DHEC Responses to Questions from the PPLS

Federalism/ states' rights

- Does South Carolina control its own medical care for its citizens?
    - **Medical care in South Carolina is generally a function of the patient-provider relationship.**

- Does the federal government/CDC control South Carolina? If so, under what circumstances?
    - **The federal government provides funding and resources to South Carolina that are, in many cases, subject to restrictions. However, decisions that affect public health in South Carolina are generally under the jurisdiction of the State or local government. DHEC is the state's public health authority and, by statute, is the sole advisor of the state in all questions involving the protection of the public health within its limits. CDC is the nation's public health agency. It is not a regulatory agency, but provides science-based, data-driven advice and recommendations to states, local jurisdictions and the general public in order to protect the public health.**

- Can we in South Carolina develop our own PPE and our own treatment modalities?
    - **Even if the State could develop its own PPE and treatment modalities, the private sector is better equipped to do this. The state does not have the resources or infrastructure to do so.**

- Can we store monoclonal antibodies and/or other treatment medicines that our citizens may need in the future?
    - **No, we cannot stockpile monoclonal antibodies because monoclonal antibodies are developed specifically and just-in-time to match and treat circulating variants of a communicable illness, such as the virus that causes COVID-19.**
    - **The Federal Government maintains a limited stockpile of medical supplies (PPE, certain vaccines, radiologic prophylactics, etc.), known as the Strategic National Stockpile.**

- Is it true that the federal government rationed monoclonal antibodies?
    - **The Federal Government determined a weekly threshold amount of COVID-19 therapeutics to be allocated for each state.**

Preparing for the next COVID type pandemic or COVID variant

- Which county in the United States and which state in the United States did the best in controlling the overall infections from COVID and the prevention of deaths (per capita)?
    - **DHEC is not aware of a study determining which county or state did the best in controlling overall infections and prevention of deaths. The state with the lowest death rate per capita is Hawaii. However, every state is unique, and it is difficult to compare states directly in this regard. The total death rates per 100,000 population for the 50 states as well as**

Washington D.C. and New York City are attached to this response. [1]

Shutdowns/ prevention of spread

- Is spread inevitable? If so, why shut down?
    - **Yes, some spread of a respiratory virus is inevitable. DHEC's role is to provide guidance based on the best available scientific information to state and local leaders. Leaders use this information and decide, based upon a myriad of factors, including but not limited to economics, individual liberty, public health, and mental health, what actions are necessary to mitigate disease-spread and deaths.**

- What about the devastating impact on learning and socialization and mental illness issues for our children?
    - **It is very important for leaders to consider the protection of children's physical and mental health when determining what actions are necessary to protect against disease-spread and deaths.** [2] [3]

- Were children without comorbidities harmed by the spread? If so, how many children did we lose, per capita?
    - **Yes. Among the 42 pediatric deaths (0-17 years old) reported in South Carolina, only 16 had confirmed comorbidities reported at the time of death. Additionally, children with or without comorbidities were impacted by the effects of Multisystem Inflammatory Syndrome in Children (MIS-C) and long COVID. MIS-C is a delayed inflammatory response to the coronavirus that can affect multiple organs, including the heart, lungs, kidneys, intestines, and brain.**

- Do children need to be vaccinated? If so, why? Do unbiased studies show the need?
    - **Yes. Vaccines, including COVID-19 vaccines, are important because they both protect the individual who receives them from developing serious illness or dying and help to reduce the spread of disease to other children and adults in the community. In a study published in the British Medical Journal, researchers reported that a two-dose vaccine schedule (including with the Moderna and Pfizer vaccines) protected against death during omicron predominance at effectiveness of 66.9% in children and 97.6% in adolescents.**
    - **MIS-C can largely be prevented by children being vaccinated against COVID-19. According to data reviewed and published by the CDC[4], the estimated effectiveness of 2 doses of Pfizer-BioNTech vaccine against MIS-C was 91% nationwide. Nationally, among critically ill MIS-C case-patients requiring life support, all were unvaccinated.**
    - **In SC less than 20% of elementary age children have completed their COVID-19 vaccine schedule and less than 44% of middle schoolers and high schoolers are fully vaccinated against COVID-19. As of February 2023, 94% (or 229) of children with MIS-C were not vaccinated. Such cases could largely be avoided if children are vaccinated.**
    - **The implications of long COVID are also a concern among the pediatric**

population, and this condition can be largely prevented with vaccination. Long COVID is separate from MIS-C, with longer-term consequences occurring even among those with milder infections. Some maladies include children not being able to return to their baseline, behavioral problems, mental clouding ("brain fog"), sleep disturbances, and in more severe cases, organ system complications such as heart, kidney, or liver problems.[5] [6]

- Will a normal human being develop immunities to fight the COVID virus and/or a variant?
    - **People with normal immune systems can develop an immune response producing protective antibodies or protective blood cells as a result of natural exposure to a disease or by vaccine-induced immunity.**

- Will immunities for one variant help with the defense of another variant? Explain.
    - **Possibly. Overall, experiences with one variant may help with your defense against another variant, depending upon the number of changes in the new variant. For instance, the emergence of the Omicron variant caused a surge in cases because of the number of critical differences between it and previous variants.**

<u>Causation</u>

- Was the Covid virus man-made or nature made? What caused the COVID virus? Where did it originate from?
    - **DHEC does not know the cause or the origin of the COVID virus.**

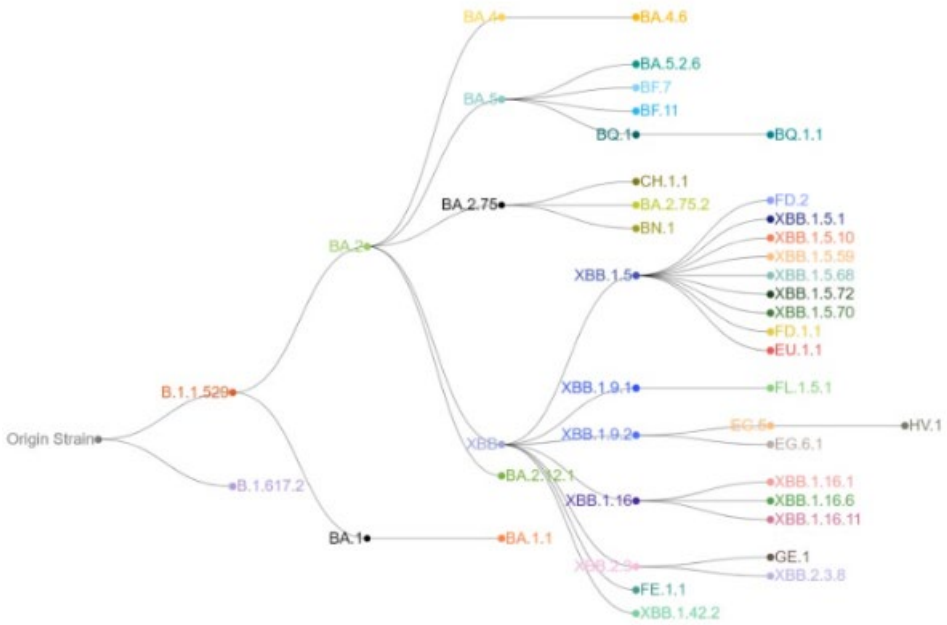
- How many variants have been identified? How many variants can we expect in the future?
    - **Since the beginning of the pandemic, we've seen a number of prominent variants, including Alpha, Beta, Gamma, Delta, Eta, Iota, Kappa, Lambda, and Omicron. Within these prominent variants there are sub-variants and even subtle changes within those sub-variants. This sort of variation is very typical of viruses; they change and mutate to better adapt to their environment to continue spreading.**
        - **See link attached for a list of active variants for the COVID-19 virus from the last year[7]**

- Identify each variant and explain how each variant is different and how do you rate the transmissibility of each variant?
    - **The below article from Yale Medicine and the British Medical Journal provides summary information for the Alpha, Beta, Delta and Omicron and it's subvariants, which have been the most impactful variants thus far. In summary:**
        - **Alpha: Some mutations in Alpha's spike protein gene were thought to make it more infectious. In the U.S., in mid-April 2021—before delta became predominant—alpha comprised 66% of cases, according to a released in June 2021 by the CDC. While it was first thought that the B.1.1.7 lineage was around 70% more**

transmissible than the original (wild type) SARS-CoV-2 virus, data now suggest that it is 30-40% more transmissible than the original.

- **Beta: The CDC linked beta with a 50% increase in transmission, but the major issue was its ability to partially evade some of the existing vaccines.**
- **Delta: Delta was a highly transmissible form of SARS-CoV-2: as much as 60% more so than the alpha variant, one study estimated. Researchers described it as an "improved" version of the alpha variant thanks to a mutation that makes it more infective in the airways. This means an increased amount of virus in the infected person such that they may expel more virus into the air, and one preprint study concluded that infected individuals had viral loads as much as 1260 times higher than people infected with wild-type SARS-CoV-2 virus.**
- **Omicron and it's subvariants: Omicron's subvariants are considered to be especially efficient spreaders of the disease, which helps explain why it is the dominant variant today. Omicron and its subvariants are the most transmissible versions of the virus thus far. One explanation was that more than 30 of Omicron's mutations are on the virus's spike protein, the part that attaches to human cells, and several of those are believed to increase the probability of infection.[8] [9]**

- **Variants and sub-variants[10]**



- **The website and diagram above show how rapidly COVID has**

changed over time. This is what viruses do if given enough time. Successful actions to limit disease spread can also limit the ability of the virus to "change their spots" which may make our actions less effective.

- How many residents of South Carolina suffered from each of the variants? How many South Carolina residents died from each variant?
    - **Most people with COVID-19 are not subtyped for which variant they have or had, therefore this information is not available**.

- What is the prescribed treatment for each variant?
    - **The patient's physician advises the appropriate treatment plan for approved COVID-19 treatments. See below for a comprehensive list of US FDA approved or authorized COVID-19 treatments.**

- What other treatments were used?
    - **Monoclonal Antibodies**
        - **Evusheld (tixagevimab co-packaged with cilgavimab; not authorized in the U.S. after January 26th, 2023)**
            - **Evusheld is a long-acting antibody therapeutic. From December 2021 – January 26, 2023, Evusheld was an option for pre-exposure prophylaxis, in other words as preventive protection from COVID-19. (ASPR, 2023)[11] Its authorization was removed as it was no longer effective for the newer variants.**
            - **Specifically, Evusheld was authorized for:**
                - **People who had moderate to severe immune compromise and may not mount an adequate immune response to COVID-19 vaccination, or**
                - **People for whom vaccination with any available COVID-19 vaccine was not recommended due to a history of severe adverse reaction to a COVID-19 vaccine and/or components of a COVID-19 vaccine.**

            - **On January 26th, 2023: The FDA revised the Emergency Use Authorization (EUA) for Evusheld to limit its use to when the combined frequency of non-susceptible SARS-CoV-2 variants nationally is less than or equal to 90%. Based on this revision, Evusheld is not currently authorized for use in the U.S. until further notice by the Agency**
                - **EUA Not Currently Authorized in U.S.[12]**
                - **FAQ for Healthcare Providers[13]**
                - **FDA's Change to Authorization for Evusheld[14]**

        - **Bebtelovimab (not authorized in the U.S. as of November 30,**

2022)

- **Bebtelovimab was a monoclonal antibody authorized for use in people with COVID-19 infection who were at moderate to high risk for severe disease, and it was notable for its activity against early Omicron variants.**
- **On November 30, 2022: The FDA announced bebtelovimab was no longer authorized for emergency use in the U.S. because it was not effective against newer Omicron subvariants BQ.1 and BQ.1.1.**
  - **EUA[15]**
  - **FAQ for Healthcare Providers[16]**

- **REGEN-COV (combination of casirivimab and imdevimab; not authorized in the U.S. as of January 24th, 2022)**
  - **REGEN-COV was a monoclonal antibody authorized for use in people with COVID-19 infection who were at moderate to high risk for severe disease, and it was notable for its activity against early Omicron variants.**
  - **On January 24th, 2022: FDA revoked the authorization for REGEN-COV due to the high frequency of the Omicron variant, which the treatment was not effective against.**
    - **EUA[17]**
    - **FAQ for Healthcare Providers[18]**

- **Bamlanivimab (not authorized in the U.S. as of April 16th, 2022)**
  - **Bamlanivimab is a monoclonal antibody designed to block viral attachment and entry into human cells, thus neutralizing the virus.**
  - **On April 16th, 2022: The FDA revoked the authorization for bamlanivimab, due to decreased effectiveness against new subvariants.**
    - **EUA[19]**
    - **EUA FAQ[20]**

- **Sotrivimab (not authorized in the U.S. as of April 5th, 2022)**
  - **On April 5th, 2022: Sotrovimab's authorization by the FDA was removed as it was not effective against the predominant subvariant in the country, Omicron BA.2.**
    - **FDA EUA[21]**
    - **FAQ for Healthcare Providers[22]**

- **Antiviral Medications**
  - **Paxlovid (nirmatrelvir co–packaged with ritonavir) - Oral antiviral medication available by prescription**
    - **Paxlovid is an FDA-approved medicine to treat adults and children 12-18 years old with mild-to-moderate**

COVID-19 infection and who are at high risk for progression to severe COVID-19, including hospitalization or death. It must be started within five days of symptom onset in order to be effective.

- **EUA[23]**
- **FAQ for Healthcare Providers[24]**
- **FAQ for FDA EUA[25]**

- **Lagevrio (molnupiravir) - Oral antiviral medication available by prescription**
  - **Lagevrio is authorized for adults aged 18 years and older with a current diagnosis of mild to moderate COVID-19 who are at high risk for progressing to severe COVID-19 including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by the FDA, such as Paxlovid, are not accessible or clinically appropriate. Data reviewed by the FDA showed Paxlovid works much better at reducing the risk of getting hospitalized with COVID-19 than molunupiravir. Molnupiravir was 30% effective at cutting the risk of getting hospitalized with COVID-19 while Paxlovid reduced the same risk by nearly 90% (FDA, 2021).**
    - **EUA[26]**
    - **FAQ for Healthcare Providers[27]**
    - **FAQ for FDA EUA[28]**
    - **FDA Briefing Document[29]**

- **Veklury (remdesivir) - commercially available IV antiviral medication**
  - **Veklury (remdesivir) is an antiviral drug that has been approved by the FDA for the treatment of adults and pediatric patients (28 days of age and older and weighing at least 3 kg). Veklury is for people who are hospitalized or not hospitalized with mild to moderate COVID-19 symptoms and are at high risk for progression to severe COVID-19, including hospitalization or death.**
  - **Veklury for non-hospitalized patients is administered as an intravenous (IV) infusion over the course of 3 days. It should be initiated within 7 days of symptom onset.**
  - **For patients who are hospitalized and require invasive mechanical ventilation and/or ECMO, the recommended total treatment duration is 10 days. Veklury should be initiated as soon as possible after diagnosis of symptomatic COVID-19.**
  - **For patients who are hospitalized and do not require invasive mechanical ventilation and/or ECMO, the recommended treatment duration is 5 days.**

- **Information for Healthcare Providers[30]**

- **Alternative Treatments:**
  - **Ivermectin**
    - **The FDA has not authorized or approved ivermectin for use in preventing or treating COVID-19 in humans or animals. Ivermectin has not been shown to be safe or effective for these indications. Ivermectin is approved for human use to treat infections caused by some parasitic worms and severe head lice and skin conditions like rosacea. Multiple studies have not found ivermectin to be effective for COVID-19.[31]**

  - **Hydroxychloroquine**
    - **Currently, The FDA and NIH state that Hydroxychloroquine should only be taken for the treatment of COVID-19 under the direction of a doctor in a clinical study. The use of Hydroxychloroquine for the treatment of COVID-19 inside or outside the hospital setting is not recommended.[32]**

  - **Silver Solution**
    - **Silver solution has not been found to be safe, effective, or recommended for the treatment or prevention of COVID-19.[33]**

  - **Olumiant (baricitinib)**
    - **Olumiant (baricitinib) is an immunomodulatory medication approved for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).**
      - **EUA[34]**
      - **EUA FAQ[35]**

  - **Actemra (tocilizumab)**
    - **On December 21, 2022, FDA approved Actemra, a biologic immunosuppressant medication, for the treatment of COVID-19 in hospitalized adult patients who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).**
      - **FDA news release[36]**
      - **FAQ EUA [37]**

- How effective were treatments concerning each variant?
  - **Monoclonal antibodies were associated with decreased risk of hospitalization and death in high-risk outpatients with mild to moderate COVID-19 caused by SARS-COV-2 variants prior to Omicron.**

(McCreary, 2022)[38]. Data from clinical trials indicated a significant reduction in hospitalization rates of up to 70% with bamlanivimab, 67% with casirivimab-imdevimab, 87% with bamlanivimab-etesevimab, and 85% with sotrovimab in high-risk patients (Al-Obaidi et al, 2022)[39]. The monoclonal antibodies were effective against the SARS-CoV-2 Delta variant to reduce hospitalization, mortality, and ICU admission rates within 30 days (Al-Obaidi, 2022). However, due to the omicron variant, data showed that these treatments were highly unlikely to be active against the omicron variant (FDA, 2022)[40]. Monoclonal antibodies are laboratory-made proteins that mimic the immune system to fight off harmful pathogens such as SARS-CoV-2.

- **The use of systemic corticosteroids have shown improvement in those hospitalized with COVID-19 "Multiple randomized trials indicate that systemic corticosteroid therapy improves clinical outcomes and reduces mortality in hospitalized patients with COVID-19 who require supplemental oxygen, presumably by mitigating the COVID-19–induced systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction." However, additional studies have shown there is no data shown to support the use of systemic corticosteroid treatments for those not in a hospital setting.[41]**

- Who controls treatment for each patient?
  - **The patient controls treatment, in collaboration with their provider.**

<u>Masks -</u>

- Do masks work? If so, what kind of masks work?
  - **Studies have demonstrated that masks reduce transmission of COVID-19 when worn properly.**
  - **N-95/KN-95 masks most effectively filter virus-sized particles when studied in laboratory conditions (Andrejko et al., 2021). As described below, surgical masks are also effective, though N-95/KN-95 are best. Data on cloth masks is mixed. However, if an individual does not have a N-95/KN-95 to wear, it is reasonable to wear a cloth mask that has two or more layers, completely covers your nose and mouth, fits snugly against the sides of your face and doesn't have gaps. [42]**

- What types of masks don't work and why?
  - **Studies have shown that single layer masks and/or masks that do not fit properly are not as effective as masks that have two or more layers and completely cover the nose and mouth with a snug fit. Multiple layers allow for more effective filtration of small aerosol particles. Masks that fail to provide adequate filtration, completely cover the nose and mouth, or that have gaps can allow small aerosol particles containing infectious material to circulate in the air. [43]**

- Discuss the effectiveness of each mask type.
  - **For all mask types, fit is a significant factor (Brooks et al., 2021). A 2021**

study (Lindsley et al.) found that N95 respirators were the most effective, blocking 99% of small aerosol particles (0 to 7 µm). The same study found that medical grade procedure masks blocked 59%, 3-ply cotton cloth face mask blocked 51%, single layer polyester neck gaiter blocked 47%, and a face shield blocked 2% of the small aerosol particles. A 2013 study (Davies et al.) similarly found that both homemade and surgical masks "significantly reduced the number of microorganisms expelled by volunteers, although the surgical mask was 3 times more effective in blocking transmission than the homemade mask." There are limitations implicit in any study; these studies cannot consider all variations of masks in each possible real-world situation.[44]

- Do we have a mask that works for each South Carolinian?
    - **No. There is not a universal mask that works in all circumstances for all people. There are masks made in sizes that properly fit individuals 2 and over.**

- Do children need to wear masks? If so, what type?
    - When at school?
        - **Depending on the circumstances and the particular disease, DHEC may recommend children wear masks that fit properly and have at least two layers.**
        - **Current DHEC guidance does not recommend wearing a mask in school for children who are healthy, free of symptoms, and who are not at high risk of getting very sick. If a child chooses to wear a mask, it should be well-fitting mask with two or more layers, completely covering the nose and mouth, fitting snugly against the sides of their face without gaps. An N-95/KN-95 is the most effective.**
    - Church?
        - **DHEC guidance also does not recommend wearing a mask in church for children who are healthy, free of symptoms, and who are not at high risk of getting very sick. If a child's family chooses to wear masks in the community, a well-fitting mask that has two or more layers, completely covers the nose and mouth, fits snugly against the sides of their face and doesn't have gaps, such as a N-95/KN-95 is the most effective.**
    - Ballfields?
        - **Masks are not currently recommended for outdoor activities.**

<u>COVID treatments</u>

- Please describe each vaccine for COVID.
    - Moderna Vaccine and Pfizer Vaccine
        - **Moderna and Pfizer are similar mRNA vaccine products.**
        - **mRNA, or messenger ribonucleic acid, is a blueprint for protein production.**
        - **The mRNA in the COVID vaccine codes for a piece of viral protein, usually part of the spike protein, on the outside of the**

virus.

- **Once the mRNA is decoded and the viral protein is created in the body, the normal immune response recognizes the foreign product and begins an immune response against the (spike) protein. In the future, when the actual virus enters the body, the person's immune system is primed to respond and fight off the infection.**
- **In addition to the mRNA component, Pfizer and Moderna vaccines contain lipids (fat-based molecules) that help stabilize the mRNA. Sugar, the same kind used in desserts or put in coffee, is also added to both vaccines; it keeps the fat molecules from sticking to each other or to the sides of the vials. Both mRNA vaccines also contain chemicals to help keep them at the appropriate pH.**
- **The Pfizer version contains four salts in this role, one of which is table salt.**
- **The Moderna version also uses four ingredients in this role: acetic acid (the main ingredient in vinegar); the salt form of acetic acid, called sodium acetate; and two chemicals in a class known as amines.**
- **The first COVID-19 mRNA vaccines manufactured covered the original strain of SARS-CoV-2 virus. As the virus mutated and Omicron strains predominated, Pfizer and Moderna produced bivalent mRNA products that covered both the original strain and BA.4/BA.5 lineages. In the summer of 2023, the FDA and CDC recommended that manufacturers adjust the COVID-19 vaccines to exclusively cover the predominant strain of Omicron, XBB.1.5.**
    - **Pfizer COVID-19 Vaccine EUA[45]**
    - **Moderna COVID-19 Vaccine EUA[46]**

- Novavax Vaccine
    - **Novavax is a protein-based COVID-19 vaccine that contains the spike protein from SARS-CoV-2 virus.**
    - **The spike protein was produced by inserting the spike protein gene into a virus that infects insect cells, so that as the cells make the virus, the spike protein is also manufactured.**
    - **The spike protein is then purified for use in the vaccine. As a result of this process, the Novavax vaccine contains small amount of viral and cellular proteins and DNA as well as some other materials that were used as nutrients during the growth process.**
    - **The proteins and DNA are not in sufficient quantities or form to cause any adverse cellular effects, and they are not of human origin.**
    - **Unlike the mRNA vaccines, Novavax contains an additive ("adjuvant"), that helps to enhance the recipient's immune response to the vaccine. This adjuvant is the same adjuvant used in the shingles vaccine.**
    - **In addition, to help with vaccine stability, Novavax contains salts,**

cholesterol, hydrochloric acid and polysorbate 80.

- **Polysorbate 80 is a chemical commonly used as an emulsifier, meaning it helps compounds with different qualities that don't normally mix to stay in solution together.**
- **Common examples of where polysorbate 80 is used in this way are ice cream, salad dressings and chocolate.**
  - **Novavax Vaccination EUA[47]**

- Janssen (Johnson & Johnson) COVID-19 Vaccine
  - **Johnson & Johnson was a viral vector vaccine. It used a type of adenovirus (a virus that can cause a cold) that couldn't replicate to carry the SARS-CoV-2 spike protein.**
  - **Its emergency use authorization (EUA) was revoked and it is no longer available for use in the US as of May 6, 2023 due to adverse events related to blood clot formation and the availability of safer and effective alternatives (Moderna, Pfizer, Novavax).**
  - **In addition to the replication incompetent adenovirus, the J&J vaccine also contained citric acid monohydrate, trisodium citrate dihydrate, ethanol, 2-hydroxypropyl-β-cyclodextrin (HBCD), polysorbate-80, sodium chloride.**

- Booster Doses
  - **The currently authorized vaccines are available as "booster" doses based on age, immunocompromise, and personal medical history.**

- Please describe each vaccine for each variant of COVID.
  - **The first COVID-19 mRNA vaccines covered the original strain of SARS-CoV-2 virus. As the virus mutated and Omicron strains predominated, a bivalent mRNA was produced that covered both the original strain and BA.4 and BA.5 lineages. The FDA and CDC recommended that manufacturers adjust the COVID-19 vaccines to exclusively cover the predominant strain of Omicron, XBB.1.5. The CDC ACIP committee will be meeting 9/12/23 to review the latest findings and studies in order to make recommendations for the general public regarding vaccinations with this new monovalent XBB.1.5 vaccine for 2023/2024 season. This is similar to how influenza vaccines are developed and approved each year.**

Immunity

- Explain what immunity is.
  - **Immunity is defined as the protection from a disease. If you are immune to a disease, you can be exposed to it without becoming infected. Immunity to a disease is often achieved through the presence of antibodies, which are disease specific and can be acquired through what's known as "active" or "passive" immunity. Active immunity is derived from exposure to illness or through vaccination. Passive immunity is derived from antibodies passed from one person to another, such as the immunity passed from a**

mother to child.

- Suppose you have a 57 score. What does that mean?
    - **Immunity scores are not accepted or endorsed as a means of determining risk of SARS-COV-2 infection or COVID-19 complications.**

- Doc says a 57 score was bulletproof. What does that mean?
    - **Immunity scores are not accepted or endorsed as a means of determining risk of SARS-COV-2 infection or COVID-19 complications.**

- Why shouldn't we determine an immunity before we require a vaccine?
    - **At the initial stages of a novel virus, such as COVID-19, it is not possible to determine what level of antibodies is protective.**

Effects of vaccine treatment

- Please describe each treatment vaccine.
    - **Please see info above about vaccination types.**
- Please describe the effectiveness of each treatment vaccine.
    - **COVID-19 vaccines have been updated in order to be more effective as the SARS-CoV-2 virus has mutated. That being the case, there is not a single value of "effectiveness" for the vaccine because factors like age and a person's immune status affect how much someone responds to vaccination. There are also differences in vaccine effectiveness at preventing any symptomatic disease versus its effectiveness at preventing severe disease, which can also vary between different populations like children and adults. Finally, as with other vaccines, effectiveness can wane over time and require "boosters" (e.g. tetanus).**
    - **The following estimates of vaccine effectiveness are reported by the CDC[48]**
        - **2 weeks to one month after vaccination, one dose of Moderna vaccine given to children 3-5 years old between July 4, 2022 and April 8, 2023 was estimated to be 40% effective at preventing symptomatic COVID-19 infection.**
        - **Complete monovalent primary series vaccination helped provide protection for children aged 3–5 years against symptomatic SARS-CoV-2 infection for at least the first 3 months after vaccination.**
        - **Waning of monovalent Moderna primary series appears to occur by 4–6 months after the second dose.**

    - **A bivalent booster COVID-19 mRNA vaccine given to immunocompetent adults aged 18-64 years of age was 68% effective at preventing hospitalization when the vaccine was given 7-59 days earlier; for adults 65 years and older, the effectiveness of preventing hospitalization was 64%. As time since vaccination increased, the vaccine's effectiveness at preventing hospitalization decreased.**

- Please describe known or suspected side effects from each vaccine.

- **Serious or severe side effects are rare. Side effects that have been reported (but are not limited to) with Pfizer-BioNTech COVID-19 Vaccine, Bivalent, Pfizer-BioNTech COVID-19 Vaccine, or Comirnaty (COVID-19 Vaccine, mRNA) include:**
  - **Severe allergic reactions**
  - **Non-severe allergic reactions such as rash, itching, hives, or swelling of the face**
  - **Myocarditis (inflammation of the heart muscle)**
  - **Pericarditis (inflammation of the lining outside the heart)**
  - **Injection site pain/tenderness**
  - **Tiredness**
  - **Headache**
  - **Muscle pain**
  - **Chills**
  - **Joint pain**
  - **Fever**
  - **Injection site swelling**
  - **Injection site redness**
  - **Nausea**
  - **Feeling unwell**
  - **Swollen lymph nodes (lymphadenopathy)**
  - **Decreased appetite**
  - **Diarrhea**
  - **Vomiting**
  - **Arm pain**
  - **Fainting in association with injection of the vaccine**
  - **Dizziness**
  - **Irritability**
  - **The Vaccine and Related Biological Products Advisory Committee (VRBPAC) briefing materials on side effects for this vaccine is attached to this document.[49]**

- **Serious or severe side effects are rare. Side effects that have been reported (but not limited to) with Spikevax (COVID-19 Vaccine mRNA), Moderna COVID-19 Vaccine, and Moderna COVID-19 Vaccine, Bivalent include:**
  - **Difficulty breathing**
  - **Swelling of your face and throat**
  - **A bad rash all over your body**
  - **Dizziness and weakness**
  - **Chest pain**
  - **Shortness of breath**
  - **Feelings of having a fast-beating, fluttering, or pounding heart**
  - **Injection site reactions: pain, tenderness and swelling of the lymph nodes in the same arm of the injection, swelling (hardness), and redness**

        - **General side effects: fatigue, headache, muscle pain, joint pain, chills, nausea and vomiting, fever, and rash**
        - **Severe allergic reaction**
        - **Myocarditis (inflammation of the heart muscle)**
        - **Pericarditis (inflammation of the lining outside the heart)**
        - **Fainting in association with injection of the vaccine**
        - **The Vaccine and Related Biological Products Advisory Committee (VRBPAC) briefing materials on side effects for this vaccine is attached to this document.[50]**

    - **Serious or severe side effects are rare. Side effects that have been reported (but not limited to) with Novavax COVID-19 Vaccine, Adjuvanted include:**
        - **Difficulty breathing**
        - **Swelling of your face and throat**
        - **A fast heartbeat**
        - **A bad rash all over your body**
        - **Dizziness and weakness**
        - **Myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart). Symptoms include:**
            - **Chest pain Revised**
            - **Shortness of breath**
            - **Feelings of having a fast-beating, fluttering, or pounding heart**
        - **Injection site reactions: pain/tenderness, swelling, redness and itching**
        - **Fatigue or generally feeling unwell**
        - **Muscle pain**
        - **Headache**
        - **Joint pain**
        - **Nausea**
        - **Vomiting**
        - **Fever**
        - **Chills**
        - **Allergic reactions such as hives and swelling of the face**
        - **Swollen lymph nodes**
        - **Paresthesia (unusual feeling in the skin such as tingling or a crawling feeling)**
        - **Hypoesthesia (decreased feeling or sensitivity, especially in the skin)**
        - **The Vaccine and Related Biological Products Advisory Committee (VRBPAC) briefing materials on side effects for this vaccine is attached to this document. [51]**

- Have studies been done to determine the side effects of each of these vaccines?
    - **COVID-19 vaccines went through extensive development and testing to generate non-clinical, clinical and manufacturing data in order for an**

Emergency Use Authorization (EUA) to be issued for use beginning in 2020. An EUA request was able to be submitted to and analyzed by the FDA based on final or interim analysis of clinical trial data. The first vaccine to prevent COVID-19 was approved for use for 16 years and older (Pfizer) and 18 years and older (Moderna) based on a randomized controlled clinical trial which found the COVID-19 vaccine to be safe and highly effective.

- **The CDC and FDA shared responsibility of post-authorization vaccination monitoring. Programs were put in place to rapidly detect any issues that may have risen post-authorization. Examples of these measures include:**
  - **The federal Vaccine Adverse Event Reporting System (VAERS) is a passive vaccine safety monitoring system that allows anyone from a patient to a provider to report potentially negative vaccine reactions for further review. These events can include anything from swelling at the injection site, to allergic reactions to vaccine ingredients, to more serious complications such as thrombosis with thrombocytopenia syndrome. Vaccine manufacturers will identify the most common side effects of vaccine administration throughout the clinical trial process, and those known side effects account for a large proportion of VAERS reports. More severe events are thoroughly investigated by federal entities to determine if a causal signal is present between vaccine administration and the event. Some additional limitations of the VAERS system are identified as follows:**
    - **VAERS reports may contain information that is incomplete, inaccurate, coincidental, or unverifiable. Reports to VAERS can also be biased. As a result, there are limitations on how the data can be used scientifically. Data from VAERS reports should always be interpreted with these limitations in mind.**
    - **VAERS accepts reports from anyone. Patients, parents, caregivers and healthcare providers (HCP) are encouraged to report adverse events after vaccination to VAERS even if it is not clear that the vaccine caused the adverse event. In addition, HCP are required to report certain adverse events after vaccination.**
  - **VAERS is not designed to detect if a vaccine caused an adverse event, but it can identify unusual or unexpected patterns of reporting that might indicate possible safety problems requiring a closer look.**

- Are we performing any studies for the protection of South Carolina citizens?
  - **No, DHEC is not performing any studies related to the COVID-19 vaccine. However, DHEC staff do regularly review the literature of published research studies, the VAERS database, and other sources to inform our recommendations and actions.**

- How many people have blood and/or heart conditions as a result of taking the vaccine?
    - **As of September 1, 2023, there have been 9,805 VAERS reports nationwide with 11,194 events involving embolism, thrombosis, myocarditis, pericarditis, and/or Thrombosis with Thrombocytopenia Syndrome (TTS). In South Carolina, there have been 111 VAERS reports with 125 events involving the same diagnoses. The specific breakdown of each reported event is attached to this document. It is important to note that each VAERS entry may contain more than one diagnosis per reported event, leading to more entries than reported events.[52] [53]**

- What other side effects, if any, are there from each of the treatment modalities?
    - **Paxlovid (nirmatrelvir co –packaged with ritonavir) Federally Allocated Oral Antiviral**
        - **Paxlovid consists of nirmatrelvir and ritonavir, and ritonavir can interact with many other medicines, which may lead to serious or life-threatening adverse reactions.**
        - **Patients should tell their health care providers all of the medicines they are taking, including over-the-counter medications and herbal supplements, when deciding whether to take Paxlovid.**
        - **Because of the importance of reducing the risk of significant drug-drug interactions with Paxlovid, the approved Prescribing Information and authorized Fact Sheet for Health Care Providers for the Paxlovid EUA include a boxed warning with instructions for providers to review all medications taken by the patient to assess for potential drug-drug interactions and determine if other medicines that a patient may be taking require a dose adjustment, interruption and/or additional monitoring.**
        - **As of July 7th, 2023, the most common side effects of taking Paxlovid include impaired sense of taste (for example, a metallic taste in the mouth) and diarrhea. Liver problems have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering Paxlovid to patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis.**
        - **Patients should talk with their health care provider if they have a history of liver or renal problems. Paxlovid is not recommended for patients with severe kidney problems, and a different dose is needed for patients with moderate kidney problems.**
        - **See Warnings and Precautions in the FDA-approved Prescribing Information and the Fact Sheet for Health Care Providers for additional information on risks associated with Paxlovid.**
            - **EUA[54]**
            - **FAQ for Healthcare Providers[55]**
            - **FAQ for FDA EUA[56]**

    - **Lagevrio (molnupiravir)-Federally Allocated Oral Antiviral**
        - **Possible side effects of Lagevrio include diarrhea, nausea, and**

dizziness.

- **Lagevrio is not recommended for use during pregnancy because findings from animal reproduction studies showed that Lagevrio may cause fetal harm when administered to pregnant individuals.**
- **Hypersensitivity, anaphylaxis, angioedema, erythema, rash, and urticaria adverse reactions have been identified during post-authorization use of Lagevrio; however, it is unclear whether these were caused by the medication.**
  - **EUA[57]**
  - **FAQ for Healthcare Providers[58]**
  - **FAQ for FDA EUA[59]**

- **Veklury (remdesivir)-Commercially Available IV Antiviral**
  - **Possible side effects include increased levels of liver enzymes, which may be a sign of liver injury; and allergic reactions, which may include changes in blood pressure and heart rate, low blood oxygen level, fever, shortness of breath, wheezing, swelling (e.g., lips, around eyes, under the skin), rash, nausea, sweating or shivering.**
  - **DHCP Letter[60]**

- **Monoclonal Antibodies**
  - **Evusheld (No longer authorized in the U.S. as of January 26th, 2023)**
    - **Possible side effects of Evusheld include the following: Allergic reactions can happen during and after injection of Evusheld.**
    - **Reactions to Evusheld may include difficulty breathing or swallowing; shortness of breath; wheezing; swelling of the face, lips, tongue or throat; rash including hives; or itching.**
    - **Everyone who receives Evusheld should be observed after injection for at least one hour to monitor for hypersensitivity reactions, and Evusheld should only be administered under the supervision of a health care provider with appropriate medical support to manage severe allergic reactions.**
    - **Clinicians should consider consulting an allergist-immunologist prior to administering Evusheld to individuals with a history of a severe allergic reaction to a COVID-19 vaccine.**
    - **The side effects of getting any medicine by intramuscular injection may include pain, bruising of the skin, soreness, swelling, and possible bleeding or infection at the injection site.**
    - **Serious cardiac adverse events (such as myocardial infarction and heart failure) were infrequent in the clinical trial evaluating Evusheld for pre-exposure prophylaxis for prevention.**
    - **However, more trial participants had serious cardiac adverse events after receiving Evusheld compared to placebo.**
    - **These participants all had risk factors for cardiac disease or a history of cardiovascular disease before participating in the**

clinical trial. It is not clear if Evusheld caused these cardiac adverse events.

- **EUA Not Currently Authorized in U.S.[61]**
- **FAQ for EUA[62]**
- **FAQ for Healthcare Providers[63]**

- **Bebtelovimab (No longer authorized in the U.S. as of November 30th, 2022)**
  - **Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of other SARS-CoV-2 monoclonal antibodies and could occur with administration of bebtelovimab.**
  - **If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.**
  - **Infusion-related reactions, which may occur up to 24 hours after the injection, have been observed in clinical trials of bebtelovimab when administered with other monoclonal antibodies and may occur with use of bebtelovimab alone.**
  - **These reactions may be severe or life threatening. Signs and symptoms of infusion-related reactions may include: fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vasovagal reactions (e.g., pre-syncope, syncope), dizziness and diaphoresis (excessive sweating).**
  - **There have been reports of clinical worsening of COVID-19 after administration of COVID-19 monoclonal antibodies under EUA; signs or symptoms may include fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), fatigue, and altered mental status.**
  - **Some of these events required hospitalization. It is not known if these events were related to COVID-19 monoclonal antibody use or were due to progression of COVID-19.**
  - **The following adverse reactions (i.e., adverse events assessed as causally related) have been observed in those who have received bebtelovimab alone or when administered with other monoclonal antibodies at the authorized dose or higher:**
    - **EUA[64]**
    - **FAQ for Healthcare Providers[65]**
    - **FAQ for EUA[66]**

- **REGEN-COV (No longer authorized in the U.S. as of January 24th, 2022)**
  - **Approximately 16,000 non-hospitalized and hospitalized subjects with symptomatic COVID-19 received REGEN-COV intravenously in clinical trials at doses of 600 mg of casirivimab and 600 mg of imdevimab or higher doses.**
  - **Approximately 2,500 subjects have received subcutaneous injections of 600 mg of casirivimab and 600 mg of imdevimab or higher doses. Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of REGEN-COV.**
  - **Infusion-related reactions have been observed with administration of REGEN-COV.**
  - **In the clinical trial in non-hospitalized patients, these reactions have been rare (infusion-related reactions of at least moderate severity were observed in 10 subjects (0.2%) who received REGEN-COV intravenously at the authorized dose or a higher dose) but may be severe or life threatening. Signs and symptoms of infusion-related reactions may include:**
    - **fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vasovagal reactions (e.g., pre-syncope, syncope), dizziness.**
  - **Based on reporting of adverse events that occurred after administration of REGEN-COV, clinical worsening of COVID-19 after administration has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization.**
  - **It is not known if these events were related to REGEN-COV use or were due to progression of COVID-19.**
  - **In a separate trial in healthy (non-hospitalized) adults, 600 mg of casirivimab and 600 mg of imdevimab were administered together subcutaneously in approximately 700 subjects.**
  - **Injection site reactions were the most reported adverse events after subcutaneous administration; and the remaining side effects with subcutaneous administration were like those observed with intravenous administration.**
  - **Injection site reactions were the commonly reported side effects with repeat dosing every 4 weeks for six months.**
  - **These are not all the possible side effects of REGEN-COV, as not a lot of people have received REGENCOV.**
    - **EUA Link[67]**
    - **FAQ for Healthcare Providers[68]**
    - **FAQ on EUA[69]**

- **Sotrivimab (No longer authorized in the U.S. as of April 5th, 2022)**
  - **Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of sotrovimab in clinical trials.**
  - **If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.**
  - **Infusion-related reactions have been observed with administration of sotrovimab.**
  - **Signs and symptoms of infusion-related reactions may include: fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, or dizziness.**
  - **There have been reports of clinical worsening of COVID-19 after administration of COVID-19 monoclonal antibodies under EUA; signs or symptoms may include fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), fatigue, and altered mental status.**
    - **EUA[70]**
    - **FAQ for Healthcare Providers[71]**
    - **FAQ for EUA[72]**

- Biden recently said the new vaccine "really works". How do you interpret that statement in reference to the early vaccines?
  - **We cannot speculate as to what President Biden meant by this statement.**

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[1] US Death Data Table

[2] DHEC worked closely with the SC Dept. of Education, individual school districts, Superintendents, school nurses, and others to provide for the safety of students and staff.

DHEC provided free resources such as COVID-19 tests, consent and attestation forms, third party COVID-19 testing vendors, opportunity for grant reimbursement to school districts performing their own tests, and many other resources and guidance documents to assist schools as they sought to provide the safest and most effective learning environment for students and staff.

DHEC provided guidance that allowed for students and staff to return in person to school sooner than advised by the CDC and stay in the classroom longer than advised by the CDC. DHEC created its own school guidance booklet and many visual materials illustrating current DHEC guidance.

DHEC provided portable room air cleaners with replacement filter kits sufficient for up to 3 years of filtration. 102 school districts and charter schools received 7,092 air cleaner units. Studies have indicated that portable HEPA air cleaners reduced exposure to SARS-CoV-2 aerosols in indoor environments.

[3] Air purifiers sent to school districts/charter schools:

School District or Charter School Name	Type	Portable Room Air Cleaner Units
Aiken County Public Schools	District	15

Anderson School District 1	District	115
Anderson School District 2	District	35
Anderson School District 4	District	30
Anderson School District 5	District	45
Bamberg County School District	District	200
Barnwell County Consolidated School District	District	30
Barnwell School District 45	District	20
Berkeley County School District	District	240
Calhoun County Schools	District	6
Charleston County School District	District	395
Chester County School District	District	70
Darlington County Schools	District	50
Department of Juvenile Justice School District	District	25
Dillon School District Four	District	540
Dorchester School District 2	District	130
Dorchester School District 4	District	75
Edgefield County School District	District	87
Fairfield County School District	District	50
Florence 1 Schools	District	325
Florence County School District 2	District	4
Florence County School District 3	District	50
Florence County School District Five	District	195
Georgetown County School District	District	45
Greenville County Schools	District	20
Hampton County School District	District	112
Horry County Schools	District	228
Jasper County School District	District	35
Kershaw County School District	District	95
Laurens County School District 56	District	6
Lee County School District	District	25
Lexington County School District 1	District	90
Lexington County School District 3	District	32
Lexington County School District 4	District	20
Marion County School District	District	30
Orangeburg County School District	District	1000
Richland County School District 1	District	250
Richland County School District 2	District	155
Saluda County School District One	District	30
School District of Oconee County	District	30
South Carolina School for the Deaf and the Blind	District	30

Spartanburg County School District 1	District	50
Spartanburg County School District 2	District	40
Spartanburg County School District 3	District	20
Spartanburg County School District 4	District	9
Spartanburg County School District 5	District	16
Spartanburg County School District 7	District	65
Sumter School District	District	735
The School District of Newberry County	District	75
Union County School District	District	75
Ware Shoals School District 51 (Greenwood)	District	35
Williamsburg County School District	District	305
York County School District 1	District	50
York County School District 2-Clover	District	80
York County School District 3-Rock Hill Schools	District	130
York County School District 4-Fort Mill School District IV	District	75
Academy of Hope	Charter	3
Advantage Academy	Charter	5
Beaufort-Jasper Academy for Career Excellence (ACE)	Charter	5
Bettis Preparatory	Charter	5
Butler Academy	Charter	22
Calhoun Falls Charter School	Charter	10
Cape Romain Environmental Education Charter School	Charter	5
Carolina Shores Acceleration Academy	Charter	5
Cherokee Charter Academy	Charter	13
Compass Collegiate Academy	Charter	9
East Cooper Montessori Charter School	Charter	5
East Point Academy	Charter	5
Felton Laboratory Charter School	Charter	5
Global Academy of South Carolina	Charter	10
Goucher Charter Academy	Charter	28
Gray Collegiate Academy	Charter	10
Green Charter Elementary/Middle School	Charter	8
GREEN Charter Lowcountry	Charter	5
GREEN Charter School	Charter	5
Green Charter School of the Midlands	Charter	3
Green Upstate High School	Charter	3
Greer Middle College Charter High School	Charter	10
Greg Mathis Charter High School	Charter	5
Horse Creek Academy	Charter	50
Lakes and Bridges Charter School	Charter	3

Lead Academy	Charter	5
Learn4Life High School-Charleston	Charter	1
Legacy Early College	Charter	5
Legion Collegiate Academy	Charter	5
Liberty Steam Charter School	Charter	10
Limestone Charter Association	Charter	9
Midlands Arts Conservatory	Charter	2
Midlands STEM Institute- Charter Institute at Erskine	Charter	30
Montessori School of Camden	Charter	8
Orangeburg High School for Health Professions	Charter	10
Pee Dee Math, Science and Technology Academy	Charter	5
Polaris Charter School	Charter	5
SC Governor's School for Agriculture at John de la Howe	Charter	5
SC Whitmore School	Charter	2
Spartanburg Preparatory School	Charter	5
Summit Classical School	Charter	3
Tall Pines STEM Academy	Charter	5
Thornwell Charter School- Charter Institute at Erskine	Charter	4
Virtus Academy of South Carolina- Charter Institute at Erskine	Charter	3
York Preparatory Academy	Charter	3
Youth Leadership Academy	Charter	5

[4] https://www.cdc.gov/mmwr/volumes/71/wr/mm7102e1.htm?s_cid=mm7102e1_w
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[13] https://www.fda.gov/media/154701/download
[14] https://aspr.hhs.gov/COVID-19/Therapeutics/Products/Evusheld/Documents/ASPR-Info-Sheet-FDA-Change-to-Authorization-of-Evusheld.pdf
[15] http://www.fda.gov/media/156151/download
[16] https://www.fda.gov/media/156152/download
[17] https://www.fda.gov/media/145610/download
[18] https://www.fda.gov/media/145611/download
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State/Territory	Total Deaths	Total Death rate per 100000
Alabama	22354	359
Alaska	1514	226.9
Arizona	29703	324.7
Arkansas	12544	337.9
California	108806	245.5
Colorado	14968	246.9
Connecticut	12286	251.8
Delaware	3456	258.6
District of Columbia	1869	280.9
Florida	79898	248.8
Georgia	36142	316.3
Hawaii	1953	97.9
Idaho	5514	261.3
Illinois	40358	262.6
Indiana	25934	326.6
Iowa	11113	269.2
Kansas	10589	300
Kentucky	19965	371.6
Louisiana	17644	329.8
Maine	3274	163.6
Maryland	18115	247.9
Massachusetts	20923	235.1
Michigan	37724	296.5
Minnesota	15530	224.6
Mississippi	14814	427.7
Missouri	22468	289.7
Montana	3870	268.5
Nebraska	5766	247.6
Nevada	11918	332.1
New Hampshire	3288	178.8
New Jersey	35312	301.8
New Mexico	9326	360.4
New York	81138	313.7
New York (excludes NYC)	41801	271.1
New York City	39337	377.4
North Carolina	33873	270.5
North Dakota	2638	282.8
Ohio	49719	334.1
Oklahoma	19524	425.8
Oregon	9286	176.6
Pennsylvania	52670	295
Rhode Island	3978	268.6
South Carolina	21259	328.3
South Dakota	3273	299.1
Tennessee	28671	345.5
Texas	102239	355.4
Utah	5520	197.2
Vermont	1020	117
Virginia	23578	234.9
Washington	15029	173.1
West Virginia	8635	347.2
Wisconsin	17150	231.8
Wyoming	2140	303.7

Actions by DHEC to minimize the impact of children's health:

- **DHEC worked closely with the SC Dept. of Education, individual school districts, Superintendents, school nurses, and others to provide for the safety of students and staff.**

- **DHEC provided free resources such as COVID-19 tests, consent and attestation forms, third party COVID-19 testing vendors, opportunity for grant reimbursement to school districts performing their own tests, and many other resources and guidance documents to assist schools as they sought to provide the safest and most effective learning environment for students and staff.**

- **DHEC provided guidance that allowed for students and staff to return in person to school sooner than advised by the CDC and stay in the classroom longer than advised by the CDC. DHEC created its own school guidance booklet and many visual materials illustrating current DHEC guidance.**

- **DHEC provided portable room air cleaners with replacement filter kits sufficient for up to 3 years of filtration. 102 school districts and charter schools received 7,092 air cleaner units. Studies have indicated that portable HEPA air cleaners reduced exposure to SARS-CoV-2 aerosols in indoor environments.**

Air purifiers sent to school districts/charter schools:

School District or Charter School Name	Type	Portable Room Air Cleaner Units
Aiken County Public Schools	District	15
Anderson School District 1	District	115
Anderson School District 2	District	35
Anderson School District 4	District	30
Anderson School District 5	District	45
Bamberg County School District	District	200
Barnwell County Consolidated School District	District	30
Barnwell School District 45	District	20
Berkeley County School District	District	240
Calhoun County Schools	District	6
Charleston County School District	District	395
Chester County School District	District	70
Darlington County Schools	District	50
Department of Juvenile Justice School District	District	25
Dillon School District Four	District	540
Dorchester School District 2	District	130
Dorchester School District 4	District	75
Edgefield County School District	District	87
Fairfield County School District	District	50
Florence 1 Schools	District	325
Florence County School District 2	District	4
Florence County School District 3	District	50
Florence County School District Five	District	195
Georgetown County School District	District	45
Greenville County Schools	District	20
Hampton County School District	District	112
Horry County Schools	District	228
Jasper County School District	District	35
Kershaw County School District	District	95
Laurens County School District 56	District	6
Lee County School District	District	25
Lexington County School District 1	District	90
Lexington County School District 3	District	32
Lexington County School District 4	District	20
Marion County School District	District	30
Orangeburg County School District	District	1000
Richland County School District 1	District	250
Richland County School District 2	District	155
Saluda County School District One	District	30
School District of Oconee County	District	30

Air purifiers sent to school districts/charter schools:

South Carolina School for the Deaf and the Blind	District	30
Spartanburg County School District 1	District	50
Spartanburg County School District 2	District	40
Spartanburg County School District 3	District	20
Spartanburg County School District 4	District	9
Spartanburg County School District 5	District	16
Spartanburg County School District 7	District	65
Sumter School District	District	735
The School District of Newberry County	District	75
Union County School District	District	75
Ware Shoals School District 51 (Greenwood)	District	35
Williamsburg County School District	District	305
York County School District 1	District	50
York County School District 2-Clover	District	80
York County School District 3-Rock Hill Schools	District	130
York County School District 4-Fort Mill School District IV	District	75
Academy of Hope	Charter	3
Advantage Academy	Charter	5
Beaufort-Jasper Academy for Career Excellence (ACE)	Charter	5
Bettis Preparatory	Charter	5
Butler Academy	Charter	22
Calhoun Falls Charter School	Charter	10
Cape Romain Environmental Education Charter School	Charter	5
Carolina Shores Acceleration Academy	Charter	5
Cherokee Charter Academy	Charter	13
Compass Collegiate Academy	Charter	9
East Cooper Montessori Charter School	Charter	5
East Point Academy	Charter	5
Felton Laboratory Charter School	Charter	5
Global Academy of South Carolina	Charter	10
Goucher Charter Academy	Charter	28
Gray Collegiate Academy	Charter	10
Green Charter Elementary/Middle School	Charter	8
GREEN Charter Lowcountry	Charter	5
GREEN Charter School	Charter	5
Green Charter School of the Midlands	Charter	3
Green Upstate High School	Charter	3
Greer Middle College Charter High School	Charter	10
Greg Mathis Charter High School	Charter	5
Horse Creek Academy	Charter	50
Lakes and Bridges Charter School	Charter	3

Air purifiers sent to school districts/charter schools:

Lead Academy	Charter	5
Learn4Life High School-Charleston	Charter	1
Legacy Early College	Charter	5
Legion Collegiate Academy	Charter	5
Liberty Steam Charter School	Charter	10
Limestone Charter Association	Charter	9
Midlands Arts Conservatory	Charter	2
Midlands STEM Institute- Charter Institute at Erskine	Charter	30
Montessori School of Camden	Charter	8
Orangeburg High School for Health Professions	Charter	10
Pee Dee Math, Science and Technology Academy	Charter	5
Polaris Charter School	Charter	5
SC Governor's School for Agriculture at John de la Howe	Charter	5
SC Whitmore School	Charter	2
Spartanburg Preparatory School	Charter	5
Summit Classical School	Charter	3
Tall Pines STEM Academy	Charter	5
Thornwell Charter School- Charter Institute at Erskine	Charter	4
Virtus Academy of South Carolina- Charter Institute at Erskine	Charter	3
York Preparatory Academy	Charter	3
Youth Leadership Academy	Charter	5

Effectiveness of BNT162b2 (Pfizer-BioNTech) mRNA Vaccination Against Multisystem Inflammatory Syndrome in Children Among Persons Aged 12–18 Years — United States, July–December 2021

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Multisystem inflammatory syndrome in children (MIS-C) is a severe postinfectious hyperinflammatory condition, which generally occurs 2–6 weeks after a typically mild or asymptomatic infection with SARS-CoV-2, the virus that causes COVID-19 (*1–3*). In the United States, the BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine is currently authorized for use in children and adolescents aged 5–15 years under an Emergency Use Authorization and is fully licensed by the Food and Drug Administration for persons aged ≥16 years (*4*). Prelicensure randomized trials in persons aged ≥5 years documented high vaccine efficacy and immunogenicity (*5*),[§] and real-world studies in persons aged 12–18 years demonstrated high vaccine effectiveness (VE) against severe COVID-19 (*6*). Recent evidence suggests that COVID-19 vaccination is associated with lower MIS-C incidence among adolescents (*7*); however, VE of the 2-dose Pfizer-BioNTech regimen against MIS-C has not been evaluated. The effectiveness of 2 doses of Pfizer-BioNTech vaccine received ≥28 days before hospital admission in preventing MIS-C was assessed using a test-negative case-control design[¶] among hospitalized patients aged 12–18 years at 24 pediatric hospitals in 20 states[**] during July 1–December 9, 2021, the period when most MIS-C patients could be temporally linked to SARS-CoV-2 B.1.617.2 (Delta) variant predominance. Patients with MIS-C (case-patients) and two groups of hospitalized controls matched to case-patients were evaluated: test-negative controls had at least one COVID-19–like symptom and negative SARS-CoV-2 reverse transcription–polymerase chain reaction (RT-PCR) or antigen-based assay results, and syndrome-negative controls were hospitalized patients without COVID-19–like illness. Among 102 MIS-C case-patients and 181 hospitalized controls, estimated effectiveness of 2 doses of Pfizer-BioNTech vaccine against MIS-C was 91% (95% CI = 78%–97%). All 38 MIS-C patients requiring life support were unvaccinated. Receipt of 2 doses of the Pfizer-BioNTech vaccine is associated with a high level of protection against MIS-C in persons aged 12–18 years, highlighting the importance of vaccination among all eligible children.

This study used a test-negative case-control design, commonly used for postauthorization VE evaluations (*6,8*). Patients were hospitalized at 24 participating sites in the Overcoming COVID-19 Network, a collaboration between CDC and approximately 70 pediatric hospitals nationwide to assess COVID-19 complications in children and young adults.[††] Given that children aged 5–11 years were not recommended to receive the Pfizer-BioNTech vaccine until November 2, 2021,[§§] this analysis focused on persons aged 12–18 years.[¶¶] VE was assessed by comparing the odds of antecedent vaccination between MIS-C patients and hospitalized controls without evidence of SARS-CoV-2 infection during July 1–December 9, 2021. Case-patients met CDC criteria for MIS-C,[***] which

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§ https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/comirnaty-and-pfizer-biontech-covid-19-vaccine

¶ In this context, the test-negative case-control design was used to compare the odds of previous Pfizer-BioNTech vaccine receipt among inpatients without evidence of SARS-CoV-2 infection with case-patients hospitalized for MIS-C. These control patients included those with respiratory virus infection who received a negative test result for SARS-CoV-2 infection (test-negative) or patients without symptoms compatible with COVID-19 (syndrome-negative), including fever, cough, shortness of breath, loss of taste, loss of smell, gastrointestinal symptoms, use of respiratory support for the acute illness, or new pulmonary findings on chest imaging consistent with pneumonia.

** This investigation included patients enrolled from 24 pediatric hospitals in 20 states: Alabama, Arkansas, California, Colorado, Georgia, Illinois, Indiana, Louisiana, Massachusetts, Michigan, Mississippi, Missouri, Nebraska, New Jersey, North Carolina, Ohio, Pennsylvania, South Carolina, Tennessee, and Texas.

†† https://overcomecovid.org/

§§ CDC recommendation for pediatric COVID-19 vaccine for children aged 5–11 years: https://www.cdc.gov/media/releases/2021/s1102-PediatricCOVID-19Vaccine.html

¶¶ The lower age bound for the study population was set at 12 years and 49 days to allow for the first vaccine dose on the patient's 12th birthday, a second dose 21 days thereafter, and a 28-day window between the patient's second dose and hospitalization for MIS-C.

*** CDC case definition criteria for MIS-C are available at https://www.cdc.gov/mis/mis-c/hcp/index.html. For the purposes of this analysis, all MIS-C case-patients were required to have laboratory evidence of current or recent infection (RT-PCR, antigen-, or antibody-based testing).

included a clinically severe illness requiring hospitalization, temperature ≥100.4°F (38°C) for ≥24 hours or subjective fever, evidence of inflammation (demonstrated by elevated levels of inflammatory markers), involvement of two or more organ systems, no alternative plausible diagnosis, and current or recent SARS-CoV-2 infection, indicated by a positive result from an RT-PCR test, serologic test, or antigen test. Two hospitalized control groups included 1) patients with one or more symptoms consistent with COVID-19, but with a negative result from a SARS-CoV-2 RT-PCR or antigen test (test-negative) and 2) patients without symptoms compatible with COVID-19 who might or might not have received SARS-CoV-2 testing (syndrome-negative).[†††] Eligible controls were matched to case-patients by site, age group (12–15 years and 16–18 years), and case-patient hospitalization date (within plus or minus approximately 3 weeks).

Vaccination status was verified through searches of state immunization information systems, electronic medical records, or other sources, including documentation from pediatricians or patient immunization cards. For this analysis, persons were categorized as unvaccinated or fully vaccinated on or before the case-patient hospitalization date. Patients were considered unvaccinated if they had received no doses of the Pfizer-BioNTech vaccine; full vaccination in terms of expected protection against MIS-C was defined as receipt of 2 doses of Pfizer-BioNTech COVID-19 vaccine, with receipt of the second dose ≥28 days before hospital admission. The 28-day window was selected because a person is considered fully vaccinated against COVID-19 ≥14 days after receipt of the second dose, and MIS-C generally occurs approximately 2–6 weeks after SARS-CoV-2 infection, with most cases occurring by the fourth week (*1–3*). Patients were excluded based on the following conditions: 1) receipt of only 1 vaccine dose; 2) receipt of the second dose within 28 days of hospital admission; 3) age 12–15 years and admission before July 1, 2021 (given that vaccination was not expanded to this age group until May 12, 2021); and 4) receipt of any COVID-19 vaccine other than Pfizer-BioNTech.

Demographic characteristics, clinical information related to the current illness, and SARS-CoV-2 testing history were obtained through parent or guardian interview conducted by trained study personnel or review of electronic medical records.[§§§] Descriptive statistics were used to compare characteristics of case-patients and hospitalized controls, and Fisher's exact or Wilcoxon rank-sum tests were used for categorical and continuous variables, respectively. VE against MIS-C was calculated by comparing the odds of full COVID-19 vaccination among MIS-C case-patients and controls using the equation VE = 100 X (1 – adjusted odds ratio). Adjusted odds ratios were calculated using multivariable logistic regression models with Firth penalization to reduce bias contributed by sparse data. Models were adjusted for U.S. Census region, age, sex, and race/ethnicity (*8*). To account for potential residual confounding by calendar time related to increasing vaccination coverage, the case-patient hospitalization date was used as a reference point for comparing antecedent vaccination in case-patients and controls. Other factors (underlying health conditions and social vulnerability index) were assessed, but not included in the final model if they did not alter the odds ratio estimate by >5%. Sensitivity analyses were conducted to evaluate VE against MIS-C among patients with serologic evidence of previous infection (because non–MIS-C acute COVID-19 patients might have a positive RT-PCR assay in the absence of serology) and to evaluate whether VE differed by control group. Statistical analyses were conducted using SAS (version 9.4; SAS Institute); statistical significance was defined as $p<0.05$. This activity was reviewed by CDC and other participating institutions and was conducted consistent with applicable federal law and CDC policy.[¶¶¶]

During July 1–December 9, 2021, among 117 MIS-C case-patients aged 12–18 years, 15 were excluded from the analysis, including six patients who received only 1 dose by the date of hospitalization, four who received their second vaccine dose within 28 days of hospital admission, and five patients aged 12–15 years who were hospitalized before July 1, 2021. The 283 patients in the primary analysis included 102 MIS-C case-patients and 181 controls (90 [50%] test-negative and 91 [50%] syndrome-negative) (Table 1). The median age among all case-patients and controls was 14.5 years, and 58% had at least one underlying condition (including obesity). COVID-19 vaccination coverage was approximately 5% among case-patients and 36% among controls.

Among the 70 children in this analysis who were fully vaccinated (with 2 doses), one syndrome-negative control patient

[†††] Vaccine effectiveness studies in the context of respiratory viruses most commonly include test-negative controls. Because of potential biases related to the selection of controls, including the potential for misclassification of test-negative patients due to false-negative tests, syndrome-negative controls were also included as a separate control group. Among the 91 syndrome-negative controls, 18 (20%) had no record of SARS-CoV-2 testing. The remaining syndrome-negative controls had a record of SARS-CoV-2 testing by RT-PCR or antigen and received negative test results.

[§§§] Among the 102 MIS-C case-patients and 181 controls enrolled, 50 (49%) and 113 (62%), respectively, had information obtained through a combination of parent interview and medical records abstraction, while 52 (51%) case-patients and 68 (38%) control patients had information obtained solely through medical records abstraction.

[¶¶¶] 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

had received a third dose. Among 102 MIS-C case-patients, five (5%) were fully vaccinated with 2 doses ≥28 days before hospitalization, and 97 (95%) were unvaccinated (Table 2). Overall, 91 (89%) case-patients had cardiovascular involvement, 84 (82%) had gastrointestinal involvement, and 68 (67%) had hematologic involvement. Sixty-two (61%) were admitted to an intensive care unit, and 38 (37%) received life support during hospitalization, including invasive mechanical ventilation, vasoactive infusions, or extracorporeal membrane oxygenation (ECMO). All 38 MIS-C patients requiring life support were unvaccinated; among these, nine patients required invasive mechanical ventilation, 35 received vasoactive infusions and one required ECMO. No deaths among these patients were reported. Hospital length of stay was similar among vaccinated and unvaccinated MIS-C patients (median = 5 days).

VE against MIS-C was 91% (95% CI = 78%–97%) (Table 3).**** In a sensitivity analysis excluding patients with positive RT-PCR or antigen-based SARS-CoV-2 test results and no positive serologic test, VE was 90% (95% CI = 75%–96%). VE against MIS-C was similar, irrespective of control group (test-negative controls: 92%, 95% CI = 77%–97%; syndrome-negative controls: 89%, 95% CI = 70%–96%); therefore, the pooled VE estimate using both control populations was deemed acceptable.

Discussion

During July–December 2021, a period of Delta variant predominance, a real-world evaluation of VE in 24 U.S. pediatric hospitals found that receipt of 2 doses of the Pfizer-BioNTech vaccine was associated with a high level of protection against MIS-C among patients aged 12–18 years who received their second vaccine dose ≥28 days before hospitalization. Most (95%) patients aged 12–18 years hospitalized with MIS-C were unvaccinated. No fully vaccinated patients with MIS-C required respiratory or cardiovascular life support, as opposed to 39% of unvaccinated MIS-C patients who did. A recent Overcoming COVID-19 hospital network investigation reported high VE (93% [95% CI = 83%–97%]) against COVID-19–related hospitalizations in persons aged 12–18 years (*6*). The current findings contribute to the growing body of evidence that vaccination is likely effective in preventing severe COVID-19–related complications in children, including MIS-C.

**** VE against MIS-C was also assessed comparing the odds of antecedent vaccination with the second dose of the Pfizer-BioNTech vaccine ≥14 days before hospital admission. Point estimates did not significantly differ from the primary analysis presented in this report. (VE after 14 days: 86%; 95% CI = 70%–93%.)

The findings in this report are subject to at least seven limitations. First, VE was not assessed against MIS-C attributed to specific variants; however, >99% of COVID-19 cases reported during July–December 2021 resulted from infections with the Delta variant (*9*). Second, VE against MIS-C attributed to the B.1.1.529 (Omicron) variant could not be assessed, given the timing of hospital admission of included patients relative to emergence of this variant in the United States. Third, timing of initial SARS-CoV-2 infection relative to vaccination could not be inferred, and this investigation cannot differentiate between protection from acquisition of SARS-CoV-2 infection versus protection against development of MIS-C after infection. Fourth, the timing at which protection against MIS-C is conferred after 2 doses of vaccine is unknown; some protection might be possible within 28 days of vaccination, and this investigation had insufficient power to evaluate VE for 1 dose of vaccine. Fifth, this analysis examines VE against MIS-C conferred only by the Pfizer-BioNTech vaccine. Sixth, although the hospital sites participating in this investigation covered a broad geographic area, the results of this analysis are not generalizable to the entire U.S. pediatric population. Finally, given the short time frame of enrollment, this analysis was not designed to evaluate waning immunity or duration of protection against MIS-C.

As of December 13, 2021, 52.3% of eligible U.S. children and adolescents aged 12–17 years had received the primary Pfizer-BioNTech 2-dose series (*10*). In a multistate hospital network, this real-world investigation found that receipt of 2 doses of Pfizer-BioNTech vaccine was strongly associated with prevention of MIS-C among adolescents. Children aged 5–11 years, who are now authorized to receive the Pfizer-BioNTech vaccine, represent the age group at highest risk for MIS-C (*1,3*). This analysis lends supportive evidence that vaccination of children and adolescents is highly protective against MIS-C and COVID-19 and underscores the importance of vaccination of all eligible children.

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TABLE 1. Characteristics of multisystem inflammatory syndrome in children case-patients and controls aged 12–18 years — 24 pediatric hospitals, 20 U.S. states,* July 1–December 9, 2021

Characteristic	No. (%) Total (N = 283)	MIS-C case-patients (n = 102)	Controls (n = 181)	p-value†
Median age, yrs (IQR)	14.5 (13.4–15.9)	14.2 (13.0–15.9)	14.7 (13.6–15.9)	0.06
Age group, yrs				
12–15	221 (78.1)	81 (79.4)	140 (77.3)	0.77
16–18	62 (21.9)	21 (20.6)	41 (22.7)	
Sex				
Female	132 (46.6)	30 (29.4)	102 (56.4)	<0.01
Race/Ethnicity				
White, non-Hispanic	105 (37.1)	32 (31.4)	73 (40.3)	0.39
Black, non-Hispanic	99 (35.0)	42 (41.2)	57 (31.5)	
Asian, non-Hispanic	8 (2.8)	1 (1.0)	7 (3.9)	
Hispanic, any race	51 (18.0)	19 (18.6)	32 (17.7)	
Multiple/Other, non-Hispanic	10 (3.5)	4 (3.9)	6 (3.3)	
Unknown	10 (3.5)	4 (3.9)	6 (3.3)	
SVI,§ median (IQR)	0.60 (0.30–0.80)	0.64 (0.43–0.78)	0.56 (0.27–0.81)	0.09
U.S. Census region*				
Northeast	8 (2.8)	3 (2.9)	5 (2.8)	0.98
Midwest	75 (26.5)	28 (27.5)	47 (26.0)	
South	159 (56.2)	56 (54.9)	103 (56.9)	
West	41 (14.5)	15 (14.7)	26 (14.4)	
Month of admission				
June	1 (0.4)	0 (—)	1 (0.6)	0.35
July	9 (3.2)	5 (4.9)	4 (2.2)	
August	49 (17.3)	16 (15.7)	33 (18.2)	
September	82 (29.0)	35 (34.3)	47 (26.0)	
October	85 (30.0)	30 (29.4)	55 (30.4)	
November	48 (17.0)	15 (14.7)	33 (18.2)	
December	9 (3.2)	1 (1.0)	8 (4.4)	
Underlying health condition¶				
At least one underlying condition (including obesity)	164 (58.0)	40 (39.2)	124 (68.5)	<0.01
Asthma	49 (17.3)	15 (14.7)	34 (18.8)	0.42
Cardiovascular system disorder	23 (8.1)	3 (2.9)	20 (11.0)	0.02
Neurologic/Neuromuscular disorder	45 (15.9)	7 (6.9)	38 (21.0)	<0.01
Active or previous oncologic disorder	9 (3.2)	1 (1.0)	8 (4.4)	0.16
Nononcologic immunosuppressive disorder	13 (4.6)	2 (2.0)	11 (6.1)	0.14
Endocrine disorder	16 (5.7)	4 (3.9)	12 (6.6)	0.43
Diabetes	9 (3.2)	2 (2.0)	7 (3.9)	0.50
Other chronic conditions**	97 (34.3)	21 (20.6)	76 (42.0)	<0.01

See table footnotes on the next page.

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TABLE 1. (*Continued*) Characteristics of multisystem inflammatory syndrome in children case-patients and controls aged 12–18 years — 24 pediatric hospitals, 20 U.S. states,* July 1–December 9, 2021

Characteristic	No. (%) Total (N = 283)	MIS-C case-patients (n = 102)	Controls (n = 181)	p-value†
Laboratory test results††				
RT-PCR or antigen-positive, antibody not performed	11 (3.9)	11 (10.8)	0 (—)	<0.01
RT-PCR or antigen-positive, antibody-positive	12 (4.2)	12 (11.8)	0 (—)	
Antibody positive only	76 (26.9)	76 (74.5)	0 (—)	
Pre-admission results available only	3 (1.1)	3 (2.9)	0 (—)	
Fully vaccinated§§	**70 (24.7)**	**5 (4.9)**	**65 (35.9)**	**<0.01**
Median interval from receipt of second vaccine dose to reference hospitalization date, days (IQR)¶¶	84 (51–122)	63 (48–89)	88 (52–122)	0.37

Abbreviations: MIS-C = multisystem inflammatory syndrome in children; RT-PCR = reverse transcription-polymerase chain reaction; SVI = social vulnerability index.

* Patients included vaccinated and unvaccinated persons aged 12–18 years enrolled from 24 pediatric hospitals in 20 states. *Northeast:* Boston Children's Hospital (Massachusetts), Children's Hospital of Philadelphia (Pennsylvania), and Saint Barnabas Medical Center (New Jersey); *Midwest:* Akron Children's Hospital (Ohio), Children's Hospital and Medical Center: Nebraska (Nebraska), Children's Hospital of Michigan (Michigan), Children's Mercy Kansas City (Missouri), Cincinnati Children's Hospital Medical Center (Ohio), Lurie Children's Hospital of Chicago (Illinois), Mayo Clinic (Minnesota), Nationwide Children's Hospital (Ohio), and Riley Children's Hospital (Indiana); *South:* Arkansas Children's Hospital (Arkansas), Children's of Alabama (Alabama), Children's Healthcare of Atlanta (Georgia), Children's Hospital of New Orleans (Louisiana), Medical University of South Carolina Children's Health (South Carolina), Monroe Carell Jr. Children's Hospital at Vanderbilt (Tennessee), Texas Children's Hospital (Texas), University of Mississippi Medical Center (Mississippi), University of North Carolina at Chapel Hill Children's Hospital (North Carolina), and University of Texas Southwestern Medical Center (Texas); *West:* Children's Hospital Colorado (Colorado), Children's Hospital Los Angeles (California), University of California San Diego-Rady Children's Hospital (California), and University of California San Francisco Benioff Children's Hospital Oakland (California).

† Testing for statistical significance was conducted using Fisher's exact test to compare categorical variables or Wilcoxon rank-sum test for medians to compare continuous data. Statistical significance was defined as p<0.05.

§ CDC/ATSDR SVI documentation is available at https://www.atsdr.cdc.gov/placeandhealth/svi/index.html. Median SVI for case-patients and controls are based on U.S. 2018 SVI data.

¶ Underlying conditions with a missing response (yes/no) were assumed not to be present.

** Other chronic conditions included rheumatologic/autoimmune disorder, hematologic disorder, renal or urologic dysfunction, gastrointestinal/hepatic disorder, metabolic or confirmed or suspected genetic disorder (including obesity), or atopic or allergic condition.

†† With the exception of the "pre-admission results available only" category, all other test results were obtained after hospital admission.

§§ COVID-19 vaccination status included the following two categories: 1) unvaccinated, defined as no receipt of any SARS-CoV-2 vaccine before hospitalization for current illness and 2) fully vaccinated, defined as receipt of both doses of a 2-dose Pfizer-BioNTech vaccination ≥28 days before illness onset.

¶¶ Dates are based on those with documented vaccination, not plausible self-report. For controls without COVID-19–like illness, a reference date was set to the admission date of their matched case-patient to account for residual confounding by hospital admission date relative to expanding vaccination coverage.

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TABLE 2. Clinical outcomes and severity among multisystem inflammatory syndrome in children case-patients aged 12–18 years, by vaccination status* — 24 pediatric hospitals, 20 U.S. states,† July–December 2021

Characteristic	No. (%) Total (N = 102)	Unvaccinated (n = 97)	Fully vaccinated ≥28 days before hospitalization (n = 5)
Organ system involvement§			
Cardiovascular	91 (89.2)	86 (88.7)	5 (100.0)
Respiratory	29 (28.4)	28 (28.9)	1 (20.0)
Hematologic	68 (66.7)	66 (68.0)	2 (40.0)
Gastrointestinal	84 (82.4)	79 (81.4)	5 (100.0)
Neurologic	9 (8.8)	8 (8.2)	1 (20.0)
Dermatologic	36 (35.3)	34 (35.1)	2 (40.0)
Renal/Urologic	35 (34.3)	33 (34.0)	2 (40.0)
Intensive care unit admission	62 (60.8)	61 (62.9)	1 (20.0)
Critically ill patients on life support	38 (37.3)	38 (39.2)	0 (—)
Invasive mechanical ventilation	9 (8.8)	9 (9.3)	0 (—)
Vasoactive infusions	35 (34.3)	35 (36.1)	0 (—)
Extracorporeal membrane oxygenation	1 (1.0)	1 (1.0)	0 (—)
Patients with discharge data	101 (99.0)	96 (99.0)	5 (100.0)
Hospital length of stay, median (IQR)	5 (4–8)	5 (4–8)	5 (2–6)

Abbreviation: BNP = brain natriuretic peptide.

* COVID-19 vaccination status included the following two categories: 1) unvaccinated, defined as no receipt of any SARS-CoV-2 vaccine before hospitalization for current illness and 2) fully vaccinated, defined as receipt of both doses of a 2-dose Pfizer-BioNTech vaccination ≥28 days before illness onset.

† Patients included vaccinated and unvaccinated persons aged 12–18 years enrolled from 24 pediatric hospitals in 20 states. *Northeast:* Boston Children's Hospital (Massachusetts), Children's Hospital of Philadelphia (Pennsylvania), and Saint Barnabas Medical Center (New Jersey); *Midwest:* Akron Children's Hospital (Ohio), Children's Hospital and Medical Center: Nebraska (Nebraska), Children's Hospital of Michigan (Michigan), Children's Mercy Kansas City (Missouri), Cincinnati Children's Hospital Medical Center (Ohio), Lurie Children's Hospital of Chicago (Illinois), Mayo Clinic (Minnesota), Nationwide Children's Hospital (Ohio), and Riley Children's Hospital (Indiana); *South:* Arkansas Children's Hospital (Arkansas), Children's of Alabama (Alabama), Children's Healthcare of Atlanta (Georgia), Children's Hospital of New Orleans (Louisiana), Medical University of South Carolina Children's Health (South Carolina), Monroe Carell Jr. Children's Hospital at Vanderbilt (Tennessee), Texas Children's Hospital (Texas), University of Mississippi Medical Center (Mississippi), University of North Carolina at Chapel Hill Children's Hospital (North Carolina), and University of Texas Southwestern Medical Center (Texas); *West:* Children's Hospital Colorado (Colorado), Children's Hospital Los Angeles (California), University of California San Diego-Rady Children's Hospital (California), and University of California San Francisco Benioff Children's Hospital Oakland (California).

§ Organ system involvement was defined with the following criteria: 1) Cardiovascular (e.g., shock, elevated troponin, BNP, N-terminal-pro hormone BNP, abnormal echocardiogram, or arrhythmia); 2) Respiratory (e.g., pneumonia, acute respiratory distress syndrome, and pulmonary embolism); 3) Renal (e.g., acute kidney injury or renal failure); 4) Gastrointestinal (e.g., abdominal pain, vomiting, diarrhea, elevated bilirubin, or elevated liver enzymes); 5) Neurologic (e.g., cerebrovascular accident, aseptic meningitis, or encephalopathy); 6) Hematologic (e.g., elevated D-dimers, thrombophilia, or thrombocytopenia); 7) Dermatologic (e.g., rash, erythema, or peeling).

TABLE 3. Effectiveness* of 2 doses of Pfizer-BioNTech vaccine against multisystem inflammatory syndrome in children among hospitalized patients aged 12–18 years — 24 pediatric hospitals, 20 U.S. states,† July–December 2021

Control groups	No. vaccinated§/Total (%) MIS-C case patients	Control patients	Adjusted VE, % (95% CI)
All controls	5/102 (4.9)	65/181 (35.9)	91 (78–97)
Test-negative	5/102 (4.9)	34/90 (37.8)	92 (77–97)
Syndrome-negative	5/102 (4.9)	31/91 (34.1)	89 (70–96)
Sensitivity analysis			
MIS-C case patients with serologic evidence present¶	5/88 (5.7)	61/161 (37.9)	90 (75–96)

Abbreviations: MIS-C = multisystem inflammatory syndrome in children; VE = vaccine effectiveness.

* VE estimates were based on odds of antecedent vaccination in MIS-C case-patients versus controls adjusted for U.S. Census region, continuous age in years, sex, and race/ethnicity (non-Hispanic White, non-Hispanic Black, non-Hispanic multiple race/other, Hispanic of any race, or unknown). Firth penalized regression was used for models with six or fewer vaccinated cases.

† Patients included vaccinated and unvaccinated persons aged 12–18 years enrolled from 24 pediatric hospitals in 20 states. *Northeast:* Boston Children's Hospital (Massachusetts), Children's Hospital of Philadelphia (Pennsylvania), and Saint Barnabas Medical Center (New Jersey); *Midwest:* Akron Children's Hospital (Ohio), Children's Hospital and Medical Center: Nebraska (Nebraska), Children's Hospital of Michigan (Michigan), Children's Mercy Kansas City (Missouri), Cincinnati Children's Hospital Medical Center (Ohio), Lurie Children's Hospital of Chicago (Illinois), Mayo Clinic (Minnesota), Nationwide Children's Hospital (Ohio), and Riley Children's Hospital (Indiana); *South:* Arkansas Children's Hospital (Arkansas), Children's of Alabama (Alabama), Children's Healthcare of Atlanta (Georgia), Children's Hospital of New Orleans (Louisiana), Medical University of South Carolina Children's Health (South Carolina), Monroe Carell Jr. Children's Hospital at Vanderbilt (Tennessee), Texas Children's Hospital (Texas), University of Mississippi Medical Center (Mississippi), University of North Carolina at Chapel Hill Children's Hospital (North Carolina), and University of Texas Southwestern Medical Center (Texas); *West:* Children's Hospital Colorado (Colorado), Children's Hospital Los Angeles (California), University of California San Diego-Rady Children's Hospital (California), and University of California San Francisco Benioff Children's Hospital Oakland (California).

§ COVID-19 vaccination status included the following two categories: 1) unvaccinated, defined as no receipt of any SARS-CoV-2 vaccine before hospitalization for current illness and 2) fully vaccinated, defined as receipt of both doses of a 2-dose Pfizer-BioNTech vaccination ≥28 days before illness onset.

¶ Analysis excluded 14 MIS-C case-patients who were positive by reverse transcription-polymerase chain reaction only with no serologic evidence of previous infection and 20 controls matched to these patients, given potential misclassification of patients with severe acute COVID-19.

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Summary

What is already known about this topic?

The Pfizer-BioNTech vaccine, currently authorized for persons aged ≥5 years, provides a high level of protection against severe COVID-19 in persons aged 12–18 years. Vaccine effectiveness against multisystem inflammatory syndrome in children (MIS-C), which can occur 2–6 weeks after SARS-CoV-2 infection, has remained uncharacterized.

What is added by this report?

Estimated effectiveness of 2 doses of Pfizer-BioNTech vaccine against MIS-C was 91% (95% CI = 78%–97%). Among critically ill MIS-C case-patients requiring life support, all were unvaccinated.

What are the implications for public health practice?

Receipt of 2 doses of Pfizer-BioNTech vaccine is highly effective in preventing MIS-C in persons aged 12–18 years. These findings further reinforce the COVID-19 vaccination recommendation for eligible children.

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Review

Prevalence and risk factor for long COVID in children and adolescents: A meta-analysis and systematic review

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ABSTRACT

Background: Millions of COVID-19 pediatric survivors are facing the risk of long COVID after recovery from acute COVID-19. The primary objective of this study was to systematically review the available literature and determine the pooled prevalence of, and risk factors for long COVID among the pediatric survivors.

Methods: Studies that assessed the prevalence of, or risk factors associated with long COVID among pediatric COVID-19 survivors were systematically searched in PubMed, Embase, and Cochrane Library up to December 11th, 2022. Random effects model was performed to estimate the pooled prevalence of long COVID among pediatric COVID-19 patients. Subgroup analyses and meta-regression on the estimated prevalence of long COVID were performed by stratification with follow-up duration, mean age, sex ratio, percentage of multisystem inflammatory syndrome, hospitalization rate at baseline, and percentage of severe illness.

Results: Based on 40 studies with 12,424 individuals, the pooled prevalence of any long COVID was 23.36 % ([95 % CI 15.27–32.53]). The generalized symptom (19.57 %, [95 % CI 9.85–31.52]) was reported most commonly, followed by respiratory (14.76 %, [95 % CI 7.22–24.27]), neurologic (13.51 %, [95 % CI 6.52–22.40]), and psychiatric (12.30 %, [95% CI 5.38–21.37]). Dyspnea (22.75 %, [95% CI 9.38–39.54]), fatigue (20.22 %, [95% CI 9.19–34.09]), and headache (15.88 %, [95 % CI 6.85–27.57]) were most widely reported specific symptoms. The prevalence of any symptom during 3–6, 6–12, and > 12 months were 26.41 % ([95 % CI 14.33–40.59]), 20.64 % ([95 % CI 17.06–24.46]), and 14.89 % ([95 % CI 6.09–26.51]), respectively. Individuals with aged over ten years, multisystem inflammatory syndrome, or had severe clinical symptoms exhibited higher prevalence of long COVID in multisystems. Factors such as older age, female, poor physical or mental health, or had severe infection or more symptoms were more likely to have long COVID in pediatric survivors.

Conclusions: Nearly one quarter of pediatric survivors suffered multisystem long COVID, even at 1 year after infection. Ongoing monitoring, comprehensive prevention and intervention is warranted for pediatric survivors, especially for individuals with high risk factors.

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Contents

Introduction

The COVID-19 pandemic continues to spread, with the global case count and number of deaths estimated at 657.4 million and 6.7 million, respectively, as of January 5th, 2023 [1]. COVID-19 survivors have reported ongoing persistent symptoms in many organ systems, long after recovery from the acute phase of COVID-19 infection [2,3]. World Health Organization creates a final consensus definition for long COVID: usually 3 months from the onset, with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis [4]. Several published epidemiological studies [5,6] and reviews [7–10] mostly focused on the long COVID or persistent symptoms of COVID-19 infection amongst adults, due to the large number and often severe symptoms in adult survivors [11,12]. However, long COVID symptoms in children has not been systematically illustrated. Understanding the long COVID burden is essential to allow timely identification and intervention of affected children and appropriate allocation of pediatric healthcare resources.

Children and adolescents are at a critical stage of physical and mental development. COVID-19 infection during this period may have important implications for their functional and social wellbeing in adulthood. Compared with the clinical features and treatment outcomes observed in adult COVID-19 patients, pediatric COVID-19 patients usually presented with milder clinical features at the acute phase [13,14]. However, children are seeing a surge of COVID-19 infections in many countries, coinciding with much lower rates of vaccination amongst children as compared to adults. Higher prevalence of COVID-19 cases in children promotes increases the number of long-COVID cases, and contributes to further spread of disease among vulnerable populations [15]. Recently, a few epidemiological studies reported the prevalence of long COVID among pediatric COVID-19 cases with the follow-up duration ranging from three months to one year [16–18]. The long COVID in pediatric COVID-19 patients generally covered multiple systems, including respiratory, neurological, and cardiovascular systems, and so on [18].

Several factors, including clinical characteristics and demographic information have been found to be associated with long COVID. Multisystem inflammatory syndrome (MIS) was identified in some pediatric COVID-19 cases, and was suspected to have a wide spectrum of presenting signs and symptoms and disease severity [19]. Hospitalization and severe acute initial infection were also suggested to have more potential of long COVID [20,21]. Moreover, evidence supports that sex and age are associated with prevalence of long COVID. Specifically, a few studies pointed out that older age, and female in pediatric survivors may be associated with high risk of long COVID [20,22].

A few studies assessed the persistent symptoms among the pediatric COVID-19 survivors. By combining data from 22 studies with over 20 thousand individuals, Behnood et al. [23] found that pooled prevalence of persistent symptoms in post-COVID participants ranged from 15 % (diarrhea) to 47 % (fatigue) after one month. In addition, a meta-analysis [24] showed that the prevalence of ongoing (4–12 weeks) and post-COVID-19 (≥ 12 weeks) symptoms was 25.24 % in children and adolescents. However, the burden and risk factor of long COVID still remained unclear in children and adolescents after infection over three months. Moreover, as the effect of important clinical characteristics including MIS, severe infection, hospitalized survivors needed to be furtherly discovered.

The primary objective of this study was to systematically review the available literature and determine the pooled prevalence of long COVID in pediatric survivors. In addition, we intended to explore the estimate of the pooled prevalence of long COVID in child and adolescent survivors with stratified demographic or clinical characteristics. Finally, we aimed to systematically review possible risk factors associated long COVID among pediatric patients.

Methods

This systematic review was performed in accordance with the Meta-Analyses of Observational Studies in Epidemiology (MOOSE; Supplement Table 1) guidelines [25] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Supplement Table 2) guidelines [26]. The PROSPERO registration number for this systematic review is CRD42021293614.

Table 1
Characteristics of the included paper.

Authors	Investigating Site	Investigating period	Study design	Follow-up duration	Sample size	Age (Mean / Median/ Range)	Male (%)	Severe illness (%)[a]	MIS (%)	Hospitalization rate at baseline (%)	Affected systems	Factors associated with outcomes
Akçay et al., 2022	Turkey	2021.2.20–2021.3.2	retrospective cohort	7.12 ± 2.34 months	74	14.8 (11–17)	44.59	NA	NA	100.00	psychiatric system	NA
Asadi-Pooya et al., 2022	Iran	2020.2.19–2020.11.20	cross-sectional	> 13 months	51	13.2 ± 3.3	45.10	19.60	NA	100.00	any, generalized, musculoskeletal, psychiatric, and respiratory systems	NA
Ashkenazi-Hoffnun et al., 2021	Israel	2020.11–2021.4	prospective cohort	112 (33–410) days	90	12 ± 5	58.33	2.22	1.11	12.20	cardiovascular, dermatological, digestive, generalized, musculoskeletal, neurologic, psychiatric, and respiratory systems	NA
Bartoszek et al., 2021	Poland	2020.11–2021.1	retrospective cohort	99 (89–104) days	19	8–17	73.68	NA	100.00	100.00	cardiovascular system, and imaging findings	NA
Blankenburg et al., 2022	Germany	2020.5–2020.6	cross-sectional	11 months	178	15	NA	NA	NA	NA	digestive, generalized, musculoskeletal, neurologic, and psychiatric systems	NA
Blomberg et al., 2021	Norway	2020.2.28–2020.4.4	prospective cohort	6 months	16	8 (6–12)	43.75	NA	NA	0	any, cardiovascular, digestive, generalized, neurologic, psychiatric, and respiratory systems	NA
Bode et al., 2022	Germany	2021.2–2021.5	cross-sectional	12 months	25	9.4 ± 3.9	47.17	0	0	0	generalized, and respiratory systems	NA
Brackel et al., 2021	Netherlands	2020.12.18–2021.2.6	cross-sectional	12 weeks	89	2–18	66.67	NA	NA	100.00	cardiovascular, dermatological, digestive, generalized, musculoskeletal, neurologic, and respiratory systems	NA
Buonsenso et al., (a) 2021	Italy	2020.3–2020.10	cross-sectional	120 days	68	11 ± 4.4	51.90	2.33	2.33	4.70	any, cardiovascular, dermatological, digestive, generalized, musculoskeletal, neurologic, psychiatric, and respiratory systems	NA
Buonsenso et al., (b) 2022	Italy	2020.9.30–2022.4.31	prospective cohort	6–9 months, > 12 months	311	< 18	49.00	0.74	NA	2.65	dermatological, digestive, generalized, musculoskeletal, neurologic, psychiatric, and respiratory systems	NA
Buonsenso et al., (c) 2022	Italy	2020.1–2021.1	cohort	3–6month, > 7 month	428	10.3 ± 3.8	43.70	NA	NA	4.30	cardiovascular, dermatological, digestive, generalized, musculoskeletal, neurologic, psychiatric, ophthalmological, and respiratory systems	NA
Denina et al., 2021	Italy	2020.3.1–2020.6.1	prospective cohort	130 (106–148) days from discharge	25	7.75 (0.4–15)	52.00	16.00	0	100.00	imaging and laboratory findings	NA

(continued on next page)

Table 1 (*continued*)

Authors	Investigating Site	Investigating period	Study design	Follow-up duration	Sample size	Age (Mean / Median/ Range)	Male (%)	Severe illness (%)[a]	MIS (%)	Hospitalization rate at baseline (%)	Affected systems	Factors associated with outcomes
Doležalová et al., 2022	Czech Republic	2021.1.6–2021.6.30	cohort	> 12 weeks	39	13.5 (8–15)	43.59	NA	NA	100.00	respiratory system, and imaging and laboratory findings	NA
Enner et al., 2022	US	2020.3–2020.8	cross-sectional	23 weeks	47	9 (5–13)	55.32	63.83	100.00	100.00	generalized, neurologic, and psychiatric systems	NA
Erol et al., 2022	Turkey	2021.3.17–2021.6.10	cohort	5.6 months	121	9.16 (10.88–17.92)	53.72	NA	NA	22.31	dermatological, digestive, generalized, neurologic, ophthalmological, and respiratory systems	NA
Esmaeilzadeh et al., 2022	Iran	2020.2–2021.1	cohort	6 months	69	< 18	60.87	NA	NA	100.00	respiratory system	NA
Fink et al., 2021	Brazil	2020.4.11–2021.8.10	cohort	4.4 months	53	14.65 (8–18)	41.51	11.32	5.66	33.96	any, dermatological, digestive, generalized, musculoskeletal, neurologic, ophthalmological, psychiatric, and respiratory systems	NA
Funk et al., 2022	8 countries	2020.3.7–2021.1.20	prospective cohort	90 days	1884	3 (0–10)	52.80	NA	NA	9.80	any, cardiovascular, digestive, generalized, musculoskeletal, neurologic, ophthalmological, psychiatric, and respiratory systems	older age, hospitalized 48 h or more, having 4 or more symptoms reported at the index emergency department visit
Gennaro et al., 2022	Italy	2021.10.1–2022.3.31	prospective cohort	12 weeks	75	10.5 ± 6.7	47.80	NA	NA	9.33	any symptom	NA
Guido et al., 2022	Italy	2021.2–2021.11	cross-sectional	3–5 months	322	9.53 ± 3.73	51.90	NA	NA	NA	any, generalized, musculoskeletal, neurologic, ophthalmological, psychiatric, and respiratory systems	NA
Heiss et al., 2022	Germany	2021.8–2021.12	cross-sectional	> 12 weeks	54	12 ± 3	56.00	0	NA	0	any, generalized, musculoskeletal, neurologic, psychiatric, and respiratory systems	NA
Matteudi et al., 2021	France	2020.2.27–2020.5.15	cohort	180 (36–345) days	137	9.1	49.49	1.03	0	13.87	any, generalized, and neurologic systems	symptomatic during the acute phase
Méndez-Echevarría et al., 2021	Spain	2020.3–2020.5	prospective cohort	186 (176–192) days	58	8.3 (2.8–13.5)	50.00	NA	12.07	36.21	laboratory findings	NA
Messiah et al., 2022	USA	2021.3–2022.1	retrospective cohort	> 120 days	240	6.65 ± 5.91	52.88	NA	8.33	85.26	any, cardiovascular, dermatological, generalized, musculoskeletal, neurologic, psychiatric, and respiratory systems	older age, female, private insurance
Mitchell et al., 2022	USA	2020.3.26–2020.7.20	retrospective cohort	6 months	25	8.3 (0.75–17)	56.00	NA	100.00	100.00	cardiovascular, and laboratory findings	NA

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Table 1 (*continued*)

Authors	Investigating Site	Investigating period	Study design	Follow-up duration	Sample size	Age (Mean / Median/ Range)	Male (%)	Severe illness (%)[a]	MIS (%)	Hospitalization rate at baseline (%)	Affected systems	Factors associated with outcomes
Namazova-Baranova et al., 2022	Russia	NA	cross-sectional	1 year	21	11.4 ± 3.5	61.30	NA	NA	NA	neurologic system	NA
Nugawela et al., 2022	UK	2021.1–2021.3	cohort	3 months	3246	11–17	37.00	NA	NA	NA	any, generalized, musculoskeletal, and psychiatric systems	older age, female, poor physical health, poor mental health, more symptoms at testing
Osmanov et al., 2022	Russia	2020.4.2–2020.8.26	prospective cohort	256 (223–271) days	518	10.4 (3–15.2)	47.90	2.72	NA	100.00	any, cardiovascular, dermatological, digestive, generalized, musculoskeletal, neurologic, psychiatric, ophthalmological, respiratory and urological systems	older age, allergic diseases
Öztürk et al., 2022	Turkey	2020.5.15–2020.8.1	retrospective cohort	3 months	50	15 (8–18)	56.00	20	NA	NA	respiratory system, and laboratory findings	NA
Palacios et al., 2022	USA	2021.2–2021.12	retrospective cohort	3.5 months	82	15.2 ± 2.3	41.50	NA	1.20	100.00	respiratory system	NA
Patnaik et al., 2021	India	NA	prospective cohort	3–4 months	16	8.4 ± 4.3	61.54	50	100.00	100.00	cardiovascular, and musculoskeletal systems	NA
Pazukhina et al., 2022	Russia	2020.4–2020.8	prospective cohort	255 (223–270) days	360	9.5	48.00	NA	NA	100.00	any, cardiovascular, dermatological, digestive, generalized, musculoskeletal, neurologic, psychiatric, and respiratory systems	neurological comorbidities, allergic respiratory diseases
Penner et al., 2021	UK	2020.4.4–2020.9.1	retrospective cohort	6 months	46	10.2 (8.8–13.3)	65.00	35.00	100.00	100.00	cardiovascular, digestive, musculoskeletal, neurological, psychiatric, and urological systems, and imaging and laboratory findings	NA
Radtke et al., 2021	Switzerland	2020.6–2021.4	prospective cohort	> 12 weeks	109	6–16	53.21	NA	NA	NA	any, digestive, generalized, neurological, psychiatric, and respiratory systems	NA
Say et al., 2021	Australia	2020.3.21–2020.10.28	cohort	3–6months	151	3 (1–8)	52.63	5.85	0.66	100.00	any, generalized, and respiratory systems	NA
Sezer et al., 2022	Turkey	2020.7–2021.7	retrospective cohort	7.8 months	123	9.6	63.40	NA	100.00	100.00	cardiovascular, digestive, generalized, and respiratory systems	NA
Sirico et al., 2022	Italy	2020.4.26–2021.10.2	retrospective cohort	207 days	23	8.25 ± 4	65.60	NA	100.00	100.00	cardiovascular system, and imaging findings	NA
Stephenson et al., 2021	UK	2021.1–2021.4	cohort	3 months	3065	11–17	36.54	NA	NA	0	any, dermatological, digestive, generalized, musculoskeletal, neurological, ophthalmological, and respiratory systems	older age, female, with lower pretest physical and mental health, positive PCR

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Table 1 (*continued*)

Authors	Investigating Site	Investigating period	Study design	Follow-up duration	Sample size	Age (Mean / Median/ Range)	Male (%)	Severe illness (%)[a]	MIS (%)	Hospitalization rate at baseline (%)	Affected systems	Factors associated with outcomes
Sterky et al., 2021	Sweden	2020.12–2021.1	cohort	219 (123–324) days	55	0–18	58.18	NA	3.64	100.00	any, cardiovascular, digestive, generalized, musculoskeletal, neurological, psychiatric, and respiratory systems	NA
Zhang et al., 2021	China	2020.7–2020.9	cohort	4 months	61	7–18	78.69	NA	NA	100.00	psychiatric system	NA

Abbreviations: MIS, multisystem inflammatory syndrome; NA, not available; PCR, polymerase chain reaction.

[a] Definition of severe COVID-19 infection was based on the National Institute of Health symptom severity criteria, guideline for scoring pediatric patients with COVID-19, the requirement of ventilation or admission to pediatric intensive care unit, or directly reported in the study.

Search strategy

Studies that assessed the prevalence of long COVID amongst pediatric COVID-19 survivors were systematically searched in PubMed, Embase, and Cochrane Library databases up to December 11th, 2022 (Supplement 1). The following search terms were used: (COVID-19 OR SARS-CoV-2 OR coronavirus OR 2019-nCoV) AND (long COVID OR post acute COVID syndrome OR PASC OR long-term OR "long term" OR "long haul*" OR "after recovery" OR prolong* OR persist* OR convalescent) AND (cohort OR follow-up OR longitudinal OR cross sectional) AND (child* OR infant*). The full search strategy is provided in the Supplement 1. The reference lists of retrieved papers and recent reviews were manually searched for additional studies that met the inclusion criteria.

All retrieved records were imported into an EndNote library. Two investigators (Zheng Y and Gao N) independently screened all articles for their eligibility. If consensus could not be reached, the third investigator (Zeng N) reviewed the full text article and resolved disagreements.

Selection criteria

To be eligible for inclusion, studies had to: (1) contain original research; (2) include pediatric COVID-19 survivors aged less than 18 years old; (3) measure long COVID symptoms, relevant laboratory or examination result (such as imaging, lung function tests or blood tests) of post-acute COVID-19; (4) assess symptoms at least 3 months after initial COVID-19 infection, as introduced elsewhere [10]; (5) provide raw data that allowed the calculation of the estimates. Exclusion criteria were as follows: (1) the study was a review article or a case report; (2) not pediatric patients; (3) the long COVID did not meet the follow-up duration. The detailed process of the literature search for the systematic review is shown in Fig. 1.

Data extraction

All data were independently extracted from the included studies by two researchers (Zheng YB and Zeng N) who subsequently cross-checked the data. We extracted the following characteristics for each study: authors and year of publication, research site (country), investigating period, study design, follow-up duration, sample size, age and gender of participants, percentage of severe illness, percentage of individuals with MIS, hospitalized rate during acute phase at baseline, the overall whole body symptoms (multiple affected systems mainly including generalized, psychiatric, neurologic, respiratory, digestive, musculoskeletal, cardiovascular, dermatological, ophthalmological, and urological symptoms, etc.), and factors associated with outcomes (Table 1).

Statistical analysis

Meta-analysis was performed to estimate the pooled prevalence of any long COVID and those affecting specific organ systems among pediatric COVID-19 patients. The overall prevalence of symptoms affecting a specific organ system was estimated by pooling the most common symptoms related to that system, if the overall prevalence was not itself reported in the study. Multiple symptoms relating to the same organ system were often reported in the same survivor, therefore the prevalence of the most common symptom was used to estimate the overall prevalence for that system. Additionally, the prevalence of reported symptoms examined in five or more studies was combined [7]. The I^2 index was calculated to assess the between-study heterogeneity and Cochrane Q-test was used to determine statistical significance. An I^2 value > 50 % or a chi-square p value < 0.05 was considered substantial heterogeneity. Pooled rates with 95 % confidence intervals (CIs) were calculated using the

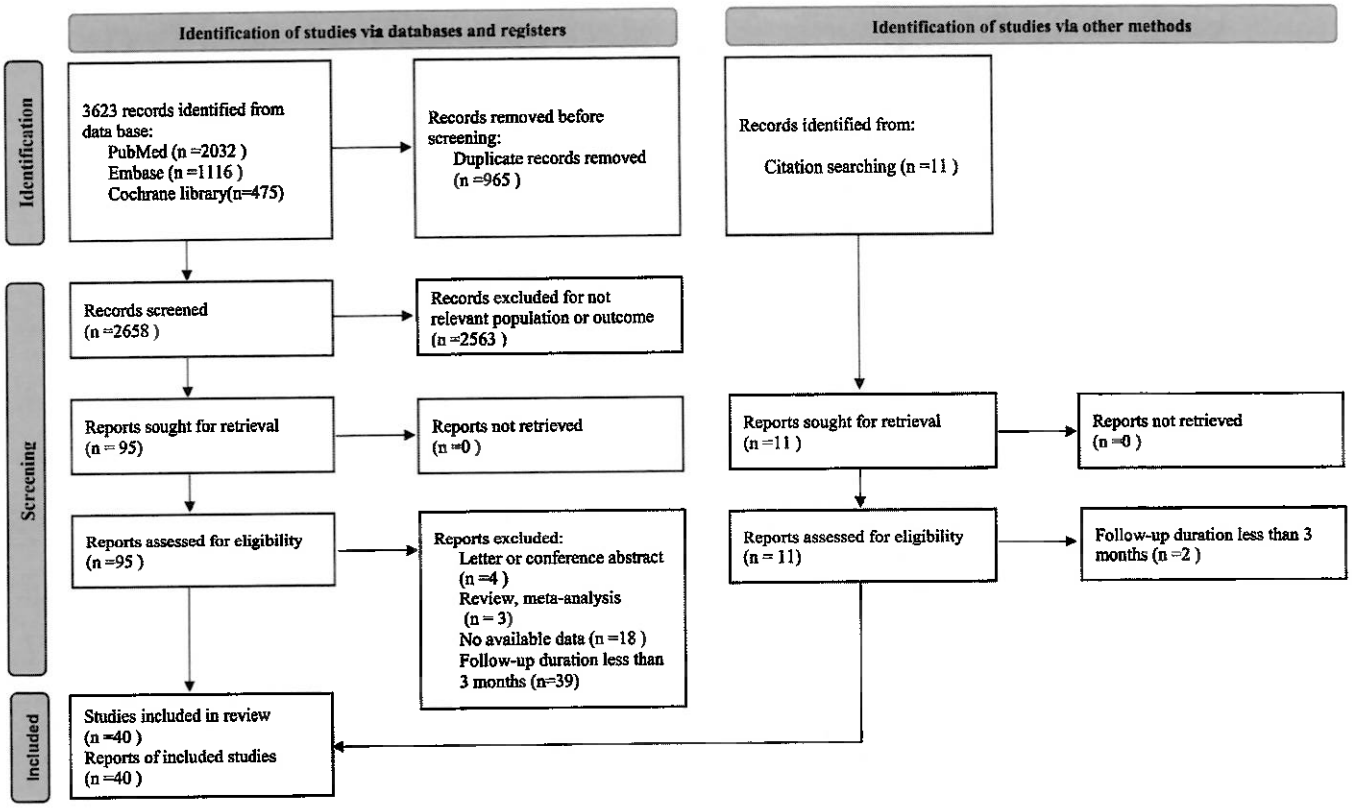


Fig. 1. Flow chart of the selection process.

random-effect model if heterogeneity existed; otherwise the fixed-effect model was used.

Subgroup analyses and meta-regressions on the estimated prevalence of any symptom in each system were performed by stratification with follow-up duration (3–6 months, 6–12 months, > 12 months), mean age of study participants (> 10 years vs. < 10 years), the sex ratio (male proportion > 50 % vs. < 50 %), presence of MIS (yes vs. no), percentage of severe illness (> 50 % vs. < 50 %), and hospitalization rate at baseline (yes vs. no). Leave-one-out sensitivity analysis was conducted to estimate the influence of each study on the pooled results. Funnel plot and the Egger test were used to assess the presence of any publication biases. All analyses were performed with R Software (version 4.0.3).

Quality assessment

The quality of the included studied was assessed using Agency for Healthcare Research and Quality methodology checklist. Two investigators (Yang YB and Chen X) appraised each item of the scale independently. The disagreement was settled by joint review with an experienced methodologist (Zheng YB).

Results

Literature search

As shown in Fig. 1, 3623 records were retrieved through the initial database search, and 965 duplicate papers were removed. Of the 2658 records remaining, the majority were excluded after the first screening based on titles or abstracts. The full texts of ninety-five papers and eleven additionally identified studies [27–37] investigating the prevalence of long COVID of pediatric COVID-19 survivors were scanned. Of these articles, four were letters, conference proceedings, abstracts or comments, three was a review or meta-analysis, eighteen had no available data, forty-one (including thirty-nine initial extracted and two additional identified studies) provided outcomes not had the symptom duration less than 3 months, and were hence excluded from analysis. Finally, a total of 40 eligible studies [16–18,20–22,27–30,32,33,35–62] were included in the final analysis.

Characteristics of the included studies

Table 1 presents the primary descriptive characteristics of the 40 eligible studies. All of the included studies were published between 2020 and 2022. A total of 12,424 participants were included in the final analysis, with the study sample sizes ranging from 16 to 3246. Among the included studies, there were nine cross-sectional and thirty-one cohort studies. The follow-up duration ranged from 3 to 13 months. Of all the included studies, 24 were conducted in Europe [17,18,21,28,29,32,33,36,39–46,50–53,55,56,60,62], 9 in Asia [16,27,30,37,38,48,57,59,61], 4 in North America [16,20,22,27,30, 37,38,47,48,54,57–59,61], and 1 in Oceania [35], South America [49], and multi continents [20], respectively. The mean or median age of the participants ranged from to 3–15.2 years old, and most of the studies included more than 50% male patients. Fifteen studies [16,17,21,27,32,35,42–45,47,49,52,57,59] reported the percentage of severe COVID-19 infection, with prevalence of severe illness ranging from 0 to 63.86 %. Eighteen studies [16,17,21,27,32,35,39,43–45,47,49,52,54,57,59,61,62] reported percentage of MIS among pediatric survivors, and seven [17,39,47,54,59,61,62] of them solely included those with MIS. Thirty-four studies [16–18,20–22,27–30,32,35–39,41–50,52–54,58–62] reported the percentage of hospitalization rate of survivors, and nineteen [16,17,21,28,35–39,45–48,54,58–62] of them were 100.00 %, while rest of them ranged from 0 % to 85.26 %. In addition, seven studies [18,20–22,32,56,60] provided information on risk factors associated with long COVID symptoms.

The pooled prevalence of long COVID by organ system and specific symptoms

We pooled the prevalence of long COVID of any one symptom and multiple organ systems. Seventeen studies [16,18,20–22,32,33,35,36,41,43,49–52,56,60] reported any symptom amongst their study population during follow-up, with the prevalence of long COVID ranging from 3.67 % to 66.49 %. By combining prevalence of any long COVID, the pooled prevalence was 23.36 % ([95 % CI 15.27–32.53], I^2 = 99 %; N = 17) among the pediatric COVID-19 participants (Fig. 2).

Estimated prevalence of long COVID by organ system is presented in Fig. 2 and Supplement Fig. 1. Overall, generalized system showed the top pooled prevalence (19.57 %, [95 % CI 9.85–31.52], I^2 = 99 %; N = 26) of long COVID among the pediatric survivors, followed by respiratory (14.76 %, [95 % CI 7.22–24.27], I^2 = 99 %; N = 25), neurologic (13.51 %, [95 % CI 6.52–22.40], I^2 = 99 %; N = 22), psychiatric (12.30 %, [95 % CI 5.38–21.37], I^2 =98 %; N = 20), digestive (11.87 %, [95 % CI 4.22–22.46], I^2 = 99 %; N = 16), musculoskeletal (9.38 %, [95 % CI 3.59–17.31], I^2 = 99 %; N = 19), cardiovascular (7.32 %, [95 % CI 2.68–13.66], I^2 = 97 %; N = 16), dermatological (6.42 %, [95 % CI 1.39–14.46], I^2 = 99 %; N = 12), ophthalmological (3.92 %, [95 % CI 0–14.34], I^2 = 99 %; N = 7), and urological systems (0.44 %, [95 % CI 0–4.02], I^2 = 62 %; N = 2).

The pooled prevalence of abnormal imaging was 13.12 % ([95 % CI 7.38–19.90], I^2 = 0; N = 5). In addition, the pooled prevalence of abnormal laboratory findings ranged from 0 (international normalized ratio: [95 % CI 0–2.51]; N = 1) to 86.71 % (IgG positivity: [95 % CI 79.95–92.36], I^2 =0; N = 3). In addition, Penner et al. [63] reported that 8.70 % ([95 % CI 1.95–18.89]; N = 1) of survivors were readmitted to the hospital after discharge. Estimation of prevalence of abnormal imaging and laboratory findings among pediatric patients is presented in Supplement Fig. 2.

The pooled prevalence of reported symptoms

We combined the pooled prevalence of specific reported symptoms examined in five or more studies. Overall, dyspnea (22.75 %, [95 % CI 9.38–39.54], I^2 =94 %; N = 11) was the top specific symptom among the pediatric survivors (Fig. 3), followed by fatigue (20.22 %, [95 % CI 9.19–34.09], I^2 =99 %; N = 21), headache (15.88 %, [95 % CI 6.85–27.57], I^2 =99 %; N = 18), shortness of breath (15.30 %, [95 % CI 3.13–33.85], I^2 =99 %; N = 7), abdominal pain (12.42 %, [95 % CI 2.94–26.81], I^2 =99 %; N = 12), concentration difficulties (11.44 %, [95% CI 1.54–28.04], I^2 =99 %; N = 10), muscle pain (11.42 %, [95 % CI 3.45–22.96], I^2 =99 %; N = 14), sleep disturbances (8.38 %, [95 % CI 1.77–18.57], I^2 =94 %; N = 9), diarrhea (8.01 %, [95 % CI 1.66–18.08], I^2 =98 %; N = 9), skin rashes (7.60 %, [95 % CI 0.38–21.62], I^2 =99 %; N = 7), heart palpitations (6.59 %, [95 % CI 0.72–16.68], I^2 =98 %; N = 8), cough (6.17 %, [95 % CI 2.16–11.78], I^2 =97 %; N = 17), dizziness (6.16 %, [95% CI 0.15–18.22], I^2 =99 %; N = 8), chest pain (5.88 %, [95 % CI 1.27–13.15], I^2 =97 %; N = 12), fever (5.02 %, [95 % CI 0.36–13.47], I^2 =95 %; N = 12), altered or loss of smell/taste (3.97 %, [95 % CI 0–12.72], I^2 =94 %; N = 6), weight loss (3.73 %, [95 % CI 0.07–11.15], I^2 =94 %; N = 5), joint pain or swelling (2.74 %, [95 % CI 0.36–6.74], I^2 =94 %; N = 7), altered or loss of smell (2.47 %, [95 % CI 0.36–5.90], I^2 =97 %; N = 9), and altered or loss of taste (1.71 %, [95 % CI 0.08–4.68], I^2 =89 %; N = 6).

The pooled prevalence of long COVID during different follow-up durations

The prevalence of any symptom exhibited a decreasing trend with the progress of follow-up (Fig. 4), they were 26.41 % ([95 % CI 14.33–40.59], I^2 =100 %; N = 11), 20.6 4% ([95 % CI 17.06–24.46], I^2 =31 %; N = 5), and 14.89 % ([95 % CI 6.09–26.51], I^2 =75 %; N = 2) during 3–6, 6–12, and > 12 months, respectively. The prevalence of long COVID among the pediatric survivors during different follow-up durations significantly different in the following specific system: respiratory (P < 0.01), psychiatric (P < 0.01), neurologic (P < 0.01), and cardiovascular (P < 0.01) systems. No significant difference of prevalence of long COVID during different follow-up duration was explored in the rest of systems.

Subgroup analysis

Fig. 5 and Supplement Table 3 shows the meta-regression results of estimation of prevalence of long COVID, and detailed prevalence of long COVID in stratified populations is presented in Supplement Fig. 3-7. Compared with patients with age < 10 years, those with age > 10 years had a higher prevalence of long COVID in generalized (36.6 % vs. 8.6 %; P = 0.04), respiratory (28.3 % vs. 1.9 %; P < 0.01), and musculoskeletal (18.9 % vs. 0.6 %; P < 0.01), and systems. MIS patients exhibited a higher prevalence of long COVID in neurologic (29.9 % vs. 5.2 %; P < 0.01), psychiatric (22.6 % vs. 2.9 %; P < 0.01), cardiovascular (9.6 % vs. 3.2 %; P < 0.01), and musculoskeletal (12.2 % vs. 1.4 %; P = 0.04), when compared with those without MIS. In addition, severe patients had a higher prevalence of neurologic (38.3 % vs. 10.5 %; P < 0.01), and psychiatric (42.5 % vs. 7.6 %; P < 0.01) symptoms than non-severe patients. No significant difference was found between prevalence of long COVID of each organ and percentage of hospitalization proportion at baseline, as well as the sex ratio of the studies.

Symtoms	No. of study	No. of events	No. of participants	Prevalence (%) (95% CI)	I^2(%)	P value
Any of the symptoms	17	3421	10426	23.36 (15.27, 32.53)	99.0	<0.01
Generalized symptoms	26	2575	11496	19.57 (9.85, 31.52)	99.0	<0.01
Subjective respiratory symptoms	25	1205	8119	14.76 (7.22, 24.27)	99.0	<0.01
Neurologic symptoms	22	951	7979	13.51 (6.52, 22.40)	99.0	<0.01
Psychiatric symptoms	20	736	7939	12.30 (5.38, 21.37)	98.0	<0.01
Digestive symptoms	16	580	7177	11.87 (4.22, 22.46)	99.0	<0.01
Musculoskeletal symptoms	19	805	10853	9.38 (3.59, 17.31)	99.0	<0.01
Cardiovascular symptoms	16	214	3933	7.32 (2.68, 13.66)	97.0	<0.01
Dermotogical symptoms	12	304	7009	6.42 (1.39, 14.46)	99.0	<0.01
Ophthalmological symptoms	7	332	6244	3.92 (0, 14.34)	99.0	<0.01
Urological symptoms	2	2	540	0.44 (0, 4.02)	62.0	0.10

Fig. 2. Estimation of prevalence of long COVID among pediatric patients.

Symtoms	No. of study	No. of events	No. of participants	Prevalence (%) (95% CI)	I^2(%)	P value
Dyspnoea	11	173	545	22.75 (9.38, 39.54)	94.0	<0.01
Fatigue	21	1950	8084	20.22 (9.19, 34.09)	99.0	<0.01
Headache	18	1287	7420	15.88 (6.85, 27.57)	99.0	<0.01
Shortness of breath	7	797	5521	15.30 (3.13, 33.85)	99.0	<0.01
Abdominal pain	12	536	4825	12.42 (2.94, 26.81)	90.0	<0.01
Concentration difficulties	10	226	3318	11.44 (1.54, 28.04)	99.0	<0.01
Muscle pain	14	727	7515	11.42 (3.45, 22.96)	99.0	<0.01
Sleep disturbance	9	113	1304	8.38 (1.77, 18.57)	94.0	<0.01
Diarrhoea	9	287	4415	8.01 (1.66, 18.08)	98.0	<0.01
Skin rashes	7	209	1521	7.60 (0.38, 21.62)	99.0	<0.01
Heart palpitations	8	165	1419	6.59 (0.72, 16.68)	98.0	<0.01
Cough	17	303	7002	6.17 (2.16, 11.78)	97.0	<0.01
Dizziness	8	595	6270	6.16 (0.15, 18.22)	99.0	<0.01
Chest pain	12	304	6598	5.88 (1.27, 13.15)	98.0	<0.01
Fever	12	250	6177	5.02 (0.36, 13.47)	95.0	<0.01
Altered or loss of smell/taste	6	40	2715	3.97 (0, 12.72)	94.0	<0.01
Weight loss	5	24	824	3.73 (0.07, 11.15)	94.0	<0.01
Joint pain or swelling	7	32	1218	2.74 (0.36, 6.74)	99.0	<0.01
Altered or loss of smell	9	433	4294	2.47 (0.36, 5.90)	97.0	<0.01
Altered or loss of taste	6	28	1120	1.71 (0.08, 4.68)	89.0	<0.01

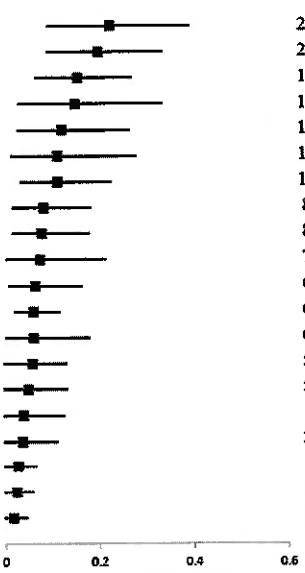


Fig. 3. Estimation of reported long COVID symptoms examined by five or more studies.

Risk factors for long COVID

Seven studies [18,20–22,32,56,60] reported risk factors for any long COVID in pediatric patients. Of these studies, five of them [18,20–22,56] pointed out the being older age was associated with higher risk for long COVID. Also, three studies [18,22,56] showed that female were more vulnerable for long COVID. Patients with poor physical or mental health were identified impacting long COVID [18,56]. In addition, those with more severe symptoms (e.g., symptomatic during the acute phase [32], hospitalized 48 h or more [20]), affected in specific organs (e.g., allergic diseases [21], and neurological comorbidities [60], etc.), and had more symptoms at initial infection [20,56], are more likely to develop long COVID. Others factors, such as insurance types [22], and polymerase chain reaction positive 3 months after diagnosis [18] were also mentioned to be associated with long COVID.

Quality control and publication bias

The quality scores of the included articles ranged from 5 to 10 points (Supplement Table 4). We observed no significant study effect when estimating the prevalence of long COVID. Applying the leave-one-out sensitivity analysis did not significantly alter the pooled estimates of prevalence of long COVID, indicating that no individual study influenced the results significantly. For those long COVID reported by over five studies, no significant publication bias was explored. These results are presented in Supplement Table 5 and Supplement Fig. 8.

Discussion

This study is, to our knowledge, the most wide-ranging systematic review to date, comprehensively summarizing current evidence on the long COVID of pediatric COVID-19 survivors. The findings suggest that nearly one quarter of pediatric patients had long COVID symptoms, which widely involved multi-organ systems. Prevalence of long COVID symptoms decreased as time went by. In addition, patients who were aged over 10 years, with MIS, and severe illness exhibited higher prevalence of long COVID. We also summarized the factors associated with long COVID in children, manly included older age, female, poor mental or physical status, as well as severe symptoms at initial infection. These findings have significant clinical implications and suggest that long-term monitoring is warranted for pediatric COVID-19 survivors.

The COVID-19 pandemic is our generation's greatest global challenge to our public health system [64–68], and children and adolescents have been affected both physically and psychologically [69,70]. In this meta-analysis and systematic review, we found that persistent COVID-19 symptoms were common among the pediatric COVID-19 survivors, with nearly one quarter reporting at least one long COVID symptom after recovery from acute illness or hospital discharge. The finding is similar to previous findings that suggesting post-COVID symptoms was 25.24 % in children and adolescents. However, the prevalence of long COVID-19 symptoms among the pediatric survivors was lower compared with adults, with at least half of them was reported having persistent long COVID [7]. These findings implicated the necessity of long-term monitoring for pediatric survivors recovered from COVID-19.

As indicated in this meta-analysis, dysponea, fatigue, and headache, occurred the most frequently, which is similar to adults with fatigue and dyspnea most prevalent [45]. However, symptoms such as myocarditis [28], splenomegaly [63], and appendicitis [71] are presented in pediatric survivors, which are serious long COVID of COVID-19 infection, albeit thankfully less common. The exact mechanism of these less common long COVID, and whether they are due to direct viral pathogenesis, requires further exploration. Apart from the symptoms mentioned above, developmental regression [27], memory impairment [27,28], and cognitive difficulties [36] have been reported in pediatric COVID-19 survivors, which may impair physical and psychological development of children in the future. Aside from the clinical assessment, imaging and laboratory findings also have implications for monitoring persistent COVID-19 symptoms amongst pediatric survivors.

We also found that the long COVID symptoms decreased as the follow-up duration, especially in respiratory, cardiovascular, psychiatric, and neurologic systems. The findings suggest that the long COVID symptoms were reversible, and the patients would be recovered despite it took a long time. However, one thing still should be taken into consideration is that some long COVID symptoms even exist after one-year follow-up duration, longer-term follow-up is

Symptoms	No. of studies	No. of events	No. of participants	Prevalence(%) (95% CI)	I^2(%)	P value
Any symptoms						
3-6 months	11	3205	9289	26.41 (14.33, 40.59)	100.0	0.41
6-12 months	5	237	1086	20.64 (17.06, 24.46)	31.0	
>12 months	2	51	411	14.89 (6.09, 26.51)	75.0	
Subjectively repiratory symptoms						
3-6 months	17	1094	7096	21.50 (9.41, 36.74)	98.0	<0.01
6-12 months	9	234	1645	13.65 (2.29, 31.55)	99.0	
>12 months	4	12	590	1.80 (0.22, 4.38)	49.0	
Psychiatric symptoms						
3-6 months	12	476	6793	13.84 (4.95, 26.08)	98.0	<0.01
6-12 months	9	331	1707	14.51 (3.26, 31.32)	99.0	
>12 months	3	10	565	1.34 (0, 5.26)	82.0	
Neurologic symptoms						
3-6 months	14	664	6784	13.01 (5.66, 22.67)	98.0	<0.01
6-12 months	9	353	1753	17.76 (3.86, 38.22)	99.0	
>12 months	3	13	534	1.89 (0.20, 4.70)	44.0	
Generalized symptoms						
3-6 months	15	2086	10077	19.50 (7.78, 34.75)	99.0	0.31
6-12 months	9	501	1842	19.30 (3.13, 43.97)	99.0	
>12 months	4	46	590	8.90 (2.96, 17.25)	88.0	
Digestive symptoms						
3-6 months	9	289	6033	12.38 (2.10, 29.02)	99.0	0.11
6-12 months	9	381	1754	14.76 (2.77, 33.23)	99.0	
>12 months	2	10	514	2.22 (0, 8.93)	90.0	
Musculoskeletal symptoms						
3-6 months	13	570	9797	8.97 (2.09, 19.52)	98.0	0.26
6-12 months	7	304	1608	13.61 (1.43, 34.52)	99.0	
>12 months	3	12	565	3.03 (0.05, 9.07)	81.0	
Dermotosis symptoms						
3-6 months	10	169	6283	7.10 (1.34, 16.46)	97.0	0.17
6-12 months	4	207	1333	11.17 (0, 40.21)	99.0	
>12 months	2	11	514	2.09 (0.97, 3.57)	0.0	
Cardiovascular symptoms						
3-6 months	9	95	3077	7.71 (1.58, 17.22)	97.0	<0.01
6-12 months	9	168	1457	8.60 (1.53, 19.68)	98.0	
>12 months	1	1	360	0.28 (0, 1.19)	/	
Ophthalmological symptoms						
3-6 months	5	197	5445	1.69 (0, 6.10)	98.0	0.52
6-12 months	2	135	799	12.63 (0, 74.04)	100.0	
Urological symptoms						
3-6 months	1	0	496	0 (0, 0.35)	/	0.11
6-12 months	2	2	540	0.44 (0, 4.02)	62.0	

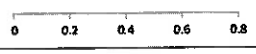
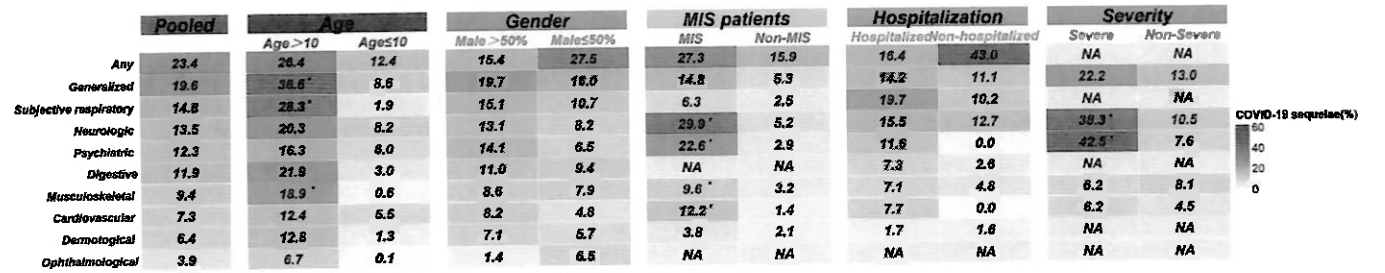


Fig. 4. Subgroup analysis of prevalence of long COVID in pediatric patients during different follow-up duration.

necessary to help define the extended natural history of pediatric survivors, even after one year or longer.

In this study, we also found children and adolescents with MIS, or had severe infection were more vulnerable to having long COVID symptoms. Children and adolescents with MIS generally exhibited serious and life-threatening illness [19,72]. Seven studies in this systematic review independently assessed the long COVID among the pediatric survivors with MIS. Overall, the pediatric survivors



Severe patients is defined as more than 50% of the patients who are seriously ill in acute phase.
* means subgroup difference p<0.05

Fig. 5. Subgroup analysis of prevalence of long COVID in pediatric patients.

with MIS had a higher prevalence of long COVID affecting multiple systems and organs. Participants with severe acute illness was also identified associated with long COVID in multi-systems. Osmanov et al. [73] associated severe acute COVID-19 with a six times greater likelihood of reporting long COVID; suggesting further characterization of which specific organ systems are most likely to be affected in severe cases of COVID-19 is still required. Moreover, by summarizing risk factors associated with long COVID, we also noticed that patients with more symptoms, or affected by specific diseases (e.g., neurologic, or allergic diseases) were more likely to develop long COVID. No statistical difference between the prevalence of long COVID affecting each specific organ system and hospitalization rate at baseline; however, more hospitalization duration was mentioned to associated with long COVID in Funk et al. findings [20]. All these findings implicated the importance of assessing the clinical conditions during the initial infection, and more attention should be paid to pediatric survivors with MIS, severe infection, or had comorbidities.

Some demographic characteristics have been mentioned to be associated with long COVID. Consistent with the findings of Behnood et al. [74], older age was associated with higher prevalence of long COVID symptoms. Despite no significant difference was explored between long COVID symptom and sex ratio in this study, several studies [18,56] implied that female are more risk for long COVID. In addition, patients with poor mental or physical health status also exhibited higher risk for long COVID. Exploring these vulnerable populations further could help policy-makers and physicians establish population-stratified support for patients most in need.

Several limitations should be pointed out in this study. First, the prevalence of long COVID among the pediatric survivors may biased due to the limited included number of studies. To the best of our knowledge, the majority of the studies focused on long COVID among the adults, as the symptoms may be more severe. As there still remained a lot of unknowns about the long COVID in pediatric COVID-19 survivors, more related researches are recommended. Second, the heterogeneity of the study could not be avoided. Many symptoms were not captured using standardized definitions or instruments, and it was difficult to compare frequency and severity. Objective measurement as well as well-designed examinations is suggested to in the near future. Third, the long COVID after COVID-19 infection were merely symptoms among the survivors; therefore, the causal relationship between COVID-19 infection and long COVID should be cautiously read. Many symptoms such as fatigue, muscle pain, and headache are highly prevalent in the general population, and it may be not necessarily caused by COVID-19 infection. Based on this consideration, it is of great necessity to introduce the comparison group to address the issue of long COVID of COVID-19 infection among the pediatric survivors. Disappointingly, few included studies set the control groups to compare the long COVID among the COVID-19 pediatric survivors, which limited us to furtherly clarify the relationship between COVID-19 infection and long COVID. Fourth, the impact of COVID-19 infection on growth and intelligence development after long period seemed to be not clear. Memory impairment, and cognitive difficulties have already been reported in pediatric COVID-19 survivors [28,51], which implied the potential side effects of COVID-19 infection on growth and intelligence development. Thus, the long period monitoring for pediatric COVID-19 survivors is necessary. Fifth, evidence of risk factors associated with long COVID symptoms was limited, which needs further investigation in the future. Patients with MIS, more severe symptoms at initial infection generally presented with higher prevalence of long COVID. Therefore, these vulnerable patients should be cautiously treated with medical service not merely during acute phase, but also be monitored after long duration.

Conclusion

In conclusion, this meta-analysis provides a comprehensive overview of the current state of knowledge of the long COVID among the pediatric COVID-19 survivors and the risk factors associated with it. Our findings suggest that pediatric COVID-19 survivors who have recovered from COVID-19 have a high burden of long COVID after hospital discharge, and the cases with multisystem inflammatory syndrome, and more severe symptoms at initial infection had higher burden. It is important to follow-up these patients and appropriately manage any persistent or emerging long COVID in both physical and psychological domains.

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CRediT authorship contribution statement

LL, and YPB proposed the topic of the systematic review. YBZ, NZ, SST, YBY, NG, and XC performed the literature search, extracted and selected articles. YBZ and NZ performed the primary analysis, and all authors help interpreted the results. YBZ and KY drafted the manuscript, ALK, AL, JS, JLY, XL, LS, JS, YPB and LL were responsible for critical revision of the manuscript, and all authors revised the manuscript, approved the final submitted version of the manuscript, and approved the decision to submit the manuscript.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors have no conflicts of interest to declare.

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None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2023.03.005.

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Morbidity and Mortality Weekly Report (*MMWR*)

Ten Great Public Health Achievements --- United States, 2001--2010

Weekly
May 20, 2011 / 60(19);619-623

During the 20th century, life expectancy at birth among U.S. residents increased by 62%, from 47.3 years in 1900 to 76.8 in 2000, and unprecedented improvements in population health status were observed at every stage of life (*1*). In 1999, *MMWR* published a series of reports highlighting 10 public health achievements that contributed to those improvements. This report assesses advances in public health during the first 10 years of the 21st century. Public health scientists at CDC were asked to nominate noteworthy public health achievements that occurred in the United States during 2001--2010. From those nominations, 10 achievements, not ranked in any order, have been summarized in this report.

Vaccine-Preventable Diseases

The past decade has seen substantial declines in cases, hospitalizations, deaths, and health-care costs associated with vaccine-preventable diseases. New vaccines (i.e., rotavirus, quadrivalent meningococcal conjugate, herpes zoster, pneumococcal conjugate, and human papillomavirus vaccines, as well as tetanus, diphtheria, and acellular pertussis vaccine for adults and adolescents) were introduced, bringing to 17 the number of diseases targeted by U.S. immunization policy. A recent economic analysis indicated that vaccination of each U.S. birth cohort with the current childhood immunization schedule prevents approximately 42,000 deaths and 20 million cases of disease, with net savings of nearly $14 billion in direct costs and $69 billion in total societal costs (*2*).

The impact of two vaccines has been particularly striking. Following the introduction of pneumococcal conjugate vaccine, an estimated 211,000 serious pneumococcal infections and 13,000 deaths were prevented during 2000--2008 (*3*). Routine rotavirus vaccination, implemented in 2006, now prevents an estimated 40,000--60,000 rotavirus hospitalizations each year (*4*). Advances also were made in the use of older vaccines, with reported cases of hepatitis A, hepatitis B, and varicella at record lows by the end of the decade. Age-specific mortality (i.e., deaths per million population) from varicella for persons age <20 years, declined by 97% from 0.65 in the prevaccine period (1990--1994) to 0.02 during 2005--2007 (*5*). Average age-adjusted mortality (deaths per million population) from hepatitis A also declined significantly, from 0.38 in the prevaccine period (1990--1995) to 0.26 during 2000--2004 (*6*).

Prevention and Control of Infectious Diseases

Improvements in state and local public health infrastructure along with innovative and targeted prevention efforts yielded significant progress in controlling infectious diseases. Examples include a 30% reduction from 2001 to 2010 in reported U.S. tuberculosis cases and a 58% decline from 2001 to 2009 in central line--associated blood stream infections (*7,8*). Major advances in laboratory techniques and technology and investments in disease surveillance have improved the capacity to identify contaminated foods rapidly and accurately and prevent further spread (*9*--*12*). Multiple efforts to extend HIV testing, including recommendations for expanded screening of persons aged 13--64 years, increased the number of persons diagnosed with HIV/AIDS and reduced the proportion with late diagnoses, enabling earlier access to life-saving treatment and care and giving infectious persons the information necessary to protect their partners (*13*). In 2002, information from CDC predictive models and reports of suspected West Nile virus transmission through blood transfusion spurred a national investigation, leading to the rapid development and implementation of new blood donor screening (*14*). To date, such screening has interdicted 3,000 potentially infected U.S. donations, removing them from the blood supply. Finally, in 2004, after more than 60 years of effort, canine rabies was eliminated in the United States, providing a model for controlling emerging zoonoses (*15,16*).

Tobacco Control

Since publication of the first Surgeon General's Report on tobacco in 1964, implementation of evidence-based policies and interventions by federal, state, and local public health authorities has reduced tobacco use significantly (*17*). By 2009, 20.6% of adults and 19.5% of youths were current smokers, compared with 23.5% of adults and 34.8% of youths 10 years earlier. However, progress in reducing smoking rates among youths and adults appears to have stalled in recent years. After a substantial decline from 1997 (36.4%) to 2003 (21.9%), smoking rates among high school students remained

relatively unchanged from 2003 (21.9%) to 2009 (19.5%) (*18*). Similarly, adult smoking prevalence declined steadily from 1965 (42.4%) through the 1980s, but the rate of decline began to slow in the 1990s, and the prevalence remained relatively unchanged from 2004 (20.9%) to 2009 (20.6%) (19). Despite the progress that has been made, smoking still results in an economic burden, including medical costs and lost productivity, of approximately $193 billion per year (20).

Although no state had a comprehensive smoke-free law (i.e., prohibit smoking in worksites, restaurants, and bars) in 2000, that number increased to 25 states and the District of Columbia (DC) by 2010, with 16 states enacting comprehensive smoke-free laws following the release of the 2006 Surgeon General's Report (21). After 99 individual state cigarette excise tax increases, at an average increase of 55.5 cents per pack, the average state excise tax increased from 41.96 cents per pack in 2000 to $1.44 per pack in 2010 (*22*). In 2009, the largest federal cigarette excise tax increase went into effect, bringing the combined federal and average state excise tax for cigarettes to $2.21 per pack, an increase from $0.76 in 2000. In 2009, the Food and Drug Administration (FDA) gained the authority to regulate tobacco products (*23*). By 2010, FDA had banned flavored cigarettes, established restrictions on youth access, and proposed larger, more effective graphic warning labels that are expected to lead to a significant increase in quit attempts (24).

Maternal and Infant Health

The past decade has seen significant reductions in the number of infants born with neural tube defects (NTDs) and expansion of screening of newborns for metabolic and other heritable disorders. Mandatory folic acid fortification of cereal grain products labeled as enriched in the United States beginning in 1998 contributed to a 36% reduction in NTDs from 1996 to 2006 and prevented an estimated 10,000 NTD-affected pregnancies in the past decade, resulting in a savings of $4.7 billion in direct costs (25--27).

Improvements in technology and endorsement of a uniform newborn-screening panel of diseases have led to earlier life-saving treatment and intervention for at least 3,400 additional newborns each year with selected genetic and endocrine disorders (28,29). In 2003, all but four states were screening for only six of these disorders. By April 2011, all states reported screening for at least 26 disorders on an expanded and standardized uniform panel (29). Newborn screening for hearing loss increased from 46.5% in 1999 to 96.9% in 2008 (*30*). The percentage of infants not passing their hearing screening who were then diagnosed by an audiologist before age 3 months as either normal or having permanent hearing loss increased from 51.8% in 1999 to 68.1 in 2008 (*30*).

Motor Vehicle Safety

Motor vehicle crashes are among the top 10 causes of death for U.S. residents of all ages and the leading cause of death for persons aged 5--34 years (*30*). In terms of years of potential life lost before age 65, motor vehicle crashes ranked third in 2007, behind only cancer and heart disease, and account for an estimated $99 billion in medical and lost work costs annually (*31,32*). Crash-related deaths and injuries largely are preventable. From 2000 to 2009, while the number of vehicle miles traveled on the nation's roads increased by 8.5%, the death rate related to motor vehicle travel declined from 14.9 per 100,000 population to 11.0, and the injury rate declined from 1,130 to 722; among children, the number of pedestrian deaths declined by 49%, from 475 to 244, and the number of bicyclist deaths declined by 58%, from 178 to 74 (*33,34*).

These successes largely resulted from safer vehicles, safer roadways, and safer road use. Behavior was improved by protective policies, including effective seat belt and child safety seat legislation; 49 states and the DC have enacted seat belt laws for adults, and all 50 states and DC have enacted legislation that protects children riding in vehicles (*35*). Graduated drivers licensing policies for teen drivers have helped reduce the number of teen crash deaths (*36*).

Cardiovascular Disease Prevention

Heart disease and stroke have been the first and third leading causes of death in the United States since 1921 and 1938, respectively (*37,38*). Preliminary data from 2009 indicate that stroke is now the fourth leading cause of death in the United States (*39*). During the past decade, the age-adjusted coronary heart disease and stroke death rates declined from 195 to 126 per 100,000 population and from 61.6 to 42.2 per 100,000 population, respectively, continuing a trend that started in the 1900s for stroke and in the 1960s for coronary heart disease (40). Factors contributing to these reductions include declines in the prevalence of cardiovascular risk factors such as uncontrolled hypertension, elevated cholesterol, and smoking, and improvements in treatments, medications, and quality of care (*41--44*)

Occupational Safety

Significant progress was made in improving working conditions and reducing the risk for workplace-associated injuries. For example, patient lifting has been a substantial cause of low back injuries among the 1.8 million U.S. health-care workers in nursing care and residential facilities. In the late 1990s, an evaluation of a best practices patient-handling program that included the use of mechanical patient-lifting equipment demonstrated reductions of 66% in the rates of workers' compensation injury claims and lost workdays and documented that the investment in lifting equipment can be

recovered in less than 3 years (*45*). Following widespread dissemination and adoption of these best practices by the nursing home industry, Bureau of Labor Statistics data showed a 35% decline in low back injuries in residential and nursing care employees between 2003 and 2009.

The annual cost of farm-associated injuries among youth has been estimated at $1 billion annually (*46*). A comprehensive childhood agricultural injury prevention initiative was established to address this problem. Among its interventions was the development by the National Children's Center for Rural Agricultural Health and Safety of guidelines for parents to match chores with their child's development and physical capabilities. Follow-up data have demonstrated a 56% decline in youth farm injury rates from 1998 to 2009 (National Institute for Occupational Safety and Health, unpublished data, 2011).

In the mid-1990s, crab fishing in the Bering Sea was associated with a rate of 770 deaths per 100,000 full-time fishers (*47*). Most fatalities occurred when vessels overturned because of heavy loads. In 1999, the U.S. Coast Guard implemented Dockside Stability and Safety Checks to correct stability hazards. Since then, one vessel has been lost and the fatality rate among crab fishermen has declined to 260 deaths per 100,000 full-time fishers (*47*).

Cancer Prevention

Evidence-based screening recommendations have been established to reduce mortality from colorectal cancer and female breast and cervical cancer (*48*). Several interventions inspired by these recommendations have improved cancer screening rates. Through the collaborative efforts of federal, state, and local health agencies, professional clinician societies, not-for-profit organizations, and patient advocates, standards were developed that have significantly improved cancer screening test quality and use (*49*,*50*). The National Breast and Cervical Cancer Early Detection Program has reduced disparities by providing breast and cervical cancer screening services for uninsured women (*49*). The program's success has resulted from similar collaborative relationships. From 1998 to 2007, colorectal cancer death rates decreased from 25.6 per 100,000 population to 20.0 (2.8% per year) for men and from 18.0 per 100,000 to 14.2 (2.7% per year) for women (*51*). During this same period, smaller declines were noted for breast and cervical cancer death rates (2.2% per year and 2.4%, respectively) (*52*).

Childhood Lead Poisoning Prevention

In 2000, childhood lead poisoning remained a major environmental public health problem in the United States, affecting children from all geographic areas and social and economic levels. Black children and those living in poverty and in old, poorly maintained housing were disproportionately affected. In 1990, five states had comprehensive lead poisoning prevention laws; by 2010, 23 states had such laws. Enforcement of these statutes as well as federal laws that reduce hazards in the housing with the greatest risks has significantly reduced the prevalence of lead poisoning. Findings of the National Health and Nutrition Examination Surveys from 1976--1980 to 2003--2008 reveal a steep decline, from 88.2% to 0.9%, in the percentage of children aged 1--5 years with blood lead levels ≥10 μg/dL. The risks for elevated blood lead levels based on socioeconomic status and race also were reduced significantly. The economic benefit of lowering lead levels among children by preventing lead exposure is estimated at $213 billion per year (*53*).

Public Health Preparedness and Response

After the international and domestic terrorist actions of 2001 highlighted gaps in the nation's public health preparedness, tremendous improvements have been made. In the first half of the decade, efforts were focused primarily on expanding the capacity of the public health system to respond (e.g., purchasing supplies and equipment). In the second half of the decade, the focus shifted to improving the laboratory, epidemiology, surveillance, and response capabilities of the public health system. For example, from 2006 to 2010, the percentage of Laboratory Response Network labs that passed proficiency testing for bioterrorism threat agents increased from 87% to 95%. The percentage of state public health laboratories correctly subtyping *Escherichia coli* O157:H7 and submitting the results into a national reporting system increased from 46% to 69%, and the percentage of state public health agencies prepared to use Strategic National Stockpile material increased from 70% to 98% (*54*). During the 2009 H1N1 influenza pandemic, these improvements in the ability to develop and implement a coordinated public health response in an emergency facilitated the rapid detection and characterization of the outbreak, deployment of laboratory tests, distribution of personal protective equipment from the Strategic National Stockpile, development of a candidate vaccine virus, and widespread administration of the resulting vaccine. These public health interventions prevented an estimated 5--10 million cases, 30,000 hospitalizations, and 1,500 deaths (CDC, unpublished data, 2011).

Existing systems also have been adapted to respond to public health threats. During the 2009 H1N1 influenza pandemic, the Vaccines for Children program was adapted to enable provider ordering and distribution of the pandemic vaccine. Similarly, President's Emergency Plan for AIDS Relief clinics were used to rapidly deliver treatment following the 2010 cholera outbreak in Haiti.

Conclusion

From 1999 to 2009, the age-adjusted death rate in the United States declined from 881.9 per 100,000 population to 741.0, a record low and a continuation of a steady downward trend that began during the last century. Advances in public health contributed significantly to this decline; seven of the 10 achievements described in this report targeted one or more of the 15 leading causes of death. Related *Healthy People 2010* data are available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6019a5_addinfo.htm. The examples in this report also illustrate the effective application of core public health tools. Some, such as the establishment of surveillance systems, dissemination of guidelines, implementation of research findings, or development of effective public health programs, are classic tools by which public health has addressed the burden of disease for decades.

Although not new, the judicious use of the legal system, by encouraging healthy behavior through taxation or by shaping it altogether through regulatory action, has become an increasingly important tool in modern public health practice and played a major role in many of the achievements described in this report (55). The creative use of the whole spectrum of available options, as demonstrated here, has enabled public health practitioners to respond effectively. Public health practice will continue to evolve to meet the new and complex challenges that lie ahead.

Reported by

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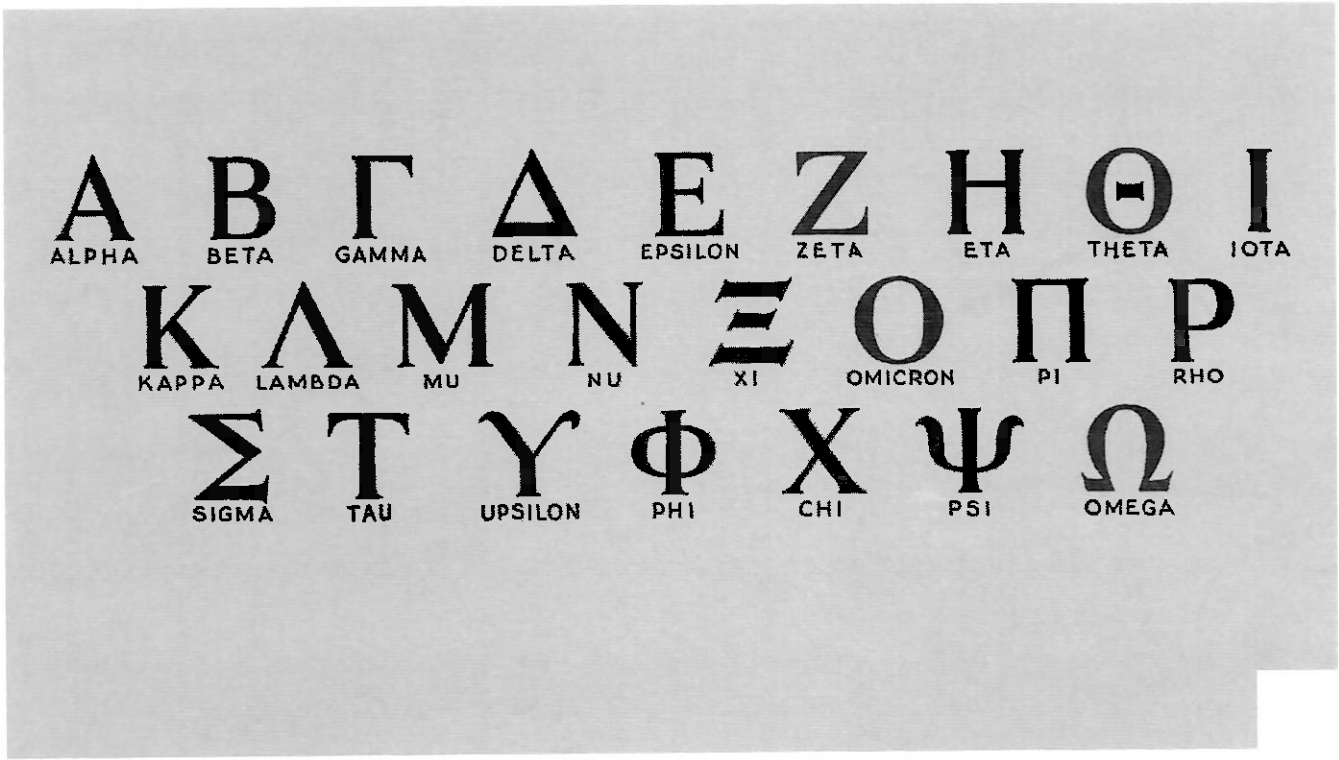
Omicron, Delta, Alpha, and More: What To Know About the Coronavirus Variants

BY **KATHY KATELLA** SEPTEMBER 1, 2023

A quick guide to the coronavirus variants that have been top-of-mind.



[Originally published: Dec. 10, 2021. Updated: Sept. 1, 2023]

Note: Information in this article was accurate at the time of original publication. Because information about COVID-19 changes rapidly, we encourage you to visit the websites of the Centers for Disease Control & Prevention (CDC), World Health Organization (WHO), and your state and local government for the latest information.

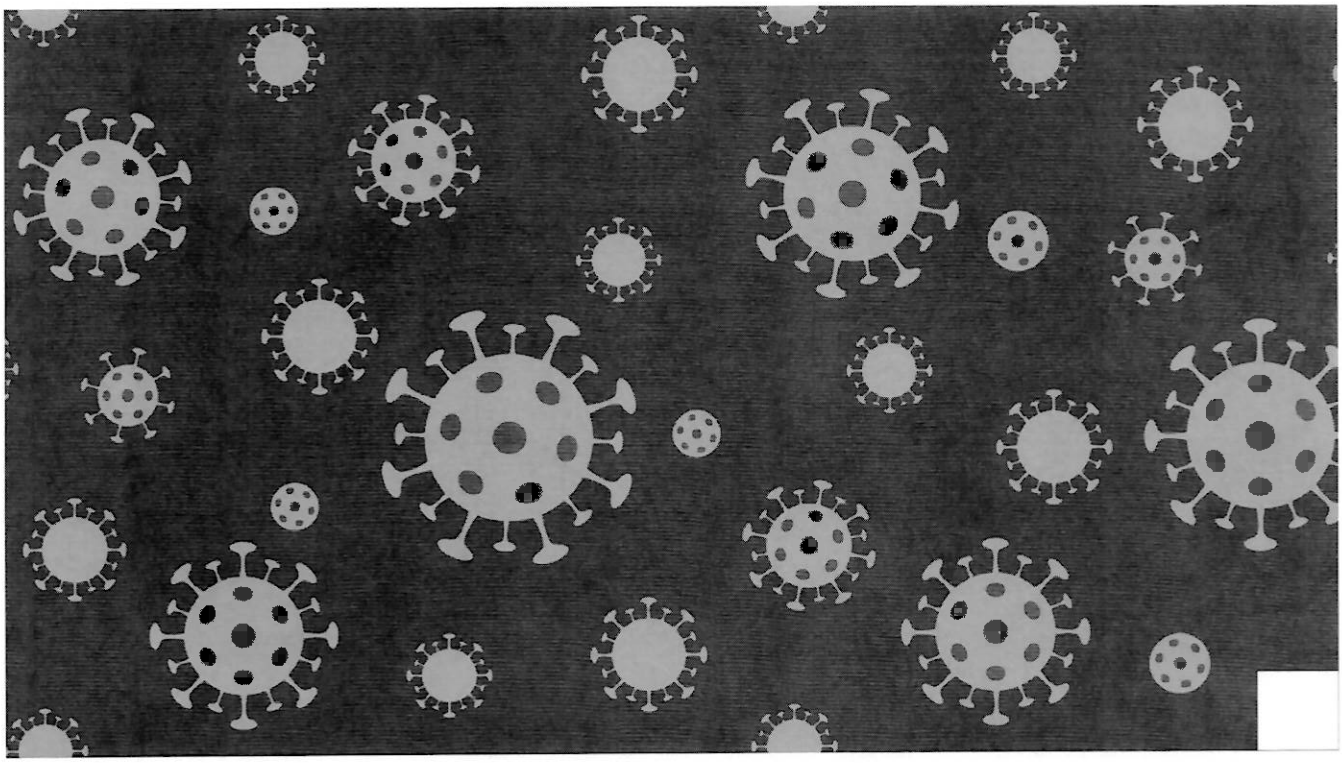
One thing we know for sure about SARS-CoV-2, the virus that causes COVID-19, is that it is changing constantly. Since the beginning of the pandemic, we've seen a number of prominent variants, including Alpha, Beta, Delta, and Omicron.

Although new variants are an expected part of the evolution of viruses, monitoring each one that surfaces is essential in ensuring we—in the U.S. and globally—are prepared. This is especially true if a new variant is more aggressive, highly transmissible, vaccine-resistant, able to cause more severe disease—or all of the above, compared with the original strain of the virus.

The World Health Organization (WHO) names new coronavirus variants using the letters of the Greek alphabet, starting with the Alpha variant, which emerged in 2020.

Below is a list of—and information about—some of the variants that have been top-of-mind.

Omicron and its subvariants



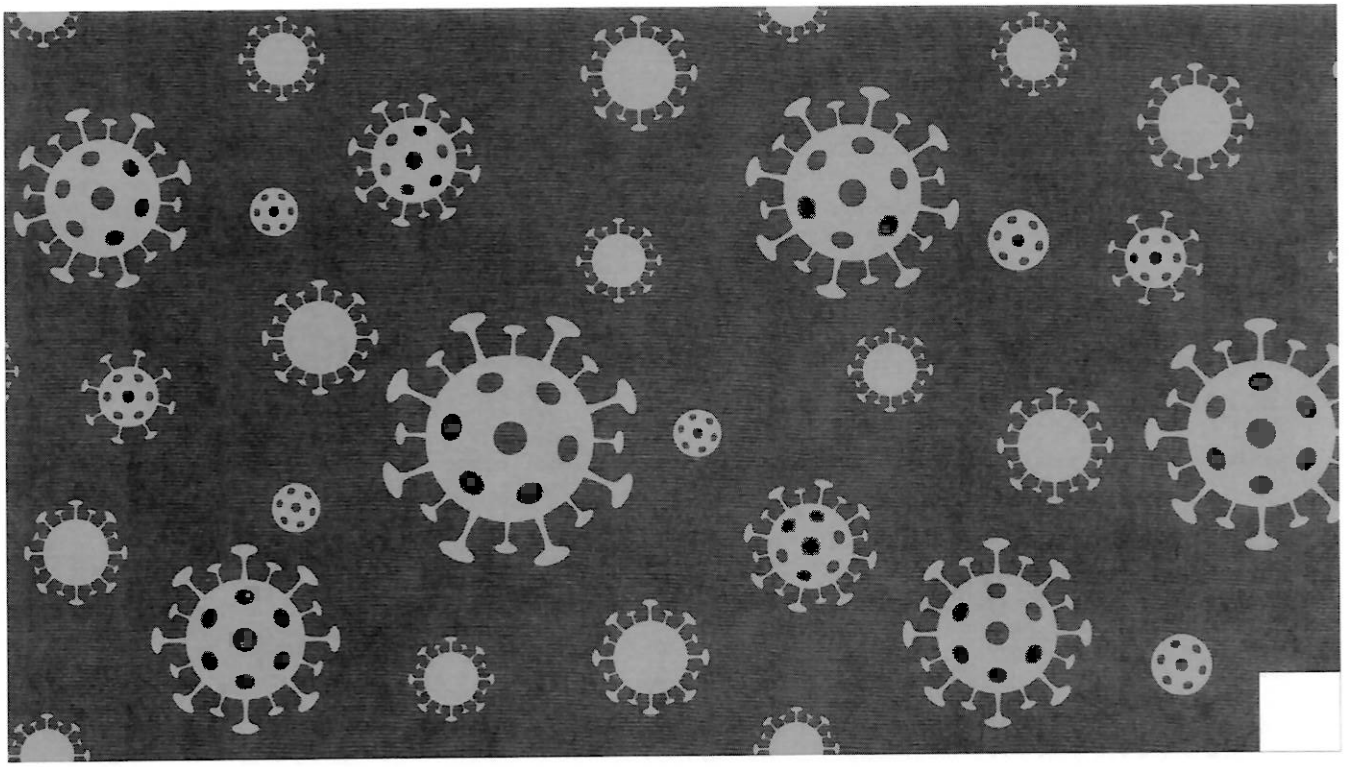
Omicron and its subvariants have ranked as the predominant SARS-CoV-2 strains in the U.S. for almost two years now. While the original Omicron strain (BA.1) is no longer circulating, Omicron subvariants are now driving most of the country's SARS-CoV-2 infections. Omicron was first identified in Botswana and South Africa in late November 2021, and cases quickly began to surface and multiply in other countries. By December of that year, Omicron was causing daily case numbers in the U.S. to skyrocket to over a million. In 2022, it had spawned a number of subvariants. In 2023, a new Omicron strain called EG.5 (nicknamed "Eris") is the dominant strain in the U.S., and experts are monitoring another new strain called BA.2.86 (nicknamed "Pirola").

How contagious is it? Omicron's subvariants are considered to be especially efficient spreaders of the disease. The original strain of Omicron was more transmissible than Delta was. One explanation was that more than 30 of Omicron's mutations are on the virus's spike protein, the part that attaches to human cells, and several of those are believed to increase the probability of infection.

Severity: Scientists are still working to learn more about whether the current Omicron strains cause more severe disease than their predecessors. Data has suggested that the original Omicron strain was less severe, in general, than previous variants, according to the CDC. But it has also been noted that surges in cases may lead to significant increases in hospitalizations and deaths, as they did during the variant's spread at the beginning of 2022, when the estimated death rates went as high or higher than they were at the time of the Delta variant surge in the previous autumn.

Can vaccination prevent it? The CDC says that while breakthrough infections in vaccinated people are expected, staying up to date with vaccinations is the best protection against Omicron. Scientists are evaluating the effectiveness of a new fall 2023 updated COVID-19 booster against EG.5 and BA.2.86, according to the CDC. Currently, the CDC says the updated vaccine is expected to be effective at reducing severe disease and hospitalization from the two recent subvariants.

Delta



Delta (B.1.617.2) was first identified in India in late 2020; it soon spread throughout the world, becoming what was the predominant version of the coronavirus—until Omicron took its place in mid-December of 2021.

How contagious is it? It's estimated that Delta caused more than twice as many infections as previous variants —in Connecticut, it was estimated to have been 80 to 90% more transmissible than the Alpha variant. In the U.S., in June 2021, after a steady decline in COVID-19 cases and hospitalizations, the arrival of Delta coincided with a rapid reversal of that trend. In the fall of 2021, there were surges even in the most vaccinated states, prompting experts to urge people to get their booster shots.

Severity: Delta caused more severe disease than other variants in people who weren't vaccinated. Early studies from Scotland and Canada, both cited by the CDC, suggested Delta was more likely to result in hospitalization in the unvaccinated. A report in the *Lancet* found that people in England had double the hospitalization risk with Delta than they did with Alpha, the previously dominant variant in that country.

Can vaccination prevent it? All three vaccines in the U.S. were considered highly effective against severe illness, hospitalizations, and death from Delta. No vaccine is 100% effective, and Delta caused breakthrough infections in some fully vaccinated people. Also, infected vaccinated people could spread the virus to others, although likely they were infectious for a shorter time.

Delta also prompted the CDC to recommend "layered prevention strategies" for both the vaccinated and the unvaccinated. That means that, in addition to staying up-to-date with their vaccines, people were advised to practice such strategies as washing hands, wearing masks, and maintaining a physical distance from one another, especially when indoors in places where there was substantial or high transmission.

Beta


Purple Variant coronavirus illustration

This variant, or B.1.351, was identified in South Africa at the end of 2020 and spread to other countries. Experts had been concerned about its several mutations and its potential to evade antibodies. Beta was not common in the U.S.

How contagious is it? The CDC said Beta was about 50% more contagious than the original coronavirus strain.

Severity: There was evidence to suggest that Beta may have been more likely than other variants to lead to hospitalization and death.

Can vaccination prevent it? South Africa stopped offering the AstraZeneca-Oxford vaccine (which is not available in the U.S.) early in 2021 after clinical trials showed it did not provide strong protection against mild and moderate disease from the Beta variant. Pfizer-BioNTech, Moderna, and Johnson & Johnson also reported less protection against Beta.

Alpha


Yellow Variant coronavirus Illustration

Alpha (B.1.1.7) was the first of the highly publicized variants. Alpha first appeared in Great Britain in November 2020 and infections surged in December of that year. It soon surfaced around the world and became the dominant variant in the U.S., where the CDC classified it as a variant of concern. Then, Alpha faded away with the rise of the more aggressive Delta variant.

How contagious is it? Some mutations in Alpha's spike protein were thought to make it more infectious. The B.1.1.7 lineage was believed to be 30 to 50% more contagious than the original SARS-CoV-2 strain. In the U.S., in mid-April 2021—before Delta became predominant—Alpha comprised 66% of cases, according to a study released in June by the CDC.

Severity: Studies have suggested the B.1.1.7 lineage was more likely to land infected people in the hospital and was deadlier than the original virus.

Can vaccinations prevent it? Pfizer, Moderna, and Johnson & Johnson all said their vaccines were effective in preventing severe disease and hospitalization in Alpha cases.

This article was medically reviewed by Yale School of Public Health epidemiologist Nathan Grubaugh, PhD.

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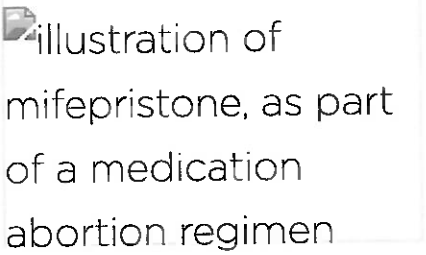

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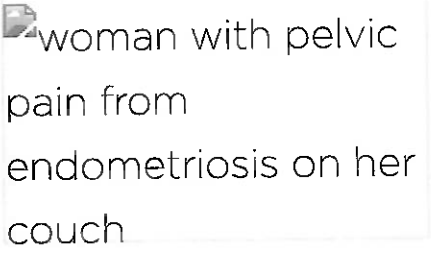

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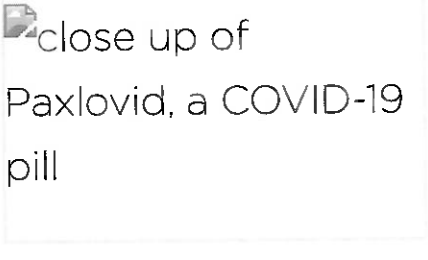

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Published: 19 August 2021

CORONAVIRUS

Covid-19: How many variants are there, and what do we know about them?

Eight notable variants of SARS-CoV-2 have been found since September 2020. **Elisabeth Mahase** reviews the line-up so far

Elisabeth Mahase

Alpha

Considered a variant of concern by the World Health Organization, alpha was first identified in Kent in the UK in September 2020 and drove the UK's second wave.

While it was first thought that this variant was around 70% more transmissible than the original (wild-type) SARS-CoV-2 coronavirus, data now suggest that it is 30-40% more transmissible than the original.[1]

Research has shown vaccine efficacy (two doses) against the alpha variant to be 74.5% with the Oxford-AstraZeneca vaccine, 93.7% with the Pfizer-BioNTech vaccine,[2] 85.6% with the Novavax vaccine,[3] and 100% with the Moderna vaccine.[4] A study looking at the Sputnik V vaccine saw some reduced neutralising activity against the alpha variant,[5] and Thailand's Public Health Ministry has reported that two doses of the Sinovac vaccine are 71-91% effective against alpha.[6] (Video 1)

Video 1 Covid-19: Variants of concern

Beta

First documented in South Africa in May 2020, beta is also considered a variant of concern by WHO.

The US Centers for Disease Control and Prevention (CDC) has linked beta with a 50% increase in transmission,[7] but the big worry is the emerging evidence of its ability to evade some of the existing vaccines.

Early studies indicate that the Pfizer vaccine has a slightly lower (72-75%) effectiveness against beta than against the wild-type SARS-CoV-2, but both Pfizer and Moderna say that their vaccines are still 95% effective against severe disease and death. Novavax (60%) and Johnson and Johnson (57%) fare slightly worse. And, while early studies of the Oxford-AstraZeneca vaccine seemed to show low efficacy against beta, real world data published on 23 July indicated 82% effectiveness in preventing severe disease and death from covid after a single vaccine dose.[8]

Sputnik V's maker claims that it is "highly effective" against beta, but at least one study has noted a reduction in neutralising activity against this variant.[5] Data on the efficacy of Sinovac's CoronaVac are lacking, although reports from Hong Kong suggested that the level of protection was 70% lower against beta than against wild-type.[9]

Gamma

Gamma was first identified in Manaus, Brazil, in November 2020 and is another variant of concern for WHO. At the time of writing it remains the dominant variant in South America.[10]

Research suggests that gamma is 1.7-2.4 times more transmissible than wild-type SARS-CoV-2.[11]

Few studies have been conducted to determine the efficacy of covid vaccines against the gamma variant. However, a report looking at an outbreak of gamma among employees of a goldmine in French Guiana noted a "strikingly high attack rate" among people fully vaccinated with the Pfizer vaccine, as 60% of the fully vaccinated people became infected, compared with 75% of unvaccinated miners without a history of infection.[12] The manufacturers of Sputnik V claim that it is "highly effective" against variants including gamma, but a study published in July looking at antibody responses found reduced neutralising activity against gamma and other variants.[13]

Delta

A WHO variant of concern now dominant in Europe and the US, delta continues to drive a steep rise in cases throughout much of Asia including Bangladesh, Iran, Iraq, Japan, Kazakhstan, Malaysia, Myanmar, Pakistan, South Korea, Thailand, and Vietnam,[14] as well as in India, where it was first identified in October 2020.

Delta is the most transmissible form of SARS-CoV-2 detected so far: as much as 60% more so than the alpha variant, one study estimated. Researchers have described it as an "improved" version of the alpha variant thanks to a mutation that makes it more infective in the airways. This means an increased amount of virus in the infected person such that they may expel more virus into the air, and one preprint study concluded that infected individuals had viral loads as much as 1260 times higher than people infected with wild-type SARS-CoV-2.[15] Another concern is that if the delta variant is better at infecting human airway cells people may become infected after lower exposure.[16]

The data so far are positive regarding existing vaccines: research suggests vaccine efficacy of 67% with the Oxford-AstraZeneca vaccine and 88% with the Pfizer-BioNTech vaccine against delta, while the

manufacturers of Sputnik V claim that it is 90% effective against it.

Another development is the emergence of delta with a K417N spike protein mutation, which has been termed delta plus. As of 23 July England had reported 45 cases of this variant. Colin Angus, a public health policy modeller and analyst, told the *Washington Post* that the delta plus cases had primarily been in younger people but that preliminary data showed that antibodies from vaccinated people were still effective against this variant.[17]

Eta

Cases of the eta variant have turned up in 72 countries including Nigeria and the UK, where it was first detected in December 2020. Little is known about eta, although the CDC said that it has the potential to reduce the neutralising ability of some monoclonal antibody treatments and convalescent plasma. WHO has declared it a "variant of interest," its second tier level of alert.

Iota

As with eta, little is known about the iota variant, which was first identified in New York City, USA, in November 2020. It has so far been reported in 53 countries, and the CDC says that it has lower susceptibility to the combination bamlanivimab-etesevimab monoclonal antibody treatment. This was enough for WHO to declare it a variant of interest.

Kappa

First documented in India in October 2020, kappa is also considered a variant of interest by WHO. The CDC says that this variant may reduce the neutralisation potential of some monoclonal antibody treatments. It has been reported in 55 countries.

Lambda

First identified in Peru in December 2020, lambda became the dominant variant within three months, accounting for 80% of all cases. The swiftness and presence of mutations that could affect transmissibility and antibodies' effectiveness have made it a variant of interest for WHO. It has been detected in 41 countries but has not yet outcompeted any of the more dominant variants.

No peer reviewed studies of lambda have been conducted, but early preprint studies indicate some reduction in neutralising antibody effects from the CoronaVac (Sinovac) vaccine,[18] as well as Pfizer and Moderna, although researchers say that they are confident that the latter two would remain protective.[19]

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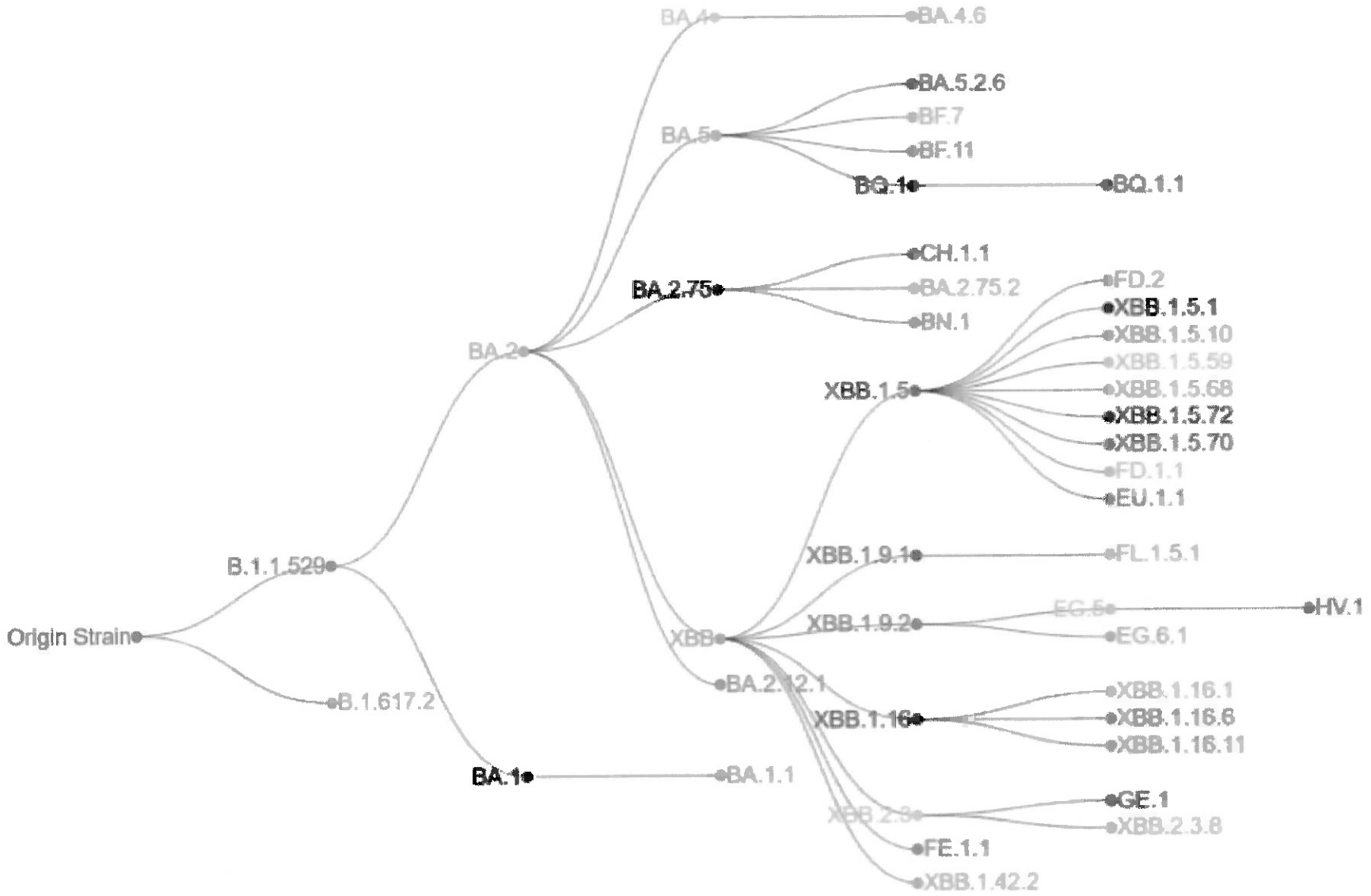
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BN.1
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BA.2.12.1
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XBB.1.5.68
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FD.1.1
EU.1.1
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ASPR Administration for Strategic Preparedness & Response

Information Sheet & Frequently Asked Questions

FDA's Change to Authorization of Evusheld

On January 26, FDA announced that Evusheld is not currently authorized for emergency use in the U.S. until further notice by the agency because the therapeutic is unlikely to be active against more than 90% of the SARS-CoV-2 variants currently circulating in the U.S. based on the latest CDC data.

There are many things that people can do to protect themselves against COVID-19. First, if vaccination is recommended for you, get vaccinated and stay up to date. This means getting the updated (bivalent) vaccine if you haven't received it yet.

Second, develop a COVID-19 Action Plan so that you have all of the information you need on hand if you get sick with COVID-19.

If you develop signs or symptoms of COVID-19, reach out to your doctor, another healthcare provider, or a Test to Treat site (in person or via telehealth) immediately, even if your symptoms are mild. As an additional option for patients who are unable to access their healthcare provider, Test to Treat sites have health clinics at the sites where people can get tested for COVID-19 and evaluated by a healthcare provider (in person or via telehealth). People who test positive and are eligible can get a prescription to treat the infection and have the prescription filled at an affiliated pharmacy.

Finally, taking multiple prevention steps can provide additional layers of protection against COVID-19:

- Wear a well-fitting, high-quality mask or respirator in public places to reduce your chances of becoming infected with COVID-19, or any other respiratory illnesses. Properly fitting respirators provide the highest level of protection.
- When indoors with others, try to improve ventilation as much as possible.
- Avoid poorly ventilated or crowded indoor settings.
- Wash your hands often with soap and water or use a hand sanitizer that contains at least 60% alcohol.
- Encourage people you live with or spend time with to stay up to date on COVID vaccines and take all necessary
- prevention actions to protect themselves against COVID-19, or hospitalization and death if exposed.
- Avoid people who are sick, including people have COVID-19, even if they do not feel or seem sick.
- Talk with your doctor in advance about what treatments may be appropriate for you and how to access the medication if you experience symptoms.

Frequently Asked Questions

What is Evusheld?

Evusheld is a long-acting antibody therapeutic. Since December 2021, Evusheld has been an option for pre-exposure prophylaxis, in other words as preventive protection from COVID-19.

Specifically, Evusheld was authorized for:

- People who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and may not mount an adequate immune response to COVID-19 vaccination, or

- People for whom vaccination with any available COVID-19 vaccine is not recommended due to a history of severe adverse reaction to a COVID-19 vaccine and/or components of a COVID-19 vaccine.

Why did FDA take action to pause the authorization of Evusheld?

Evusheld is not currently authorized for emergency use in the U.S. because it is unlikely to be active against more than 90% of the SARS-CoV-2 variants currently circulating in the U.S. The latest CDC NOWCAST estimate shows that these variants are causing more than 90% of the cases today.

This FDA action follows several previous announcements and guidance updates for Evusheld by federal agencies over the past few months, including:

- At the beginning of October, FDA informed health care providers and individuals taking Evusheld of its loss of activity against some Omicron variants and the increased risk of breakthrough infections, especially as resistant variants became more prevalent as they are today.
- On December 20, the Centers for Disease Control and Prevention (CDC) issued a Health Alert Network (HAN) Health Update to supplement the CDC HAN Health Advisories issued on April 25, 2022 and May 24, 2022 to emphasize to healthcare providers, public health departments, and reduced susceptibility to Evusheld.
- On January 6, 2023 FDA released additional communication stating that they were closely monitoring the emergence of the XBB.1.5 subvariant, a SARS-CoV-2 Omicron variant that is currently increasing in prevalence in the U.S. Because of its similarity to variants that are not neutralized by Evusheld (e.g., XBB), FDA does not anticipate that Evusheld will neutralize XBB.1.5.
- On January 10, 2023, NIH's COVID-19 Treatment Guidelines Panel released a statement indicating that the prevalence of SARS-CoV-2 subvariants likely to be resistant to Evusheld was increasing.

I am immunocompromised and used Evusheld for protection. What does this decision mean for me?

If you've already received Evusheld, it's important to know that it does not provide protection against the variants of COVID-19 that are most common today. Because of this, you may now have less protection from developing COVID-19 if you are exposed to currently circulating variants.

If vaccination is recommended for you, get vaccinated and stay up to date to protect yourself against COVID-19. This means getting the updated (bivalent) vaccine if you haven't received it yet.

If you haven't already, consider developing a COVID-19 Action Plan so you have all of the information you need on hand if you get sick with COVID-19. Talk with your doctor in advance about what treatments may be appropriate for you and how to access the medication if you do get sick.

If you develop signs or symptoms of COVID-19, reach out to your doctor immediately, even if your symptoms are mild. If your doctor recommends treatment, start it right away. There are several approved and authorized treatments for COVID-19. Timely treatment can reduce your risk of getting very sick, being hospitalized, or dying.

What treatments are available for people who might be at higher risk of getting sick now that Evusheld is no longer available?

There are several treatments available for COVID-19 infections.

Currently available data supports their use in reducing the risk of progression to severe disease, including hospitalization and death. Paxlovid (nirmatrelvir/ritonavir) and Veklury

(remdesivir) are the medicines recommended for most people. If those medicines are not available or someone cannot take them, Lagevrio (molnupiravir) is the next choice. COVID-19 convalescent plasma may be another option for certain immunocompromised patients.

If you have signs or symptoms of COVID-19, contact your doctor right away to find out if you should start one of these treatments. You should also talk with your doctor in advance about what treatments may be appropriate for you and how to access the medication if you experience symptoms.

More specifically:

Paxlovid is authorized to treat mild-to-moderate COVID-19 in adults and children 12 years of age and older

weighing at least 40 kg, (approximately 88 lbs.) and who are at high risk of developing severe COVID-19 leading to hospitalization or death.

Veklury is approved to treat adults and children 28 days of age and older and weighing at least 3 kg (approximately 6.6 lbs.) who have mild-to-moderate COVID-19 and are at high risk of developing severe COVID-19 leading to hospitalization or death.

Lagevrio is authorized to treat mild-to-moderate COVID-19 in adults who are at high risk of developing severe COVID-19 leading to hospitalization or death, and who do not have access to alternative COVID-19 treatments that are approved or authorized by FDA or for whom these treatments are not clinically appropriate.

COVID-19 convalescent plasma with high titers of anti-SARS- CoV-2 antibodies is authorized to treat COVID-19 in patients with immunosuppressive disease or who are receiving immunosuppressive treatment in in-patient or out-patient settings.

What is HHS doing to ensure access to treatments for individuals who are immunocompromised or who cannot get vaccinated now that Evusheld is no longer available?

Over the past year, HHS has dramatically increased access to Paxlovid and Lagevrio, both of which are pills. Supplies of these medicines are now widely available at pharmacies, Test to Treat pharmacies, long-term care facilities, and other locations.

We are encouraging states to support local health departments and health systems in setting up infusion clinics for Veklury (remdesivir) to make it easier for people to get this treatment as soon as possible after being diagnosed with COVID-19.

HHS, state and local health departments, and other healthcare partners also continue to work to ensure access to COVID-19 vaccines, including the updated (bivalent) vaccine.

I am immunocompromised. Is there anything I can do to boost my immunity or protect myself?

Yes: people for whom COVID-19 vaccination is recommended, including people who are immunocompromised, should get and stay up to date with vaccinations. This means getting the updated (bivalent) vaccine, no matter how many boosters you received before the bivalent vaccine became available in September 2022.

Will Evusheld be an option in the future if the variants change?

FDA will continue to work with ASPR, the CDC, and the National Institutes of Health on surveillance of variants that may impact the use of the therapies authorized for emergency use. We will provide further updates and consider additional action as new information becomes available.

Why haven't more prevention and treatment options that work against the current variants been approved or authorized, and when will they be available?

Several approved or authorized treatments are expected to remain active to fight against the currently circulating variants and are widely available.

The FDA has worked around the clock throughout the pandemic and used the best available data to ensure options are available to prevent and treat COVID-19. This work is particularly important for people who are unable to get vaccinated and for immunocompromised people who may not mount an adequate immune response to vaccination.

Disease experts at HHS continually watch for new variants of any viruses and continue to monitor the potential impact that new variants might have on existing therapies. By taking this approach, we can identify the need for new medical products and ways to expedite development of new medical products to address emerging variants. For example, nearly two years ago, the FDA provided guidance to industry on how to efficiently generate non-clinical and chemistry, manufacturing and controls data that could potentially support an Emergency Use Authorization for monoclonal antibody products that had potential to be effective against emerging variants.

In December 2022, FDA and European Medicines Agency (EMA) convened a workshop to bring together the expertise of academics, clinicians, industry, and regulatory bodies to address the acceptability and challenges of alternative strategies to support the development of novel monoclonal antibody therapies including those based on prototype products that have

demonstrated safety and efficacy in clinical trials. FDA is committed to working with industry sponsors to expedite the development of new drug products to meet unmet needs, such as the need for new preventive therapies for immune suppressed patients who are unlikely to respond to vaccination.

For More Information

People Who Are Immunocompromised | CDC

How to Protect Yourself and Others | CDC

FDA announces Evusheld is not currently authorized for emergency use in the U.S.

FDA announces Evusheld is not currently authorized for emergency use in the U.S.

Update [1/26/2023] The U.S. Food and Drug Administration today revised the Emergency Use Authorization (/media/154704/download?attachment) (EUA) for Evusheld (tixagevimab co-packaged with cilgavimab) to limit its use to when the combined frequency of non-susceptible SARS-CoV-2 variants nationally is less than or equal to 90%. Based on this revision, **Evusheld is not currently authorized for use in the U.S. until further notice by the Agency.**

Data show Evusheld is unlikely to be active against certain SARS-CoV-2 variants. According to the most recent CDC Nowcast data (https://covid.cdc.gov/covid-data-tracker/), these variants are projected to be responsible for more than 90% of current infections in the U.S. This means that Evusheld is not expected to provide protection against developing COVID-19 if exposed to those variants.

Today's action to limit the use of Evusheld prevents exposing patients to possible side effects of Evusheld such as allergic reactions, which can be potentially serious, at a time when fewer than 10% of circulating variants in the U.S. causing infection are susceptible to the product.

Monoclonal antibodies are laboratory-made proteins that mimic the immune system's ability to fight off harmful pathogens such as viruses, like SARS-CoV-2. And like other viruses, SARS-CoV-2 can mutate over time, resulting in certain products not working against certain variants. This is the case with Evusheld and prompted the changes to the authorization that FDA is making today.

Should a patient become infected with SARS-CoV-2 and develop symptoms of COVID-19, they should seek medical attention, including starting treatment for COVID-19 as appropriate. There are several treatments (/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs) – Paxlovid, Veklury (remdesivir) and Lagevrio (molnupiravir) – that are expected to work against currently circulating variants, and that are authorized or approved to treat certain patients with mild-to-moderate COVID-19 who are at high risk for progression to severe disease, including hospitalization or death. Healthcare providers should assess whether treatments are right for their patients.

The U.S. Government recommends that facilities and providers with Evusheld retain all product in the event that SARS-CoV-2 variants which are neutralized by Evusheld become more prevalent in the U.S. in the future. Retained product must be appropriately held in accordance with storage conditions detailed in the authorized Fact Sheet for Health Care Providers (/media/154701/download?attachment) and the Letter of Authorization (/media/154704/download?attachment).

FDA will continue to work with ASPR, the CDC, and the National Institutes of Health on surveillance of variants that may impact the use of the therapies authorized for emergency use. We will provide further updates and consider additional action as new information becomes available. Any updates will be made available on FDA's website (/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs).

FDA releases important information about risk of COVID-19 due to certain variants not neutralized by Evusheld

Update [1/6/2023] FDA is closely monitoring the emergence of the XBB.1.5 subvariant, a SARS-CoV-2 Omicron variant that is currently estimated (https://covid.cdc.gov/covid-data-tracker/#variant-proportions) to account for 28% of circulating variants in the U.S. Because of its similarity to variants that are not neutralized by Evusheld (e.g., XBB), FDA does not anticipate that Evusheld will neutralize XBB.1.5. This means that Evusheld may not provide protection against developing COVID-19 for individuals who have received Evusheld and are later exposed to XBB.1.5. However, we are awaiting additional data to verify that Evusheld is not active against XBB.1.5. We will provide further updates as new information becomes available.

Health care providers should inform individuals of the increased risk, compared to other variants, for COVID-19 due to SARS-CoV-2 variants not neutralized by Evusheld.

If signs and symptoms of COVID-19 occur, advise individuals to test for COVID-19 and seek medical attention, including starting treatment for COVID-19 as appropriate.

Update [10/3/2022] FDA added important information to the authorized Fact Sheets for Evusheld (tixagevimab co-packaged with cilgavimab) to inform health care providers and individuals receiving Evusheld of the increased risk for developing COVID-19 when exposed to variants of SARS-CoV-2 that are not neutralized by Evusheld. Detailed neutralization data can be found in the revised authorized **Fact Sheet for Healthcare Providers.** (https://www.fda.gov/media/154701/download) Health care professionals should inform

patients of this risk and advise patients who develop signs or symptoms of COVID-19 to test for SARS-CoV-2 infection and promptly seek medical attention, including starting treatment for COVID-19, as appropriate if they test positive.

Evusheld is currently the only option for pre-exposure prophylaxis (PrEP) of COVID-19 and is authorized under **Emergency Use Authorization (https://www.fda.gov/media/154704/download)** (EUA) for use in immunocompromised individuals who may not mount an adequate response to COVID-19 vaccination, and for individuals for whom COVID-19 vaccination is not recommended due to a history of a severe adverse reaction. It is authorized to be administered every six months. Use of Evusheld is not a substitute for COVID-19 vaccination, and individuals for whom COVID-19 vaccination is recommended should get vaccinated. Individuals who received Evusheld but who develop COVID-19 remain eligible for use of any of the available treatments for COVID-19 if the criteria for use are met.

FDA continues to recommend Evusheld as an appropriate option for PrEP to prevent COVID-19, in combination with other preventative measures like getting vaccinated and boosted as recommended, as Evusheld still offers protection against many of the currently circulating variants and may offer protection against future variants.

What Patients Should Know:

- Talk with your health care provider about appropriate treatment options in case you develop COVID-19. There are several approved and authorized treatments for COVID-19 that are expected to retain activity against currently circulating SARS-CoV-2 variants.
- If you develop COVID-19 symptoms, tell your health care provider and test right away. It's not possible to know which variant of SARS-CoV-2 you may have contracted. Timely treatment can reduce your risk of developing severe disease, including decreasing your risk of hospitalization or death.
- If recommended by your health care provider, get vaccinated or boosted with a bivalent booster dose to help your body increase your protection against SARS-CoV-2 infection. Follow CDC's guidelines (https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html) on additional prevention strategies to protect yourself from getting sick.

What Health Care Providers Should Know:

- Prescribers should monitor CDC regional variant frequency data (https://covid.cdc.gov/covid-data-tracker/#variant-proportions) and refer to the table of variants detailed in the Fact Sheet for Health Care Providers (https://www.fda.gov/media/154701/download) for the latest data on the neutralization

activity of Evusheld against SARS-CoV-2 variants in your area. Prescribers should discuss the risk of developing COVID-19 infection with patients receiving Evusheld.

- There are several treatments (https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs) – Paxlovid, Veklury (remdesivir), bebtelovimab, and Lagevrio (molnupiravir) – that are expected to retain activity against currently circulating variants, and that are authorized or approved to treat certain patients with mild-to-moderate COVID-19 who are at high risk for progression to severe disease, including hospitalization or death. Health care providers should assess whether these treatments are right for their patient in the event the patient develops mild-to-moderate COVID-19.
- FDA has also updated the list of medical conditions or treatments that may result in moderate to severe immune compromise. The conditions listed in the Fact Sheet for Health Care Providers (https://www.fda.gov/media/154701/download) are not intended to be an all-inclusive list. Patients with other conditions not listed may also have moderate to severe immune compromise and therefore be eligible for Evusheld therapy, assuming the remaining terms and conditions of the authorization are met.

FDA authorizes revisions to Evusheld dosing

Update [6/29/2022] There are different variants (and subvariants) of SARS-CoV-2, and FDA continues to evaluate how well Evusheld (tixagevimab co-packaged with cilgavimab) neutralizes them. Currently, the Omicron BA.2, BA.2.12.1, BA.4, and BA.5 subvariants are circulating in the United States. Nonclinical data and pharmacokinetic modeling suggest that activity against these subvariants may be retained for six months at drug concentrations achieved following an Evusheld dose of 300 mg of tixagevimab and 300 mg cilgavimab.

Therefore, on June 29, 2022, FDA revised the Evusheld Fact Sheet for Healthcare Providers (https://www.fda.gov/media/154701/download) to recommend repeat dosing every six months with a dose of 300 mg of tixagevimab and 300 mg cilgavimab if patients need ongoing protection. The previous Fact Sheet for Healthcare Providers did not provide a specific recommendation on the dosing interval.

We continue to monitor the neutralizing activity of Evusheld against emerging SARS-CoV-2 variants and will provide additional updates as needed.

For further details please refer to the Frequently Asked Questions for Evusheld. (https://www.fda.gov/media/154703/download)

[2/24/2022] The U.S. Food and Drug Administration has revised the emergency use authorization for Evusheld (tixagevimab co-packaged with cilgavimab) (https://www.fda.gov/media/154704/download) to change the initial dose for the authorized use as pre-exposure prophylaxis (prevention) of COVID-19 in certain adults and pediatric patients.
Based on the most recent information and data available, Evusheld may be less active against certain Omicron subvariants. The dosing regimen was revised because available data indicate that a higher dose of Evusheld may be more likely to prevent infection by the COVID-19 Omicron subvariants BA.1 and BA.1.1 than the originally authorized Evusheld dose.

Previously, the authorized Evusheld dosage was 150 mg of tixagevimab and 150 mg of cilgavimab administered as two separate consecutive intramuscular injections, with repeat doses every six months while SARS-CoV-2 remains in circulation. With this EUA revision, FDA has increased the initial authorized dose to 300 mg of tixagevimab and 300 mg of cilgavimab. Patients who have already received the previously authorized dose (150 mg of tixagevimab and 150 mg of cilgavimab) should receive an additional dose of 150 mg of tixagevimab and 150 mg of cilgavimab as soon as possible to raise their monoclonal antibody levels to those expected for patients receiving the higher dose.

Evusheld is authorized for the emergency use as pre-exposure prophylaxis (PrEP) for prevention of COVID-19 in certain adults and pediatric patients (12 years of age and older weighing at least 40 kg). Health care providers should only administer it to individuals who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to someone infected with SARS-CoV-2. Evusheld is only authorized for those:

- who have moderate-to-severe immune compromise due to a medical condition or who have received immunosuppressive medications or treatments and may not mount an adequate immune response to COVID-19 vaccination or
- for whom vaccination with any available approved or authorized COVID-19 vaccine is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s).

The duration of protection provided by Evusheld against symptomatic SARS-CoV-2 infection may not be as long as was shown in the clinical trial supporting the initial authorization because the clinical trial data came from a time period before the emergence of the BA.1 and BA.1.1 subvariants. However, it is not known whether BA.1 and BA1.1 will still be circulating in the coming months or whether another Omicron subvariant, BA.2, for which Evusheld is expected to have greater neutralizing activity, will become dominant. Because it is unclear which SARS-CoV-2 variant or Omicron subvariant will become dominant in the United States over the next few months, the recommended timing for repeat dosing cannot be provided at this time. We will

continue to monitor the situation closely and will provide updates with redosing recommendations in the near future when more data are available to determine the appropriate timing of redosing (e.g., 3 months or 6 months after the prior dose).

What should patients know:

- Patients who previously received an initial lower dose of Evusheld (150 mg of tixagevimab and 150 mg of cilgavimab) should contact their health care provider and return for an additional 150 mg of tixagevimab and 150 mg of cilgavimab dose as soon as possible. Any subsequent repeat dosing will be timed from the date of this additional Evusheld dose.
- Patients who have not received any doses of Evusheld should talk to their health care provider to determine whether, based on their individual circumstances, they are eligible to receive it. If they are eligible, they should receive the 300 mg of tixagevimab and 300 mg of cilgavimab dose.
- Patients with any additional questions should contact their health care provider.

What health care professionals should know:

- Health care professionals should contact patients who received the previously authorized Evusheld dose to return for an additional 150 mg tixagevimab and 150 mg cilgavimab dose as soon as possible.
- The volume of each injection for the new, higher dose will be larger, 3 mL instead of 1.5 mL. This means that the injections should be limited to large muscles on the body that can accommodate this volume (e.g., the gluteal muscles).
- Health care professionals should review the updated Fact Sheets and Dear Health Provider Letter for Evusheld.
- As part of the EUA, FDA requires health care providers who prescribe Evusheld to report all medication errors and serious adverse events considered to be potentially related to Evusheld through FDA's MedWatch Adverse Event Reporting program (https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program). Providers can complete and submit the report online (https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home); or download and complete the form, then submit it via fax at 1-800-FDA-0178.

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR EVUSHELD™ (tixagevimab co-packaged with cilgavimab)

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use EVUSHELD™ under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for EVUSHELD.

EVUSHELD (tixagevimab) injection; (cilgavimab) injection, co-packaged for intramuscular use
Original EUA Authorized Date: 12/2021
Revised EUA Authorized Date: 01/2023

----------RECENT MAJOR CHANGES----------

Limitations of Authorized Use: updated based on variant susceptibility	01/2023
Microbiology (12.4): updated neutralizing data	01/2023
Microbiology (12.4): updated neutralizing data	12/2022
Microbiology (12.4): updated neutralizing data	11/2022
Emergency Use Authorization (1): updated examples	10/2022
Warnings and Precautions (5.3, 17): addition of a new warning	10/2022
Microbiology (12.4): updated neutralizing data	10/2022
Dosage and Administration (2.1, 17): modification of initial dosage and repeat dosing	06/2022
Microbiology (12.4): updated neutralizing data	06/2022
Warnings and Precautions (5.2): addition of new warning	05/2022
Dosage and Administration (2.3)	05/2022
Adverse Reactions (6.1, 12.3): addition of TACKLE data	02/2022

----------EUA FOR EVUSHELD----------

The U.S. Food and Drug Administration has issued an EUA for the emergency use of the unapproved product EVUSHELD (tixagevimab co-packaged with cilgavimab), SARS-CoV-2 spike protein-directed attachment inhibitor, for the pre-exposure prophylaxis of coronavirus disease 2019 (COVID-19) in adults and pediatric individuals (12 years of age and older weighing at least 40 kg):

- Who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 **and**
  - Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments **and** may not mount an adequate immune response to COVID-19 vaccination **or**
  - For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s).

EVUSHELD may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which EVUSHELD belongs (i.e., anti-infectives).

EVUSHELD has been authorized by FDA for the emergency use described above. EVUSHELD is not FDA-approved for any use, including use for pre-exposure prophylaxis of COVID-19. (1)

EVUSHELD is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of EVUSHELD under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

LIMITATIONS OF AUTHORIZED USE

- EVUSHELD is not authorized for use in individuals:
  - For treatment of COVID-19, or
  - For post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2.
- EVUSHELD is authorized for use only when the combined frequency of non-susceptible variants nationally is less than or equal to 90%, based on available information including variant susceptibility to EVUSHELD and national variant frequencies.
- Pre-exposure prophylaxis with EVUSHELD is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended. Individuals for whom COVID-19 vaccination is recommended, including individuals with moderate to severe immune compromise who may derive benefit from COVID-19 vaccination, should receive COVID-19 vaccination.
- In individuals who have received a COVID-19 vaccine, EVUSHELD should be administered at least two weeks after vaccination.

See Full Fact Sheet for Healthcare Providers for examples of medical conditions or treatments that may result in moderate to severe immune compromise and an inadequate immune response to COVID-19 vaccination, the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19. (1)

----------DOSAGE AND ADMINISTRATION----------

The dosage of EVUSHELD for emergency use is:

- Initial dose: 300 mg of tixagevimab and 300 mg of cilgavimab administered as two separate consecutive intramuscular injections. (2.1)
- Dosing for Individuals Who Initially Received 150 mg of Tixagevimab and 150 mg Cilgavimab
  For individuals who initially received 150 mg tixagevimab and 150 mg cilgavimab:
  - Initial dose ≤3 months prior: 150 mg tixagevimab and 150 mg cilgavimab.
  - Initial dose >3 months prior: 300 mg tixagevimab and 300 mg cilgavimab. (2.1)
- Repeat dose: 300 mg of tixagevimab and 300 mg of cilgavimab every 6 months. Repeat dosing should be timed from the date of the most recent EVUSHELD dose. (2.1)

See Full Fact Sheet for Healthcare Providers for detail on preparation and administration. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Injection:

- tixagevimab 150 mg/1.5 mL (100 mg/mL) in a single-dose vial. (3)
- cilgavimab 150 mg/1.5 mL (100 mg/mL) in a single-dose vial. (3)

----------CONTRAINDICATIONS----------

EVUSHELD is contraindicated in individuals with previous severe hypersensitivity reactions, including anaphylaxis, to EVUSHELD. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity Including Anaphylaxis: Serious hypersensitivity reactions, including anaphylaxis, have been observed with EVUSHELD. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy. Clinically monitor individuals after injections and observe for at least 1 hour. (5.1)
- Risk of Cross-Hypersensitivity with COVID-19 Vaccines: EVUSHELD contains polysorbate 80, which is in some COVID-19 vaccines and is structurally similar to polyethylene glycol (PEG), an ingredient in other COVID-19 vaccines. For individuals with a history of severe hypersensitivity reaction to a COVID-19 vaccine, consider consultation with an allergist-immunologist prior to EVUSHELD administration. (5.2)
- Risk for COVID-19 Due to SARS-CoV-2 Viral Variants Not Neutralized by EVUSHELD: Certain SARS-CoV-2 viral variants may not be neutralized by monoclonal antibodies such as tixagevimab and cilgavimab, the components of EVUSHELD. EVUSHELD may not be effective at preventing COVID-19 caused by these SARS-CoV-2 viral variants. Inform individuals of the increased risk, compared to other variants, for COVID-19 due to SARS-CoV-2 viral variants not neutralized by EVUSHELD. If signs and symptoms of COVID-19 occur, advise individuals to test for COVID-19 and seek medical attention, including starting treatment for COVID-19 as appropriate. (5.3)

- Clinically Significant Bleeding Disorders: As with any other intramuscular injection, EVUSHELD should be given with caution to individuals with thrombocytopenia or any coagulation disorder. (5.4)
- Cardiovascular Events: A higher proportion of subjects who received EVUSHELD versus placebo reported myocardial infarction and cardiac failure serious adverse events. All of the subjects with events had cardiac risk factors and/or a prior history of cardiovascular disease, and there was no clear temporal pattern. A causal relationship between EVUSHELD and these events has not been established. Consider the risks and benefits prior to initiating EVUSHELD in individuals at high risk for cardiovascular events, and advise individuals to seek immediate medical attention if they experience any signs or symptoms suggestive of a cardiovascular event. (5.5)

ADVERSE REACTIONS

Most common adverse events (all grades, incidence ≥3%) are headache, fatigue, and cough. (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to EVUSHELD (1) by submitting FDA Form 3500 online, (2) by downloading this form and then submitting by mail or fax, or (3) contacting the FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to *AstraZeneca* by Fax at 1-866-742-7984 or call 1-800-236-9933. (6.4)

See PATIENT AND PARENTS/CAREGIVER FACT SHEET.

Revised: 01/2023

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* Sections or subsections omitted from the EUA are not listed

FULL FACT SHEET FOR HEALTHCARE PROVIDERS

1 EMERGENCY USE AUTHORIZATION

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of the unapproved product EVUSHELD (tixagevimab co-packaged with cilgavimab) for the pre-exposure prophylaxis of coronavirus disease 2019 (COVID-19) in adults and pediatric individuals (12 years of age and older weighing at least 40 kg):

- Who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 **and**
  - Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments **and** may not mount an adequate immune response to COVID-19 vaccination **or**
  - For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s) *[see Warnings and Precautions (5.2)]*.

EVUSHELD may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which EVUSHELD belongs (i.e., anti-infectives).

EVUSHELD has been authorized by FDA for the emergency use described above. EVUSHELD is not FDA-approved for any use, including use for pre-exposure prophylaxis of COVID-19.

EVUSHELD is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of EVUSHELD under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Medical conditions or treatments that may result in moderate to severe immune compromise and an inadequate immune response to COVID-19 vaccination **include but are not limited to**:

- Active treatment for solid tumor and hematologic malignancies
- Hematologic malignancies associated with poor responses to COVID-19 vaccines regardless of current treatment status (e.g., chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, acute leukemia)
- Receipt of solid-organ transplant or an islet transplant and taking immunosuppressive therapy
- Receipt of chimeric antigen receptor (CAR)-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)
- Moderate or severe primary immunodeficiency (e.g., common variable immunodeficiency disease, severe combined immunodeficiency, DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Advanced or untreated HIV infection (people with HIV and CD4 cell counts <200/mm^3, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV)
- Active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely

immunosuppressive, and biologic agents that are immunosuppressive or immunomodulatory (e.g., B-cell depleting agents)

LIMITATIONS OF AUTHORIZED USE

- EVUSHELD is not authorized for use in individuals:
  - For treatment of COVID-19, or
  - For post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2.
- EVUSHELD is authorized for use only when the combined frequency of non-susceptible variants nationally is less than or equal to 90%, based on available information including variant susceptibility to EVUSHELD and national variant frequencies[1].
- Pre-exposure prophylaxis with EVUSHELD is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended. Individuals for whom COVID-19 vaccination is recommended, including individuals with moderate to severe immune compromise who may derive benefit from COVID-19 vaccination, should receive COVID-19 vaccination.
- In individuals who have received a COVID-19 vaccine, EVUSHELD should be administered at least two weeks after vaccination.

Justification for Emergency Use of Drugs During the COVID-19 Pandemic

There is currently an outbreak of COVID-19 caused by SARS-CoV-2, a novel coronavirus. The Secretary of HHS has declared that:

- A public health emergency related to COVID-19 has existed since January 27, 2020.
- Circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic (March 27, 2020 declaration).

An EUA is a FDA authorization for the emergency use of an unapproved product or unapproved use of an approved product (i.e., drug, biological product, or device) in the United States under certain circumstances including, but not limited to, when the Secretary of HHS declares that there is a public health emergency that affects the national security or the health and security of United States citizens living abroad, and that involves biological agent(s) or a disease or condition that may be attributable to such agent(s). Criteria for issuing an EUA include:

- The biological agent(s) can cause a serious or life-threatening disease or condition;
- Based on the totality of the available scientific evidence (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that
  - The product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition; and
  - The known and potential benefits of the product - when used to diagnose, prevent, or treat such disease or condition - outweigh the known and potential risks of the product, taking into consideration the material threat posed by the biological agent(s);
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the serious or life-threatening disease or condition.

[1] FDA will monitor conditions to determine whether use is consistent with the scope of authorization, referring to available information, including information on variant susceptibility (e.g., Section 12.4 of the authorized Fact Sheet for Healthcare Providers) and CDC variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions.

Information Regarding Available Alternatives for the EUA Authorized Use
There are no adequate, approved and available alternatives to EVUSHELD for the pre-exposure prophylaxis of COVID-19 in individuals who may not mount an adequate immune response to COVID-19 vaccination or for whom COVID-19 vaccination is not recommended due to a history of severe adverse reaction to a COVID-19 vaccine or its components.

For information on clinical studies of EVUSHELD and other therapies for the prophylaxis of COVID-19, see www.clinicaltrials.gov.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Emergency Use of EVUSHELD

Initial Dosing
The initial dosage of EVUSHELD in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) is **300 mg of tixagevimab and 300 mg of cilgavimab** administered as two separate consecutive intramuscular (IM) injections *[see Clinical Pharmacology (12.3)]*. Refer to Table 1 below.

Dosing for Individuals Who Initially Received 150 mg of Tixagevimab and 150 mg of Cilgavimab
Individuals who have already received the previously authorized initial dose (150 mg of tixagevimab and 150 mg of cilgavimab) **should receive an additional EVUSHELD dose as soon as possible, with the dose based on the following criteria:**

- If the patient received their initial dose ≤ 3 months ago, the patient should receive a dose of 150 mg of tixagevimab and 150 mg of cilgavimab, refer to Table 2 below.
- If the patient received their initial dose > 3 months ago, the patient should receive a dose of 300 mg of tixagevimab and 300 mg of cilgavimab, refer to Table 1 below.

Repeat Dosing
The repeat dosage of EVUSHELD in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) is **300 mg of tixagevimab and 300 mg of cilgavimab** administered every 6 months, refer to Table 1 below. Repeat dosing should be timed from the date of the most recent EVUSHELD dose.

The recommendations for dosing are based on the totality of the scientific evidence including clinical pharmacology data, antiviral activity data, and clinical trial data *[see Clinical Pharmacology (12.3), Microbiology (12.4), and Clinical Studies (14)]*. EVUSHELD has only been studied for the prophylaxis of COVID-19 at the EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) dose. There are no data available in a prophylaxis setting for the EVUSHELD (300 mg of tixagevimab and 300 mg of cilgavimab) dose. The clinical safety of the EVUSHELD (300 mg of tixagevimab and 300 mg of cilgavimab) dose is supported by safety data from a treatment study in subjects with mild to moderate COVID-19 *[see Adverse Reactions (6.1)]*. There are limited safety and no efficacy data available with repeat dosing.

To access the most recent EVUSHELD Fact Sheets, please visit http://www.evusheld.com or scan the QR code:

2.2 Dosage Adjustment in Specific Populations

No dosage adjustment is recommended in pregnant or lactating individuals, in geriatrics, and in individuals with renal impairment *[see Use in Specific Populations (8)]*.

2.3 Dose Preparation and Administration

Each EVUSHELD carton contains two vials; one of each antibody. Each vial contains an overfill to allow the withdrawal of 150 mg (1.5 mL).

Table 1 Dosage of 300 mg of Tixagevimab and 300 mg of Cilgavimab

EVUSHELD* (tixagevimab co-packaged with cilgavimab)	Antibody dose	Number of vials needed	Volume to withdraw from vial(s)
	tixagevimab 300 mg	2 vials	3 mL
	cilgavimab 300 mg	2 vials	3 mL

* 300 mg of tixagevimab and 300 mg of cilgavimab are to be administered as separate, consecutive intramuscular injections

Table 2 Dosage of 150 mg of Tixagevimab and 150 mg of Cilgavimab

EVUSHELD* (tixagevimab co-packaged with cilgavimab)	Antibody dose	Number of vials needed	Volume to withdraw from vial
	tixagevimab 150 mg	1 vial	1.5 mL
	cilgavimab 150 mg	1 vial	1.5 mL

* 150 mg of tixagevimab and 150 mg of cilgavimab are to be administered as separate, consecutive intramuscular injections

Preparation

- Tixagevimab and cilgavimab must be prepared by a qualified healthcare provider.
- Tixagevimab and cilgavimab are each supplied in individual single-dose vials. Do not shake the vials.
- Visually inspect the vials for particulate matter and discoloration. Tixagevimab and cilgavimab are clear to opalescent, colorless to slightly yellow solutions. Discard the vials if the solution is cloudy, discolored or visible particles are observed.
- Administer EVUSHELD as TWO separate, consecutive intramuscular (IM) injections, 1 injection of tixagevimab and 1 injection of cilgavimab.

- Withdraw the appropriate amount of tixagevimab solution and the appropriate amount of cilgavimab solution into TWO separate syringes (see Table 1 and Table 2). Discard unused portion in vials.
- This product is preservative-free and therefore, the prepared syringes should be administered immediately. If immediate administration is not possible, and the prepared tixagevimab and cilgavimab syringes need to be stored, the total time from vial puncture to administration must not exceed 4 hours:
    - in a refrigerator at 2°C to 8°C (36°F to 46°F), or
    - at room temperature up to 25°C (77°F).

Administration

- Tixagevimab and cilgavimab should be administered by a qualified healthcare provider with appropriate medical support to manage severe hypersensitivity reactions.
- Administer the two components of EVUSHELD consecutively.
- Administer the IM injections at different injection sites, preferably one in each of the gluteal muscles, one after the other.
    - For the 300 mg tixagevimab and 300 mg cilgavimab dose, ensure that the administration sites are appropriate for the volume (3 mL per injection).
- Clinically monitor individuals after injections and observe for at least 1 hour *[see Warnings and Precautions (5.1, 5.2)]*.

3 DOSAGE FORMS AND STRENGTHS

EVUSHELD is available as an individual single-dose vial of tixagevimab as a clear to opalescent, colorless to slightly yellow solution co-packaged with an individual single-dose vial of cilgavimab as a clear to opalescent, colorless to slightly yellow solution as:

- Injection: 150 mg/1.5 mL (100 mg/mL) of tixagevimab
- Injection: 150 mg/1.5 mL (100 mg/mL) of cilgavimab

4 CONTRAINDICATIONS

EVUSHELD is contraindicated in individuals with previous severe hypersensitivity reactions, including anaphylaxis, to EVUSHELD *[see Warnings and Precautions (5.1, 5.2)]*.

5 WARNINGS AND PRECAUTIONS

There are limited clinical data available for EVUSHELD. Serious and unexpected adverse events may occur that have not been previously reported with EVUSHELD use.

5.1 Hypersensitivity Including Anaphylaxis

Serious hypersensitivity reactions, including anaphylaxis, have been observed with EVUSHELD *[see Adverse Reactions (6.1)]*. Signs and symptoms of hypersensitivity reactions may include: dyspnea, chills, fatigue/asthenia, tachycardia, chest pain or discomfort, nausea/vomiting, angioedema, dizziness, urticaria, wheezing, pruritus, flushing, hyperhidrosis, myalgia, vaso-vagal reactions (e.g., pre-syncope, syncope), or throat irritation.

Administration of EVUSHELD should be done under the supervision of a healthcare provider with appropriate medical support to manage severe hypersensitivity reactions. If signs and symptoms of a

clinically significant hypersensitivity reaction or anaphylaxis occur while taking EVUSHELD, immediately discontinue administration and initiate appropriate medications and/or supportive care. Clinically monitor individuals after injections and observe for at least 1 hour.

5.2 Risk of Cross-Hypersensitivity with COVID-19 Vaccines

EVUSHELD contains polysorbate 80, which is in some COVID-19 vaccines and is structurally similar to polyethylene glycol (PEG), an ingredient in other COVID-19 vaccines *[see Description (11)]*. For individuals with a history of a severe hypersensitivity reaction to a COVID-19 vaccine, consider consultation with an allergist-immunologist prior to EVUSHELD administration.

Administration of EVUSHELD should be done under the supervision of a healthcare provider with appropriate medical support to manage severe hypersensitivity reactions. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur while taking EVUSHELD, immediately discontinue administration and initiate appropriate medications and/or supportive care. Clinically monitor individuals after injections and observe for at least 1 hour.

5.3 Risk for COVID-19 Due to SARS-CoV-2 Viral Variants Not Neutralized by EVUSHELD

Certain SARS-CoV-2 viral variants may not be neutralized by monoclonal antibodies such as tixagevimab and cilgavimab, the components of EVUSHELD. EVUSHELD may not be effective at preventing COVID-19 caused by these SARS-CoV-2 viral variants. The *in-vitro* neutralization activity of EVUSHELD against SARS-CoV-2 viral variants is shown in Table 6 *[see Microbiology (12.4)]*.

Inform individuals of the increased risk, compared to other variants, for COVID-19 due to SARS-CoV-2 viral variants not neutralized by EVUSHELD. If signs or symptoms of COVID-19 occur, advise individuals to test for COVID-19 and seek medical attention, including starting treatment for COVID-19 as appropriate. Symptoms of COVID-19 may include: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, or diarrhea[2].

5.4 Clinically Significant Bleeding Disorders

As with any other intramuscular injection, EVUSHELD should be given with caution to individuals with thrombocytopenia or any coagulation disorder.

5.5 Cardiovascular Events

In PROVENT there was a higher rate of cardiovascular serious adverse events (SAEs), including myocardial infarction (one fatal SAE) and cardiac failure, in subjects who received EVUSHELD compared to placebo *[see Adverse Reactions (6.1)]*. All subjects who experienced cardiac SAEs had cardiac risk factors and/or a prior history of cardiovascular disease, and there was no clear temporal pattern. A causal relationship between EVUSHELD and these events has not been established. There was no signal for cardiac toxicity or thrombotic events identified in the nonclinical studies.

[2] For additional information on the symptoms of COVID-19, please see https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.

Consider the risks and benefits prior to initiating EVUSHELD in individuals at high risk for cardiovascular events, and advise individuals to seek immediate medical attention if they experience any signs or symptoms suggestive of a cardiovascular event.

6 ADVERSE REACTIONS

6.1 Adverse Reactions from Clinical Studies

The following adverse events have been observed in the clinical studies of EVUSHELD that supported the EUA. The adverse event rates observed in these clinical studies cannot be directly compared to rates in the clinical studies of other products and may not reflect the rates observed in clinical practice. Additional adverse events associated with EVUSHELD may become apparent with more widespread use.

Approximately 4,220 subjects have been exposed to EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) in two ongoing Phase III trials, PROVENT and STORM CHASER, for the prophylaxis of COVID-19. The primary safety analysis was based on data through to event driven efficacy data cut-offs, such that individual subjects had variable follow-up times *[see Clinical Studies (14)]*, with a median (range) of follow-up of 83 days (3-166 days) for PROVENT and 49 days (5-115 days) for STORM CHASER. An additional data cut-off was conducted to provide updated analyses with a median (range) of follow-up of 6.5 months (3-282 days) for PROVENT and approximately 6 months (5-249 days) for STORM CHASER. The median and range of follow-up times were similar between EVUSHELD and placebo recipients in each trial.

Four hundred and fifty two (452) non-hospitalized subjects (with the exception of those hospitalized for isolation purposes) with mild to moderate COVID-19 have been exposed to EVUSHELD (300 mg of tixagevimab and 300 mg of cilgavimab) in one ongoing Phase III clinical trial, TACKLE. The median (range) duration of follow-up was 84 days (1-183 days). EVUSHELD is not authorized for treatment of COVID-19 *[see Limitations of Authorized Use (1)]*.

In all studies, adults received EVUSHELD administered as two separate, consecutive IM injections of tixagevimab and cilgavimab or placebo *[see Clinical Studies (14)]*.

PROVENT (EVUSHELD [150 mg of tixagevimab and 150 mg of cilgavimab])
PROVENT enrolled adults ≥18 years of age who were either ≥60 years of age, had pre-specified co-morbidities *[see Clinical Studies (14)]*, or were at increased risk of SARS-CoV-2 infection due to their living situation or occupation. Subjects could not have previously received a COVID-19 vaccine or have known prior or current SARS-CoV-2 infection. Subjects received a single dose of EVUSHELD (N= 3,461) or placebo (N= 1,736).

Adverse events were reported in 1,221 (35%) subjects receiving EVUSHELD and 593 (34%) receiving placebo. SAEs were reported in 50 (1%) subjects receiving EVUSHELD and 23 (1%) receiving placebo. There was 1 adverse event reported as anaphylaxis among subjects who received EVUSHELD. The event began within minutes of EVUSHELD administration and was treated with epinephrine. The event resolved.

Of the reported adverse events (N= 4,507), the majority were mild (73%) or moderate (24%) in severity. All adverse events, occurring in at least 1% of subjects, were reported at similar incidence rates among subjects receiving EVUSHELD compared to those receiving placebo (difference <1%).

The most common treatment-emergent adverse events, occurring in at least 3% of subjects receiving EVUSHELD or placebo are shown in Table 3.

Table 3 Adverse Events (All Grades) Regardless of Causality Occurring in at Least 3% of Subjects Receiving EVUSHELD or Placebo in Primary Safety Analysis

	EVUSHELD N= 3,461	Placebo N= 1,736
Headache	6%	5%
Fatigue	4%	3%
Cough	3%	3%

At the additional data cut-off (median follow-up 6.5 months), the overall adverse event profile for subjects who received EVUSHELD remained similar to events displayed in Table 3.

Cardiac Serious Adverse Events
Through the additional data cut-off in PROVENT, a higher proportion of subjects who received EVUSHELD versus placebo in PROVENT reported myocardial infarction SAEs, one of which resulted in death, and cardiac failure SAEs (see Table 4 below). All subjects who experienced cardiac SAEs had cardiac risk factors and/or a prior history of cardiovascular disease at baseline. There was no clear temporal pattern, with events reported from several hours after EVUSHELD receipt through the end of the follow-up period.

Table 4 Cardiac SAEs Regardless of Causality in PROVENT with Onset Prior to Day 183 Using the Median 6-Month Data Cut-off Date

	EVUSHELD N= 3,461	Placebo N= 1,736
Subjects with any cardiac SAE*	22 (0.6%)	3 (0.2%)
SAEs related to coronary artery disease or myocardial ischemia†	10 (0.3%)	2 (0.1%)
Myocardial infarctions‡	8 (0.2%)	1 (0.1%)
SAEs related to cardiac failure§	6 (0.2%)	1 (0.1%)
SAEs related to an arrhythmia¶	4 (0.1%)	1 (0.1%)
Other (cardiomegaly, cardiomyopathy, and cardio-respiratory arrest)	3 (0.1%)	0

* One EVUSHELD recipient and one placebo recipient had two cardiac SAEs each.
† Includes the preferred terms angina pectoris, coronary artery disease, arteriosclerosis, troponin increased, acute myocardial infarction, and myocardial infarction.
‡ Includes the preferred terms acute myocardial infarction, myocardial infarction, and troponin increased (with a discharge diagnosis of myocardial infarction).
§ Includes the preferred terms cardiac failure congestive, acute left ventricular failure, cardiac failure, and cardiac failure acute.
¶ Includes the preferred terms atrial fibrillation, arrhythmia, paroxysmal atrioventricular block, and heart rate irregular.

<u>STORM CHASER (EVUSHELD [150 mg tixagevimab and 150 mg cilgavimab])</u>
STORM CHASER enrolled adults ≥18 years of age following potential exposure (within 8 days) to an identified individual with a laboratory-confirmed SARS-CoV-2 infection (symptomatic or asymptomatic). Subjects could not have previously received a COVID-19 vaccine, have symptoms consistent with COVID-19, or have a known prior SARS-CoV-2 infection. Subjects received a single dose of EVUSHELD (N= 749) or placebo (N= 372).

Adverse events were reported in 162 (22%) subjects receiving EVUSHELD and 111 (30%) receiving placebo. SAEs were reported in 5 (<1%) subjects receiving EVUSHELD and 3 (<1%) receiving placebo. Of the reported adverse events (N= 777), the majority were mild (75%) or moderate (23%) in severity.

At the additional data cut-off (median follow-up approximately 6 months), the overall adverse event profile for subjects who received EVUSHELD remained similar to earlier results. EVUSHELD is not authorized for post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2 *[see Emergency Use Authorization (1)]*.

Cardiac Serious Adverse Events
In STORM CHASER (N= 1,121) no cardiac SAEs were reported (median follow-up approximately 6 months). Compared to PROVENT, the subjects in STORM CHASER were younger (median age 48 versus 57 years) and had fewer baseline cardiac risk factors (24% versus 36% with hypertension, 11% versus 14% with diabetes, and 3% versus 8% with cardiovascular disease in STORM CHASER versus PROVENT, respectively).

TACKLE (EVUSHELD [300 mg tixagevimab and 300 mg cilgavimab])
TACKLE enrolled adults ≥18 years of age with mild to moderate COVID-19 who were within ≤7 days of symptom onset. Approximately 90% of study subjects had risk factors that put them at high risk for progression to severe COVID-19. Subjects received a single dose of EVUSHELD (N= 452) or placebo (N= 451).

Adverse events were reported in 132 (29%) subjects receiving EVUSHELD and 163 (36%) receiving placebo. Serious adverse events were reported in 33 (7%) subjects receiving EVUSHELD and 54 (12%) receiving placebo. Of the reported adverse events (N= 520), the majority were mild (56%) or moderate (27%) in severity. There were no reports of anaphylaxis or serious hypersensitivity reactions.

Adverse events of insomnia (1% vs. <1%) and dizziness (1% vs. none) were reported at a higher rate with EVUSHELD compared to placebo. No other treatment-emergent adverse events, occurring in at least 1% of subjects, were reported at higher incidence rates (difference ≥1%) among subjects receiving EVUSHELD compared to those receiving placebo.

Cardiac Serious Adverse Events
In TACKLE (N= 903) four subjects reported cardiac SAEs. Acute myocardial infarction was reported for two subjects who received EVUSHELD (one of whom also experienced cardiac failure leading to death) and sudden cardiac death was reported for one subject who received EVUSHELD. One subject who received placebo reported arrhythmia. All subjects who experienced cardiac SAEs had cardiac risk factors and/or a prior history of cardiovascular disease at baseline.

6.4 Required Reporting for Serious Adverse Events and Medication Errors

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events* and medication errors potentially related to EVUSHELD within 7 calendar days from the healthcare provider's awareness of the event, using FDA Form 3500 (for information on how to access this form, see below). The FDA requires that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race)
- A statement "EVUSHELD use for COVID-19 under Emergency Use Authorization (EUA)" under the "**Describe Event, Problem, or Product Use/Medication Error**" heading
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes)
- Patient's preexisting medical conditions and use of concomitant products
- Information about the product (e.g., dosage, route of administration, NDC #)

Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax to 1-800-FDA-0178, or
- Call 1-800-FDA-1088 to request a reporting form

In addition, please provide a copy of all FDA MedWatch forms to AstraZeneca:

- Fax 1-866-742-7984

and to report adverse events please:

- Visit https://contactazmedical.astrazeneca.com, or
- Call AstraZeneca at 1-800-236-9933.

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of EVUSHELD.

*Serious adverse events are defined as:

- Death
- A life-threatening adverse event;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- Other important medical event, which may require a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly;
- Inpatient hospitalization or prolongation of existing hospitalization.

6.5 Other Reporting Requirements

Healthcare facilities and providers will report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

7 DRUG INTERACTIONS

Drug-drug interaction studies have not been performed.

Tixagevimab and cilgavimab are not renally excreted or metabolized by cytochrome P450 (CYP) enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. EVUSHELD should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

Nonclinical reproductive toxicity studies have not been conducted with tixagevimab and cilgavimab. In a tissue cross-reactivity study assessing off-target binding of tixagevimab and cilgavimab to human fetal tissues no binding of clinical concern was observed. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, tixagevimab and cilgavimab have the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of tixagevimab and cilgavimab provides any treatment benefit or risk to the developing fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2 Lactation

Risk Summary
There are no available data on the presence of tixagevimab or cilgavimab in human milk or animal milk, the effects on the breastfed infant, or the effects of the drug on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EVUSHELD and any potential adverse effects on the breastfed infant from EVUSHELD.

8.4 Pediatric Use

EVUSHELD is not authorized for use in pediatric individuals under 12 years of age or weighing less than 40 kg. The safety and effectiveness of EVUSHELD have not been established in pediatric individuals. The dosing regimen is expected to result in comparable serum exposures of tixagevimab and cilgavimab in individuals 12 years of age and older and weighing at least 40 kg as observed in adults, since adults with similar body weight have been included in the trials PROVENT, STORM CHASER and TACKLE *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

8.5 Geriatric Use

Of the 2,555 subjects in the pooled pharmacokinetics (PK) analysis (Phase I and Phase III studies), 21% (N= 533) were 65 years of age or older and 3% (N= 81) were 75 years of age or older. There is no clinically meaningful difference in the PK of tixagevimab and cilgavimab in geriatric subjects (≥65 years) compared to younger subjects.

8.6 Renal Impairment

Tixagevimab and cilgavimab are not eliminated intact in the urine, renal impairment is not expected to affect the exposure of tixagevimab and cilgavimab. Similarly, dialysis is not expected to impact the PK of tixagevimab and cilgavimab.

8.7 Hepatic Impairment

The effect of hepatic impairment on the PK of tixagevimab and cilgavimab is unknown.

8.8 Other Specific Populations

Based on a population PK analysis, the PK profile of tixagevimab and cilgavimab was not affected by sex, age, race, or ethnicity. Population PK model-based simulations suggest that body weight had no clinically relevant effect on the PK of tixagevimab and cilgavimab in healthy adults over the range of 36 kg to 177 kg.

10 OVERDOSAGE

Treatment of overdose with EVUSHELD should consist of general supportive measures including the monitoring of the clinical status of the individual. There is no specific treatment for overdose with EVUSHELD.

11 DESCRIPTION

Tixagevimab, a SARS-CoV-2 spike protein-directed attachment inhibitor, is a human immunoglobulin G1 (IgG1κ) monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. The molecular weight is approximately 149 kDa.

Tixagevimab injection is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow solution supplied in a single-dose vial for intramuscular use. The vial stoppers are not made with natural rubber latex. Each 1.5 mL contains 150 mg tixagevimab, L- histidine (2.4 mg), L- histidine hydrochloride monohydrate (3.0 mg), polysorbate 80 (0.6 mg), sucrose (123.2 mg), and Water for Injection, USP. The pH is 6.0.

Cilgavimab, a SARS-CoV-2 spike protein-directed attachment inhibitor, is a human IgG1κ monoclonal antibody produced in CHO cells by recombinant DNA technology. The molecular weight is approximately 152 kDa.

Cilgavimab injection is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow solution supplied in a single-dose vial for intramuscular use. The vial stoppers are not made with natural rubber latex. Each 1.5 mL contains 150 mg cilgavimab, L- histidine (2.4 mg), L- histidine

hydrochloride monohydrate (3.0 mg), polysorbate 80 (0.6 mg), sucrose (123.2 mg), and Water for Injection, USP. The pH is 6.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tixagevimab and cilgavimab are two recombinant human IgG1κ monoclonal antibodies with amino acid substitutions to extend antibody half-life (YTE), reduce antibody effector function, and minimize the potential risk of antibody-dependent enhancement of disease (TM). Tixagevimab and cilgavimab can simultaneously bind to non-overlapping regions of the receptor binding domain (RBD) of SARS-CoV-2 spike protein. Tixagevimab, cilgavimab, and their combination bind to spike protein with equilibrium dissociation constants of K_D = 2.76 pM, 13.0 pM and 13.7 pM, respectively, blocking its interaction with human ACE2, the SARS-CoV-2 receptor, which is required for virus attachment. Tixagevimab, cilgavimab, and their combination blocked RBD binding to human ACE2 with IC_{50} values of 0.32 nM (48 ng/mL), 0.53 nM (80 ng/mL), and 0.43 nM (65 ng/mL), respectively.

12.3 Pharmacokinetics

A summary of PK parameters and properties of tixagevimab and cilgavimab following administration of a single EVUSHELD (300 mg of tixagevimab and 300 mg of cilgavimab) intramuscular dose is provided in Table 5.

Table 5 Summary of PK Parameters and Properties of Tixagevimab and Cilgavimab Following a Single EVUSHELD (300 mg Tixagevimab and 300 mg Cilgavimab) Intramuscular Dose

PK Parameters	Tixagevimab	Cilgavimab
C_{max} (µg/mL)*	21.9 (61.7)	20.3 (63.6)
T_{max} (day)†	14.9 (1.1 – 86)	15.0 (1.1 – 85)
C_2 (µg/mL)‡	9.5 (77)	9.1 (80)
C_{84} (µg/mL)§	15 (48)	14 (51)
$AUC_{0\text{-}84}$ (day•µg/mL)*	1408 (54)	1307 (58)
Absorption		
Bioavailability#¶	68.5	65.8
Distribution		
Apparent Volume of Distribution (L)#	7.7 (1.97)	8.7 (2.73)
Elimination		
Half-life (days)#¶	87.9 (13.9)	82.9 (12.3)
Apparent Clearance (L/day)#	0.062 (0.019)	0.074 (0.028)
Metabolism	Catabolic pathways; Same manner as endogenous IgG	
Excretion	Not likely to undergo renal excretion	

* Geomean (geometric %CV)
† Median (range)
‡ Observed geomean (geometric %CV) concentration 2 day after dosing
§ Observed geomean (geometric %CV) concentration 84 days after dosing
# Arithmetic mean (SD)
¶ Based on a single EVUSHELD (150 mg tixagevimab and 150 mg cilgavimab)

In the PROVENT repeat dose sub-study, following a second IM dose of EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) administered 10 to 14 months after the initial IM dose of EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) (N= 53), the geometric mean serum concentration was 26.4 µg/mL on post-administration Day 29. This serum concentration was similar to the geometric mean drug concentration on post-administration Day 29 (23.3 µg/mL) following the initial IM EVUSHELD dose (150 mg of tixagevimab and 150 mg of cilgavimab) in the PROVENT parent study.

The primary analysis in the clinical efficacy study PROVENT was conducted prior to the emergence of the Omicron variant; the dominant variants in circulation at that time were Alpha, Beta, Gamma, and Delta. Pharmacokinetic and pharmacodynamic modeling using cell-based EC_{50} values of EVUSHELD against the currently circulating variants in the U.S. suggest in vivo activity against these variants may be retained at drug concentrations achieved following a single EVUSHELD initial dose of 300 mg tixagevimab and 300 mg cilgavimab for 6 months *[see Dosage and Administration (2.1)]*.

Specific Populations
The PK profile of tixagevimab and cilgavimab were not affected by sex, age, race or ethnicity. Body weight had no clinically relevant effect on the PK of tixagevimab and cilgavimab in adults over the range of 36 kg to 177 kg.

Pediatric Population
The PK of tixagevimab and cilgavimab in pediatric individuals have not been evaluated.

The dosing regimen is expected to result in comparable plasma exposures of tixagevimab and cilgavimab in pediatric individuals ages 12 years of age or older who weigh at least 40 kg as observed in adult individuals *[see Use in Specific Populations (8.4)]*.

Renal impairment
Tixagevimab and cilgavimab are not eliminated intact in the urine.

Renal impairment is not expected to impact the PK of tixagevimab and cilgavimab, since monoclonal antibodies with molecular weight >69 kDa are known not to undergo renal elimination. Similarly, dialysis is not expected to impact the PK of tixagevimab and cilgavimab.

There is no difference in the clearance of tixagevimab and cilgavimab in individuals with mild or moderate renal impairment compared to individuals with normal renal function. There were insufficient subjects with severe renal impairment to draw conclusions *[see Use in Specific Populations (8.6)]*.

Hepatic impairment
No specific studies have been conducted to examine the effects of hepatic impairment on the PK of tixagevimab and cilgavimab. The impact of hepatic impairment on the PK of tixagevimab and cilgavimab is unknown *[see Use in Specific Populations (8.7)]*.

Drug Interaction Studies
Drug-drug interaction studies have not been performed. Based on key elimination pathways, tixagevimab and cilgavimab interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely *[see Drug Interactions (7)]*.

12.4 Microbiology

Antiviral Activity
In a neutralization assay on Vero E6 cells, tixagevimab, cilgavimab, and their combination neutralized SARS-CoV-2 (USA-WA1/2020 isolate) with EC_{50} values of 60.7 pM (9 ng/mL), 211.5 pM (32 ng/mL), and 65.9 pM (10 ng/mL), respectively.

Tixagevimab, cilgavimab, and their combination showed reduced or no antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), or antibody-dependent natural killer cell activation (ADNKA) in cell culture studies. Tixagevimab, cilgavimab, and their combination did not mediate antibody-dependent complement deposition (ADCD) activity with guinea pig complement proteins.

Antibody Dependent Enhancement (ADE) of Infection
The potential of tixagevimab and cilgavimab to mediate antibody-dependent viral entry was assessed in FcγRII-expressing Raji cells co-incubated with recombinant virus-like particles (VLPs) pseudotyped with SARS-CoV-2 spike protein, with antibody concentrations at a range of 6.6 nM (1 µg/mL) to 824 pM (125 ng/mL). Tixagevimab, cilgavimab, and their combination did not mediate entry of VLPs into these cells under the tested conditions.

The potential for ADE was also evaluated in a non-human primate model of SARS-CoV-2 using EVUSHELD. Intravascular administration prior to virus inoculation resulted in a dose-dependent improvement in all measured outcomes (total viral RNA in the lungs or nasal mucosae, infectious virus levels in the lungs based on $TCID_{50}$ measurements, or lung injury and pathology based on histology measurements). No evidence of enhancement of viral replication or disease was observed at any dose evaluated, including sub-neutralizing doses down to 0.04 mg/kg.

Antiviral Resistance
There is a potential risk of treatment failure due to the development of viral variants that are resistant to tixagevimab and cilgavimab. Prescribing healthcare providers should consider the prevalence of SARS-CoV-2 variants in their area, where data are available, when considering prophylactic treatment options.

Escape variants were identified following serial passage in cell culture of SARS-CoV-2 or replication competent recombinant vesicular stomatitis virus (VSV) expressing SARS-CoV-2 spike protein in the presence of tixagevimab or cilgavimab individually or in combination. Tixagevimab selected a variant expressing F486S in the spike protein with a >800-fold reduction in susceptibility to tixagevimab. Cilgavimab selected variants that expressed spike protein amino acid substitutions R346G, R346I, K444E, K444N, K444Q, K444R, K444T or N450D were each associated with a >200-fold reduction in susceptibility to cilgavimab. No escape variants to the tixagevimab and cilgavimab combination were selected.

In neutralization assays using recombinant VLPs pseudotyped with SARS-CoV-2 spike and harboring individual spike amino acid substitutions identified in circulating SARS-CoV-2, variants with reduced susceptibility to cilgavimab alone included those with R346I (>200-fold), K444E (>200-fold), K444Q (>200-fold), K444R (>200-fold), V445A (21- to 51-fold), G446V (4.2-fold), N450K (9.1-fold), or L452R (5.8-fold) substitutions. Variants with reduced susceptibility to tixagevimab alone included those with Q414R (4.6-fold), L455F (2.5- to 4.7-fold), G476S (3.3-fold), E484D (7.1-fold), E484K (6.2- to 12-fold), E484Q (3.0-fold), F486S (>600-fold), F486V (121- to 149-fold), Q493K (2.4- to 3.2-fold), Q493R

(7.9-fold), E990A (6.1-fold), or T1009I (8.2-fold) substitutions. Variants harboring an E484K (2.4- to 5.4-fold), Q493R (3.4-fold), E990A (5.7-fold), or T1009I (4.5-fold) substitution exhibited low level reduced susceptibility to tixagevimab and cilgavimab in combination.

VLPs pseudotyped with the SARS-CoV-2 spike of variant strains with reduced susceptibility to cilgavimab included those with R346K+E484K+N501Y (Mu, 21-fold), and those with reduced susceptibility to tixagevimab included those harboring E484K (Alpha, 18.5-fold; Beta, 3.5- to 15-fold; Zeta, 7.3-fold). Similar results were observed, where data were available, in neutralization assays using authentic SARS-CoV-2 variant strains.

VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BA.1 or BA.1.1 (BA.1+R346K) showed reduced susceptibility to tixagevimab (>600- to >1,000-fold or 460-fold, respectively) and to cilgavimab (>700- to >1,000-fold or >500-fold, respectively). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BA.2 or BA.2.12.1 showed reduced susceptibility to tixagevimab (>1,000-fold or >500-fold, respectively) but not to cilgavimab (1.9-fold or 2-fold, respectively). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BA.2.75 or BA.2.75.2 showed reduced susceptibility to tixagevimab (7- to 53-fold or >3,333- to >10,000-fold, respectively) and to cilgavimab (6- to 40-fold or >769- to >5,000-fold, respectively). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BA.3 showed reduced susceptibility to tixagevimab (>5,000-fold) but not to cilgavimab (4-fold). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BA.4/BA.5 showed reduced susceptibility to tixagevimab (>10,000-fold) and cilgavimab (7.5- to 9-fold). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BA.4.6 showed reduced susceptibility to tixagevimab (>1,000-fold) and to cilgavimab (>1,000-fold). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BF.7 or BJ.1 showed reduced susceptibility to tixagevimab (>3,333- to >10,000-fold or 85- to 172-fold, respectively) and to cilgavimab (>769- to >5,000-fold or >769- to >5,000-fold, respectively). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BQ.1 or BQ.1.1 showed reduced susceptibility to tixagevimab (>1,250- to >10,000-fold) and to cilgavimab (>667- to >5,000-fold). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BA.5.2.6 or BF.11 showed reduced susceptibility to tixagevimab (>333-fold) and to cilgavimab (>77-fold). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BN.1 or XBB showed reduced susceptibility to tixagevimab (24- to 44-fold or >2,600- to >10,000-fold, respectively) and to cilgavimab (>3,700- to >5,000-fold or >565- to >5,000-fold, respectively). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron XBB.1.5 showed reduced susceptibility to tixagevimab (>10,000-fold) and to cilgavimab (>2,900-fold). The effects of the individual substitutions in Omicron spike glycoproteins on neutralization susceptibility are being investigated.

The neutralizing activity of tixagevimab and cilgavimab in combination was tested against pseudotyped VLPs and/or authentic SARS-CoV-2 variant strains harboring all spike substitutions identified in Alpha (B.1.1.7, 0.5- to 5.2-fold), Beta (B.1.351, 1.0- to 3.8-fold), Gamma (P.1, 0.4- to 2.0-fold), Delta (B.1.617.2, 0.6- to 1.2-fold), and Delta [+K417N] (AY.1/ AY.2, 1.0-fold) variants of concern, and Eta (B.1.525, 3.1-fold), Iota (B.1.526, 0.3- to 3.4-fold), Kappa (B.1.617.1, 0.5- to 3.4-fold) Lambda (C.37, 0.7-fold), and Mu (B.1.621, 7.5-fold) variants of interest. Tixagevimab and cilgavimab in combination was also tested against Epsilon (B.1.427 / B.1.429, 0.8- to 3.5-fold), R.1 (3.5-fold), B.1.1.519 (1.4-fold), C.36.3 (2.3-fold), B.1.214.2 (0.8-fold), and B.1.619.1 (3.3-fold) variant alerts for further monitoring and B.1.616 (0.5-fold), A.23.1 (0.4-fold), A.27 (0.8-fold), and AV.1 (5.9-fold) variants de-escalated from further monitoring (Table 6).

Preliminary data for the neutralizing activities of tixagevimab and cilgavimab in combination against circulating Omicron subvariants are available. VLPs pseudotyped with the SARS-CoV-2 spike of

Omicron BA.1 or BA.1.1 (BA.1+R346K) showed reduced neutralizing activity (132- to 183-fold or 424-fold, respectively), Omicron BA.2 showed no change in neutralizing activity (3.2-fold). VLPs pseudotyped with the spike of Omicron BA.2.12.1, BA.2.75, BA.2.75.2, BA.3, BA.4/BA.5, or BA.4.6 showed 5-fold, 2.4- to 15-fold, >5,000- to >10,000-fold, 16-fold, 33- to 65-fold, or >1,000-fold reductions in neutralizing activity, respectively. VLPs pseudotyped with the spike of Omicron BF.7, BJ.1, BQ.1 or BQ.1.1 showed >5,000- to >10,000-fold, 228- to 424-fold, >2,000- to >10,000-fold or >2,000- to >10,000-fold reductions in neutralizing activity, respectively. VLPs pseudotyped with the spike of Omicron BA.5.2.6, BF.11, BN.1, XBB, or XBB.1.5 showed >500-fold, >500-fold, 68-fold, >1,400- to >10,000-fold, or >5,000-fold reductions in neutralizing activity, respectively. Authentic Omicron BA.1, BA.1.1, BA.2, or BA.5 viruses showed 12- to 30-fold, 176-fold, 5.4-fold, or 2.8- to 16-fold reductions in susceptibility, respectively.

Data collection is ongoing to better understand how the reductions in activity seen in pseudotyped VLP assays or authentic SARS-CoV-2 assays may correlate with clinical outcomes. Emerging Omicron subvariants that are resistant to neutralization by cilgavimab harbor the spike substitution R346T or K444T, while those resistant to neutralization by tixagevimab harbor the spike substitution F486S or F486V. EVUSHELD is unlikely to neutralize SARS-CoV-2 Omicron subvariants harboring R346T or K444T in combination with F486S or F486V.

Table 6 EVUSHELD Pseudotyped Virus-Like Particles and Authentic SARS-CoV-2 Neutralization Data for SARS-CoV-2 Variants

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested	Fold Reduction in Susceptibility* (Pseudotyped VLPs†)	Fold Reduction in Susceptibility* (Authentic virus‡)
B.1.1.7	UK	Alpha	N501Y	0.5- to 5.2-fold	No Change§
B.1.351	South Africa	Beta	K417N+E484K+N501Y	No Change§	No Change§
P.1	Brazil	Gamma	K417T+E484K+N501Y	No Change§	No Change§
B.1.617.2	India	Delta	L452R+T478K	No Change§	No Change§
AY.1/ AY.2	India	Delta [+K417N]	K417N+L452R+T478K	No Change§	No Change§
BA.1	Botswana	Omicron (BA.1)	G339D+S371L+S373P+ S375F+K417N+N440K+ G446S+S477N+T478K+ E484A+Q493R+G496S+ Q489R+N501Y+Y505H	132- to 183-fold#	12- to 30-fold
BA.1.1	Multiple country origin	Omicron (BA.1.1) [+R346K]	BA.1+R346K	424-fold	176-fold
BA.2	Multiple country origin	Omicron (BA.2)	G339D+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ S477N+T478K+E484A+ Q493R+Q498R+N501Y+ Y505H	No Change§	5.4-fold
BA.2.12.1	United States	Omicron (BA.2.12.1)	BA.2+L452Q	5-fold	ND
BA.2.75	India	Omicron (BA.2.75)	G339H+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ G446S+N460K+S477N+ T478K+E484A+Q498R+ N501Y+ Y505H	2.4- to 15-fold	ND

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested	Fold Reduction in Susceptibility* (Pseudotyped VLPs†)	Fold Reduction in Susceptibility* (Authentic virus‡)
BA.2.75.2	India	Omicron (BA.2.75.2)	BA.2.75+R346T+F486S	>5000-fold[þ]	ND
BA.3	Multiple country origin	Omicron (BA.3)	G339D+S371F+S373P+ S375F+D405N+K417N+ N440K+G446S+S477N+ T478K+E484A+Q493R+ Q498R+N501Y+Y505H	16-fold	ND
BA.4	Multiple country origin	Omicron (BA.4)	G339D+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ L452R+S477N+T478K+ E484A+F486V+Q498R+ N501Y+Y505H	33- to 65-fold	ND
BA.4.6	United States	Omicron (BA.4.6)	BA.4+R346T	>1000-fold[þ]	ND
BA.5	Multiple country origin	Omicron (BA.5)	G339D+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ L452R+S477N+T478K+ E484A+F486V+Q498R+ N501Y+Y505H	33- to 65-fold	2.8- to 16-fold
BA.5.2.6	Multiple country origin	Omicron (BA.5.2.6)	G339D+R346T+S371F+ S373P+S375F+T376A+ D405N+R408S+K417N+ N440K+L452R+S477N+ T478K+E484A+F486V+ Q498R+N501Y+Y505H	>500-fold	ND
BF.7	United States/Belgium	Omicron (BF.7)	BA.4+R346T	>5000-fold[þ]	ND
BF.11	Multiple country origin	Omicron (BF.11)	G339D+R346T+S371F+ S373P+ S375F+T376A+ D405N+R408S+K417N+ N440K+L452R+S477N+ T478K+E484A+F486V+ Q498R+N501Y+Y505H	>500-fold	ND
BJ.1	Multiple country origin	Omicron (BJ.1)	G339H+R346T+L368I+ S371F+S373P+S375F+ T376A+D405N+R408S+ K417N+N440K+V445P+ G446S+S477N+T478K+ V483A+E484A+F490V+ Q493R+Q498R+N501Y+ Y505H	228- to 424-fold	ND
BN.1	Multiple country origin	Omicron (BN.1)	G339D+R346T+K356T+ S371F+S373P+S375F+ D405N+ R408S+ K417N+N440K+G446S+ N460K+S477N+T478K+ E484A+F490S+ Q493R+Q498R+Y505H	68-fold	ND
BQ.1	Nigeria	Omicron (BQ.1)	BA.5+K444T+N460K	>2000-fold[þ]	ND
BQ.1.1	Multiple country origin	Omicron (BQ.1.1)	BA.5+R346T+K444T+ N460K	>2000-fold[þ]	ND

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested	Fold Reduction in Susceptibility* (Pseudotyped VLPs†)	Fold Reduction in Susceptibility* (Authentic virus‡)
XBB	Multiple country origin	Omicron (XBB)	G339H+R346T+L368I+ S371F+S373P+S375F+ T376A+D405N+R408S+ K417N+N440K+V445P+ G446S+N460K+S477N+ T478K+ E484A+F486S+ F490S+Q498R+N501Y+ Y505H	>1400-fold[Þ]	ND
XBB.1.5	Multiple country origin	Omicron (XBB.1.5)	G339H+R346T+L368I+ S371F+S373P+S375F+ T376A+D405N+R408S+ K417N+N440K+V445P+ G446S+N460K+S477N+ T478K+E484A+F486P+ F490S+Q498R+N501Y +Y505H	>5000-fold[Þ]	ND
B.1.525	Multiple country origin	Eta	E484K	No Change[§]	ND
B.1.526	United States	Iota	E484K	No Change[§]	No Change[§]
B.1.617.1	India	Kappa	L452R+E484Q	No Change[§]	No Change[§]
C.37	Peru	Lambda	L452Q+F490S	No Change[§]	ND
B.1.621	Colombia	Mu	R346K+E484K +N501Y	7.5-fold	ND
B.1.427 / B.1.429	United States	Epsilon	L452R	No Change[§]	No Change[§]
R.1	Multiple country origin	-	E484K	No Change[§]	ND
B.1.1.519	Multiple country origin	-	T478K	No Change[§]	ND
C.36.3	Multiple country origin	-	R346S:L452R	No Change[§]	ND
B.1.214.2	Multiple country origin	-	Q414K:N450K	No Change[§]	ND
B.1.619.1	Multiple country origin	-	N440K:E484K	No Change[§]	ND
P.2	Brazil	Zeta	E484K	No Change[§]	ND
B.1.616	France	-	V483A	No Change[§]	ND
A.23.1	UK	-	V367F	No Change[§]	ND
A.27	Multiple country origin	-	L452R+N501Y	No Change[§]	ND
AV.1	Multiple country origin	-	N439K+E484K	5.9-fold	ND

* Range of reduced potency across multiple variants of each lineage using research-grade pseudotyped VLP neutralization assays; mean fold change in half maximal effective concentration (EC_{50}) of mAb required for a 50% reduction in infection compared to wild type reference strain

† Pseudotyped virus-like particles expressing the entire SARS-CoV-2 spike variant protein and individual characteristic spike substitutions except L452Q were tested including Alpha (+L455F, E484K, F490S, Q493R, and/or S494P), and Delta (+K417N) harboring additional indicated RBD substitutions that are no longer detected or detected at extremely low levels within these lineages

‡ Authentic SARS-CoV-2 expressing the entire variant spike protein were tested including Alpha (+E484K or S494P) harboring additional indicated RBD substitutions that are no longer detected or detected at extremely low levels within these lineages

§ No change: <5-fold reduction in susceptibility

EC_{50} value = 1.13 – 1.83 nM (171 - 277 ng/mL)

Þ Tixagevimab and cilgavimab together are unlikely to be active against this variant.

ND, not determined; RBD, receptor binding domain

It is not known how pseudotyped VLPs or authentic SARS-CoV-2 neutralization susceptibility data correlate with clinical outcome.

In PROVENT, illness visit sequencing data were available for 21 of 33 subjects with SARS-CoV-2 infection (6 who received tixagevimab and cilgavimab and 15 placebo). Fourteen subjects were infected with variants of concern or variants of interest, including 8 subjects with Alpha (B.1.1.7) (8 who received placebo), 1 subject with Beta (B.1.351) (1 who received tixagevimab and cilgavimab), 3 subjects with Delta (B.1.617.2) (3 who received placebo), and 2 subjects with Epsilon (B.1.429) (2 who received tixagevimab and cilgavimab). Seven additional subjects were infected with B.1.375 (1 who received tixagevimab and cilgavimab) or the A_1 set of lineages containing a constellation of spike protein substitutions including D614G and P681H or Q677P (3 who received tixagevimab and cilgavimab and 3 placebo). Additional spike protein RBD substitutions detected at low frequency (between 3% and 24%) included V503F in the tixagevimab and cilgavimab group.

In STORM CHASER, illness visit sequencing data was available for 19 of 19 subjects with SARS-CoV-2 infections (12 of 12 who received tixagevimab and cilgavimab and 7 of 7 placebo). At an allele fraction ≥25%, 12 of 19 subjects were infected with variants of concern or variants of interest, including 9 subjects with Alpha (B.1.1.7) (5 who received tixagevimab and cilgavimab and 4 placebo) and 3 subjects with Epsilon (B.1.427 / B.1.429) (2 who received tixagevimab and cilgavimab and 1 placebo). Seven additional subjects were infected with B.1.1.519 (1 who received tixagevimab and cilgavimab) or the A_1 set of lineages containing a constellation of spike protein substitutions including D614G and D138H, Q675H, Q677H, or V1176F (4 who received tixagevimab and cilgavimab and 2 placebo). Additional spike protein RBD substitutions detected at an allele fraction ≥3% included S325P, Del342, C361W, Del428, F429V, and F515C in the tixagevimab and cilgavimab group.

Evaluation of neutralization susceptibility of variants identified through global surveillance and in subjects who received tixagevimab and cilgavimab is ongoing.

It is possible that variants resistant to tixagevimab and cilgavimab could have cross-resistance to other monoclonal antibodies targeting the RBD of SARS-CoV-2. The combination of tixagevimab and cilgavimab retained activity against pseudotyped VLPs harboring individual SARS-CoV-2 spike substitutions (K417E/N, D420N, K444Q, V445A, Y453F, L455F, N460K/S/T, E484D/K/Q, F486V, F490S, Q493K/R, and S494P) identified in neutralization escape variants of other monoclonal antibodies targeting the RBD of SARS-CoV-2 spike protein.

12.6 Immunogenicity

There are no immunogenicity data available for the currently authorized dosing regimen (EVUSHELD [300 mg of tixagevimab and 300 mg cilgavimab] administered every 6 months).

There was no apparent clinically significant effect of anti-EVUSHELD antibodies (ADA) on the safety or effectiveness of EVUSHELD in PROVENT (EVUSHELD [150 mg of tixagevimab and 150 mg cilgavimab]), but data are limited at this time. There is up to a 26% decrease, on average, in serum concentrations of EVUSHELD over time through 183 days post-administration in subjects with positive ADA after the initial dose compared to subjects who tested negative for ADA after the initial dose; the clinical significance of this decrease is unknown.

In PROVENT, following a single IM dose of EVUSHELD (150 mg of tixagevimab and 150 mg cilgavimab) (baseline: study Day 1) through study Day 183, treatment-emergent anti-tixagevimab, anti-cilgavimab and anti-EVUSHELD antibodies were detected in 3% (101/3152), 4% (113/3068) and 5% (156/3158) ADA-evaluable participants, respectively, who received EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab). The average Day 8, 29, and 183 serum concentrations of EVUSHELD were approximately 0%, 12%, and 26% lower, respectively, in subjects who tested positive for ADA after the initial dose versus subjects who tested negative for ADA after the initial dose.

In the PROVENT repeat dose sub-study, following a subsequent single IM dose of EVUSHELD (150 mg of tixagevimab and 150 mg cilgavimab) (baseline: sub-study Day 1) through sub-study Day 29, treatment-emergent anti-tixagevimab, anti-cilgavimab and anti-EVUSHELD antibodies were detected in 0% (0/49), 10% (5/49) and 10% (5/49) ADA-evaluable subjects, respectively. The average Day 29 concentration of EVUSHELD was approximately 14% lower in subjects who tested positive for ADA after the second dose versus subjects who tested negative for ADA after the second dose. The time between repeat doses was 10 to 14 months (first IM dose administered in the original PROVENT study to second IM dose administered in the PROVENT sub-study).

The observed incidence of ADA is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described above with the incidence of ADA in other studies.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, genotoxicity, and reproductive toxicology studies have not been conducted with tixagevimab and cilgavimab.

13.2 Animal Toxicology and Pharmacology

In a toxicology study in cynomolgus monkeys, tixagevimab and cilgavimab had no adverse effects when administered via IM injection.

In tissue cross-reactivity studies with tixagevimab and cilgavimab using human adult and fetal tissues no binding of clinical concern was detected.

Tixagevimab and cilgavimab have been assessed in rhesus macaque and cynomolgus macaque models of SARS-CoV-2 infection. Prophylactic administration of tixagevimab and cilgavimab (N= 4 rhesus macaque; N= 3 cynomolgus macaque) three days prior to infection prevented SARS-CoV-2 infection of the upper and lower respiratory tracts in dose-dependent manner. Prophylactic administration of 4 mg/kg tixagevimab and cilgavimab resulted in a 7-$\log_{10}$ reduction in viral sub-genomic messenger RNA (sgmRNA) in nasopharyngeal swabs and 5 to 6-$\log_{10}$ reduction in sgmRNA or infectious virus titer in bronchoalveolar lavage samples at Day 2 post-challenge in all animals relative to placebo-treated animals. Compared to placebo, prophylactic administration of tixagevimab and cilgavimab (N= 3 cynomolgus macaque) reduced lung injury associated with SARS-CoV-2 infection.

The applicability of these findings to a clinical setting is not known.

14 CLINICAL STUDIES

The data supporting this EUA are based on analyses from the Phase III trials PROVENT (NCT04625725) and STORM CHASER (NCT04625972). Both trials are evaluating the safety and efficacy of EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) for the prophylaxis SARS-CoV-2 symptomatic illness (COVID-19).

Efficacy Data from PROVENT

PROVENT is an ongoing Phase III, randomized (2:1), double-blind, placebo-controlled clinical trial studying EVUSHELD for the pre-exposure prophylaxis of COVID-19 in adults ≥18 years of age. All subjects were either ≥60 years of age, had a pre-specified co-morbidity (obesity, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, immunocompromised state, or previous history of severe or serious adverse event after receiving any approved vaccine), or were at increased risk of SARS-CoV-2 infection due to their living situation or occupation. Subjects could not have previously received a COVID-19 vaccine. Subjects received a single dose (administered as two IM injections) of EVUSHELD or placebo. The study excluded subjects with a history of laboratory-confirmed SARS-CoV-2 infection or SARS-CoV-2 antibody positivity at screening. Once COVID-19 vaccines were locally available, subjects were permitted on request to unblind to make an informed decision on vaccine timing and to receive COVID-19 vaccination.

The baseline demographics were balanced across the EVUSHELD and placebo arms. The median age was 57 years (with 43% of subjects aged 60 years or older), 46% of subjects were female, 73% were White, 3% were Asian 17% were Black/African American, and 15% were Hispanic/Latino. Of the 5,197 subjects, 78% had baseline co-morbidities or characteristics associated with an increased risk for severe COVID-19, including obesity (42%), diabetes (14%), cardiovascular disease (8%), cancer, including a history of cancer (7%), chronic obstructive pulmonary disease (5%), chronic kidney disease (5%), chronic liver disease (5%), immunosuppressive medications (3%) and immunosuppressive disease (<1%).

For the primary endpoint, a subject was defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurred after administration and prior to Day 183. The primary analysis included 5,172 subjects who were SARS-CoV-2 RT-PCR-negative at baseline, of which 3,441 received EVUSHELD and 1,731 received placebo. Only events that occurred prior to unblinding or vaccine receipt were included. EVUSHELD receipt resulted in a statistically significant (p-value <0.001) 77% reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness (COVID-19) when compared to placebo (Table 7). At the time of analysis the median follow-up time post-administration was 83 days (range 3 to 166 days).

Similar results were observed for EVUSHELD recipients compared to placebo recipients in the reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness or death from any cause (12/3,441 versus 19/1,731, respectively) with relative risk reduction of 69% (95% CI: 36, 85; p-value= 0.002), and in the reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness regardless of unblinding or vaccine receipt (10/3,441 versus 22/1,731, respectively) with relative risk reduction of 77% (95% CI: 52, 89 ; p-value <0.001).

Table 7 Incidence of Symptomatic COVID-19 in Adults (PROVENT)

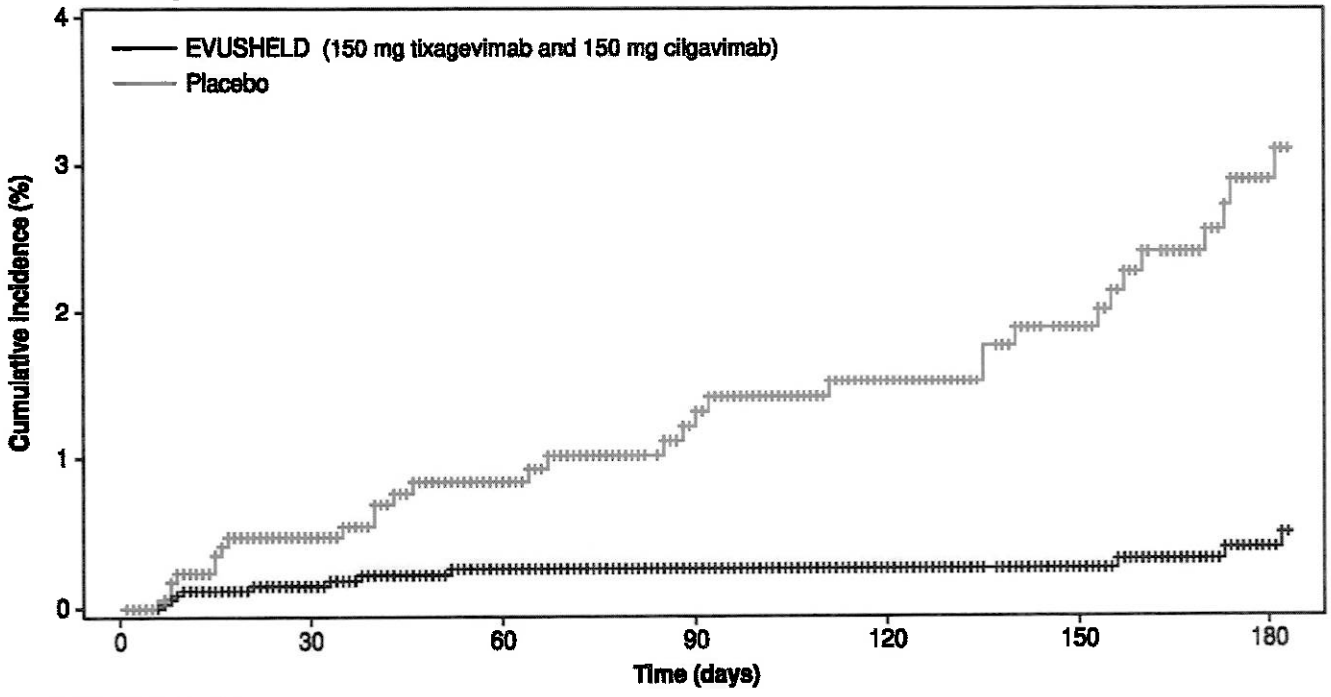
	N*	Number of events, n (%)	Relative Risk Reduction, % (95% CI)
EVUSHELD†	3,441	8 (0.2%)	77% (46, 90)
Placebo	1,731	17 (1.0%)	

N = number of subjects in analysis; CI = Confidence Interval
* subjects were censored after receiving the vaccine or being unblinded to consider the vaccine, whichever occurred earlier
† EVUSHELD dose (150 mg tixagevimab and 150 mg cilgavimab)

Among subjects who received EVUSHELD, there were no severe/critical COVID-19 events (defined as SARS-CoV-2 RT-PCR-positive symptomatic illness characterized by a minimum of either pneumonia [fever, cough, tachypnoea or dyspnea, and lung infiltrates] or hypoxemia [SpO_2 <90% in room air and/or severe respiratory distress] and a WHO Clinical Progression Scale score of 5 or higher) compared to one event (0.1%) among subjects who received placebo.

An additional data cut was conducted to provide post-hoc updated efficacy and safety analysis, the median follow-up was 6.5 months for subjects in both EVUSHELD and placebo arms. The relative risk reduction of SARS-CoV-2 RT-PCR-positive symptomatic illness was 83% (95% CI: 66, 91) with 11/3,441 (0.3%) events in the EVUSHELD arm and 31/1,731 (1.8%) events in the placebo arm, see Figure 1. These results are consistent with the duration of protection predicted by population PK modelling. Among subjects who received EVUSHELD there were no severe/critical COVID-19 events compared to five events among subjects who received placebo.

Figure 1 Kaplan Meier: Cumulative Incidence of Symptomatic COVID-19* (PROVENT)



Number of participants at risk

EVUSHELD	3441	2957	2393	2054	1815	1667	1044
Placebo	1731	1483	1177	991	856	774	472

* Subjects who do not experience a primary endpoint event (and had not discontinued) are censored at Day 183. Subjects who were unblinded/vaccinated prior to an event are also censored at the earlier time of unblinding/vaccination.

Efficacy Data from STORM CHASER

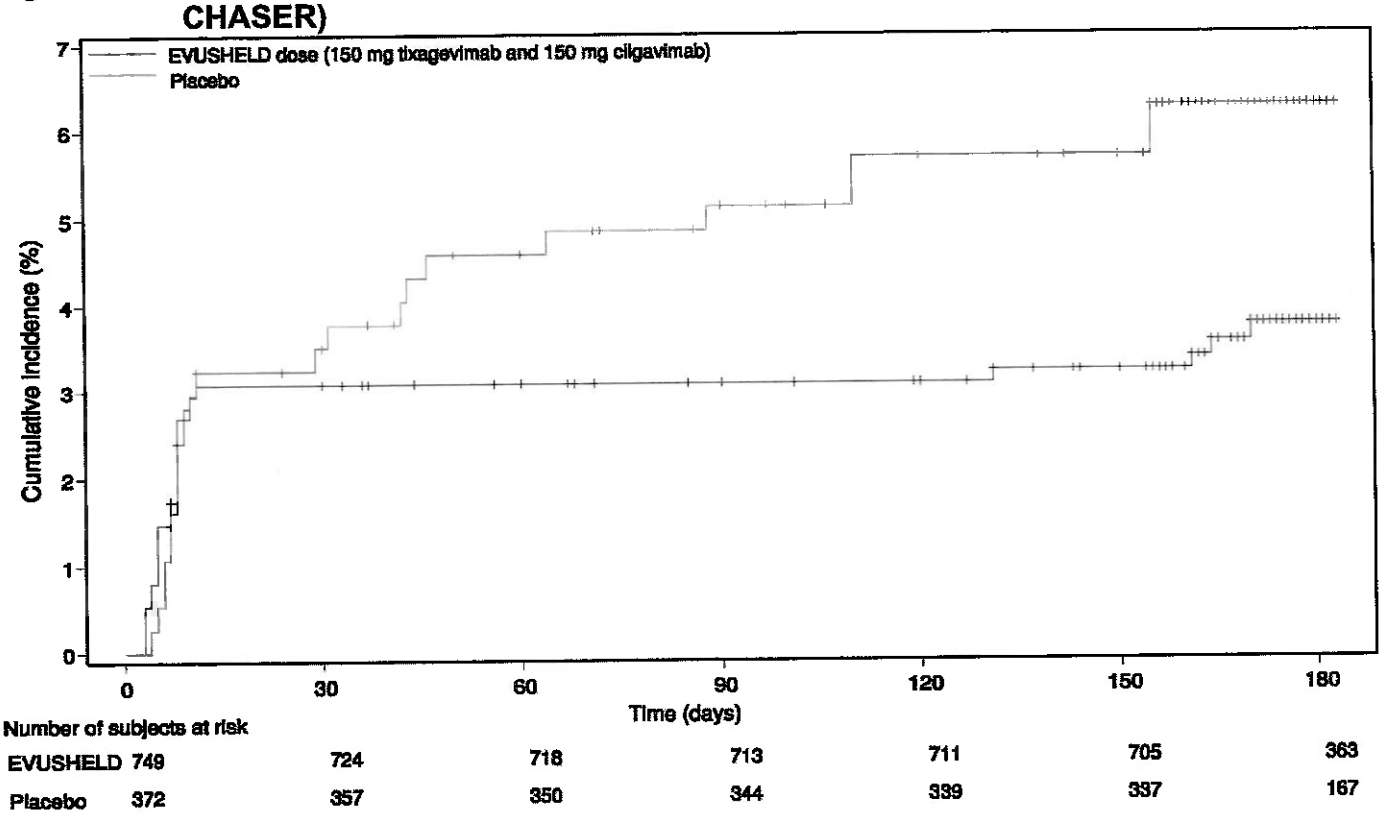
STORM CHASER is an ongoing Phase III randomized (2:1), double-blind, placebo-controlled clinical trial of EVUSHELD for the post-exposure prophylaxis of COVID-19 in adults ≥18 years of age. Subjects who had not previously received a COVID-19 vaccine were enrolled following potential exposure (within 8 days) to an identified individual with a laboratory-confirmed SARS-CoV-2 infection (symptomatic or asymptomatic). Subjects received a single dose (administered as two IM injections) of EVUSHELD or placebo. The study excluded subjects with a history of laboratory-confirmed SARS-CoV-2 infection or SARS-CoV-2 antibody positivity at screening. Once COVID-19 vaccines were locally available, subjects were permitted on request to unblind to make an informed decision on vaccine timing and to receive COVID-19 vaccination.

Of the 1,121 subjects who were randomized and received EVUSHELD (N= 749) or placebo (N= 372), 48 subjects were positive for SARS-CoV-2 (RT-PCR analysis of nasopharyngeal swabs) at baseline.

The primary efficacy analysis, comparison of the incidence of a subject's first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post-dose and before Day 183, did not demonstrate a statistically significant effect for EVUSHELD versus placebo with 23 cases of symptomatic COVID-19 in the EVUSHELD arm (3.1%) and 17 cases in the placebo arm (4.6%) (relative risk reduction of 33%, 95% CI: -26, 65). At the time of analysis the median follow-up time post-administration was 49 days (range 5 to 115 days).

The study did not demonstrate benefit for EVUSHELD in preventing symptomatic COVID-19 in the first 30 days after randomization, leading to the limitation of use for post-exposure prophylaxis *[see Emergency Use Authorization (1)]*. However, there was a higher proportion of symptomatic COVID-19 cases among placebo recipients after Day 29 (see Figure 2 below, data from the post-hoc updated efficacy analysis with a median follow-up time of 6.5 months). EVUSHELD is not authorized for post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2.

Figure 2 Kaplan Meier: Cumulative Incidence of Symptomatic COVID-19* (STORM CHASER)



* Subjects who do not experience a primary endpoint event (and had not discontinued) are censored at Day 183.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Each EVUSHELD co-packaged carton contains two vials (Table 8):

- 1 single-dose vial of tixagevimab injection as a sterile, preservative-free, clear to opalescent and colorless to slightly yellow solution.
- 1 single-dose vial of cilgavimab injection as a sterile, preservative-free, clear to opalescent and colorless to slightly yellow solution.

Table 8 EVUSHELD co-packaged carton contents

Carton (2 vials per pack)	Components	
	1 vial of Tixagevimab 150 mg/1.5 mL (100 mg/mL) **(dark grey cap)**	**1 vial of Cilgavimab** 150 mg/1.5 mL (100 mg/mL) **(white cap)**
NDC 0310-7442-02	NDC 0310-8895-01	NDC 0310-1061-01
NDC 0310-8861-02		

Storage and Handling

Store unopened vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Discard any unused portion.

DO NOT FREEZE. DO NOT SHAKE.

17 PATIENT COUNSELING INFORMATION

As a prescribing healthcare practitioner, you must communicate to the patient, parent and caregiver information consistent with the "FACT SHEET FOR PATIENTS, PARENTS OR CAREGIVERS" and provide them with a copy of this Fact Sheet prior to administration of EVUSHELD.

Dosing
Inform individuals that they will need to receive additional doses of EVUSHELD every 6 months if ongoing protection is needed *[see Dosage and Administration (2.1), and Clinical Pharmacology (12.3)]*.

Risk for COVID-19 Due to SARS-CoV-2 Viral Variants Not Neutralized by EVUSHELD
Certain SARS-CoV-2 viral variants may not be neutralized by monoclonal antibodies such as tixagevimab and cilgavimab, the components of EVUSHELD. EVUSHELD may not be effective at preventing COVID-19 caused by these SARS-CoV-2 viral variants. Inform individuals of the increased risk, compared to other variants, for COVID-19 due to SARS-CoV-2 viral variants not neutralized by EVUSHELD. If signs and symptoms of COVID-19 occur, advise individuals to test for COVID-19 and seek medical attention, including starting treatment for COVID-19 as appropriate *[see Warnings and Precautions (5.3)]*.

Cardiovascular Events
Inform individuals that a higher proportion of subjects who received EVUSHELD versus placebo reported cardiovascular serious adverse events (myocardial infarctions and heart failure). Advise individuals to seek immediate medical attention if they experience any signs or symptoms suggestive of a cardiovascular event *[see Warnings and Precautions (5.5)]*.

For additional information, please visit the website or call the telephone number provided below.

To access the most recent EVUSHELD Fact Sheets, please scan the QR code provided below.

Website	Telephone number
http://www.evusheld.com	1-800-236-9933

18 MANUFACTURER INFORMATION

Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

ASPR Administration for Strategic Preparedness & Response

Information Sheet & Frequently Asked Questions

FDA's Change to Authorization of Evusheld

On January 26, FDA announced that Evusheld is not currently authorized for emergency use in the U.S. until further notice by the agency because the therapeutic is unlikely to be active against more than 90% of the SARS-CoV-2 variants currently circulating in the U.S. based on the latest CDC data.

There are many things that people can do to protect themselves against COVID-19. First, if vaccination is recommended for you, get vaccinated and stay up to date. This means getting the updated (bivalent) vaccine if you haven't received it yet.

Second, develop a COVID-19 Action Plan so that you have all of the information you need on hand if you get sick with COVID-19.

If you develop signs or symptoms of COVID-19, reach out to your doctor, another healthcare provider, or a Test to Treat site (in person or via telehealth) immediately, even if your symptoms are mild. As an additional option for patients who are unable to access their healthcare provider, Test to Treat sites have health clinics at the sites where people can get tested for COVID-19 and evaluated by a healthcare provider (in person or via telehealth). People who test positive and are eligible can get a prescription to treat the infection and have the prescription filled at an affiliated pharmacy.

Finally, taking multiple prevention steps can provide additional layers of protection against COVID-19:

- Wear a well-fitting, high-quality mask or respirator in public places to reduce your chances of becoming infected with COVID-19, or any other respiratory illnesses. Properly fitting respirators provide the highest level of protection.
- When indoors with others, try to improve ventilation as much as possible.
- Avoid poorly ventilated or crowded indoor settings.
- Wash your hands often with soap and water or use a hand sanitizer that contains at least 60% alcohol.
- Encourage people you live with or spend time with to stay up to date on COVID vaccines and take all necessary
- prevention actions to protect themselves against COVID-19, or hospitalization and death if exposed.
- Avoid people who are sick, including people have COVID-19, even if they do not feel or seem sick.
- Talk with your doctor in advance about what treatments may be appropriate for you and how to access the medication if you experience symptoms.

Frequently Asked Questions

What is Evusheld?

Evusheld is a long-acting antibody therapeutic. Since December 2021, Evusheld has been an option for pre-exposure prophylaxis, in other words as preventive protection from COVID-19.

Specifically, Evusheld was authorized for:

- People who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and may not mount an adequate immune response to COVID-19 vaccination, or

- People for whom vaccination with any available COVID-19 vaccine is not recommended due to a history of severe adverse reaction to a COVID-19 vaccine and/or components of a COVID-19 vaccine.

Why did FDA take action to pause the authorization of Evusheld?

Evusheld is not currently authorized for emergency use in the U.S. because it is unlikely to be active against more than 90% of the SARS-CoV-2 variants currently circulating in the U.S. The latest CDC NOWCAST estimate shows that these variants are causing more than 90% of the cases today.

This FDA action follows several previous announcements and guidance updates for Evusheld by federal agencies over the past few months, including:

- At the beginning of October, FDA informed health care providers and individuals taking Evusheld of its loss of activity against some Omicron variants and the increased risk of breakthrough infections, especially as resistant variants became more prevalent as they are today.
- On December 20, the Centers for Disease Control and Prevention (CDC) issued a Health Alert Network (HAN) Health Update to supplement the CDC HAN Health Advisories issued on April 25, 2022 and May 24, 2022 to emphasize to healthcare providers, public health departments, and reduced susceptibility to Evusheld.
- On January 6, 2023 FDA released additional communication stating that they were closely monitoring the emergence of the XBB.1.5 subvariant, a SARS-CoV-2 Omicron variant that is currently increasing in prevalence in the U.S. Because of its similarity to variants that are not neutralized by Evusheld (e.g., XBB), FDA does not anticipate that Evusheld will neutralize XBB.1.5.
- On January 10, 2023, NIH's COVID-19 Treatment Guidelines Panel released a statement indicating that the prevalence of SARS-CoV-2 subvariants likely to be resistant to Evusheld was increasing.

I am immunocompromised and used Evusheld for protection. What does this decision mean for me?

If you've already received Evusheld, it's important to know that it does not provide protection against the variants of COVID-19 that are most common today. Because of this, you may now have less protection from developing COVID-19 if you are exposed to currently circulating variants.

If vaccination is recommended for you, get vaccinated and stay up to date to protect yourself against COVID-19. This means getting the updated (bivalent) vaccine if you haven't received it yet.

If you haven't already, consider developing a COVID-19 Action Plan so you have all of the information you need on hand if you get sick with COVID-19. Talk with your doctor in advance about what treatments may be appropriate for you and how to access the medication if you do get sick.

If you develop signs or symptoms of COVID-19, reach out to your doctor immediately, even if your symptoms are mild. If your doctor recommends treatment, start it right away. There are several approved and authorized treatments for COVID-19. Timely treatment can reduce your risk of getting very sick, being hospitalized, or dying.

What treatments are available for people who might be at higher risk of getting sick now that Evusheld is no longer available?

There are several treatments available for COVID-19 infections.

Currently available data supports their use in reducing the risk of progression to severe disease, including hospitalization and death. Paxlovid (nirmatrelvir/ritonavir) and Veklury

(remdesivir) are the medicines recommended for most people. If those medicines are not available or someone cannot take them, Lagevrio (molnupiravir) is the next choice. COVID-19 convalescent plasma may be another option for certain immunocompromised patients.

If you have signs or symptoms of COVID-19, contact your doctor right away to find out if you should start one of these treatments. You should also talk with your doctor in advance about what treatments may be appropriate for you and how to access the medication if you experience symptoms.

More specifically:

Paxlovid is authorized to treat mild-to-moderate COVID-19 in adults and children 12 years of age and older

weighing at least 40 kg, (approximately 88 lbs.) and who are at high risk of developing severe COVID-19 leading to hospitalization or death.

Veklury is approved to treat adults and children 28 days of age and older and weighing at least 3 kg (approximately 6.6 lbs.) who have mild-to-moderate COVID-19 and are at high risk of developing severe COVID-19 leading to hospitalization or death.

Lagevrio is authorized to treat mild-to-moderate COVID-19 in adults who are at high risk of developing severe COVID-19 leading to hospitalization or death, and who do not have access to alternative COVID-19 treatments that are approved or authorized by FDA or for whom these treatments are not clinically appropriate.

COVID-19 convalescent plasma with high titers of anti-SARS- CoV-2 antibodies is authorized to treat COVID-19 in patients with immunosuppressive disease or who are receiving immunosuppressive treatment in in-patient or out-patient settings.

What is HHS doing to ensure access to treatments for individuals who are immunocompromised or who cannot get vaccinated now that Evusheld is no longer available?

Over the past year, HHS has dramatically increased access to Paxlovid and Lagevrio, both of which are pills. Supplies of these medicines are now widely available at pharmacies, Test to Treat pharmacies, long-term care facilities, and other locations.

We are encouraging states to support local health departments and health systems in setting up infusion clinics for Veklury (remdesivir) to make it easier for people to get this treatment as soon as possible after being diagnosed with COVID-19.

HHS, state and local health departments, and other healthcare partners also continue to work to ensure access to COVID-19 vaccines, including the updated (bivalent) vaccine.

I am immunocompromised. Is there anything I can do to boost my immunity or protect myself?

Yes: people for whom COVID-19 vaccination is recommended, including people who are immunocompromised, should get and stay up to date with vaccinations. This means getting the updated (bivalent) vaccine, no matter how many boosters you received before the bivalent vaccine became available in September 2022.

Will Evusheld be an option in the future if the variants change?

FDA will continue to work with ASPR, the CDC, and the National Institutes of Health on surveillance of variants that may impact the use of the therapies authorized for emergency use. We will provide further updates and consider additional action as new information becomes available.

Why haven't more prevention and treatment options that work against the current variants been approved or authorized, and when will they be available?

Several approved or authorized treatments are expected to remain active to fight against the currently circulating variants and are widely available.

The FDA has worked around the clock throughout the pandemic and used the best available data to ensure options are available to prevent and treat COVID-19. This work is particularly important for people who are unable to get vaccinated and for immunocompromised people who may not mount an adequate immune response to vaccination.

Disease experts at HHS continually watch for new variants of any viruses and continue to monitor the potential impact that new variants might have on existing therapies. By taking this approach, we can identify the need for new medical products and ways to expedite development of new medical products to address emerging variants. For example, nearly two years ago, the FDA provided guidance to industry on how to efficiently generate non-clinical and chemistry, manufacturing and controls data that could potentially support an Emergency Use Authorization for monoclonal antibody products that had potential to be effective against emerging variants.

In December 2022, FDA and European Medicines Agency (EMA) convened a workshop to bring together the expertise of academics, clinicians, industry, and regulatory bodies to address the acceptability and challenges of alternative strategies to support the development of novel monoclonal antibody therapies including those based on prototype products that have

demonstrated safety and efficacy in clinical trials. FDA is committed to working with industry sponsors to expedite the development of new drug products to meet unmet needs, such as the need for new preventive therapies for immune suppressed patients who are unlikely to respond to vaccination.

For More Information

People Who Are Immunocompromised | CDC

How to Protect Yourself and Others | CDC

FDA U.S. FOOD & DRUG ADMINISTRATION

October 27, 2022

Eli Lilly and Company
Attention: Christine Phillips, PhD, RAC
Advisor Global Regulatory Affairs - US
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

RE: Emergency Use Authorization 111

Dear Ms. Phillips:

This letter is in response to Eli Lilly and Company's ("Lilly") request that the Food and Drug Administration (FDA or Agency) issue an Emergency Use Authorization (EUA) for the emergency use of bebtelovimab for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in certain adults and pediatric patients who are at high-risk for progression to severe COVID-19, including hospitalization or death, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §360bbb-3).

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19).[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[2]

On February 11, 2022, the FDA issued an EUA for the emergency use of bebtelovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high-risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

[1] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3.* February 4, 2020.
[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).

Bebtelovimab is a neutralizing IgG1 monoclonal antibody that binds to an epitope within the receptor binding domain of the spike protein of SARS-CoV-2. Bebtelovimab is not FDA-approved for any uses, including use as treatment for COVID-19.

FDA subsequently reissued the Letter of Authorization (LOA) on August 5, 2022.[3]

On October 27, 2022, having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the August 5, 2022 letter in its entirety, to incorporate clarifying revisions to Condition W of this letter. Condition V was also revised to require that all printed matter, advertising and promotional materials relating to the use of bebtelovimab under this authorization be submitted to FDA for consideration at least 14 calendar days prior to initial dissemination or first use.

Based on the review of the data from the BLAZE-4 clinical trial (NCT04634409), a Phase 1/2 randomized, single-dose clinical trial studying bebtelovimab for the treatment of non-hospitalized patients with mild-to-moderate COVID-19, as well as available pharmacokinetic data and nonclinical viral neutralization data for Omicron and other variants of concern, it is reasonable to believe that bebtelovimab may be effective for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high-risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate, as described in the Scope of Authorization (Section II), and when used under the conditions described in this authorization, the known and potential benefits of bebtelovimab outweigh the known and potential risks of such product.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of bebtelovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high-risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of bebtelovimab for treatment of mild-to-moderate COVID-19, when administered as described in the Scope of Authorization (Section II), meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

1. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that bebtelovimab may be effective for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who

[3] In its August 5, 2022 revision, FDA revised the LOA with revisions to the scope of authorization no longer requiring directed distribution of bebtelovimab by the United States Government.

are at high-risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (section II), and that, when used under the conditions described in this authorization, the known and potential benefits of bebtelovimab outweigh the known and potential risks of such product; and

3. There is no adequate, approved, and available alternative[4] to the emergency use of bebtelovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric (12 years of age and older weighing at least 40 kg) patients as further described in the Scope of Authorization (section II).[5]

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Bebtelovimab may only be used for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg):
    - With positive results of direct SARS-CoV-2 viral testing, and
    - Who are at high-risk[6] for progression to severe COVID, including hospitalization or death, and
    - For whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

- Bebtelovimab is **not** authorized for use in the following patient populations[7]:
    - Adults or pediatric patients who are hospitalized due to COVID-19, or
    - Adults or pediatric patients who require oxygen therapy and/or respiratory support due to COVID-19, or
    - Adults or pediatric patients who require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 in those patients on chronic oxygen therapy and/or oxygen support due to underlying non-COVID-19-related comorbidity;

- Bebtelovimab is **not** authorized for treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible

[4] Although Veklury (remdesivir) is an approved alternative to treat COVID-19 in adults and pediatric patients within the scope of this authorization, FDA does not consider it to be an adequate alternative for certain patients for whom it may not be feasible or practical (e.g., it requires a 3-day treatment duration).
[5] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.
[6] For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html.
[7] Treatment with bebtelovimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bebtelovimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

SARS-CoV-2 variant, based on available information including variant susceptibility to these drugs and regional variant frequency.[8]

- Bebtelovimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary;

- The use of bebtelovimab covered by this authorization must be in accordance with the authorized Fact Sheets.

Product Description

Bebtelovimab injection (NDC 0002-7589-01) is a sterile, preservative-free clear to opalescent and colorless to slightly yellow to slightly brown solution supplied in a single-dose vial. Each carton contains a single vial of bebtelovimab, which is labeled "For Use Under Emergency Use Authorization (EUA)".

The authorized storage and handling information is included in the authorized Fact Sheet for Healthcare Providers.

Bebtelovimab is authorized for emergency use with the following product-specific information required to be made available to healthcare providers and to patients, parents, and caregivers, respectively, through Lilly's website www.LillyAntibody.com/bebtelovimab (referred to as the "authorized labeling"):

- Fact Sheet for Healthcare Providers: Emergency Use Authorization (EUA) for bebtelovimab
- Fact Sheet for Patients, Parents, and Caregivers: Emergency Use Authorization (EUA) of bebtelovimab for Coronavirus Disease 2019 (COVID-19)

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of bebtelovimab, when used for the treatment of COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh the known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that bebtelovimab may be effective for the treatment of COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

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[8] FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility (see, e.g., section 12.4 of authorized Fact Sheet for Health Care Providers), and CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions. FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that bebtelovimab (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of bebtelovimab under this EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), bebtelovimab is authorized for the treatment of COVID-19 as described in this Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

Lilly and Authorized Distributors[9]

A. Lilly and authorized distributor(s) will ensure that the authorized bebtelovimab is distributed and the authorized labeling (i.e., Fact Sheets) will be made available to healthcare facilities and/or healthcare providers consistent with the terms of this letter.

B. Lilly and authorized distributor(s) will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., U.S. government agencies, state and local government authorities, authorized distributors, healthcare facilities, healthcare providers) involved in distributing or receiving bebtelovimab. Lilly will provide to all relevant stakeholders a copy of this Letter of Authorization and communicate any subsequent amendments that might be made to this Letter of Authorization and its authorized accompanying materials (i.e., Fact Sheets).

C. Lilly may request changes to this authorization, including to the authorized Fact Sheets for bebtelovimab. Any request for changes to this EUA must be submitted to the Office of Infectious Diseases/Office of New Drugs/Center for Drug Evaluation and Research. Such changes require appropriate authorization prior to implementation.[10]

[9] "Authorized Distributor(s)" are identified by Lilly as an entity or entities allowed to distribute the authorized bebtelovimab.

[10] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study; (8) new strengths of the authorized product, new product sources (e.g., of active pharmaceutical ingredient) or of product components. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), (7), or (8), review and concurrence is required from the Counter-Terrorism and

D. Lilly may develop and disseminate instructional and educational materials (e.g., materials providing information on product administration and/or patient monitoring) that are consistent with the authorized emergency use of bebtelovimab as described in this Letter of Authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs. Any instructional and educational materials that are inconsistent with the authorized labeling for bebtelovimab are prohibited. If the Agency notifies Lilly that any instructional and educational materials are inconsistent with the authorized labeling, Lilly must cease distribution of such instructional and educational materials. Furthermore, as part of its notification, the Agency may also require Lilly to issue corrective communication(s).

E. Lilly will report to FDA all serious adverse events and medication errors potentially related to bebtelovimab use that are reported to Lilly using either of the following options.

Option 1: Submit reports through the Safety Reporting Portal (SRP) as described on the FDA SRP web page.

Option 2: Submit reports directly through the Electronic Submissions Gateway (ESG) as described on the FAERS electronic submissions web page.

Submitted reports under both options must state: "Bebtelovimab use for COVID-19 under Emergency Use Authorization (EUA)." For reports submitted under Option 1, include this language at the beginning of the question "Describe Event" for further analysis. For reports submitted under Option 2, include this language at the beginning of the "Case Narrative" field.

F. All manufacturing, packaging, and testing sites for both drug substance and drug product used for EUA supply will comply with current good manufacturing practice requirements of Section 501(a)(2)(B) of the Act.

G. Lilly will submit information to the Agency within three working days of receipt of any information concerning significant quality problems with distributed drug product of bebtelovimab that includes the following:

- Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or
- Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the established specifications.

Emergency Coordination Staff/Office of the Center Director/CDER and the Office of Counterterrorism and Emerging Threats/Office of the Chief Scientist.

If a significant quality problem affects unreleased product and may also impact product(s) previously released and distributed, then information must be submitted for all potentially impacted lots.

Lilly will include in its notification to the Agency whether the batch, or batches, in question will be recalled. If FDA requests that these, or any other batches, at any time, be recalled, Lilly must recall them.

If not included in its initial notification, Lilly must submit information confirming that Lilly has identified the root cause of the significant quality problems, taken corrective action, and provide a justification confirming that the corrective action is appropriate and effective. Lilly must submit this information as soon as possible but no later than 45 calendar days from the initial notification.

H. Lilly will manufacture bebtelovimab to meet all quality standards and per the manufacturing process and control strategy as detailed in Lilly's EUA request. Lilly will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product, without notification to and concurrence by the Agency as described under condition D.

I. Lilly will list bebtelovimab with a unique product NDC under the marketing category of Emergency Use Authorization. Further, the listing will include each establishment where manufacturing is performed for the drug and the type of operation performed at each such establishment.

J. Through a process of inventory control, Lilly and authorized distributor(s) will maintain records regarding distribution of bebtelovimab (i.e., lot numbers, quantity, receiving site, receipt date).

K. Lilly will establish a process for monitoring genomic database(s) for the emergence of global viral variants of SARS-CoV-2. A summary of Lilly's process should be submitted to the Agency as soon as practicable, but no later than 30 calendar days of the issuance of this letter, and within 30 calendar days of any material changes to such process. Lilly will provide reports to the Agency on a monthly basis summarizing any findings as a result of its monitoring activities and, as needed, any follow-up assessments planned or conducted.

L. FDA may require Lilly to assess the activity of the authorized bebtelovimab against any global SARS-CoV-2 variant(s) of interest (e.g., variants that are prevalent or becoming prevalent that harbor substitutions in the target protein or in protein(s) that interact with the target protein). Lilly will perform the required assessment in a manner and timeframe agreed upon by Lilly and the Agency. Lilly will submit to FDA a preliminary summary report immediately upon completion of its assessment followed by a detailed study report within 30 calendar days of study completion. Lilly will submit any relevant proposal(s) to revise the authorized labeling based on the results of its assessment, as may be necessary or appropriate based on the foregoing assessment.

M. Lilly shall provide samples as requested of the authorized bebtelovimab to the HHS for evaluation of activity against emerging global viral variants of SARS-CoV-2, including specific amino acid substitution(s) of interest (e.g., variants that are highly prevalent or that harbor substitutions in the target protein) within 5 business days of any request made by HHS. Analyses performed with the supplied quantity of authorized bebtelovimab may include, but are not limited to, cell culture potency assays, protein binding assays, cell culture variant assays (pseudotyped virus-like particles and/or authentic virus), and *in vivo* efficacy assays.

N. Lilly must provide the following information to the Agency:

1. Lilly will submit a study report to FDA characterizing the development of SARS-CoV-2 resistance to bebtelovimab in cell culture passage experiments no later than 30 days of the completion of these experiments.
2. Lilly will submit to FDA all sequencing data assessing bebtelovimab, including sequencing of any participant samples from the full analysis population from PYAH arms 9-14 that have not yet been completed no later than March 31, 2022.
3. Lilly will submit a proposed clinical trial protocol to further evaluate bebtelovimab for the treatment of mild-to-moderate COVID-19 in non-hospitalized patients no later than March 1, 2022.

O. Lilly and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

Healthcare Facilities to Whom Bebtelovimab Is Distributed and Healthcare Providers Administering bebtelovimab

P. Healthcare facilities and healthcare providers will ensure that they are aware of the letter of authorization, and the terms herein, and that the authorized Fact Sheets are made available to healthcare providers and to patients and caregivers, respectively, through appropriate means, prior to administration of bebtelovimab as described in the Scope of Authorization (Section II) under this EUA.

Q. Healthcare facilities and healthcare providers receiving bebtelovimab will track all serious adverse events and medication errors that are considered to be potentially related to bebtelovimab use and must report these to FDA in accordance with the Fact Sheet for Healthcare Providers. Complete and submit a MedWatch form (www.fda.gov/medwatch/report.htm), or complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178) (these forms can be found via link above). Call 1-800-FDA-1088 for questions. Submitted reports must state, "Bebtelovimab use for COVID-19 under Emergency Use Authorization" at the beginning of the question "Describe Event" for further analysis.

R. Healthcare facilities and healthcare providers will ensure that appropriate storage is maintained until the product is administered consistent with the terms of this letter and the authorized labeling.

S. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensing and administration of bebtelovimab for the use authorized in this letter (i.e., lot numbers, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered).

T. Healthcare facilities will ensure that any records associated with this EUA are maintained until notified by Lilly and/or FDA. Such records will be made available to Lilly, HHS, and FDA for inspection upon request.

U. Healthcare facilities and providers will report therapeutics information and utilization data as directed by HHS.

Conditions Related to Printed Matter, Advertising, and Promotion

V. All descriptive printed matter, advertising, and promotional materials relating to the use of bebtelovimab under this authorization shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in Section 502(a) and (n) of the Act, as applicable, and FDA implementing regulations. References to "approved labeling", "permitted labeling" or similar terms in these requirements shall be understood to refer to the authorized labeling for the use of bebtelovimab under this authorization. In addition, such materials shall:

- Be tailored to the intended audience.
- Not take the form of reminder advertisements, as that term is described in 21 CFR 202.1(e)(2)(i), 21 CFR 200.200 and 21 CFR 201.100(f).
- Present the same risk information relating to the major side effects and contraindications concurrently in the audio and visual parts of the presentation for advertising and promotional materials in audio-visual format.
- Be accompanied by the authorized labeling, if the promotional materials are not subject to Section 502(n) of the Act.
- Be submitted to FDA accompanied by Form FDA-2253 for consideration at least 14 calendar days prior to initial dissemination or first use.

W. Lilly may disseminate descriptive printed matter, advertising, and promotional materials relating to the emergency use of bebtelovimab that provide accurate descriptions of safety results and efficacy results on a clinical endpoint(s) from the clinical trial(s) summarized in the authorized labeling. Such materials must include any limitations of the clinical trial data as described in the authorized labeling. Lilly may not imply that bebtelovimab is FDA-approved for its authorized use by making statements such as "bebtelovimab is safe and effective for the treatment of COVID-19."

X. All descriptive printed matter, advertising, and promotional material, relating to the use of bebtelovimab under this authorization clearly and conspicuously shall state that:

- Bebtelovimab has not been approved, but has been authorized for emergency use by FDA under an EUA, for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high-risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate; and

- The emergency use of bebtelovimab is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

If the Agency notifies Lilly that any descriptive printed matter, advertising or promotional materials do not meet the terms set forth in conditions V through X of this EUA, Lilly must cease distribution of such descriptive printed matter, advertising, or promotional materials in accordance with the Agency's notification. Furthermore, as part of its notification, the Agency may also require Lilly to issue corrective communication(s).

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

--/S/--

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR BEBTELOVIMAB

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use BEBTELOVIMAB under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for BEBTELOVIMAB.

BEBTELOVIMAB injection for intravenous use
Original EUA Authorized Date: 02/2022
Revised EUA Authorized Date: 11/2022

----------RECENT MAJOR CHANGES----------

Dosage and Administration, Dose Preparation and Administration (2.3): updated administration materials	03/2022
Use in Specific Populations, Pregnancy (8.1): added hypersensitivity reactions in pregnant women	05/2022
Clinical Pharmacology, Microbiology (12.4): updated neutralizing data	11/2022

----------EMERGENCY USE AUTHORIZATION----------

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of bebtelovimab for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg):

- with positive results of direct SARS-CoV-2 viral testing, **and**
- who are at high risk for progression to severe COVID-19, including hospitalization or death, **and**
- for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate. (14.4)

LIMITATIONS OF AUTHORIZED USE

- Bebtelovimab is not authorized for treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to this drug and regional variant frequency.
  - FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility, and CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions. (12.4)
  - FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs
- Bebtelovimab is not authorized for use in patients who:
  - are hospitalized due to COVID-19, OR
  - require oxygen therapy and/or respiratory support due to COVID-19, OR
  - require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 and are on chronic oxygen therapy and/or respiratory support due to underlying non-COVID-19 related comorbidity.

Bebtelovimab is not approved for any use, including for use as treatment of COVID-19. (1)

Bebtelovimab is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of bebtelovimab under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

See Full Fact Sheet for Healthcare Providers for the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19.

----------DOSAGE AND ADMINISTRATION----------

The dosage in adults (18 years and older) and pediatric patients (≥12 years of age and weighing at least 40 kg) is bebtelovimab 175 mg administered as a single intravenous injection over at least 30 seconds. Administer bebtelovimab as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 7 days of symptom onset. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 175 mg/2 mL (87.5 mg/mL) in a single-dose vial. (3)

----------CONTRAINDICATIONS----------

No contraindications have been identified based on the limited available data for the emergency use of bebtelovimab authorized under this EUA. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions: Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of other SARS-CoV-2 monoclonal antibodies and could occur with administration of bebtelovimab. If clinically significant hypersensitivity reactions occur, discontinue and initiate appropriate supportive care. Infusion-related reactions may occur up to 24 hours post injection. These reactions may be severe or life threatening. (5.1)
- Clinical Worsening After SARS-CoV-2 Monoclonal Antibody Administration: Clinical worsening of COVID-19 after administration of SARS-CoV-2 monoclonal antibody treatment has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to SARS-CoV-2 monoclonal antibody use or were due to progression of COVID-19. (5.2)
- Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19: Treatment with bebtelovimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bebtelovimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. (5.3)

----------ADVERSE REACTIONS----------

Most common adverse reactions are infusion-related reactions (0.3%), pruritus (0.3%), and rash (0.8%). (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to bebtelovimab (1) by submitting FDA Form 3500 online, (2) by downloading this form and then submitting by mail or fax, or (3) contacting the FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to Eli Lilly and Company, Global Patient Safety: Fax: 1-317-277-0853; E-mail: mailindata_gsmtindy@lilly.com; or call 1-855-LillyC19 (1-855-545-5921) to report adverse events. (6.4).

----------DRUG INTERACTIONS----------

Bebtelovimab is not renally excreted or metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely. (7)

See FACT SHEET FOR PATIENTS, PARENTS, AND CAREGIVERS.

TABLE OF CONTENTS*

* Sections or subsections omitted from the EUA are not listed

FULL FACT SHEET FOR HEALTHCARE PROVIDERS

1 EMERGENCY USE AUTHORIZATION

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of bebtelovimab for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg):

- with positive results of direct SARS-CoV-2 viral testing, **and**
- who are at high risk[1] for progression to severe COVID-19, including hospitalization or death, **and**
- for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate *[see Clinical Studies (14.4)]*.

LIMITATIONS OF AUTHORIZED USE

- Bebtelovimab is not authorized for treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to this drug and regional variant frequency.
    - FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.[2]
- Bebtelovimab is not authorized for use in patients, who:
    - are hospitalized due to COVID-19, OR
    - require oxygen therapy and/or respiratory support due to COVID-19, OR
    - require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 and are on chronic oxygen therapy and/or respiratory support due to underlying non-COVID-19 related comorbidity.

Treatment with bebtelovimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bebtelovimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation *[see Warnings and Precautions (5.3)]*.

Bebtelovimab is not FDA-approved for any use, including for use as treatment of COVID-19 *[see Emergency Use Authorization (1)]*.

Bebtelovimab is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of bebtelovimab under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Justification for Emergency Use of Drugs During the COVID-19 Pandemic
There is currently an outbreak of Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2, a novel coronavirus. The Secretary of HHS has declared that:

[1] For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html. Healthcare providers should consider the benefit-risk for an individual patient.
[2] FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility *[see Microbiology (12.4)]*, and CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions.

- A public health emergency related to COVID-19 has existed since January 27, 2020.
- Circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic (March 27, 2020 declaration).

An EUA is a FDA authorization for the emergency use of an unapproved product or unapproved use of an approved product (i.e., drug, biological product, or device) in the United States under certain circumstances including, but not limited to, when the Secretary of HHS declares that there is a public health emergency that affects the national security or the health and security of United States citizens living abroad, and that involves biological agent(s) or a disease or condition that may be attributable to such agent(s). Criteria for issuing an EUA include:

- The biological agent(s) can cause a serious or life-threatening disease or condition;
- Based on the totality of the available scientific evidence (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that
    - the product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition; and
    - The known and potential benefits of the product - when used to diagnose, prevent, or treat such disease or condition - outweigh the known and potential risks of the product, taking into consideration the material threat posed by the biological agent(s);
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the serious or life-threatening disease or condition.

Information Regarding Available Alternatives for the EUA Authorized Use

Veklury (remdesivir) is FDA-approved for the treatment of COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, who are not hospitalized and have mild-to-moderate COVID-19, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Veklury is administered via intravenous infusion for a total treatment duration of 3 days.

Although Veklury is an approved alternative treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, FDA does not consider Veklury to be an adequate alternative to bebtelovimab for this authorized use because it may not be feasible or practical for certain patients (e.g., it requires a 3-day treatment duration).

Other therapeutics are currently authorized for the same use as bebtelovimab. For additional information on all products authorized for treatment or prevention of COVID-19, please see https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

For information on clinical studies of bebtelovimab and other therapies for the treatment of COVID-19, see www.clinicaltrials.gov.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

The dosage in adults (18 years and older) and pediatric patients (≥12 years of age and weighing at least 40 kg) is bebtelovimab 175 mg.

Administer bebtelovimab as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 7 days of symptom onset.

Bebtelovimab must be administered as a single intravenous injection over at least 30 seconds.

2.2 Dosage Adjustment in Specific Populations

No dosage adjustment is recommended in pregnant or lactating individuals, in geriatrics, in individuals with renal impairment, or in individuals with mild hepatic impairment *[see Clinical Pharmacology (12.3)]*.

2.3 Dose Preparation and Administration

General Information

- Bebtelovimab should be prepared by a qualified healthcare professional using aseptic technique.
- Inspect bebtelovimab vial visually for particulate matter and discoloration. Bebtelovimab is clear to opalescent and colorless to slightly yellow to slightly brown solution. Discard the vial if the solution is cloudy, discolored or visible particles are observed.
- Bebtelovimab may only be administered in settings in which healthcare providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.
- **Clinically monitor patients for possible infusion-related reactions during administration and observe patients for at least 1 hour after injection is complete.**

Materials Needed for Administration

- 1 bebtelovimab vial (175 mg/2 mL)
- 1 disposable polypropylene dosing syringe capable of holding 2 mL
- 0.9% Sodium Chloride Injection for flushing
- Optional: 1 syringe extension set made of polyethylene or polyvinylchloride with or without di-ethylhexylphthalate (DEHP)

Preparation

- Remove bebtelovimab vial from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake vial. Inspect the vial.**
- Withdraw 2 mL from the vial into the disposable syringe.
- Discard any product remaining in the vial.
- This product is preservative-free and therefore, should be administered immediately.

- If immediate administration is not possible, store the syringe for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) and up to 7 hours at room temperature (20°C to 25°C [68°F to 77°F]). If refrigerated, allow the prepared syringe to equilibrate to room temperature for approximately 20 minutes prior to administration.
- If used, attach and prime the syringe extension set.
- Administer the entire contents of the syringe via IV injection over at least 30 seconds.
- After the entire contents of the syringe have been administered, **flush the injection line** with 0.9% Sodium Chloride to ensure delivery of the required dose.

3 DOSAGE FORMS AND STRENGTHS

Bebtelovimab is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow to slightly brown solution available as:

- Injection: 175 mg/2 mL (87.5 mg/mL) in a single-dose vial

4 CONTRAINDICATIONS

No contraindications have been identified based on the limited available data for the emergency use of bebtelovimab authorized under this EUA.

5 WARNINGS AND PRECAUTIONS

There are limited clinical data available for bebtelovimab. Serious and unexpected adverse events may occur that have not been previously reported with bebtelovimab use.

5.1 Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of other SARS-CoV-2 monoclonal antibodies and could occur with administration of bebtelovimab. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related reactions, which may occur up to 24 hours after the injection, have been observed in clinical trials of bebtelovimab when administered with other monoclonal antibodies and may occur with use of bebtelovimab alone. These reactions may be severe or life threatening.

Signs and symptoms of infusion-related reactions may include:

- fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vasovagal reactions (e.g., pre-syncope, syncope), dizziness and diaphoresis.

Administer appropriate medications and/or supportive care if an infusion-related reaction occurs.

Hypersensitivity reactions occurring more than 24 hours after the injection have also been reported with the use of SARS-CoV-2 monoclonal antibodies under Emergency Use Authorization.

5.2 Clinical Worsening After SARS-CoV-2 Monoclonal Antibody Administration

Clinical worsening of COVID-19 after administration of SARS-CoV-2 monoclonal antibody treatment has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to SARS-CoV-2 monoclonal antibody use or were due to progression of COVID-19.

5.3 Limitations of Benefit and Potential for Risk in Patients with Severe COVID 19

Treatment with bebtelovimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bebtelovimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Therefore, bebtelovimab is not authorized for use in patients, regardless of age, who:

- are hospitalized due to COVID-19, OR
- require oxygen therapy and/or respiratory support due to COVID-19, OR
- require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 and are on chronic oxygen therapy and/or respiratory support due to underlying non-COVID-19 related comorbidity.

6 ADVERSE REACTIONS

6.1 Adverse Reactions from Clinical Studies

The following adverse reactions have been observed in the clinical studies of bebtelovimab that supported the EUA. The adverse reaction rates observed in these clinical studies cannot be directly compared to rates in the clinical studies of other products and may not reflect the rates observed in clinical practice. Additional adverse events associated with bebtelovimab may become apparent with more widespread use.

The safety of bebtelovimab is primarily based on exposure of 602 ambulatory (non-hospitalized) subjects who received doses of bebtelovimab, alone or in combination with bamlanivimab and etesevimab, in the phase 1 and phase 2 portions of BLAZE-4, a randomized, single-dose clinical trial.

The following adverse reactions (i.e., adverse events assessed as causally related) have been observed in those who have received bebtelovimab, alone or in combination with bamlanivimab and etesevimab, at the authorized dose or higher:

- Infusion-related reactions (n=2, 0.3%)
- Pruritus (n=2, 0.3%)
- Rash (n=5, 0.8%)

The most common treatment-emergent adverse events observed in subjects treated with bebtelovimab, alone or in combination with bamlanivimab and etesevimab, at the authorized dose or higher, included nausea (0.8%) and vomiting (0.7%).

6.4 Required Reporting for Serious Adverse Events and Medication Errors

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events* and medication errors potentially related to bebtelovimab

within 7 calendar days from the healthcare provider's awareness of the event, using FDA Form 3500 (for information on how to access this form, see below). The FDA requires that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race)
- A statement "Bebtelovimab use for COVID-19 under Emergency Use Authorization (EUA)" under the "**Describe Event, Problem, or Product Use/Medication Error**" heading
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes).
- Patient's preexisting medical conditions and use of concomitant products
- Information about the product (e.g., dosage, route of administration, NDC #).

Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax to 1-800-FDA-0178, or
- Call 1-800-FDA-1088 to request a reporting form

In addition, please provide a copy of all FDA MedWatch forms to:

Eli Lilly and Company, Global Patient Safety
Fax: 1-317-277-0853
E-mail: mailindata_gsmtindy@lilly.com
Or call Eli Lilly and Company at 1-855-LillyC19 (1-855-545-5921) to report adverse events.

The prescribing health care provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of bebtelovimab.

*Serious adverse events are defined as:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- Other important medical event, which may require a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

7 DRUG INTERACTIONS

Bebtelovimab is not renally excreted or metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Severe hypersensitivity reactions and infusion-related reactions, have been observed with administration of bebtelovimab, including in pregnant patients *[see Warnings and Precautions (5.1)]*. There are risks to the mother and fetus associated with untreated COVID-19 in pregnancy as well as potential risks to the fetus associated with severe maternal hypersensitivity and infusion-related reactions *(see Clinical Considerations)*.

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Bebtelovimab should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy *(see Clinical Considerations)*.

Data
Nonclinical reproductive toxicity studies have not been performed with bebtelovimab. In tissue cross reactivity studies using human fetal tissues, no binding of clinical concern was detected for bebtelovimab. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, bebtelovimab has the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of bebtelovimab provides any treatment benefit or risk to the developing fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations
Disease-associated maternal and/or embryo-fetal risk
COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

Maternal Adverse Reactions
Pregnant patients who develop severe hypersensitivity and infusion-related reactions should be managed appropriately, including obstetrical care *[see Warnings and Precautions (5.1)]*.

8.2 Lactation

Risk Summary

There are no available data on the presence of bebtelovimab in human or animal milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for bebtelovimab and any potential adverse effects on the breastfed child from bebtelovimab or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

8.4 Pediatric Use

Bebtelovimab is not authorized for use in pediatric individuals under 12 years of age or weighing less than 40 kg. The safety and effectiveness of bebtelovimab have not been assessed in pediatric patients. The recommended dosing regimen in patients 12 years to less than 18 years of age, weighing at least 40 kg, is expected to result in comparable serum exposures of bebtelovimab as those observed in adults.

8.5 Geriatric Use

Of the 602 patients receiving bebtelovimab in BLAZE-4, 10.5% were 65 years of age and older and 3.3% were 75 years of age and older. Based on population PK analyses of samples from 573 patients over an age range of 14 to 89 years, there was no impact of age on PK. Therefore, there is no difference in the PK of bebtelovimab in geriatric patients compared to younger patients.

10 OVERDOSAGE

Doses up to 1750 mg of bebtelovimab (10 times the authorized dose of bebtelovimab) have been administered in clinical trials without dose-limiting toxicity. Treatment of overdose with bebtelovimab should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with bebtelovimab.

11 DESCRIPTION

Bebtelovimab is a human immunoglobulin G-1 (IgG1 variant) monoclonal antibody consisting of 2 identical light chain polypeptides composed of 215 amino acids each and 2 identical heavy chain polypeptides composed of 449 amino acids produced by a Chinese Hamster Ovary (CHO) stable bulk culture or cell line with a molecular weight of 144 kDa.

Bebtelovimab injection is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow to slightly brown solution in a single-dose vial for intravenous injection.

Each mL contains 87.5 mg of bebtelovimab, L-histidine (0.4 mg), L-histidine hydrochloride monohydrate (0.6 mg), sodium chloride (2.9 mg), sucrose (60 mg), polysorbate 80 (0.5 mg), and Water for Injection. The bebtelovimab solution has a pH range of 5.5-6.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bebtelovimab is a recombinant neutralizing human IgG1λ monoclonal antibody (mAb) to the spike protein of SARS-CoV-2 and is unmodified in the Fc region. Bebtelovimab binds the spike protein with a dissociation constant K_D = 0.046 to 0.075 nM and blocks spike protein attachment to the human ACE2 receptor with an IC_{50} value of 0.39 nM (0.056 mcg/mL).

12.2 Pharmacodynamics

The exposure-response relationships of bebtelovimab for viral loads and clinical outcomes are unknown.

12.3 Pharmacokinetics

A summary of PK parameters of bebtelovimab following administration of a single dose of 175 mg bebtelovimab is provided in Table 1.

Table 1: Pharmacokinetic Parameters of Bebtelovimab Administered IV in Adults and Pediatric Patients (12 years of age and older weighing at least 40 kg)

	Bebtelovimab (175 mg) N=585
Systemic Exposure	
Geometric Mean (%CV) C_{max}, mcg/mL	59.9 (31.9)
Geometric Mean (%CV) $C_{day\ 29}$, mcg/mL	4.55 (70.9)
Geometric Mean (%CV) AUC_{inf}, mcg day/mL	539 (41.5)
Distribution	
Geometric Mean (%CV) Vss (L)	4.55 (25.8)
Elimination	
Geometric Mean (%CV) Elimination Half-Life (day)	11.5 (27.0)
Geometric Mean (%CV) Clearance (L/day)	0.325 (41.5)

Abbreviations: CV = coefficient of variation; C_{max} = maximum concentration; $C_{day,29}$ = drug concentration on day 29; AUC_{inf} = area under the concentration versus time curve from zero to infinity; Vss = steady-state volume of distribution.

Specific Populations:
The PK profile of bebtelovimab was not affected by age, sex, race, or baseline viral load based on a population PK analysis. Body weight had no clinically relevant effect on the PK of bebtelovimab in adults with COVID-19 over the body weight range of 45 kg to 194 kg.

Patients with renal impairment
Renal impairment is not expected to impact the PK of bebtelovimab, since mAbs with molecular weight >69 kDa are known not to undergo renal elimination. Similarly, dialysis is not expected to impact the PK of bebtelovimab.

Patients with hepatic impairment
Bebtelovimab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as other IgG monoclonal antibodies and human endogenous IgG antibodies.

Based on population PK analysis, there is no significant difference in PK of bebtelovimab in patients with mild hepatic impairment compared to patients with normal hepatic function. Bebtelovimab has not been studied in patients with moderate or severe hepatic impairment.

Drug Interactions:
Bebtelovimab is not renally excreted or metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

12.4 Microbiology

Antiviral Activity
The cell culture neutralization activity of bebtelovimab against SARS-CoV-2 was measured in a dose-response model quantifying plaque reduction using cultured Vero E6 cells. Bebtelovimab neutralized the USA/WA/1/2020 isolate of SARS-CoV-2 with an estimated EC_{50} value = 0.044 nM (6.4 ng/mL).

Bebtelovimab demonstrated antibody-dependent cell-mediated cytotoxicity on Jurkat reporter cells expressing FcγRIIIa following engagement with target cells expressing spike protein. Bebtelovimab did not elicit complement-dependent cytotoxicity activity in cell-based assays.

Antibody Dependent Enhancement (ADE) of Infection
The risk that bebtelovimab could mediate viral uptake and replication by immune cells was studied in THP-1 and Raji cell lines and primary human macrophages. In general, experiments with bebtelovimab did not demonstrate productive viral infection in immune cells exposed to SARS-CoV-2 at concentrations of mAb down to 60,000-fold below the approximate EC_{50} value for neutralization.

Antiviral Resistance
There is a potential risk of treatment failure due to the development of viral variants that are resistant to bebtelovimab.

Nonclinical selection studies using a directed evolution of a yeast displayed Spike RBD identified that substitutions at residues K444, V445, G446, and P499 interfered with bebtelovimab's ability to block the Spike RBD:ACE-2 interaction. Pseudotyped virus-like particle (VLP) neutralization assays confirmed a 5-fold or greater reduction in susceptibility to bebtelovimab of viral variants with the following substitutions: K444E (>862), K444N (>1,901-fold), K444Q (208-fold), K444T (>1,814-fold), V445A (111-fold), V445F (369-fold), V445G (>730-fold), G446D (69-fold), G446R (7-fold), G446V (8-fold), P499H (>1,606-fold), P499R (>1,870-fold), and P499S (25-fold). In the context of Delta spike protein, G446V substitution had reduced susceptibility of 16.4-fold.

Pseudotyped VLP assessment using the full-length spike genes from different variant lineages indicate that bebtelovimab retains activity (<5-fold reduction) against the Alpha (B.1.1.7, UK origin), Beta (B.1.351, South Africa origin), Gamma (P.1, Brazil origin), Delta (B.1.617.2, India origin), Delta [+K417N] (AY.1/AY.2, India origin), Epsilon (B.1.427/B.1.429, California origin), Iota (B.1.526, New York origin), Kappa (B.1.617.1, India origin), Lambda (C.37, Peru origin), Omicron (B.1.1.529/BA.1, South Africa origin), Omicron [+R346K] (BA.1.1), Omicron BA.2, Omicron BA.2 [+L452Q] (BA.2.12.1), Omicron BA.2 [+D339H, G446S, N460K, R493Q (reversion)] (BA.2.75), Omicron BA.2 [BA.2.75+R346T+F486S] (BA.2.75.2), Omicron BA.4/BA.5, and Omicron BA.4 [+R346T] (BA.4.6/BF.7) variant lineages (Table 2). The Mu (B.1.621, Colombia origin) variant showed a reduction in susceptibility to bebtelovimab of 5.3-fold. The Omicron BA.5 [+N444T, N460K] (BQ.1),

and Omicron BA.5 [+R346T, N444T, N460K] (BQ.1.1) variants showed a large reduction in susceptibility to bebtelovimab of >672-fold.

Table 2: Bebtelovimab Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Spike Protein Variants

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested[a]	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y	No change[b]
B.1.351	South Africa	Beta	K417N + E484K + N501Y	No change[b]
P.1	Brazil	Gamma	K417T + E484K + N501Y	No change[b]
B.1.617.2/AY.3	India	Delta	L452R + T478K	No change[b]
AY.1/AY.2 (B.1.617.2 sublineages)	India	Delta [+K417N]	L452R + T478K + K417N	No change[b]
B.1.427/B.1.429	USA (California)	Epsilon	L452R	No change[b]
B.1.526[c]	USA (New York)	Iota	E484K	No change[b]
B.1.617.1	India	Kappa	L452R + E484Q	No change[b]
C.37	Peru	Lambda	L452Q + F490S	No change[b]
B.1.621	Colombia	Mu	R346K + E484K + N501Y	5.3
B.1.1.529/BA.1	South Africa	Omicron [BA.1]	G339D + S371L + S373P + S375F + K417N + N440K + G446S + S477N + T478K + E484A + Q493R + G496S + Q498R + N501Y + Y505H	No change[b]
BA.1.1	South Africa	Omicron [+R346K]	BA.1 + R346K	No change[b]
BA.2	South Africa	Omicron [BA.2]	G339D + S371F + S373P + S375F + T376A + D405N + R408S + K417N + N440K + S477N + T478K + E484A + Q493R + Q498R + N501Y + Y505H	No change[b]
BA.2.12.1	USA	Omicron [BA.2+L452Q]	BA.2 + L452Q	No change[b]
BA.2.75	India	Omicron [BA.2+D339H, G446S, N460K, R493Q (reversion)]	BA.2 + D339H + G446S + N460K + R493Q (reversion)	No change[b]
BA.2.75.2	India	Omicron [BA.2.75+R346T+F486S]	BA.2.75 + R346T + F486S	No change[b]
BA.4/BA.5	South Africa	Omicron [BA.4/BA.5]	G339D + S371F + S373P + S375F + T376A + D405N + R408S + K417N +	No change[b]

			N440K + L452R + S477N + T478K + E484A + F486V + Q498R + N501Y + Y505H	
BA.4.6/BF.7	USA/Belgium	Omicron [BA.4+R346T]	BA.4 + R346T	No change[b]
BQ.1	Nigeria	Omicron [BA.5+K444T+N460K]	BA.5 + K444T + N460K	>672[d]
BQ.1.1	Multiple	Omicron [BA.5+R346T+K444T+N460K]	BA.5 + R346T + K444T + N460K	>672[d]

[a] Key substitutions occurring in the receptor binding domain of spike protein are listed. Pseudotyped VLP contained the full-length spike protein reflective of the consensus sequence for each of the variant lineages with the exception of BA.2.75.2 which is a full-length spike of BA.2.75+R346T+F486S substitutions.

[b] No change: <5-fold reduction in susceptibility.

[c] Isolates of the B.1.526 lineage harbor several spike protein amino acid substitutions, and not all isolates contain the E484K substitution (as of February 2021).

[d] Bebtelovimab is unlikely to be active against this variant.

In authentic SARS-CoV-2 assays, bebtelovimab retained activity (<5-fold reduction) against variant virus isolates from the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2/AY.3), Omicron (B.1.1.529/BA.1), Omicron [+R346K] (BA.1.1), Omicron BA.2, Omicron BA.2 [+L452Q] (BA.2.12.1), Omicron BA.2 [+D339H, G446S, N460K, R493Q (reversion)] (BA.2.75), Omicron BA.4, Omicron BA.4 [+R346T] (BA.4.6), and Omicron BA.5 lineages, as well as SARS-CoV-2 (USA/WA/1/2020 isolate) engineered to express the L452R substitution present in the Epsilon (B.1.427/B.1.429) lineage or the E484K substitution present in the Iota (B.1.526) lineage (Table 3).

Table 3: Authentic[a] SARS-CoV-2 Neutralization Data for Bebtelovimab

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested[b]	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y	No change[c]
B.1.351	South Africa	Beta	K417N, E484K, N501Y	No change[c,d]
P.1	Brazil	Gamma	K417T, E484K, N501Y	No change[c]
B.1.617.2/AY.3	India	Delta	L452R, T478K	No change[c,d]
B.1.427/B.1.429	USA (California)	Epsilon	L452R	No change[c]
B.1.526[e]	USA (New York)	Iota	E484K	No change[c]
B.1.1.529/BA.1	South Africa	Omicron	G339D + S371L + S373P + S375F + K417N + N440K + G446S + S477N + T478K + E484A + Q493R + G496S + Q498R + N501Y + Y505H	No change[c,d]
BA.1.1	South Africa	Omicron [+R346K]	BA.1 + R346K	No change[c]
BA.2	South Africa	Omicron [BA.2]	G339D + S371F + S373P + S375F + T376A + D405N + R408S + K417N + N440K + S477N + T478K + E484A + Q493R + Q498R + N501Y + Y505H	No change[c,d]
BA.2.12.1	USA	Omicron [BA.2+L452Q]	BA.2 + L452Q	No change[c]
BA.2.75	India	Omicron [BA.2+D339H, G446S, N460K, R493Q (reversion)]	BA.2 + D339H + G446S + N460K + R493Q (reversion)	No change[c,d]
BA.4	South Africa	Omicron [BA.4]	G339D + S371F + S373P + S375F + T376A + D405N + R408S + K417N + N440K + L452R + S477N + T478K + E484A + F486V + Q498R + N501Y + Y505H	No change[c]
BA.4.6	USA	Omicron [BA.4+R346T]	BA.4 + R346T	No change[c]
BA.5	South Africa	Omicron [BA.4/BA.5]	G339D + S371F + S373P + S375F + T376A + D405N + R408S + K417N + N440K + L452R + S477N + T478K + E484A + F486V + Q498R + N501Y + Y505H	No change[c]

[a] The B.1.1.7, B.1.351, B.1.617.2, B.1.1.529/BA.1, and BA.2 variants were assessed using cell culture-expanded virus isolates and tested using a plaque reduction assay; the B.1.351, P.1, B.1.617.2, B.1.1.529/BA.1, BA.1.1, BA.2, BA.2.12.1, BA.2.75, BA.4, BA.4.6, and BA.5 variants were assessed using cell culture-expanded isolates and tested using a microneutralization assay with a CPE-based endpoint titer to determine the $IC_{>99}$; the B.1.526/E484K, B.1.427/B.1.429/L452R, and BA.2.75 spike substitutions were assessed using recombinant SARS-CoV-2 (USA/WA/1/2020 isolate with E484K, L452R, or full spike of BA.2.75) and tested using a plaque reduction assay.

[b] Key substitutions occurring in receptor binding domain of spike protein which are associated with each lineage.

[c] No change: <5-fold reduction in susceptibility when compared to ancestral control isolate using the same methodology.

[d] These viral variants have been tested with two different neutralization methodologies, both yielding <5-fold reductions in susceptibility.

[e] Isolates of the B.1.526 lineage harbor several spike protein amino acid substitutions, and not all isolates contain the E484K substitution (as of February 2021).

Genotypic analysis and phenotypic testing are ongoing to monitor for potential bebtelovimab-resistance-associated spike variations in clinical trials. Baseline sequencing data are available for 611 of the subjects in the BLAZE-4 (Arms 9-14) Study. Of these, 552 (90.3%) were infected with a variant of interest or concern, as designated by the WHO. No subject was infected with virus of the Omicron lineage or sub-lineages. The majority of subjects in the trial were infected with Delta (49.9%) and Alpha (28.6%). These were distributed across the treatment groups with Delta and Alpha infection rates of 60.2% and 23.1% in placebo, 31.3% and 41.8% in bebtelovimab alone arms, and 58.3% and 21.9% in the bebtelovimab with bamlanivimab and etesevimab arms, respectively. Gamma and Mu infections comprised 5.6% and 3.8% of the total infections respectively. Subjects infected with Beta, Delta [+K417N], Iota, and Lambda variants were the minority with 0.5%, 0.8%, 0.7%, and 0.5% total infections, respectively. All other subjects in the trial had SARS-CoV-2 infections from either non-WHO classified viruses (3.3%), or the lineage was not able to be determined based on the baseline sequence data (6.4%). Detection of viral variants with a 5-fold or greater reduction in susceptibility to bebtelovimab at baseline has been rare, with only one G446V substitution (8-fold shift) observed transiently out of 611 subjects in the BLAZE-4 (Arms 9-14) study that had baseline sequencing available (0.2%, 1/611).

Analysis of treatment-emergent variants focused on changes at amino acid positions with known phenotypically confirmed bebtelovimab-associated variations (i.e., K444, V445, G446, and P499) in serial viral samples obtained in the BLAZE-4 (Arms 9-14) bebtelovimab Phase 2 Study. Treatment-emergent substitutions detected at ≥15% or ≥50% allele fractions at these positions included K444E/N, V445G, G446V, and P499H/R. These substitutions resulted in a 5-fold or greater reduction in susceptibility to bebtelovimab in pseudotyped VLP assays: K444E (>862), K444N (>1,901-fold), V445G (>730-fold), G446V (8-fold), P499H (>1,606-fold), and P499R (>1,870-fold). Additional treatment-emergent substitutions detected at ≥15% or >50% allele fractions outside the epitope in at least 2 subjects included C379F (n=2) and G404C (n=2), seen in bebtelovimab in combination with bamlanivimab and etesevimab arms.

Considering all substitutions detected at ≥15% allele fraction at positions K444, V445, G446, and P499, 5.5% (11/199) of subjects treated with bebtelovimab alone harbored a variant that was treatment-emergent. This was more frequent than observed in the placebo arm (0%, 0/112), or when bebtelovimab was administered together with bamlanivimab and etesevimab (0.3%, 1/312). The appearance of these treatment-emergent bebtelovimab resistance-associated substitutions was associated with higher viral loads in the subjects in whom they were detected, but none of these subjects were hospitalized. The majority of the variants were first detected on Day 5 (n=3) and Day 7 (n=6) following treatment initiation.

It is possible that bebtelovimab resistance-associated variants could have cross-resistance to other mAbs targeting the receptor binding domain of SARS-CoV-2. The clinical impact is not known.

Immune Response Attenuation

There is a theoretical risk that antibody administration may attenuate the endogenous immune response to SARS-CoV-2 and make patients more susceptible to re-infection.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis, mutagenesis, and reproductive toxicology studies with bebtelovimab have not been conducted.

13.2 Animal Toxicology and/or Pharmacology

In toxicology studies, bebtelovimab had no adverse effects when administered intravenously to rats.

In tissue cross reactivity studies using human adult and fetal tissues, no binding of clinical concern was detected for bebtelovimab.

Antiviral Activity In Vivo
Prophylactic administration of bebtelovimab to male Syrian golden hamsters (n=5 to 8 per group) resulted in 2 to 4 $\log_{10}$ decreases in viral genomic RNA and viral replication (subgenomic RNA) from lung tissue, as well as decreases in lung weight and improvements in body weight compared to controls.

The applicability of these findings to a treatment setting is not known.

14 CLINICAL STUDIES

The data supporting this EUA for treatment of mild-to-moderate COVID-19 are primarily based on analyses of data from the Phase 2 portion of the BLAZE-4 trial (NCT04634409) that enrolled both low risk and high risk subjects (treatment arms 9-14). This trial evaluated the clinical efficacy data from subjects receiving 175 mg bebtelovimab alone and together with 700 mg bamlanivimab and 1,400 mg of etesevimab.

BLAZE-4 is a Phase 1/2, randomized, single-dose clinical trial evaluating treatment of subjects with mild-to-moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized). Efficacy of bebtelovimab, alone and together with bamlanivimab and etesevimab, was evaluated in low risk adults (i.e., those not at high-risk to progress to severe COVID-19) in a randomized part of the trial which included a placebo control arm (treatment arms 9-11). Low risk adults were randomized with a 1:1:1 ratio. High-risk adults and pediatric subjects (12 years of age and older weighing at least 40 kg) received open-label active treatments. One cohort of high risk subjects was randomized with 2:1 ratio (treatment arms 12 and 13). Another cohort of high risk subject was enrolled with no randomization (treatment arm 14). The trial enrolled subjects who were not hospitalized and had 1 or more COVID-19 symptoms that were at least mild in severity. Treatment was initiated within 3 days of obtaining the clinical sample for the first positive SARS-CoV-2 viral infection determination.

BLAZE-4 was conducted prior to the emergence of the Omicron variant. No subject in BLAZE-4 was infected with virus of the Omicron lineage or sub-lineages. The majority of participants in the trial were infected with Delta (49.8%) and Alpha (28.6%).

14.1 Phase 2 Data from the Placebo-Controlled Portion of BLAZE-4 (Low Risk Subjects; Treatment Arms 9-11)

In this portion of the trial, adult subjects were treated with a single infusion of bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg (N=127), 175 mg bebtelovimab alone (N=125), or placebo (N=128). The majority (96.8%) of the subjects enrolled in these treatment arms did not meet the criteria for high-risk.

At baseline, median age was 35 years (with 1 placebo subject aged 65 or older); 56% of subjects were female, 79% were White, 36% were Hispanic or Latino, and 19% were Black or African American. Subjects had mild (74%) to moderate (26%) COVID-19; the mean duration of symptoms was 3.6 days; mean viral load by cycle threshold (CT) was 24.63 at baseline. The baseline demographics and disease characteristics were well balanced across treatment arms with the exception of baseline serology status. A higher percentage of subjects in the placebo arm were positive for baseline serology (15% vs. 9% for bamlanivimab, etesevimab, and bebtelovimab together, and 7% for bebtelovimab alone). Participants enrolled in these treatment arms had not received SARS-CoV-2 vaccine at baseline.

The primary endpoint was the proportion of subjects with persistently high viral load (PHVL) by Day 7. PHVL occurred in 26 subjects treated with placebo (21%) as compared to 16 (13%) subjects treated with bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg together [p=0.098], and 17 (14%) subjects treated with bebtelovimab 175 mg alone [p=0.147], a 38% (95% CI: -9%, 65%) and 34% (95% CI: -15%, 62%) relative reduction, respectively.

Secondary endpoints included mean change in viral load from baseline to Day 3, 5, 7, and 11 (Figure 1).

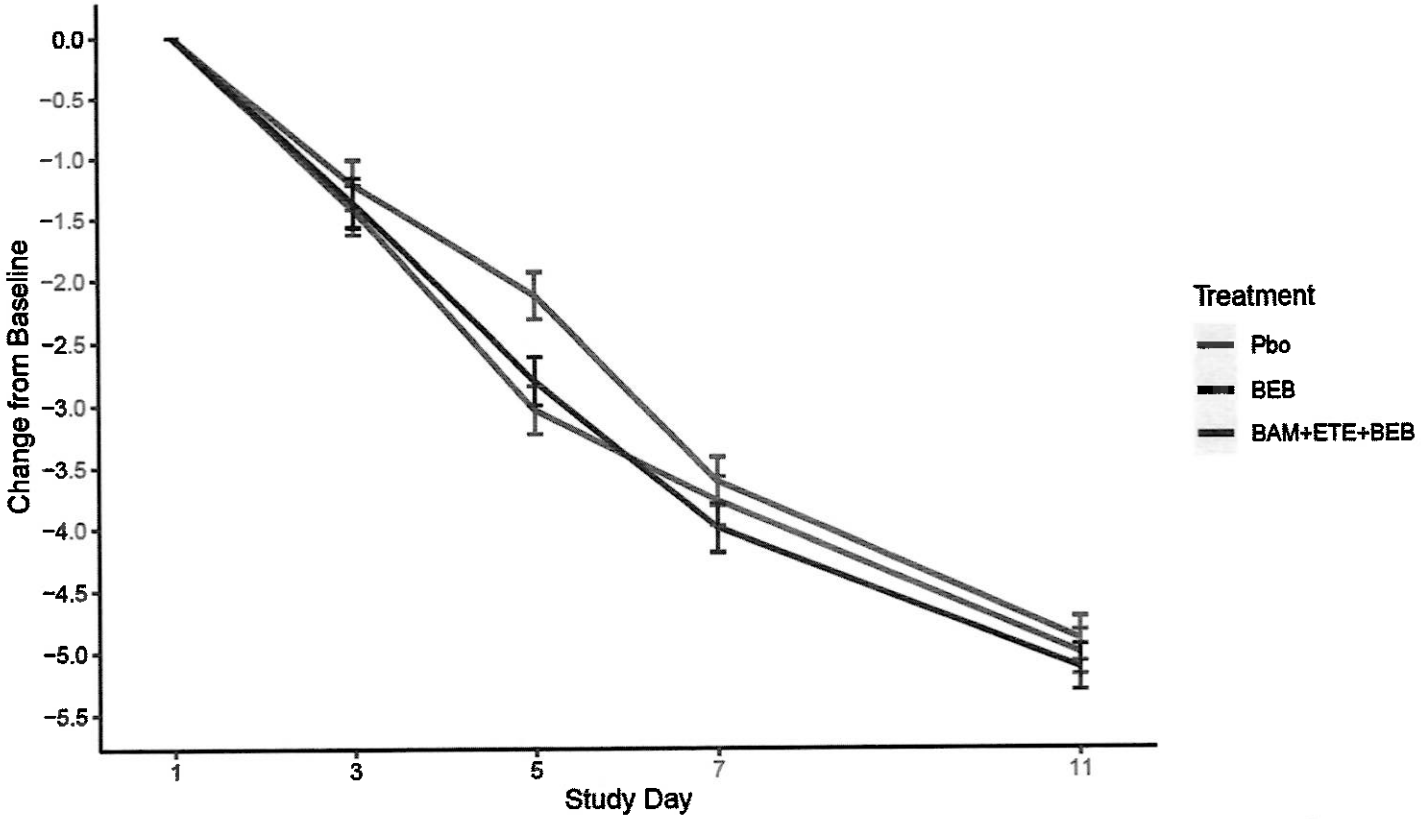

Figure 1: SARS-CoV-2 Viral Load Change from Baseline (Mean ± SE) by Visit from the Placebo-Controlled Portion of BLAZE-4 in Low Risk Adults (700 mg bamlanivimab, 1,400 mg etesevimab, 175 mg bebtelovimab together and 175 mg bebtelovimab alone).

For the secondary endpoint of COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death by any cause by Day 29, these events occurred in 2 (1.6%) subjects treated with placebo as compared with 3 (2.4%) events in subjects treated with bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg together and 2 (1.6%) events in subjects treated with bebtelovimab 175 mg alone. There was 1 subject treated with bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg together who died on Day 5. Conclusions are limited as COVID-19 related hospitalization and death rates are expected to be low in a low risk population.

The median time to sustained symptom resolution as recorded in a trial specific daily symptom diary was 7 days (95%CI: 6, 8 days) for subjects treated with bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg together [p=0.289] and 6 days (95% CI: 5, 7 days) for subjects treated with bebtelovimab 175 mg alone [p=0.003] as compared with 8 days (95% CI: 7, 9 days) for subjects treated with placebo. Symptoms assessed were cough, shortness of breath, feeling feverish, fatigue, body aches and pains, sore throat, chills, and headache. Sustained symptom resolution was defined as absence of any of these symptoms, except for allowance of mild fatigue and cough, in two consecutive assessments.

14.2 Phase 2 Data from the Randomized, Open-Label Portion of BLAZE-4 (High Risk Subjects; Treatment Arms 12-13)

In this portion of the trial, subjects were treated with a single infusion of bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg (N=50) or 175 mg bebtelovimab alone (N=100). The majority (91.3%) of the subjects enrolled in these dose arms meet the criteria for high-risk.

At baseline, median age was 50 years (with 28 subjects aged 65 or older); 52% of subjects were female, 75% were White, 18% were Hispanic or Latino, and 18% were Black or African American. Subjects had mild (75%) to moderate (25%) COVID-19; the mean duration of symptoms was 4.7 days; mean viral load by cycle threshold (CT) was 26.66 at baseline; and 20.7% of subjects had at least one dose of a COVID-19 vaccine. There were 2 pediatric patients enrolled (ages 14 and 17), one in each treatment arm. The baseline demographics and disease characteristics were well balanced across treatment groups.

The primary objective for these treatment arms was to characterize the safety profile of bebtelovimab 175 mg by evaluating adverse events and serious adverse events. Efficacy endpoints included the proportion of subjects with COVID-19 related hospitalization or death by any cause by Day 29, mean change in viral load from baseline to Days 3, 5, 7, and 11 and time to sustained symptom resolution.

The proportion of subjects with COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death by any cause was assessed by Day 29. Events occurred in 2 (4%) subjects treated with bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg together and 3 (3%) subjects treated with bebtelovimab 175 mg alone. There was 1 subject treated with bebtelovimab 175 mg alone who died on Day 34.

Mean changes in viral load from baseline to Day 3, 5, 7, and 11 are shown in Figure 2.

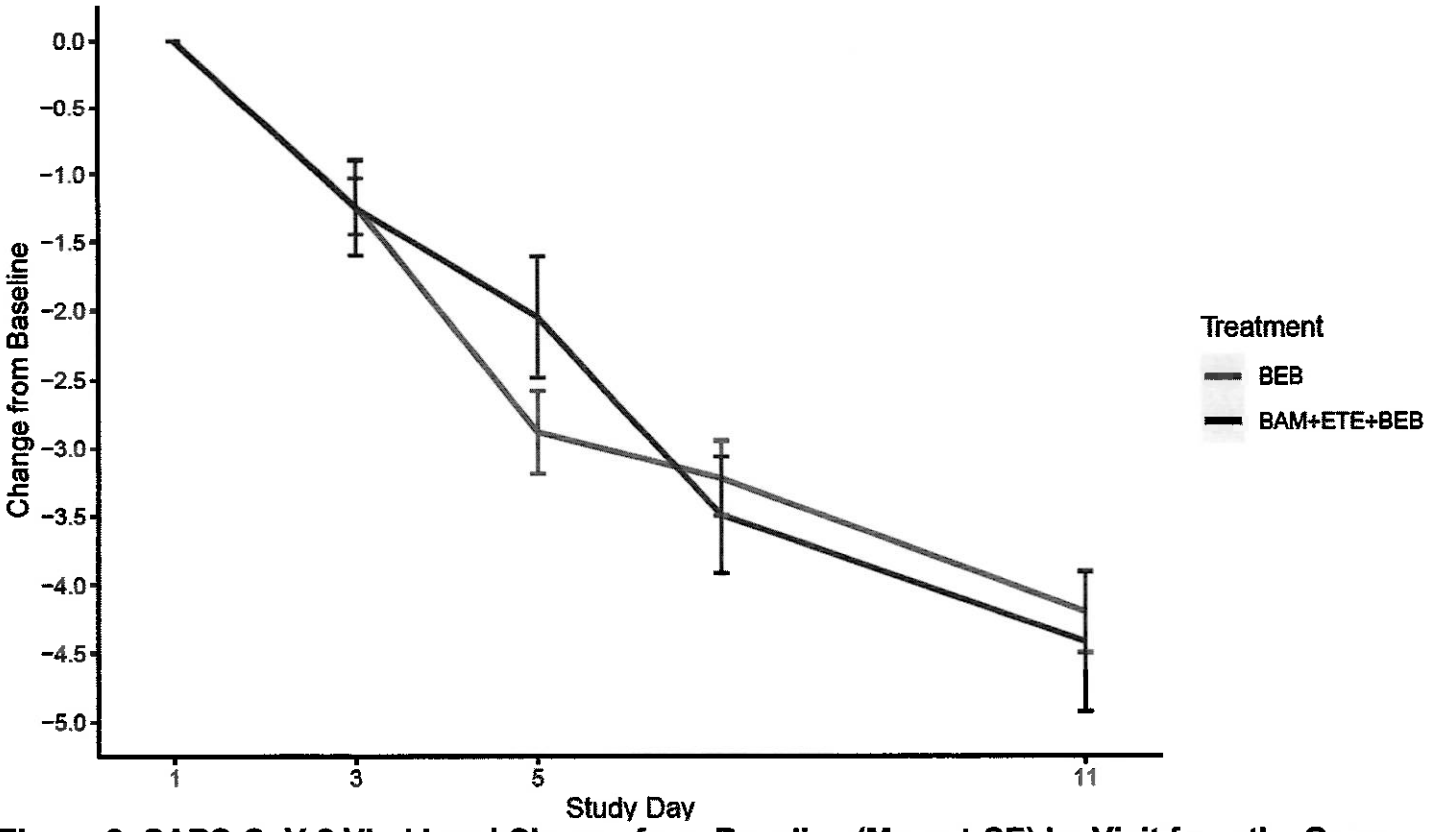

Figure 2: SARS-CoV-2 Viral Load Change from Baseline (Mean ± SE) by Visit from the Open-Label Portion of BLAZE-4 (700 mg bamlanivimab, 1,400 mg etesevimab, 175 mg bebtelovimab together and 175 mg bebtelovimab alone).

The median time to sustained symptom resolution as recorded in a trial specific daily symptom diary was 7 days for subjects treated with bebtelovimab 175 mg alone.

14.3 Phase 2 Data from the Non-Randomized, Open-Label Portion of BLAZE-4 (High Risk Subjects; Treatment Arm 14)

In this portion of the trial, subjects were treated with a single infusion of bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg (N=176). The majority (97.7%) of the subjects enrolled meet the criteria for high-risk.

At baseline, median age was 51 years (with 35 subjects aged 65 or older); 56% of subjects were female, 80% were White, 28% were Hispanic or Latino, and 16% were Black or African American. Subjects had mild (73%) to moderate (27%) COVID-19; the mean duration of symptoms was 4 days; mean viral load by cycle threshold (CT) was 23.45 at baseline; and 31% of subjects had at least one dose of a COVID-19 vaccine. There were 2 pediatric patients enrolled (ages 14 and 15).

The primary objective for this treatment arm was to characterize the safety profile of bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg by evaluating adverse events and serious adverse events. Efficacy endpoints included the proportion of subjects with COVID-19 related hospitalization or death by any cause by Day 29, mean change in viral load from baseline to Days 3, 5, 7, and 11, and time to sustained symptom resolution.

The proportion of subjects with COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death by any cause was assessed by Day 29. Events occurred in 3 subjects (1.7%), and no subjects died.

Mean changes in viral load from baseline to Day 3, 5, 7, and 11 were -1.4, -3.1, -4.0, and -5.4, respectively.

The median time to sustained symptom resolution as recorded in a trial specific daily symptom diary was 8 days.

14.4. Overall Benefit-Risk Assessment and Limitations of Data Supporting the Benefits of the Product

Based on the data from BLAZE-4, bebtelovimab has been shown to improve symptoms in patients with mild-to-moderate COVID-19. Additionally, a reduction in SARS-CoV-2 viral load on Day 5 was observed relative to placebo, though the clinical significance of this is unclear. The placebo-controlled phase 2 data are limited by enrollment of only subjects without risk factors for progression to severe COVID-19, and the trial was not powered or designed to determine a difference in the clinical outcomes of hospitalization or death between the placebo and bebtelovimab treatment arms *[see Clinical Studies (14.1)]*. Bebtelovimab has been studied in individuals who have risk factors for progression to severe COVID-19, but the efficacy analyses are limited due to the lack of a concurrent placebo control arm for this population *[see Clinical Studies (14.2, 14.3)]*.

However, based on the totality of scientific evidence available, including the available Phase 2 and pharmacokinetic data, along with the nonclinical viral neutralization data for Omicron and other variants of concern, it is reasonable to believe that bebtelovimab may be effective for the treatment of patients with mild-to-moderate COVID-19 to reduce the risk of progression to hospitalization or death. In addition, the mechanism of action for bebtelovimab is similar to other neutralizing SARS-CoV-2 monoclonal antibodies, including bamlanivimab and etesevimab, that have data from Phase 3 clinical trials showing a reduction in hospitalization or death in high risk patients infected with other SARS-CoV-2 variants. The safety profile of bebtelovimab is acceptable with monitorable risks and is comparable to other SARS-CoV-2 monoclonal antibodies, including bamlanivimab and etesevimab. Considered together, these data support that the known and potential benefits of treatment with bebtelovimab outweigh the known and potential risks in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

Clinical data summarized above were similar for bebtelovimab alone as compared to the combination of bamlanivimab, etesevimab and bebtelovimab administered together. Bebtelovimab retains activity against currently circulating variants *[see Microbiology (12.4)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Bebtelovimab injection is a sterile, preservative-free clear to opalescent and colorless to slightly yellow to slightly brown solution supplied in a single-dose vial.

Antibody	Concentration	Package Size	NDC
Bebtelovimab	175 mg/2 mL (87.5 mg/mL)	One vial per carton	0002-7589-01

Storage and Handling
Bebtelovimab is preservative-free. Discard unused portion.

Store unopened vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.

DO NOT FREEZE, SHAKE, OR EXPOSE TO DIRECT LIGHT.

17 PATIENT COUNSELING INFORMATION

As a healthcare practitioner, you must communicate to the patient and/or caregiver information consistent with the "FACT SHEET FOR PATIENTS, PARENTS AND CAREGIVERS" and provide them with a copy of this Fact Sheet prior to administration of bebtelovimab. However, if providing this information will delay the administration of bebtelovimab to a degree that would endanger the life of a patient, the information must be provided to the parent and/or caregiver as soon as feasible after bebtelovimab administration.

Remind patients treated with bebtelovimab that they should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect "high touch" surfaces, and frequent handwashing) according to CDC guidelines.

For additional information visit: www.LillyAntibody.com/bebtelovimab

If you have questions, please contact: 1-855-LillyC19 (1-855-545-5921)

18 MANUFACTURER INFORMATION

Eli Lilly and Company, Indianapolis, IN 46285, USA

Literature revised November 04, 2022

A2.0-BEB-0008-EUA HCP-2001104

FDA U.S. FOOD & DRUG ADMINISTRATION

January 24, 2022

Regeneron Pharmaceuticals, Inc.
Attention: Yunji Kim, PharmD
Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591

RE: Emergency Use Authorization 091

Dear Dr. Kim:

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19).[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[2]

On November 21, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of REGEN-COV (casirivimab and imdevimab, administered together)[3] for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization. Casirivimab and imdevimab are recombinant human IgG1 monoclonal antibodies that target the receptor binding domain of the spike protein of SARS-CoV-2. They are investigational drugs and are not approved for any indication.

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[1] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3.* February 4, 2020.

[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).

[3] The November 21, 2020 EUA referred to the authorized product as "casirivimab and imdevimab, administered together". Regeneron subsequently requested, and FDA concurred, that the authorized labeling be revised to add references to authorized products' trade name, "REGEN-COV".

FDA reissued the Letter of Authorization on the following dates: February 3, 2021,[4] February 25, 2021,[5] June 3, 2021,[6] July 30, 2021,[7] September 9, 2021,[8] and November 17, 2021.[9]

On January 24, 2022, again having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the November 17, 2021 letter in its entirety, to further limit the use of REGEN-COV for treatment of COVID-19 or as post-exposure prophylaxis of COVID-19 to exclude geographic regions where, based on available information including variant susceptibility to this drug and regional variant frequency, infection or exposure is likely due to a variant that is non-susceptible to REGEN-COV. Corresponding revisions have also been made to the authorized Fact Sheets.

Based on the review of the analysis of phase 3 data from COV-2067[10] (NCT04425629), a phase 1/2/3 randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of a single intravenous infusion of 600 mg casirivimab and 600 mg imdevimab in outpatients (non-hospitalized) with SARS-CoV-2 infection, it is reasonable to believe that REGEN-COV may be effective for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral

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[4] In the February 3, 2021 revision, FDA revised the condition on requesting changes to this authorization, including changes to the authorized Fact Sheets. New conditions were also incorporated relating to the development of instructional or educational materials, as well as certain mandatory reporting requirements for healthcare facilities and providers. In addition to certain editorial and/or clarifying revisions, the Fact Sheet for Healthcare Providers was revised to include information on the new mandatory reporting requirements on therapeutics information and utilization data for healthcare facilities and providers. Updated safety information and details on possible side effects were also incorporated into the authorized Fact Sheets.

[5] In the February 25, 2021 revision, FDA revised the condition on instructional and educational materials. New conditions were also incorporated on the establishment of a process for monitoring genomic databases for the emergence of global viral variants of SARS-CoV-2 and the assessment, if requested by FDA, of the activity of the authorized REGEN-COV against any global SARS-CoV-2 variant(s) of interest.

[6] In the June 3, 2021 revision, FDA revised the authorized use statement for REGEN-COV. Additionally, FDA authorized a change in dosing of REGEN-COV from 2400 mg (1200 mg casirivimab and 1200 mg imdevimab) to 1200 mg (600 mg casirivimab and 600 mg imdevimab), and the addition of a new presentation consisting of a single vial containing casirivimab and imdevimab co-formulated in a 1:1 ratio for either intravenous infusion or subcutaneous injection. New conditions were incorporated on the provision of samples of the authorized REGEN-COV to the U.S. Department of Health and Human Services, upon request, and the submission of certain genomic sequencing and virology information to the FDA by a specified date. Revisions to existing conditions on advertising and promotion and manufacturing practices and other editorial changes were also incorporated.

[7] In the July 30, 2021 revision, FDA authorized REGEN-COV for emergency use as post-exposure prophylaxis for COVID-19 in certain adults and pediatric individuals. Clarifying revisions to the conditions on good manufacturing practices as well as advertising and promotion were also incorporated.

[8] In the September 9, 2021 revision, FDA authorized a co-packaged presentation of REGEN-COV which consists of individual vials of both casirivimab and imdevimab inside a single carton. FDA also authorized a document entitled *Casirivimab and Imdevimab Co-Packaged Product Quick Reference Guide* that must accompany in hardcopy format the authorized co-packaged formulation of REGEN-COV that is labeled "For pandemic use". Revisions to the Fact Sheet for Healthcare Providers associated with the co-packaged presentation of REGEN-COV and clarifying revisions on the preparation of more than one dose from a single-dose vial were also incorporated.

[9] In the November 17, 2021 revision, FDA revised the product description in this Letter of Authorization with updated storage and handling information for the authorized dose pack bags of REGEN-COV, co-packaged REGEN-COV, and subcutaneous injection presentation of REGEN-COV. Corresponding revisions on storage and handling of the subcutaneous injection presentation of REGEN-COV and minor revisions to section 15 ("Virology") were also incorporated in the Fact Sheet for Healthcare Providers.

[10] Referred to as trial R10933-10987-COV-2067 in previous iterations of this Letter of Authorization.

testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and that, when used under the conditions described in this authorization, the known and potential benefits of REGEN-COV outweigh the known and potential risks of such product.

Additionally, based on the review of the topline analysis of phase 3 data from COV-2069 (NCT04452318), a phase 3 randomized, double-blind, placebo-controlled trial in household contacts with close exposure to a household member known to be infected with SARS-CoV-2 (index case), but who were themselves asymptomatic; and the analysis of phase 1 data from COV-2093 (NCT 04519437), an ongoing, phase 1, randomized, double-blind, placebo-controlled clinical trial assessing the safety and pharmacokinetics of repeat subcutaneous doses of REGEN-COV in subjects who are SARS-CoV-2 negative at baseline, it is reasonable to believe that REGEN-COV may be effective for use as post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (Section II), and that, when used under such conditions, the known and potential benefits of REGEN-COV outweigh the known and potential risks of such product.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of REGEN-COV for treatment and as post-exposure prophylaxis of COVID-19, as described in the Scope of Authorization (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of REGEN-COV for treatment and as post-exposure prophylaxis of COVID-19, when administered as described in the Scope of Authorization (Section II), meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

1. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe the following:

    - REGEN-COV may be effective for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, as further described in the Scope of Authorization (Section II)

    - REGEN-COV may be effective for use as post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, as further described in the Scope of Authorization (Section II)

And that, when used under the conditions described in the Scope of Authorization (Section II), the known and potential benefits of REGEN-COV outweigh the known and potential risks of such products; and

3. There is no adequate, approved, and available alternative to the emergency use of REGEN-COV for treatment and as post-exposure prophylaxis of COVID-19, as described in the Scope of Authorization (Section II).[11]

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Distribution of the authorized REGEN-COV will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Regeneron will supply REGEN-COV to authorized distributor(s)[12], who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed;

Treatment of COVID-19

- REGEN-COV will be used only by healthcare providers to treat mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19, including hospitalization or death;

  The monoclonal antibodies that comprise REGEN-COV, casirivimab and imdevimab, may only be administered together;

- REGEN-COV is **not** authorized for use in the following patient populations[13]:
  - Adults or pediatric patients who are hospitalized due to COVID-19, or
  - Adults or pediatric patients who require oxygen therapy due to COVID-19, or
  - Adults or pediatric patients who require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity.

- REGEN-COV is **not** authorized for treatment of mild to moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible

[11] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.
[12] "Authorized Distributor(s)" are identified by Regeneron as an entity or entities allowed to distribute authorized REGEN-COV.
[13] Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

SARS-CoV-2 variant, based on available information including variant susceptibility to this drug and regional variant frequency.[14]

- REGEN-COV may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

- REGEN-COV is authorized for intravenous infusion. Subcutaneous injection is authorized as an alternative route of administration when intravenous infusion is not feasible and would lead to delay in treatment.

- The use of REGEN-COV covered by this authorization must be in accordance with the authorized Fact Sheets.

Post-Exposure Prophylaxis

- REGEN-COV may only be used in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

    - not fully vaccinated[15] **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications[16]) **and**
        - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[17] **or**
        - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other

[14] FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility (see, e.g., section 15 of authorized Fact Sheet for Healthcare Providers), and the CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions. FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.

[15] Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as the Johnson & Johnson/ Janssen vaccine). See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated.

[16] See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html

[17] Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example). See this website for additional details: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html

individuals in the same institutional setting (for example, nursing homes, prisons).

- The monoclonal antibodies that comprise REGEN-COV, casirivimab and imdevimab, may only be administered together;

- REGEN-COV is **not** authorized for post-exposure prophylaxis of COVID-19 in geographic regions where exposure is likely to have been to a non-susceptible SARS-CoV-2 variant, based on available information including variant susceptibility to these drugs and regional variant frequency.[18]

- REGEN-COV may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

- REGEN-COV is authorized for either intravenous infusion or subcutaneous injection when administered for post-exposure prophylaxis under this authorization.

- The use of REGEN-COV covered by this authorization must be in accordance with the authorized Fact Sheets.

- Post-exposure prophylaxis with REGEN-COV (casirivimab with imdevimab) is **not** intended to be a substitute for vaccination against COVID-19.

- REGEN-COV is **not** authorized for pre-exposure prophylaxis for prevention of COVID-19.

Product Description

Casirivimab and imdevimab are recombinant neutralizing human IgG1 monoclonal antibodies that target the receptor binding domain of the spike protein of SARS-CoV-2. REGEN-COV is available in three distinct presentations: (1) REGEN-COV co-packaged in an individual carton, (2) REGEN-COV in dose pack bags, and (3) co-formulated solution of REGEN-COV.[19]

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[18] Supra at Note 14.

[19] Individual vials of casirivimab and imdevimab distributed in interstate commerce prior to the reissuance of this letter on February 3, 2021 remain authorized for emergency use. FDA is not requiring that such product be repackaged given the public health need for the product. The use of the individual vials of casirivimab and imdevimab must be consistent with the terms and conditions of this authorization. Individual vial labels for casirivimab and imdevimab and carton labeling may be clearly marked with either "Caution: New Drug - Limited by Federal (or United States) law to investigational use" or with "For use under Emergency Use Authorization (EUA)". Some vial labels and carton labeling of casirivimab and imdevimab may be instead labeled with the Investigational New Drug (IND) clinical trial code name as "REGN10933" and "REGN10987", respectively.

(1) *Co-packaged REGEN-COV:* Co-packaged REGEN-COV is comprised of one vial each of both casirivimab and imdevimab inside a single carton. Individual vial and carton container labeling for casirivimab and imdevimab covered in the authorized co-packaged presentation will be clearly marked with either "For pandemic use" or "For Use under Emergency Use Authorization."

Casirivimab is available as 300 mg/2.5 mL (120 mg/mL) or 1332 mg/11.1 mL (120 mg/mL) sterile, preservative-free aqueous solution to be diluted prior to infusion. Imdevimab is available as 300 mg/2.5 mL (120 mg/mL) or 1332 mg/11.1 mL (120 mg/mL) sterile, preservative-free aqueous solution to be diluted prior to infusion. Co-packaged REGEN-COV supplied in the 1332 mg/11.1 mL strength presentation will include a sufficient number of vials of casirivimab and imdevimab to prepare more than one dose.

The authorized storage and handling information for the co-packaged REGEN-COV is included in the authorized Fact Sheet for Healthcare Providers.

(2) *Dose pack bags:* Dose pack bags of REGEN-COV will include a sufficient number of vials of casirivimab and imdevimab to prepare more than one dose. Individual vials and carton container labeling for casirivimab and imdevimab included in dose pack bags are clearly marked "For Use under Emergency Use Authorization." Casirivimab and imdevimab are recombinant neutralizing human IgG1 monoclonal antibodies that target the receptor binding domain of the spike protein of SARS-CoV-2.

Casirivimab is available as 300 mg/2.5 mL (120 mg/mL) or 1332 mg/11.1 mL (120 mg/mL) sterile, preservative-free aqueous solution to be diluted prior to infusion. Imdevimab is available as 300 mg/2.5 mL (120 mg/mL) or 1332 mg/11.1 mL (120 mg/mL) sterile, preservative-free aqueous solution to be diluted prior to infusion.

The authorized storage and handling information for the dose pack bags of REGEN-COV is included in the authorized Fact Sheet for Healthcare Providers.

(3) *Co-formulated solution of REGEN-COV*: The co-formulated solution of REGEN-COV contains two antibodies in a 1:1 ratio in a single dose vial consisting of 600 mg casirivimab and 600 mg of imdevimab per 10 mL (60 mg/60 mg per mL). Individual vials of co-formulated REGEN-COV are clearly marked "For Use under Emergency Use Authorization."

Co-formulated casirivimab and imdevimab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution. Co-formulated REGEN-COV may be administered via intravenous infusion or subcutaneous injection.

The authorized storage and handling information for the co-formulated solution of REGEN-COV is included in the authorized Fact Sheet for Healthcare Providers.

Any presentation of REGEN-COV described above may be prepared for intravenous infusion or subcutaneous injection.[20]

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[20] Certain carton labeling for the co-packaged presentation of REGEN-COV is labeled as "casirivimab and

REGEN-COV is authorized for emergency use with the following product-specific information required to be made available to healthcare providers and patients/caregivers, respectively, through Regeneron's website at www.REGENCOV.com:

- Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of REGEN-COV (casirivimab and imdevimab)

- Fact Sheet for Patients, Parents and Caregivers: Emergency Use Authorization (EUA) of REGEN-COV (casirivimab and imdevimab) for Coronavirus Disease 2019 (COVID-19)

The co-packaged presentation of REGEN-COV that is labeled "For pandemic use" is also authorized for emergency use with the document entitled *Casirivimab and Imdevimab Co-Packaged Product Quick Reference Guide*, which must accompany this authorized co-packaged presentation of REGEN-COV in hardcopy format.

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of REGEN-COV, when used for treatment and as post-exposure prophylaxis of COVID-19 as described in this Scope of Authorization (Section II), outweigh the known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that REGEN-COV may be effective for treatment and as post-exposure prophylaxis of COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that REGEN-COV (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of your product under an EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), REGEN-COV is authorized for treatment and as post-exposure prophylaxis of COVID-19 as described in this Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

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imdevimab 120 mg/mL concentrate for solution for infusion. The vials in the carton for the co-packaged presentation of REGEN-COV may be used to prepare and administer REGEN-COV for either intravenous infusion or subcutaneous injection despite this labeling.

Regeneron and Authorized Distributors

A. Regeneron and authorized distributor(s) will ensure that the authorized REGEN-COV is distributed as directed by the U.S. government, and the authorized labeling (i.e., Fact Sheets) will be made available to healthcare facilities and/or healthcare providers consistent with the terms of this letter.

B. Regeneron and authorized distributor(s) will ensure that appropriate storage and cold chain is maintained until the product is delivered to healthcare facilities and/or healthcare providers.

C. Regeneron and authorized distributor(s) will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., U.S. government agencies, state and local government authorities, authorized distributors, healthcare facilities, healthcare providers) involved in distributing or receiving authorized REGEN-COV. Regeneron will provide to all relevant stakeholders a copy of this letter of authorization and communicate any subsequent amendments that might be made to this letter of authorization and its authorized accompanying materials (i.e., Fact Sheets).

D. Regeneron may request changes to this authorization, including to the authorized Fact Sheets for REGEN-COV. Any request for changes to this EUA must be submitted to the Office of Infectious Diseases/Office of New Drugs/Center for Drug Evaluation and Research. Such changes require appropriate authorization prior to implementation.[21]

E. Regeneron may develop and disseminate instructional and educational materials (e.g., materials providing information on product administration and/or patient monitoring) that are consistent with the authorized emergency use of REGEN-COV as described in this letter of authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs. Any instructional and educational materials that are inconsistent with the authorized labeling for REGEN-COV are prohibited. Should the Agency become aware of any instructional or educational materials that are inconsistent with the authorized labeling for REGEN-COV, the Agency will require Regeneron to cease distribution of such instructional and educational materials.

[21] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study; (8) new strengths of the authorized product, new product sources (e.g., of active pharmaceutical ingredient) or of product components. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), (7), or (8), review and concurrence is required from the Counter-Terrorism and Emergency Coordination Staff/Office of the Center Director/CDER and the Office of Counterterrorism and Emerging Threats/Office of the Chief Scientist.

F. Regeneron will report to FDA serious adverse events and all medication errors associated with the use of the authorized REGEN-COV that are reported to Regeneron using either of the following options.

Option 1: Submit reports through the Safety Reporting Portal (SRP) as described on the FDA SRP web page.

Option 2: Submit reports directly through the Electronic Submissions Gateway (ESG) as described on the FAERS electronic submissions web page.

Submitted reports under both options must state: "REGEN-COV use for COVID-19 under Emergency Use Authorization (EUA)." For reports submitted under Option 1, include this language at the beginning of the question "Describe Event" for further analysis. For reports submitted under Option 2, include this language at the beginning of the "Case Narrative" field.

G. All manufacturing, packaging, and testing sites for both drug substance and drug product will comply with current good manufacturing practice requirements of Section 501(a)(2)(B) of the Act.

H. Regeneron will submit information to the Agency within three working days of receipt of any information concerning significant quality problems with distributed drug product of REGEN-COV that includes the following:

- Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or
- Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the product to meet the established specifications.

If a significant quality problem affects unreleased product and may also impact product(s) previously released and distributed, then information must be submitted for all potentially impacted lots.

Regeneron will include in its notification to the Agency whether the batch, or batches, in question will be recalled. If FDA requests that these, or any other batches, at any time, be recalled, Regeneron must recall them.

If not included in its initial notification, Regeneron must submit information confirming that Regeneron has identified the root cause of the significant quality problems and taken corrective action, and provide a justification confirming that the corrective action is appropriate. Regeneron must submit this information as soon as possible but no later than 45 calendar days from the initial notification.

I. Regeneron will manufacture REGEN-COV to meet all quality standards and per the manufacturing process and control strategy as detailed in Regeneron's EUA request.

Regeneron will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product, without notification to and concurrence by the Agency as described under condition D.

J. Regeneron will list the single dose pack bag, the co-packaged product, and the co-formulated product containing casirivimab and imdevimab with unique NDC product codes from each other and the NDC product codes of the single ingredient listings under the marketing category of Unapproved Drug-Other. As applicable, different vial sizes should be identified by a different package NDC within the product NDC. Further, the listing will include each establishment where manufacturing is performed for the drug and the type of operation performed at such establishment.

K. Through a process of inventory control, Regeneron and authorized distributor(s) will maintain records regarding distribution of the authorized casirivimab and imdevimab (i.e., lot numbers, quantity, receiving site, receipt date).

L. Regeneron and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

M. Regeneron will establish a process for monitoring genomic database(s) for the emergence of global viral variants of SARS-CoV-2. A summary of Regeneron's process should be submitted to the Agency as soon as practicable, but no later than 30 calendar days of the issuance of this letter, and within 30 calendar days of any material changes to such process. Regeneron will provide reports to the Agency on a monthly basis summarizing any findings as a result of its monitoring activities and, as needed, any follow-up assessments planned or conducted.

N. FDA may require Regeneron to assess the activity of the authorized REGEN-COV against any global SARS-CoV-2 variant(s) of interest (e.g., variants that are prevalent or becoming prevalent that harbor substitutions in the target protein or in protein(s) that interact with the target protein). Regeneron will perform the required assessment in a manner and timeframe agreed upon by Regeneron and the Agency. Regeneron will submit to FDA a preliminary summary report immediately upon completion of its assessment followed by a detailed study report within 30 calendar days of study completion. Regeneron will submit any relevant proposal(s) to revise the authorized labeling based on the results of its assessment, as may be necessary or appropriate based on the foregoing assessment.

O. Regeneron shall provide samples as requested of the authorized REGEN-COV to the U.S. Department of Health and Human Services (HHS) for evaluation of activity against emerging global viral variants of SARS-CoV-2, including specific amino acid substitution(s) of interest (e.g., variants that are highly prevalent or that harbor substitutions in the target protein) within 5 business days of any request made by HHS. Analyses performed with the supplied quantity of authorized REGEN-COV may include, but are not limited to, cell culture potency assays, protein binding assays, cell culture variant assays (pseudotyped virus-like particles and/or authentic virus), and *in vivo* efficacy assays.

P. Regeneron will submit to FDA all sequencing data assessing REGEN-COV, including sequencing of any participant samples from the full analysis population from COV-2067 that have not yet been completed no later than July 30, 2021. Regeneron will provide the Agency with a frequency table reporting all substitutions detected for all participants at all available time points at a frequency ≥5%.

Q. Regeneron will submit to FDA all SARS-CoV-2 nasopharyngeal viral shedding and blood viral load data, including quantitation of viral load for any participant samples from the full analysis population for which REGEN-COV is currently authorized from COV-2067 that have not yet been completed, no later than July 30, 2021.

Healthcare Facilities to Whom the Authorized REGEN-COV Is Distributed and Healthcare Providers Administering the Authorized Casirivimab and Imdevimab

R. Healthcare facilities and healthcare providers will ensure that they are aware of the letter of authorization, and the terms herein, and that the authorized Fact Sheets are made available to healthcare providers and to patients and caregivers, respectively, through appropriate means, prior to administration of REGEN-COV.

S. Healthcare facilities and healthcare providers receiving REGEN-COV will track serious adverse events and medication errors that are considered to be potentially attributable to REGEN-COV use and must report these to FDA in accordance with the Fact Sheet for Healthcare Providers. Complete and submit a MedWatch form (www.fda.gov/medwatch/report.htm), or Complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178) (these forms can be found via link above). Call 1-800-FDA-1088 for questions. Submitted reports must state, "REGEN-COV use for COVID-19 under Emergency Use Authorization" at the beginning of the question "Describe Event" for further analysis.

T. Healthcare facilities and healthcare providers will ensure that appropriate storage and cold chain is maintained until the product is administered consistent with the terms of this letter.

U. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensed authorized REGEN-COV (i.e., lot numbers, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered).

V. Healthcare facilities will ensure that any records associated with this EUA are maintained until notified by Regeneron and/or FDA. Such records will be made available to Regeneron, HHS, and FDA for inspection upon request.

W. Healthcare facilities and providers will report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

Conditions Related to Printed Matter, Advertising and Promotion

X. All descriptive printed matter, advertising, and promotional materials relating to the use of the REGEN-COV under this authorization shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in section 502(a) and (n) of the Act and FDA implementing regulations, as applicable. References to "approved labeling", "permitted labeling" or similar terms in these requirements shall be understood to refer to the authorized labeling for the use of REGEN-COV under this authorization. In addition, such materials shall:

- Be tailored to the intended audience.
- Not take the form of reminder advertisements, as that term is described in 21 CFR 202.1(e)(2)(i), 21 CFR 200.200 and 21 CFR 201.100(f).
- Present the same risk information relating to the major side effects and contraindications concurrently in the audio and visual parts of the presentation for advertising and promotional materials in audio-visual format.
- Be accompanied by the authorized labeling, if the promotional materials are not subject to Section 502(n) of the Act.
- Be submitted to FDA accompanied by Form FDA-2253 at the time of initial dissemination or first use.

If the Agency notifies Regeneron that any descriptive printed matter, advertising or promotional materials do not meet the terms set forth in conditions X-Z of this EUA, Regeneron must cease distribution of such descriptive printed matter, advertising, or promotional materials in accordance with the Agency's notification. Furthermore, as part of its notification, the Agency may also require Regeneron to issue corrective communication(s).

Y. No descriptive printed matter, advertising, or promotional materials relating to the use of REGEN-COV under this authorization may represent or suggest that REGEN-COV is safe or effective when used for the treatment of COVID-19 or when used as post-exposure prophylaxis as described in the Scope of Authorization (Section II).

Z. All descriptive printed matter, advertising, and promotional material, relating to the use of the REGEN-COV under this authorization shall clearly and conspicuously state that:

- REGEN-COV has not been approved, but has been authorized for emergency use by FDA under an EUA, for treatment and as post-exposure prophylaxis of COVID-19 in certain adults and pediatric individuals (12 years of age and older weighing at least 40 kg) with high risk for progression to severe COVID-19, including hospitalization or death, and

- The emergency use of REGEN-COV is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19

pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

--/S/--

Jacqueline A. O'Shaughnessy, Ph.D.
Acting Chief Scientist
Food and Drug Administration

FACT SHEET FOR HEALTH CARE PROVIDERS
EMERGENCY USE AUTHORIZATION (EUA) OF REGEN-COV®
(casirivimab and imdevimab)

AUTHORIZED USE

TREATMENT

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adult and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Limitations of Authorized Use

- REGEN-COV is not authorized for treatment of mild to moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information such as variant susceptibility to this drug and regional variant frequency.
    - FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.[1]
- REGEN-COV (casirivimab and imdevimab) is not authorized for use in patients:
    - who are hospitalized due to COVID-19, OR
    - who require oxygen therapy due to COVID-19, OR
    - who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.
- Monoclonal antibodies, such as REGEN-COV, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

POST-EXPOSURE PROPHYLAXIS

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated[2] **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with

[1] FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility *[see Microbiology/Resistance Information (15)]*, and CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions.
[2] Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as Johnson & Johnson's Janssen vaccine). See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated

immunocompromising conditions including those taking immunosuppressive medications[3]) **and**

- have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[4] **or**
- who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

Limitations of Authorized Use

- REGEN-COV is not authorized for post-exposure prophylaxis of COVID-19 in geographic regions where exposure is likely to have been to a non-susceptible SARS-CoV-2 variant, based on available information including variant susceptibility to this drug and regional variant frequency.
  - FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.[5]
- Post-exposure prophylaxis with REGEN-COV (casirivimab and imdevimab) is not a substitute for vaccination against COVID-19.
- REGEN-COV (casirivimab and imdevimab) is not authorized for pre-exposure prophylaxis for prevention of COVID-19.

RECENT MAJOR CHANGES

- Limitations of Authorized Use: updated Limitations of Authorized Use for treatment and post-exposure prophylaxis — Revised 1/2022
- Box-Removed SARS-CoV-2 viral variant section — Revised 1/2022
- Antiviral Resistance (Section 15): addition of information on susceptibility of SARS-CoV-2 variants to REGEN-COV (Tables 9 and 10) and updates based on latest viral surveillance report — Revised 12/2021, 8/2021
- Dosage and Administration (Section 2.4) and How Supplied/ Storage and Handling (Section 19): updated storage temperature range and duration — Revised 11/2021
- Dosage and Administration (Box, Section 2.4, Section 3, Section 19): addition of co-packaged carton — Revised 09/2021
- Dosage and Administration (Section 2.4): addition of 5% Dextrose as diluent — Revised 09/2021
- Authorized Use: addition of new indication for post-exposure

[3] See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html

[4] Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example). See this website for additional details: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html

[5] FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility *[see Microbiology/Resistance Information (15)]*, and CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions.

prophylaxis of COVID-19 Revised 07/2021

- Dosage and Administration (Box, and Section 2.2): updated authorized dosage for post-exposure prophylaxis of COVID-19 Revised 07/2021
- Authorized Use: expanded the definition of progression of severe COVID-19 to include death Revised 06/2021
- Dosage and Administration (Box, and Section 2.2): updated authorized dosage Revised 06/2021
- Dosage and Administration (Box, Section 2.2 and 2.4): updated with subcutaneous route of administration as an alternative for those who cannot receive intravenous infusion Revised 06/2021
- Dosage and Administration (Box, Section 2.2 and 2.4): updated with co-formulation Revised 06/2021
- Warnings: Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions (Section 5.1): addition of vasovagal reactions Revised 06/2021
- Overall Safety Summary, Clinical Trials Experience (Section 6.1): addition of Phase 3 results and safety with subcutaneous dosing Revised 06/2021
- Clinical Trial Results and Supporting Data for EUA, Mild to Moderate COVID-19 (Section 18.1): addition of Phase 3 data for the authorized dose Revised 06/2021
- Dosage and Administration (Box and Section 2.1): updated high risk criteria for patient selection Revised 05/2021
- Dose Preparation and Administration Instructions (Section 2.4): provides updated minimum infusion times based on size of infusion bag used Revised 03/2021
- New proprietary name: REGEN-COV Revised 02/2021
- Warnings: Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions (Section 5.1) – addition of new symptoms Revised 02/2021
- Warnings: Clinical Worsening After REGEN-COV Administration (Section 5.2) – new warning added Revised 02/2021

REGEN-COV has been authorized by FDA for the emergency uses described above.

REGEN-COV is not FDA-approved for these uses.

REGEN-COV is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of REGEN-COV under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Treatment

This EUA is for the use of the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, for the treatment of mild to moderate COVID-19 in adult and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death *[see Limitations of Authorized Use (1.1)]*.

Post-Exposure Prophylaxis

This EUA is for the use of the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- **not fully vaccinated[2] or who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications[3]) and**
  - **have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Center for Disease Control and Prevention (CDC)[4] or**
    who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) ***[see Limitations of Authorized Use (1.2)].***

Criteria for Identifying High Risk Individuals

The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example, age ≥65 years of age)
- Obesity or being overweight (for example, BMI >25 kg/m^2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19))

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of REGEN-COV under the EUA is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID, see the CDC website:

https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

Available Dosage Forms of REGEN-COV:

REGEN-COV (casirivimab and imdevimab) is available as:

1. A single vial which contains two antibodies co-formulated in a 1:1 ratio of casirivimab and imdevimab or
2. Individual antibody solutions in separate vials, which may be supplied in separate cartons or together in a single carton (also referred to as a co-packaged carton), or in a dose pack.

Routes of Administration for REGEN-COV:

REGEN-COV may be administered by intravenous infusion or subcutaneous injection.

FOR TREATMENT, INTRAVENOUS INFUSION IS STRONGLY RECOMMENDED. SUBCUTANEOUS INJECTION IS AN ALTERNATIVE ROUTE OF ADMINISTRATION WHEN INTRAVENOUS INFUSION IS NOT FEASIBLE AND WOULD LEAD TO DELAY IN TREATMENT.

FOR POST-EXPOSURE PROPHYLAXIS, EITHER SUBCUTANEOUS INJECTION OR INTRAVENOUS INFUSION CAN BE USED.

Treatment Dosage

- The authorized dosage is 600 mg of casirivimab and 600 mg of imdevimab administered together as a single intravenous infusion or by subcutaneous injection as soon as possible after positive SARS-CoV-2 viral testing and within 10 days of symptom onset *[see Dosage and Administration (2.2) and Clinical Trial Results and Supporting Data for EUA (18.1)]*.
- The authorized dosage of 600 mg of casirivimab and 600 mg of imdevimab for subcutaneous administration for treatment is selected based on the totality of the scientific evidence, incorporating clinical data, viral load reduction data (pharmacodynamics) and pharmacokinetic data *[see Clinical Pharmacology (14.2) and (14.3)]*.

Post-exposure Prophylaxis Dosage

- The authorized dosage is 600 mg of casirivimab and 600 mg of imdevimab administered by subcutaneous injection or together as a single intravenous infusion as soon as possible following exposure to SARS-CoV-2.
- For individuals in whom repeat dosing is determined to be appropriate for ongoing exposure to SARS-CoV-2 for longer than 4 weeks and who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination, the initial dose is 600 mg of casirivimab and 600 mg of imdevimab by subcutaneous injection or intravenous infusion followed by subsequent repeat dosing of 300 mg of casirivimab and 300 mg of imdevimab by subcutaneous injection or intravenous infusion once every 4 weeks for the duration of ongoing exposure.

- The authorized dosage including dosage for repeat dosing is based on the totality of the scientific evidence including clinical pharmacology data and clinical trial data *[see Clinical Trial Results and Supporting Data for EUA (18.2) and Clinical Pharmacology (14.3)]*.

For Intravenous Infusion:

- Co-formulated casirivimab and imdevimab solution in a vial and casirivimab and imdevimab solutions in individual vials must be diluted prior to intravenous administration.
- Administer casirivimab and imdevimab together as a single intravenous infusion via pump or gravity (see Table 1, Table 2, Table 3 and Table 4).
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

For Subcutaneous Injection:

- Administer casirivimab and imdevimab using the co-formulated solution in a vial or using the individual vials (see Table 5 and Table 6).
- Clinically monitor patients after injections and observe patients for at least 1 hour after injections.
- For treatment, subcutaneous injection is an alternative route of administration when intravenous administration is not feasible and would lead to delay in treatment. For post-exposure prophylaxis, either subcutaneous injection or intravenous infusion can be administered.

REGEN-COV may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion or hypersensitivity reactions, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

Health care providers must submit a report on **ALL MEDICATION ERRORS and ALL SERIOUS ADVERSE EVENTS** potentially related to REGEN-COV. See Sections 8 and 9 of the Full EUA Prescribing Information for reporting instructions below.

- Patients treated with REGEN-COV should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect "high touch" surfaces, and frequent handwashing) according to CDC guidelines.

The authorized dosage may be updated as additional data from clinical trials becomes available.

For information on clinical trials that are testing the use of REGEN-COV in COVID-19, please see www.clinicaltrials.gov.

Contraindications

REGEN-COV is contraindicated in individuals with previous severe hypersensitivity reactions, including anaphylaxis, to REGEN-COV *[see Warnings and Precautions (5.1)]*.

Dosing

Patient Selection for Treatment and Post-Exposure Prophylaxis

This section provides essential information on the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied in individual vials to be administered together in adult and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death for:

- Treatment of mild to moderate COVID-19 in adult and pediatric patients with positive results of direct SARS-CoV-2 viral testing *[see Limitations of Authorized Use (1.1)]*.
- Post-exposure prophylaxis of COVID-19 in high risk individuals who are:
    - not fully vaccinated[2] **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications[3]) **and**
        - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[4] **or**
        - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

Criteria for Identifying High Risk Individuals

The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example, age ≥65 years of age)
- Obesity or being overweight (for example, BMI >25 kg/m^2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19))

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of REGEN-COV under the EUA is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

Dosage

Treatment:
The dosage in adult and pediatric patients (12 years of age and older weighing at least 40 kg) is 600 mg of casirivimab and 600 mg of imdevimab administered together as a single intravenous infusion or by subcutaneous injection. Casirivimab and imdevimab should be given together as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset.

Post-Exposure Prophylaxis:
The dosage in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) is 600 mg of casirivimab and 600 mg of imdevimab administered by subcutaneous injection or together as a single intravenous infusion. Casirivimab and imdevimab should be given together as soon as possible following exposure to SARS-CoV-2.

For individuals in whom repeat dosing is determined to be appropriate for ongoing exposure to SARS-CoV-2 for longer than 4 weeks and who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination, the initial dose is 600 mg of casirivimab and 600 mg of imdevimab by subcutaneous injection or intravenous infusion followed by subsequent repeat dosing of 300 mg of casirivimab and 300 mg of imdevimab by subcutaneous injection or intravenous infusion once every 4 weeks for the duration of ongoing exposure.

For Intravenous Infusion:
- Casirivimab and imdevimab solution co-formulated in a vial and in individual vials, including co-packaged carton and dose pack, must be diluted prior to intravenous administration.
- Administer casirivimab and imdevimab together as a single intravenous infusion via pump or gravity (see Table 1, Table 2, Table 3 and Table 4).
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

For Subcutaneous Injection:
- Administer casirivimab and imdevimab using the co-formulated vial or using the individual vials by subcutaneous injection (see Table 5 and Table 6).
- Clinically monitor patients after injections and observe patients for at least 1 hour.

Dosage Adjustment in Specific Populations

No dosage adjustment is recommended in pregnant or lactating women and in patients with renal impairment *[see Full EUA Prescribing Information, Use in Specific Populations (11)]*.

Preparation and Administration

There are TWO different formulations of REGEN-COV:

- Casirivimab and imdevimab co-formulated solution containing two antibodies in a 1:1 ratio in a vial.
- Casirivimab and imdevimab available as individual antibody solutions in separate vials supplied as follows:
  - Individual vials in individual cartons, or
  - together in a single carton (as referred to as a co-packaged carton), or
  - in a dose pack. The dose pack contains individual vials of casirivimab and imdevimab, configurations that may vary in vial size, strength and appearance and are available in dose pack configurations that include 2, 5, and 8 cartons *[see Full EUA Prescribing Information, How Supplied/Storage and Handling (19)]*.

For treatment, intravenous infusion is strongly recommended. Subcutaneous injection is an alternative route of administration when intravenous infusion is not feasible and would lead to delay in treatment.

For post-exposure prophylaxis, either subcutaneous injection or intravenous infusion can be used.

There are differences in the way the two formulations are prepared. Carefully follow the preparation procedures below.

- Casirivimab and imdevimab co-formulated solution in a vial and casirivimab or imdevimab as individual antibody solutions in separate 11.1 mL vials may be used to prepare more than one dose simultaneously as appropriate, either in intravenous bags or in syringes for subcutaneous injection. Discard any product remaining in the vial.
- Store unopened casirivimab and imdevimab vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Unopened vials may be stored in the original carton at room temperature [up to 25°C (77°F)] and must be used within 30 days. If not used in the 30 days, discard vials.

Under the EUA, a single-dose vial may be used to prepare more than one dose.

<u>Preparation for Intravenous Infusion</u>

For treatment, the preferred route of administration for casirivimab and imdevimab is by intravenous infusion after dilution.

Casirivimab and imdevimab solution for intravenous infusion should be prepared by a qualified healthcare professional using aseptic technique:

1. Remove the casirivimab and imdevimab vials from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake the vials**.
2. Inspect casirivimab and imdevimab vials visually for particulate matter and discoloration prior to administration. Should either be observed, the vial must be discarded and replaced with a new vial.
   - The solution for each vial should be clear to slightly opalescent, colorless to pale yellow.

3. Obtain a prefilled intravenous infusion bag containing either 50 mL, 100 mL, 150 mL, or 250 mL of either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.
4. Withdraw the appropriate amount of casirivimab and imdevimab from each respective vial(s) and inject into a prefilled infusion bag containing either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP (see Table 1 and Table 2). If using one vial to prepare more than one infusion bag, then prepare all infusion bags at the same time. The product is preservative-free, therefore do not store unused solution in vial(s).
5. Gently invert infusion bag by hand approximately 10 times to mix. **Do not shake.**
6. This product is preservative-free and therefore, the diluted infusion solution should be administered immediately (see Table 3 and Table 4).
    - If immediate administration is not possible, store the diluted casirivimab and imdevimab infusion solution in the refrigerator between 2°C to 8°C (36°F to 46°F) for no more than 36 hours or at room temperature up to 25°C (77°F) for no more than 4 hours. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.

Table 1: Recommended Dilution Instructions for 600 mg of Casirivimab and 600 mg of Imdevimab for Intravenous Infusion

Size of Prefilled 0.9% Sodium Chloride or 5% Dextrose Infusion Bag	**Preparing Using Co-Formulated Casirivimab and Imdevimab Vial**	**Preparing Casirivimab and Imdevimab Using Individual Vials[a]**
50 mL	Add 10 mL of co-formulated casirivimab and imdevimab (1 vial) into a prefilled 0.9% Sodium Chloride or 5% Dextrose infusion bag and administer as instructed below	Add: • 5 mL of casirivimab (may use 2 vials of 2.5 mL OR 1 vial of 11.1 mL) and • 5 mL of imdevimab (may use 2 vials of 2.5 mL OR 1 vial of 11.1 mL) and inject into a prefilled 0.9% Sodium Chloride or 5% Dextrose infusion bag and administer as instructed below
100 mL		
150 mL		
250 mL		

[a] 600 mg of casirivimab and 600 mg of imdevimab are added to the same infusion bag and administered together as a single intravenous infusion.

Table 2: Recommended Dilution Instructions for 300 mg of Casirivimab and 300 mg of Imdevimab for Intravenous Infusion for Repeat Dosing[a]

Size of Prefilled 0.9% Sodium Chloride or 5%	**Preparing Using Co-Formulated Casirivimab and Imdevimab Vial**	**Preparing Casirivimab and Imdevimab Using Individual Vials[b]**

Dextrose Infusion Bag		
50 mL	Add 5 mL of co-formulated casirivimab and imdevimab into a prefilled 0.9% Sodium Chloride or 5% Dextrose infusion bag and administer as instructed below	Add: • 2.5 mL of casirivimab (may use 1 vial of 2.5 mL OR 1 vial of 11.1 mL) and • 2.5 mL of imdevimab (may use 1 vial of 2.5 mL OR 1 vial of 11.1 mL) and inject into a prefilled 0.9% Sodium Chloride or 5% Dextrose infusion bag and administer as instructed below
100 mL		
150 mL		
250 mL		

[a] Subsequent repeat dosing every 4 weeks after initial 600 mg casirivimab and 600 mg imdevimab dosing for the duration of ongoing exposure.

[b] 300 mg of casirivimab and 300 mg of imdevimab are added to the same infusion bag and administered together as a single intravenous infusion.

Administration by Intravenous Infusion

Casirivimab and imdevimab infusion solution should be administered by a qualified healthcare professional using aseptic technique.

- Gather the recommended materials for infusion:
  - Polyvinyl chloride (PVC), polyethylene (PE)-lined PVC, or polyurethane (PU) infusion set
  - In-line or add-on 0.2 micron polyethersulfone (PES) filter
- Attach the infusion set to the intravenous bag.
- Prime the infusion set.
- Administer the entire infusion solution in the bag via pump or gravity through an intravenous line containing a sterile, in-line or add-on 0.2-micron polyethersulfone (PES) filter (see Table 3 and Table 4). Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.
- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of casirivimab and imdevimab injection with intravenous solutions and medications other than 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP is not known.
- After infusion is complete, flush the tubing with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to ensure delivery of the required dose.
- Discard unused product.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.

Table 3: Recommended Administration Rate for 600 mg of Casirivimab and 600 mg of Imdevimab for Intravenous Infusion

Size of Prefilled 0.9% Sodium Chloride or 5% Dextrose Infusion Bag used	Maximum Infusion Rate	Minimum Infusion Time
50 mL[a]	180 mL/hr	20 minutes
100 mL	310 mL/hr	21 minutes
150 mL	310 mL/hr	31 minutes
250 mL	310 mL/hr	50 minutes

[a] The minimum infusion time for patients administered casirivimab and imdevimab together using the 50 mL prefilled 0.9% Sodium Chloride or 5% Dextrose infusion bag must be at least 20 minutes to ensure safe use.

Table 4: Recommended Administration Rate for 300 mg of Casirivimab and 300 mg of Imdevimab for Intravenous Infusion for Repeat Dosing[a]

Size of Prefilled 0.9% Sodium Chloride or 5% Dextrose Infusion Bag used	Maximum Infusion Rate	Minimum Infusion Time
50 mL[b]	165 mL/hr	20 minutes
100 mL	310 mL/hr	20 minutes
150 mL	310 mL/hr	30 minutes
250 mL	310 mL/hr	49 minutes

[a] Subsequent repeat dosing every 4 weeks after initial 600 mg casirivimab and 600 mg imdevimab dosing for the duration of ongoing exposure.
[b] The minimum infusion time for patients administered casirivimab and imdevimab together using the 50 mL prefilled 0.9% Sodium Chloride or 5% Dextrose infusion bag must be at least 20 minutes to ensure safe use.

Preparation for Subcutaneous Injection

Remove the casirivimab and imdevimab vial(s) from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake the vials.**

Inspect casirivimab and imdevimab vial(s) visually for particulate matter and discoloration prior to administration. Should either be observed, the vial must be discarded and replaced with a new vial. The solution for each vial should be clear to slightly opalescent, colorless to pale yellow.

1. Casirivimab and imdevimab should be prepared using the appropriate number of syringes (see Table 5 and Table 6). Obtain 3 mL or 5 mL polypropylene Luer Lock syringes with luer connection and 21-gauge 1½ inch transfer needles.
2. Withdraw the appropriate amount of solution into each syringe (see Table 5 and Table 6). Prepare all syringes at the same time.
3. Replace the 21-gauge transfer needle with a 25-gauge or 27-gauge needle for subcutaneous injection.
4. This product is preservative-free and therefore, the prepared syringes should be administered immediately. If immediate administration is not possible, store the prepared casirivimab and imdevimab syringes in the refrigerator between 2°C to 8°C (36°F to 46°F) for no more than 24 hours, or at room temperature up to 25°C (77°F) for no more than 8 hours. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 20 minutes prior to administration.

Table 5: Preparation of 600 mg of Casirivimab and 600 mg of Imdevimab for Subcutaneous Injections

Prepare 600 mg of Casirivimab and 600 mg of Imdevimab	Preparation of 4 Syringes
Using Casirivimab and Imdevimab Co-formulated Vial	Withdraw 2.5 mL solution per syringe into FOUR separate syringes.
Using Casirivimab and Imdevimab Individual Vials	• **Casirivimab:** Withdraw 2.5 mL solution per syringe into TWO separate syringes. • **Imdevimab:** Withdraw 2.5 mL solution per syringe into TWO separate syringes. For total of 4 syringes.

Table 6: Preparation of 300 mg of Casirivimab and 300 mg of Imdevimab for Subcutaneous Injections for Repeat Dosing[a]

Prepare 300 mg of Casirivimab and 300 mg of Imdevimab	Preparation of 2 Syringes
Using Casirivimab and Imdevimab Co-formulated Vial	Withdraw 2.5 mL solution per syringe into TWO separate syringes.
Using Casirivimab and Imdevimab Individual Vials	• **Casirivimab:** Withdraw 2.5 mL solution into ONE syringe. • **Imdevimab:** Withdraw 2.5 mL solution into ONE syringe. For total of 2 syringes.

[a] Subsequent repeat dosing every 4 weeks after initial 600 mg casirivimab and 600 mg imdevimab dosing for the duration of ongoing exposure.

Administration for Subcutaneous Injection

- For the administration of 600 mg of casirivimab and 600 mg of imdevimab, gather 4 syringes (see Table 5) and prepare for subcutaneous injections.
- For the administration of 300 mg of casirivimab and 300 mg of imdevimab, gather 2 syringes (see Table 6) and prepare for subcutaneous injections.
- Administer the subcutaneous injections consecutively, each at a different injection site, into the thigh, back of the upper arm, or abdomen, except for 2 inches (5 cm) around the navel. The waistline should be avoided.
- When administering the subcutaneous injections, it is recommended that providers use different quadrants of the abdomen or upper thighs or back of the upper arms to space apart each 2.5 mL subcutaneous injection of casirivimab and imdevimab. DO NOT inject into skin that is tender, damaged, bruised, or scarred.
- Clinically monitor patients after injections and observe patients for at least 1 hour.

Storage

Store unopened casirivimab and imdevimab vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Unopened vials may be stored in the original carton at room temperature [up to 25°C (77°F)] and must be used within 30 days. If not used in the 30 days, discard vials.

Warnings

There are limited clinical data available for REGEN-COV (casirivimab and imdevimab). Serious and unexpected adverse events may occur that have not been previously reported with REGEN-COV use.

Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of REGEN-COV (casirivimab and imdevimab). If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy.

Infusion-related reactions, occurring during the infusion and up to 24 hours after the infusion, have been observed with administration of REGEN-COV. These reactions may be severe or life-threatening.

Signs and symptoms of infusion-related reactions may include:

- fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vasovagal reactions (e.g., pre-syncope, syncope), dizziness, and diaphoresis.

Consider slowing or stopping the infusion and administer appropriate medications and/or supportive care if an infusion-related reaction occurs.

Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of REGEN-COV under Emergency Use Authorization.

Clinical Worsening After REGEN-COV Administration

Clinical worsening of COVID-19 after administration of REGEN-COV has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to REGEN-COV use or were due to progression of COVID-19.

Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19

Monoclonal antibodies, such as REGEN-COV, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Therefore, REGEN-COV is not authorized for use in patients *[see Limitations of Authorized Use (1.1)]*:

- who are hospitalized due to COVID-19, OR
- who require oxygen therapy due to COVID-19, OR
- who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

Side Effects

Adverse events have been reported with REGEN-COV (casirivimab and imdevimab) [*see Full EUA Prescribing Information, Clinical Trials Experience (6.1)*].

Additional adverse events associated with REGEN-COV, some of which may be serious, may become apparent with more widespread use.

INSTRUCTIONS FOR HEALTH CARE PROVIDERS

As the health care provider, you must communicate to your patient or parent/caregiver, as age appropriate, information consistent with the "Fact Sheet for Patients, Parents and Caregivers" (and provide a copy of the Fact Sheet) prior to the patient receiving REGEN-COV (casirivimab and imdevimab), including:

- FDA has authorized the emergency use of REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, for the treatment of mild to moderate COVID-19 in adult and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death *[see Limitations of Authorized Use (1.1)]*.
- FDA has authorized the emergency use of REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated[2] **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications[3]) **and**
  - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Center for Disease Control and Prevention (CDC)[4] **or**
  - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

- The patient or parent/caregiver has the option to accept or refuse REGEN-COV.
- The significant known and potential risks and benefits of REGEN-COV, and the extent to which such risks and benefits are unknown.
- Information on available alternative treatments and the risks and benefits of those alternatives, including clinical trials.
- Patients treated with REGEN-COV should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect "high touch" surfaces, and frequent handwashing) according to CDC guidelines.

For information on clinical trials that are testing the use of REGEN-COV related to COVID-19, please see www.clinicaltrials.gov.

MANDATORY REQUIREMENTS FOR REGEN-COV UNDER EMERGENCY USE AUTHORIZATION:

In order to mitigate the risks of using this unapproved product under EUA and to optimize the potential benefit of REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, the following items are required. Use of REGEN-COV under this EUA is limited to the following (all requirements **must** be met):

1. Treatment of mild to moderate COVID-19 in adult and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for severe COVID-19, including hospitalization or death *[see Limitations of Authorized Use (1.1)]*.
2. Post-exposure prophylaxis of COVID-19 in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:
   a. not fully vaccinated[2] **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications[3]) and
      - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Center for Disease Control and Prevention (CDC)[4] **or**
      - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in

other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

3. As the health care provider, communicate to your patient or parent/caregiver, as age appropriate, information consistent with the "Fact Sheet for Patients, Parents and Caregivers" prior to the patient receiving REGEN-COV. Health care providers (to the extent practicable given the circumstances of the emergency) must document in the patient's medical record that the patient/caregiver has been:
    a. Given the "Fact Sheet for Patients, Parents and Caregivers",
    b. Informed of alternatives to receiving REGEN-COV, and
    c. Informed that REGEN-COV is an unapproved drug that is authorized for use under this Emergency Use Authorization.
4. Patients with known hypersensitivity to any ingredient of REGEN-COV must not receive REGEN-COV.
5. The prescribing health care provider and/or the provider's designee are/is responsible for mandatory reporting of all medication errors and serious adverse events* potentially related to REGEN-COV treatment within 7 calendar days from the onset of the event. The reports must include unique identifiers and the words "REGEN-COV use for COVID-19 under Emergency Use Authorization (EUA)" in the description section of the report.

    - Submit adverse event reports to FDA MedWatch using one of the following methods:
        - Complete and submit the report online: www.fda.gov/medwatch/report.htm, or
        - Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
            - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
            - Fax (1-800-FDA-0178), or
        - Call 1-800-FDA-1088 to request a reporting form
        - Submitted reports must include in the field name, "Describe Event, Problem, or Product Use/Medication Error" a statement "REGEN-COV use for COVID-19 under Emergency Use Authorization (EUA)."

    *Serious Adverse Events are defined as:
    - death;
    - a life-threatening adverse event;
    - inpatient hospitalization or prolongation of existing hospitalization;
    - a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
    - a congenital anomaly/birth defect;
    - a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

6. The prescribing health care provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of REGEN-COV.

7. OTHER REPORTING REQUIREMENTS
    - Healthcare facilities and providers must report therapeutics information and utilization data through HHS Protect, Teletracking or National Healthcare Safety Network (NHSN) as directed by the U.S. Department of Health and Human Services.

    - In addition, please provide a copy of all FDA MedWatch forms to:
      Regeneron Pharmaceuticals, Inc
      Fax: 1-888-876-2736
      E-mail: medical.information@regeneron.com
      Or call Regeneron Pharmaceuticals at 1-844-734-6643 to report adverse events.

APPROVED AVAILABLE ALTERNATIVES

Veklury (remdesivir) is FDA-approved for the treatment of COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, who are not hospitalized and have mild-to-moderate COVID-19, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Veklury is administered via intravenous infusion for a total treatment duration of 3 days.

Although Veklury is an approved alternative treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, FDA does not consider Veklury to be an adequate alternative to REGEN-COV for this authorized use because it may not be feasible or practical for certain patients (e.g., it requires a 3-day treatment duration).

There is no adequate, approved and available alternative to REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated[2] **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications[3]) **and**
    - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per CDC[4] **or**
    - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

Additional information on COVID-19 treatments can be found at https://www.cdc.gov/coronavirus/2019-ncov/index.html. The health care provider should visit https://clinicaltrials.gov/ to determine whether the patient may be eligible for enrollment in a clinical trial.

AUTHORITY FOR ISSUANCE OF THE EUA

The Secretary of the Department of Health and Human Services (HHS) has declared a public health emergency that justifies the emergency use of drugs and biological products during the COVID-19 pandemic.

FDA has issued this EUA, requested by Regeneron Pharmaceuticals, Inc. for the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, for the treatment of mild to moderate COVID-19 in adult and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death.[6] As a health care provider, you must comply with the mandatory requirements of the EUA (see above).

FDA has issued this EUA, requested by Regeneron Pharmaceuticals, Inc. for the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated[2] **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications[3]) **and**
    - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[4] **or**
      who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

Although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, may be effective for the treatment of COVID-19 or for post-exposure prophylaxis of COVID-19 in individuals as specified in this Fact Sheet. You may be contacted and asked to provide information to help with the assessment of the use of the product during this emergency.

This EUA for REGEN-COV will end when the Secretary determines that the circumstances justifying the EUA no longer exist or when there is a change in the approval status of the product such that an EUA may no longer be needed.

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[6] The health care provider should visit https://clinicaltrials.gov/ to determine whether there is an active clinical trial for the product in this disease/condition and whether enrollment of the patient(s) in a clinical trial is more appropriate than product use under this EUA.

CONTACT INFORMATION

For additional information visit www.REGENCOV.com
If you have questions, please contact Regeneron at 1-844-734-6643.

END SHORT VERSION FACT SHEET
Long Version Begins on Next Page

FULL EUA PRESCRIBING INFORMATION

FULL EUA PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

1 AUTHORIZED USE

1.1 TREATMENT

REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, is authorized for use under an EUA for the treatment of mild to moderate COVID-19 in adult and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Limitations of Authorized Use

- REGEN-COV is not authorized for treatment of mild to moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information such as variant susceptibility to this drug and regional variant frequency.
  - FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.[7]
- REGEN-COV (casirivimab and imdevimab) is not authorized for use in patients:
  - who are hospitalized due to COVID-19, OR
  - who require oxygen therapy due to COVID-19, OR

[7] FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility *[see Microbiology/Resistance Information (15)]*, and CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions.

- who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

- Monoclonal antibodies, such as REGEN-COV, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation *[see Warnings and Precautions (5.2)]*.

1.2 POST-EXPOSURE PROPHYLAXIS

REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, is authorized for use under an EUA for the post-exposure prophylaxis of COVID-19 in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated[8] **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications[9]) **and**
  - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[10] **or**
  - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons).

Limitations of Authorized Use

- REGEN-COV is not authorized for post-exposure prophylaxis of COVID-19 in geographic regions where exposure is likely to have been to a non-susceptible SARS-CoV-2 variant, based on available information including variant susceptibility to this drug and regional variant frequency.
  - FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.[11]

- Post-exposure prophylaxis with REGEN-COV (casirivimab and imdevimab) is not a substitute for vaccination against COVID-19.

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[8] Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as Johnson & Johnson's Janssen vaccine). See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated

[9] See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html

[10] Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example). See this website for additional details: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html

[11] FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility *[see Microbiology/Resistance Information (15)]*, and CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions.

- REGEN-COV (casirivimab and imdevimab) is not authorized for pre-exposure prophylaxis for prevention of COVID-19.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

The optimal dosing regimen for treatment of COVID-19 has not yet been established.
The recommended dosing regimen may be updated as data from clinical trials become available.

Patient Selection for Treatment and Post-Exposure Prophylaxis

Treatment:
This section provides essential information on the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, for the treatment of adult and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death *[see Limitations of Authorized Use (1.1)]*.

Post-Exposure Prophylaxis:
This section provides essential information on the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied in individual vials to be administered together, in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for the post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated[2] **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications[3]) **and**
  - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[4] **or**
  - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example, age ≥65 years of age)
- Obesity or being overweight (for example, BMI >25 kg/m^2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- Pregnancy
- Chronic kidney disease

- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19))

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of REGEN-COV under the EUA is not limited to the medical conditions or factors listed above.

For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

2.2 Dosage

Treatment:
The dosage in adult and pediatric patients (12 years of age and older weighing at least 40 kg) is 600 mg of casirivimab and 600 mg of imdevimab administered together as a single intravenous infusion or by subcutaneous injection. Casirivimab and imdevimab should be given together as soon as possible after a positive viral test for SARS-CoV-2 and within 10 days of symptom onset.

Post-Exposure Prophylaxis:
The dosage in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) is 600 mg of casirivimab and 600 mg of imdevimab administered by subcutaneous injection or together as a single intravenous infusion. Casirivimab and imdevimab should be given together as soon as possible following exposure to SARS-CoV-2.

For individuals whom repeat dosing is determined to be appropriate for ongoing exposure to SARS-CoV-2 for longer than 4 weeks and who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination, the initial dose is 600 mg of casirivimab and 600 mg of imdevimab by subcutaneous injection or intravenous infusion followed by subsequent repeat dosing of 300 mg of casirivimab and 300 mg of imdevimab by subcutaneous injection or intravenous infusion once every 4 weeks for the duration of ongoing exposure.

For Intravenous Infusion:

- Casirivimab and imdevimab solution co-formulated in a vial and in individual vials, including co-packaged carton and dose pack, must be diluted prior to intravenous administration.
- Administer casirivimab and imdevimab together as a single intravenous infusion via pump or gravity (see Table 1, Table 2, Table 3 and Table 4).
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

For Subcutaneous Injection:

- Administer casirivimab and imdevimab using the co-formulated vial or using the individual vials by subcutaneous injection (see Table 5 and Table 6).
- Clinically monitor patients after injections and observe patients for at least 1hour.

2.3 Dose Adjustment in Specific Populations

Pregnancy or Lactation

No dosage adjustment is recommended in pregnant or lactating women *[see Use in Specific Populations (11.1, 11.2)]*.

Pediatric Use

No dosage adjustment is recommended in pediatric patients who weigh at least 40 kg and are older than 12 years of age. REGEN-COV (casirivimab and imdevimab) is not recommended for pediatric patients weighing less than 40 kg or those less than 12 years of age *[see Use in Specific Populations (11.3)]*.

Renal Impairment

No dosage adjustment is recommended in patients with renal impairment *[see Use in Specific Populations (11.5)]*.

2.4 Dose Preparation and Administration

There are TWO different formulations of REGEN-COV:

- Casirivimab and imdevimab co-formulated solution containing two antibodies in a 1:1 ratio in a vial.
- Casirivimab and imdevimab available as individual antibody solutions in separate vials supplied as follows:
    - Individual vials in individual cartons, or
    - together in a single carton (also referred to as a co-packaged carton), or
    - in a dose pack. The dose pack contains individual vials of casirivimab and imdevimab, configurations that may vary in vial size, strength and appearance and are available in dose pack configurations that include 2, 5, and 8 cartons *[see Full EUA Prescribing Information, How Supplied/Storage and Handling (19)]*.

For treatment, intravenous infusion is strongly recommended. Subcutaneous injection is an alternative route of administration when intravenous infusion is not feasible and would lead to delay in treatment.

For post-exposure prophylaxis, either subcutaneous injection or intravenous infusion can be used.

There are differences in the way the two formulations are prepared. Carefully follow the preparation procedures below.

- Casirivimab and imdevimab co-formulated solution in a vial and casirivimab or imdevimab as individual antibody solutions in separate 11.1 mL vials may be used to prepare more than one dose simultaneously as appropriate, either in intravenous bags or in syringes for subcutaneous injection. Discard any product remaining in the vial.
- Store unopened casirivimab and imdevimab vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Unopened vials may be stored in the original carton at room temperature [up to 25°C (77°F)] and must be used within 30 days. If not used in the 30 days, discard vials.

Under the EUA, a single-dose vial may be used to prepare more than one dose.

Preparation for Intravenous Infusion

For treatment, the preferred route of administration for casirivimab and imdevimab is by intravenous infusion after dilution.

Casirivimab and imdevimab solution for intravenous infusion should be prepared by a qualified healthcare professional using aseptic technique:

1. Remove the casirivimab and imdevimab vials from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake the vials.**
2. Inspect casirivimab and imdevimab vials visually for particulate matter and discoloration prior to administration. Should either be observed, the vial must be discarded and replaced with a new vial.
   - The solution for each vial should be clear to slightly opalescent, colorless to pale yellow.
3. Obtain a prefilled intravenous infusion bag containing either 50 mL, 100 mL, 150 mL, or 250 mL of either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.
4. Withdraw the appropriate amount of casirivimab and imdevimab from each respective vial(s) and inject into a prefilled infusion bag containing either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP, (see Table 1 and Table 2). If using one vial to prepare more than one infusion bag, then prepare all infusion bags at the same time. The product is preservative-free, therefore do not store unused solution in vial(s).
5. Gently invert infusion bag by hand approximately 10 times to mix. **Do not shake.**

6. This product is preservative-free and therefore, the diluted infusion solution should be administered immediately (see Table 3 and Table 4).
   - If immediate administration is not possible, store the diluted casirivimab and imdevimab infusion solution in the refrigerator between 2°C to 8°C (36°F to 46°F) for no more than 36 hours or at room temperature up to 25°C (77°F) for no more than 4 hours. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.

Table 1: Recommended Dilution Instructions for 600 mg of Casirivimab and 600 mg of Imdevimab for Intravenous Infusion

Size of Prefilled 0.9% Sodium Chloride or 5% Dextrose Infusion Bag	Preparing Using Co-Formulated Casirivimab and Imdevimab Vial	Preparing Casirivimab and Imdevimab Using Individual Vials[a]
50 mL	Add 10 mL of co-formulated casirivimab and imdevimab (1 vial) into a prefilled 0.9% Sodium Chloride or 5% Dextrose infusion bag and administer as instructed below	Add: • 5 mL of casirivimab (may use 2 vials of 2.5 mL OR 1 vial of 11.1 mL) and • 5 mL of imdevimab (may use 2 vials of 2.5 mL OR 1 vial of 11.1 mL) and inject into a prefilled 0.9% Sodium Chloride or 5% Dextrose infusion bag and administer as instructed below
100 mL		
150 mL		
250 mL		

[a] 600 mg of casirivimab and 600 mg of imdevimab are added to the same infusion bag and administered together as a single intravenous infusion.

Table 2: Recommended Dilution Instructions for 300 mg of Casirivimab and 300 mg of Imdevimab for Intravenous Infusion for Repeat Dosing[a]

Size of Prefilled 0.9% Sodium Chloride or 5% Dextrose Infusion Bag	Preparing Using Co-Formulated Casirivimab and Imdevimab Vial	Preparing Casirivimab and Imdevimab Using Individual Vials[b]
50 mL	Add 5 mL of co-formulated casirivimab and imdevimab into a prefilled 0.9% Sodium Chloride or	Add: • 2.5 mL of casirivimab (may use 1 vial of 2.5

100 mL	5% Dextrose infusion bag and administer as instructed below	mL OR 1 vial of 11.1 mL) and • 2.5 mL of imdevimab (may use 1 vial of 2.5 mL OR 1 vial of 11.1 mL) and inject into a prefilled 0.9% Sodium Chloride or 5% Dextrose infusion bag and administer as instructed below
150 mL		
250 mL		

[a] Subsequent repeat dosing every 4 weeks after initial 600 mg casirivimab and 600 mg imdevimab dosing for the duration of ongoing exposure.

[b] 300 mg of casirivimab and 300 mg of imdevimab are added to the same infusion bag and administered together as a single intravenous infusion.

Administration by Intravenous Infusion

Casirivimab and imdevimab infusion solution should be administered by a qualified healthcare professional using aseptic technique.

- Gather the recommended materials for infusion:
  - Polyvinyl chloride (PVC), polyethylene (PE)-lined PVC, or polyurethane (PU) infusion set
  - In-line or add-on 0.2 micron polyethersulfone (PES) filter
- Attach the infusion set to the intravenous bag.
- Prime the infusion set.
- Administer the entire infusion solution in the bag via pump or gravity through an intravenous line containing a sterile, in-line or add-on 0.2-micron polyethersulfone (PES) filter (see Table 3 and Table 4). Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.
- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of casirivimab and imdevimab injection with intravenous solutions and medications other than 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP is not known.
- After infusion is complete, **flush the tubing** with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to ensure delivery of the required dose.
- Discard unused product.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.

Table 3: Recommended Administration Rate for 600 mg of Casirivimab and 600 mg of Imdevimab for Intravenous Infusion

Size of Prefilled 0.9% Sodium Chloride or 5% Dextrose Infusion Bag used	Maximum Infusion Rate	Minimum Infusion Time
50 mL[a]	180 mL/hr	20 minutes
100 mL	310 mL/hr	21 minutes
150 mL	310 mL/hr	31 minutes
250 mL	310 mL/hr	50 minutes

[a] The minimum infusion time for patients administered casirivimab and imdevimab together using the 50 mL prefilled 0.9% Sodium Chloride or 5% Dextrose infusion bag must be at least 20 minutes to ensure safe use.

Table 4: Recommended Administration Rate for 300 mg of Casirivimab and 300 mg of Imdevimab for Intravenous Infusion for Repeat Dosing[a]

Size of Prefilled 0.9% Sodium Chloride or 5% Dextrose Infusion Bag used	Maximum Infusion Rate	Minimum Infusion Time
50 mL[b]	165 mL/hr	20 minutes
100 mL	310 mL/hr	20 minutes
150 mL	310 mL/hr	30 minutes
250 mL	310 mL/hr	49 minutes

[a] Subsequent repeat dosing every 4 weeks after initial 600 mg casirivimab and 600 mg imdevimab dosing for the duration of ongoing exposure.
[b] The minimum infusion time for patients administered casirivimab and imdevimab together using the 50 mL prefilled 0.9% Sodium Chloride or 5% Dextrose infusion bag must be at least 20 minutes to ensure safe use.

Preparation for Subcutaneous Injection

Remove the casirivimab and imdevimab vial(s) from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake the vials.**

Inspect casirivimab and imdevimab vial(s) visually for particulate matter and discoloration prior to administration. Should either be observed, the vial must be discarded and replaced with a new vial. The solution for each vial should be clear to slightly opalescent, colorless to pale yellow.

1. Casirivimab and imdevimab should be prepared using the appropriate number of syringes (see Table 5 and Table 6). Obtain 3 mL or 5 mL polypropylene Luer Lock syringes with luer connection and 21-gauge 1½ inch transfer needles.
2. Withdraw the appropriate amount of solution into each syringe (see Table 5 and Table 6). Prepare all syringes at the same time.
3. Replace the 21-gauge transfer needle with a 25-gauge or 27-gauge needle for subcutaneous injection.

4. This product is preservative-free and therefore, the prepared syringes should be administered immediately. If immediate administration is not possible, store the prepared casirivimab and imdevimab syringes in the refrigerator between 2°C to 8°C (36°F to 46°F) for no more than 24 hours, or at room temperature up to 25°C (77°F) for no more than 8 hours. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 20 minutes prior to administration.

Table 5: Preparation of 600 mg of Casirivimab and 600 mg of Imdevimab for Subcutaneous Injections

Prepare 600 mg of Casirivimab and 600 mg of Imdevimab	**Preparation of 4 Syringes**
Using Casirivimab and Imdevimab Co-formulated Vial	Withdraw 2.5 mL solution per syringe into FOUR separate syringes.
Using Casirivimab and Imdevimab Individual Vials	• **Casirivimab:** Withdraw 2.5 mL solution per syringe into TWO separate syringes. • **Imdevimab:** Withdraw 2.5 mL solution per syringe into TWO separate syringes. For total of 4 syringes.

Table 6: Preparation of 300 mg of Casirivimab and 300 mg of Imdevimab for Subcutaneous Injections for Repeat Dosing[a]

Prepare 300 mg of Casirivimab and 300 mg of Imdevimab	**Preparation of 2 Syringes**
Using Casirivimab and Imdevimab Co-formulated Vial	Withdraw 2.5 mL solution per syringe into TWO separate syringes.

Using Casirivimab and Imdevimab Individual Vials	• **Casirivimab:** Withdraw 2.5 mL solution into ONE syringe. • **Imdevimab:** Withdraw 2.5 mL solution into ONE syringe. For total of 2 syringes.

[a] Subsequent repeat dosing every 4 weeks after initial 600 mg casirivimab and 600 mg imdevimab dosing for the duration of ongoing exposure.

Administration for Subcutaneous Injection

- For the administration of 600 mg of casirivimab and 600 mg of imdevimab, gather 4 syringes (see Table 5) and prepare for subcutaneous injections.
- For the administration of 300 mg of casirivimab and 300 mg of imdevimab, gather 2 syringes (see Table 6) and prepare for subcutaneous injections.
- Administer the subcutaneous injections consecutively, each at a different injection site, into the thigh, back of the upper arm, or abdomen, except for 2 inches (5 cm) around the navel. The waistline should be avoided.
- When administering the subcutaneous injections, it is recommended that providers use different quadrants of the abdomen or upper thighs or back of the upper arms to space apart each 2.5 mL subcutaneous injection of casirivimab and imdevimab. DO NOT inject into skin that is tender, damaged, bruised, or scarred.
- Clinically monitor patients after injections and observe patients for at least 1 hour.

3 DOSAGE FORMS AND STRENGTHS

REGEN-COV (casirivimab and imdevimab) is available as:

1. A single vial which contains two antibodies co-formulated in a 1:1 ratio of casirivimab and imdevimab. Co-formulated casirivimab and imdevimab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution available as:
    - Injection: 600 mg of casirivimab and 600 mg of imdevimab per 10 mL (60 mg/60 mg per mL) in a single-dose[12] vial

2. Individual antibody solutions in separate single-dose[4] vials, which may be supplied in separate cartons or together in a single carton (also referred to as a co-packaged carton), or as dose pack.
    - Casirivimab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution available as:

[12] Under the EUA, a single-dose vial may be used to prepare more than one dose.

- Injection: 300 mg/2.5 mL (120 mg/mL) or 1,332 mg/11.1 mL (120 mg/mL)

- Imdevimab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution available as:
  - Injection: 300 mg/2.5 mL (120 mg/mL) or 1,332 mg/11.1 mL (120 mg/mL)

- Each REGEN-COV dose pack contains 1,200 mg of casirivimab [REGN10933] and 1,200 mg of imdevimab [REGN10987] *[see How Supplied/Storage and Handling (19)]*. Casirivimab and imdevimab vial labels and carton labeling may instead be labeled REGN10933 and REGN10987, respectively.

4 CONTRAINDICATIONS

REGEN-COV is contraindicated in individuals with previous severe hypersensitivity reactions, including anaphylaxis, to REGEN-COV *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

There are limited clinical data available for REGEN-COV (casirivimab and imdevimab). Serious and unexpected adverse events may occur that have not been previously reported with REGEN-COV use.

5.1 Hypersensitivity including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported with administration of REGEN-COV (casirivimab and imdevimab). If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related reactions, occurring during the infusion and up to 24 hours after the infusion, have been observed with administration of REGEN-COV. These reactions may be severe or life threatening.
Signs and symptoms of infusion related reactions may include:

- fever, difficulty breathing, reduced oxygen saturation, chills, nausea, arrhythmia (e.g., atrial fibrillation, tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vasovagal reactions (e.g., pre-syncope, syncope), dizziness, fatigue, and diaphoresis *[see Overall Safety Summary (6.1)]*.

If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care.

Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of REGEN-COV under Emergency Use Authorization.

5.2 Clinical Worsening After REGEN-COV Administration

Clinical worsening of COVID-19 after administration of REGEN-COV has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to REGEN-COV use or were due to progression of COVID-19.

5.3 Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19

Monoclonal antibodies, such as REGEN-COV, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Therefore, REGEN-COV is not authorized for use in patients *[see Limitations of Authorized Use (1.1)]*:

- who are hospitalized due to COVID-19, OR
- who require oxygen therapy due to COVID-19, OR
- who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

6 OVERALL SAFETY SUMMARY

6.1 Clinical Trials Experience

Overall, approximately 16,000 subjects have been exposed to REGEN-COV (casirivimab and imdevimab) in clinical trials in hospitalized and non-hospitalized subjects. Approximately 13,500 subjects received intravenous infusions and 2,500 subjects received subcutaneous injections.

The safety of REGEN-COV (casirivimab and imdevimab) is based on analyses from COV-2067, a Phase 1/2/3 trial of ambulatory (non-hospitalized) subjects with COVID-19; COV-2069, a Phase 3 post-exposure prophylaxis trial for prevention of COVID-19; and COV-2093, a Phase 1 trial evaluating the safety and pharmacokinetics of REGEN-COV repeat subcutaneous dosing every 4 weeks for 24 weeks.

COV-2067

This is a randomized, double-blind, placebo-controlled clinical trial in subjects with mild to moderate COVID-19 who had a sample collected for the first positive SARS-CoV-2 viral infection determination within 3 days prior to the start of the infusion. In the phase 3 portion of the trial, subjects were treated with a single intravenous infusion of 600 mg of casirivimab and 600 mg of imdevimab (n=827), or 1,200 mg of casirivimab and 1,200 mg of imdevimab (n=1,849), or 4,000 mg of casirivimab and 4,000 mg of imdevimab (n=1,012), or placebo (n=1,843). REGEN-COV is not authorized at the 4,000 mg of casirivimab and 4,000 mg of imdevimab dose. The 1,200 mg of casirivimab and 1,200 mg of imdevimab is no longer authorized under this EUA *[see Clinical Trial Results and Supporting Data for EUA (18)]*.

In pooled phase 1/2/3 analysis, infusion-related reactions (adverse event assessed as causally related by the investigator) of grade 2 or higher severity have been observed in 10/4,206 (0.2%) of those who received REGEN-COV at the authorized dose or a higher dose *[see Warnings and Precautions (5.1)]*.

Overall, in Phase 1/2/3, three subjects receiving the 8,000 mg dose of REGEN-COV, and one subject receiving the 1,200 mg of casirivimab and 1,200 mg of imdevimab infusion-related reactions (urticaria, pruritus, flushing, pyrexia, shortness of breath, chest tightness, nausea, vomiting, rash) which resulted in permanent discontinuation of the infusion. All events resolved [*see Warnings and Precautions (5.1)*].

Anaphylactic reactions have been reported in the clinical program in subjects receiving REGEN-COV. The events began within 1 hour of completion of the infusion, and in at least one case required treatment including epinephrine. The events resolved.

COV-2069

This is a randomized, double-blind, placebo-controlled clinical trial assessing the efficacy and safety of REGEN-COV (casirivimab and imdevimab) for post-exposure prophylaxis of COVID-19 in household contacts of individuals infected with SARS-CoV-2. Subjects who were SARS-CoV-2 negative at baseline were enrolled in Cohort A and received a single dose of 600 mg of casirivimab and 600 mg of imdevimab subcutaneously (n=1,311) or placebo (n=1,306).

Adverse events were reported in 265 subjects (20%) in the REGEN-COV group and 379 subjects (29%) in the placebo group. Injection site reactions (all grade 1 and 2) occurred in 55 subjects (4%) in the REGEN-COV group and 19 subjects (2%) in the placebo group. The most common signs and symptoms of injection site reactions which occurred in at least 1% of subjects in the REGEN-COV group were erythema and pruritus. Hypersensitivity reactions occurred in 2 subjects (0.2%) in the REGEN-COV group and all hypersensitivity reactions were grade 1 in severity. There were no cases of anaphylaxis.

Subjects who were SARS-CoV-2 positive at baseline were enrolled in Cohort B and received a single dose of 600 mg of casirivimab and 600 mg of imdevimab subcutaneously (n=155) or placebo (n=156).

Adverse events were reported in 52 subjects (34%) in the REGEN-COV group and 75 subjects (48%) in the placebo group. Injection site reactions, all of which were grade 1 or 2, occurred in 6 subjects (4%) in the REGEN-COV group and 1 subject (1%) in the placebo group. The most common signs and symptoms of injection site reactions which occurred in at least 1% of subjects in the REGN-COV group were ecchymosis and erythema. There were no cases of hypersensitivity reaction or anaphylaxis.

COV-2093

This is a randomized double-blind, placebo-controlled Phase 1 trial evaluating the safety, pharmacokinetic and immunogenicity of repeated doses of 600 mg of casirivimab and 600 mg of imdevimab administered subcutaneously in healthy adult subjects. In COV-2093, subjects were

randomized 3:1 to REGEN-COV (n=729) or placebo (n=240) administered every 4 weeks for 24 weeks. Adverse events were reported in 380 subjects (52%) in the REGEN-COV group and 111 subjects (46%) in the placebo group. Injection site reactions occurred in 12% and 4% of subjects following single dose administration in the REGEN-COV and placebo groups, respectively; the remaining safety findings following subcutaneous administration in the REGEN-COV group were similar to the safety findings observed with intravenous administration of REGEN-COV in COV-2067.

With repeat dosing, injection site reactions occurred in 252 subjects (35%) in the REGEN-COV group and 38 subjects (16%) in the placebo group; all injection site reactions were grade 1 or 2 in severity. Hypersensitivity reactions occurred in 8 subjects (1%) in the REGEN-COV group; and all hypersensitivity reactions were grade 1 or 2 in severity. There were no cases of anaphylaxis.

The authorized dosage for repeat dosing for post-exposure prophylaxis of COVID-19 for certain individuals who remain at high risk of exposure for longer than 4 weeks is the initial dose of 600 mg casirivimab and 600 mg imdevimab followed by 300 mg of casirivimab and 300 mg of imdevimab administered every 4 weeks *[see Dosage and Administration (2.2)]*.

7 PATIENT MONITORING RECOMMENDATIONS

Clinically monitor patients during dose administration and observe patients for at least 1 hour after intravenous infusion or subcutaneous dosing is complete *[see Warnings and Precautions (5.1) and Clinical Trials Experience (6.1)]*.

8 ADVERSE REACTIONS AND MEDICATION ERRORS REPORTING REQUIREMENTS AND INSTRUCTIONS

Clinical trials evaluating the safety of REGEN-COV (casirivimab and imdevimab) are ongoing *[see Overall Safety Summary (6)]*.

Completion of an FDA MedWatch Form to report all medication errors and serious adverse events* occurring during REGEN-COV use and considered to be potentially related to REGEN-COV is mandatory and must be done by the prescribing healthcare provider and/or the provider's designee. These adverse events must be reported within 7 calendar days from the onset of the event:

*Serious Adverse Events are defined as:

- death;
- a life-threatening adverse event;
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly/birth defect;

- a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

If a serious and unexpected adverse event occurs and appears to be associated with the use of REGEN-COV, the prescribing health care provider and/or the provider's designee must complete and submit a MedWatch form to FDA using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm, or
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax (1-800-FDA-0178), or
- Call 1-800-FDA-1088 to request a reporting form

IMPORTANT: When reporting adverse events or medication errors to MedWatch, please complete the entire form with detailed information. It is important that the information reported to FDA be as detailed and complete as possible. Information that must be included:

- Patient demographics (e.g., patient initials, date of birth)
- Pertinent medical history
- Pertinent details regarding admission and course of illness
- Concomitant medications
- Timing of adverse event(s) in relationship to administration of REGEN-COV
- Pertinent laboratory and virology information
- Outcome of the event and any additional follow-up information if it is available at the time of the MedWatch report. Subsequent reporting of follow-up information should be completed if additional details become available.

The following steps are highlighted to provide the necessary information for safety tracking:

1. In section A, box 1, provide the patient's initials in the Patient Identifier
2. In section A, box 2, provide the patient's date of birth or age
3. In section B, box 5, description of the event:
   a. Write "REGEN-COV use for COVID-19 under Emergency Use Authorization (EUA)" as the first line
   b. Provide a detailed report of medication error and/or adverse event. It is important to provide detailed information regarding the patient and adverse event/medication error for ongoing safety evaluation of this unapproved drug. Please see information to include listed above.
4. In section G, box 1, name and address:
   a. Provide the name and contact information of the prescribing health care provider or institutional designee who is responsible for the report
   b. Provide the address of the treating institution (NOT the health care provider's office address).

9 OTHER REPORTING REQUIREMENTS

Healthcare facilities and providers must report therapeutics information and utilization data through HHS Protect, Teletracking or National Healthcare Safety Network (NHSN) as directed by the U.S. Department of Health and Human Services.

In addition, please provide a copy of all FDA MedWatch forms to:
Regeneron Pharmaceuticals, Inc
Fax: 1-888-876-2736
E-mail: medical.information@regeneron.com
Or call Regeneron Pharmaceuticals at 1-844-734-6643 to report adverse events.

10 DRUG INTERACTIONS

REGEN-COV consists of 2 monoclonal antibodies (mAbs), casirivimab and imdevimab, which are not renally excreted or metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk Summary

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. REGEN-COV (casirivimab and imdevimab) should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

Nonclinical reproductive toxicity studies have not been conducted with casirivimab and imdevimab. In a tissue cross-reactivity study with casirivimab and imdevimab using human fetal tissues, no binding of clinical concern was detected. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, casirivimab and imdevimab have the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of casirivimab and imdevimab provides any treatment benefit or risk to the developing fetus. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy *(see Clinical Considerations)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk
COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

11.2 Lactation

Risk Summary

There are no available data on the presence of casirivimab and/or imdevimab in human milk or animal milk, the effects on the breastfed infant, or the effects of the drug on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for REGEN-COV (casirivimab and imdevimab) and any potential adverse effects on the breastfed child from REGEN-COV or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

11.3 Pediatric Use

REGEN-COV is not authorized for use in pediatric patients under 12 years of age or weighing less than 40 kg. The safety and effectiveness of casirivimab and imdevimab are being assessed in pediatric and adolescent patients in an ongoing clinical trial. The recommended dosing regimen is expected to result in comparable serum exposures of casirivimab and imdevimab in patients 12 years of age and older and weighing at least 40 kg as observed in adults, since adults with similar body weight have been included in Trials COV-2067, COV-2069, and COV-2093.

11.4 Geriatric Use

Of the 4,567 subjects with SARS-CoV-2 infection randomized in Trial COV-2067, 14% were 65 years or older, and 4% were 75 years of age or older. Of the 3,029 subjects randomized in Trial COV-2069, 9% were 65 years or older and 2% were 75 years of age or older. Of the 974 subjects randomized in Trial COV-2093, 13% were 65 years or older and 2% were 75 years of age or older. The difference in pharmacokinetics (PK) of casirivimab and imdevimab in geriatric patients compared to younger patients is unknown *[see Clinical Trial Results and Supporting Data for EUA (18.1)]*.

11.5 Renal Impairment

Casirivimab and imdevimab are not eliminated intact in the urine, thus renal impairment is not expected to affect the exposure of casirivimab and imdevimab.

11.6 Hepatic Impairment

The effect of hepatic impairment on PK of casirivimab and imdevimab is unknown.

11.7 Other Specific Populations

The effect of other covariates (e.g., sex, race, body weight, disease severity) on PK of casirivimab and imdevimab is unknown.

12 OVERDOSAGE

Doses up to 8,000 mg (4,000 mg each of casirivimab and imdevimab, greater than 3 times the recommended dose) have been administered in clinical trials without dose-limiting toxicity. Treatment of overdose should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with REGEN-COV (casirivimab and imdevimab).

13 PRODUCT DESCRIPTION

Casirivimab, a human immunoglobulin G-1 (IgG1) monoclonal antibody (mAb), is a covalent heterotetramer consisting of 2 heavy chains and 2 light chains produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture and has an approximate molecular weight of 145.23 kDa.

Casirivimab injection is a sterile, preservative-free, clear to slightly opalescent and colorless to pale yellow solution in a vial for subcutaneous use or intravenous infusion after dilution available as a 300 mg/2.5 mL (120 mg/mL) or 1,332 mg/11.1 mL (120 mg/mL) solution and must be administered with imdevimab. The vial stoppers are not made with natural rubber latex.

- Casirivimab: Each 2.5 mL of solution contains 300 mg of casirivimab, L-histidine (1.9 mg), L-histidine monohydrochloride monohydrate (2.7 mg), polysorbate 80 (2.5 mg), sucrose (200 mg), and Water for Injection, USP. The pH is 6.0.

- Casirivimab: Each 11.1 mL of solution contains 1,332 mg of casirivimab, L-histidine (8.3 mg), L-histidine monohydrochloride monohydrate (12.1 mg), polysorbate 80 (11.1 mg), sucrose (888 mg), and Water for Injection, USP. The pH is 6.0.

Imdevimab, a human IgG1 mAb, is a covalent heterotetramer consisting of 2 heavy chains and 2 light chains produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture and has an approximate molecular weight of 144.14 kDa.

Imdevimab injection is a sterile, preservative-free, clear to slightly opalescent and colorless to pale yellow solution in a vial for subcutaneous use or intravenous infusion after dilution available as a 300 mg/2.5 mL (120 mg/mL) or 1,332 mg/11.1 mL (120 mg/mL) solution and must be administered with casirivimab. The vial stoppers are not made with natural rubber latex.

- Imdevimab: Each 2.5 mL of solution contains 300 mg of imdevimab, L-histidine (1.9 mg), L-histidine monohydrochloride monohydrate (2.7 mg), polysorbate 80 (2.5 mg), sucrose (200 mg), and Water for Injection, USP. The pH is 6.0.

- Imdevimab: Each 11.1 mL of solution contains 1,332 mg of imdevimab, L-histidine (8.3 mg), L-histidine monohydrochloride monohydrate (12.1 mg), polysorbate 80 (11.1 mg), sucrose (888 mg), and Water for Injection, USP. The pH is 6.0.

REGEN-COV (casirivimab and imdevimab solution) injection is a sterile, preservative-free, clear to slightly opalescent, and colorless to pale yellow 10 mL solution in a vial for intravenous infusion after dilution. The vial stoppers are not made with natural rubber latex.

- Each 10 mL of solution contains 600 mg of casirivimab, 600 mg of imdevimab, L-histidine (7.4 mg), L-histidine monohydrochloride monohydrate (10.9 mg), polysorbate 80 (10.0 mg), sucrose (800 mg), and Water for Injection, USP. The pH is 6.0.

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

Casirivimab (IgG1κ) and imdevimab (IgG1λ) are two recombinant human mAbs which are unmodified in the Fc regions. Casirivimab and imdevimab bind to non-overlapping epitopes of the spike protein receptor binding domain (RBD) of SARS-CoV-2 with dissociation constants K_D = 45.8 pM and 46.7 pM, respectively. Casirivimab, imdevimab and casirivimab and imdevimab together blocked RBD binding to the human ACE2 receptor with IC_{50} values of 56.4 pM, 165 pM and 81.8 pM, respectively and prevents viral attachment to host cells [*see Microbiology/Resistance Information (15)*].

14.2 Pharmacodynamics

Trial COV-2067 evaluated REGEN-COV (casirivimab and imdevimab) with doses of up to 6.66 times the recommended dose (600 mg of casirivimab and 600 mg of imdevimab; 1,200 mg of casirivimab and 1,200 mg of imdevimab; 4,000 mg of casirivimab and 4,000 mg of imdevimab) in ambulatory patients with COVID-19. A flat dose-response relationship for efficacy was identified for REGEN-COV at all doses, based on viral load and clinical outcomes. Similar reductions in viral load (log10 copies/mL) were observed in subjects for the (600 mg of casirivimab and 600 mg of imdevimab) intravenous and (600 mg of casirivimab and 600 mg of imdevimab) subcutaneous doses; however, only limited clinical outcome data are available for the subcutaneous route of administration for the treatment of symptomatic patients.

14.3 Pharmacokinetics

Both casirivimab and imdevimab exhibited linear and dose-proportional pharmacokinetics (PK) between (600 mg of casirivimab and 600 mg of imdevimab) to (4,000 mg of casirivimab and 4,000 mg of imdevimab) doses of REGEN-COV (casirivimab and imdevimab) following intravenous administration of single dose. A summary of PK parameters after a single (600 mg of casirivimab and 600 mg of imdevimab) intravenous dose, for each antibody is provided in Table 7.

Table 7: Summary of PK Parameters for Casirivimab and Imdevimab After a Single 600 mg of Casirivimab and 600 mg of Imdevimab Intravenous Dose of REGEN-COV in Study COV-2067

PK Parameter[1]	Casirivimab	Imdevimab
C_{eoi} (mg/L)[2]	192 (80.9)	198 (84.8)
C_{28} (mg/L)[3]	46.2 (22.3)	38.5 (19.7)

[1] Mean (SD)
[2] concentration at end of 1-hour infusion
[3] observed concentration 28 days after dosing, i.e., on day 29, as defined in the protocol

A summary of PK parameters after a single 600 mg of casirivimab and 600 mg of imdevimab subcutaneous dose is shown in Table 8.

Table 8: Summary of PK Parameters for Casirivimab and Imdevimab After a Single 600 mg of Casirivimab and 600 mg of Imdevimab Subcutaneous Dose of REGEN-COV

PK Parameter[1,5]	Casirivimab	Imdevimab
C_{max} (mg/L)	55.6 (22.2)	52.7 (22.5)
t_{max} (day)[2]	8.00 (4.00, 87.0)	7.00 (4.00, 15.0)
AUC_{0-28} (mg•day/L)	1060 (363)	950 (362)
AUC_{inf} (mg•day/L)[3]	2580 (1349)	1990 (1141)
C_{28} (mg/L)[4]	30.7 (11.9)	24.8 (9.58)
Half-life (day)	31.8 (8.35)	26.9 (6.80)

[1] Mean (SD)
[2] Median (range)
[3] Value reported for subjects with $\%AUC_{inf}$ extrapolated <20%
[4] Observed concentration 28 days after dosing, i.e., on day 29
[5] Mean (SD) concentration at 24 hours (C_{24}) of casirivimab and imdevimab in serum with 1200 SC dosing, 22.5 (11.0) mg/L and 25.0 (16.4) mg/L, respectively

For the repeat dose prophylaxis intravenous and subcutaneous regimens, population pharmacokinetic simulations predicted that trough concentrations in serum at steady-state after an initial 600 mg casirivimab and 600 mg imdevimab intravenous or subcutaneous dose followed by monthly (every 4 weeks) 300 mg casirivimab and 300 mg imdevimab intravenous or

subcutaneous doses are similar to slightly higher than observed mean day 29 concentrations in serum for a single 600 mg casirivimab and 600 mg imdevimab subcutaneous dose.

Specific Populations

The effect of different covariates (e.g., age, sex, race, body weight, disease severity, hepatic impairment) on the PK of casirivimab and imdevimab is unknown. Renal impairment is not expected to impact the PK of casirivimab and imdevimab, since mAbs with molecular weight >69 kDa are known not to undergo renal elimination. Similarly, dialysis is not expected to impact the PK of casirivimab and imdevimab.

Drug-Drug Interactions

Casirivimab and imdevimab are mAbs which are not renally excreted or metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely *[see Drug Interactions (10)]*.

15 MICROBIOLOGY/RESISTANCE INFORMATION

Antiviral Activity

In a SARS-CoV-2 virus neutralization assay in Vero E6 cells, casirivimab, imdevimab, and casirivimab and imdevimab together neutralized SARS-CoV-2 (USA-WA1/2020 isolate) with EC_{50} values of 37.4 pM (0.006 μg/mL), 42.1 pM (0.006 μg/mL), and 31.0 pM (0.005 μg/mL), respectively.

Antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) were assessed using Jurkat target cells expressing SARS-CoV-2 spike protein. Casirivimab, imdevimab and casirivimab and imdevimab together mediated ADCC with human natural killer (NK) effector cells. Casirivimab, imdevimab and casirivimab and imdevimab together mediated ADCP with human macrophages. Casirivimab, imdevimab and casirivimab and imdevimab together did not mediate complement-dependent cytotoxicity in cell-based assays.

Antibody Dependent Enhancement (ADE) of Infection

The potential of casirivimab and of imdevimab to mediate viral entry was assessed in immune cell lines co-incubated with recombinant vesicular stomatitis virus (VSV) virus-like particles (VLP) pseudotyped with SARS-CoV-2 spike protein at concentrations of mAb(s) down to approximately 10-fold below the respective neutralization EC_{50} values. Casirivimab and imdevimab together and imdevimab alone, but not casirivimab alone, mediated entry of pseudotyped VLP into $Fc\gamma R2^+$ Raji and $Fc\gamma R1^+/Fc\gamma R2^+$ THP1 cells (maximum infection in total cells of 1.34% and 0.24%, respectively, for imdevimab; 0.69% and 0.06%, respectively for casirivimab and imdevimab together), but not any other cell lines tested (IM9, K562, Ramos and U937 cells).

Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to casirivimab and imdevimab administered together. Prescribing healthcare providers should consider the prevalence of SARS-CoV-2 variants in their area, where data are available, when considering treatment options.

Escape variants were identified following two passages in cell culture of recombinant VSV encoding SARS-CoV-2 spike protein in the presence of casirivimab or imdevimab individually, but not following two passages in the presence of casirivimab and imdevimab together. Variants which showed reduced susceptibility to casirivimab alone included those with spike protein amino acid substitutions K417E (182-fold), K417N (7-fold), K417R (61-fold), Y453F (>438-fold), L455F (80-fold), E484K (25-fold), F486V (>438-fold) and Q493K (>438-fold). Variants which showed reduced susceptibility to imdevimab alone included substitutions K444N (>755-fold), K444Q (>548-fold), K444T (>1,033-fold), and V445A (>548-fold). Casirivimab and imdevimab together showed reduced susceptibility to variants with K444T (6-fold) and V445A (5-fold) substitutions.

In neutralization assays using VSV VLP pseudotyped with spike protein variants identified in circulating SARS-CoV-2, variants with reduced susceptibility to casirivimab alone included those with E406D (51-fold), G476S (5-fold), E484Q (19-fold), G485D (5-fold), F486L (61-fold), F486S (>715-fold), Q493E (446-fold), Q493R (77-fold), and S494P (5-fold) substitutions, and variants with reduced susceptibility to imdevimab alone included those with P337L (5-fold), N439K (463-fold), N439V (4-fold), N440K (28-fold), K444L (153-fold), K444M (1,577-fold), G446V (135-fold), N450D (9-fold), Q498H (17-fold), P499S (206-fold) substitutions. The G476D substitution had an impact (4-fold) on casirivimab and imdevimab together. Substitutions tested concurrently which had reduced susceptibility to casirivimab and imdevimab together included N440K+E484K (21-fold), found in the B.1.619/B.1.625 lineages, and N439K+E484K (23-fold), found in the AV.1 lineage; variants harboring these concurrent substitutions have been detected rarely in the US.

Casirivimab and imdevimab individually and together retained neutralization activity against pseudotyped VLP expressing all spike protein substitutions found in the B.1.1.7 lineage (Alpha; UK origin) and against pseudotyped VLP expressing only N501Y found in B.1.1.7 and other circulating lineages (Table 9). Casirivimab and imdevimab together retained neutralization activity against pseudotyped VLP expressing all spike protein substitutions, or individual substitutions K417N, E484K or N501Y, found in the B.1.351 lineage (Beta; South Africa origin), and all spike protein substitutions or key substitutions K417T, E484K, or N501Y, found in the P.1 lineage (Gamma; Brazil origin), although casirivimab alone, but not imdevimab, had reduced activity against pseudotyped VLP expressing K417N (7-fold) or E484K (25-fold). The E484K substitution is also found in the B.1.526 lineage (Iota; USA [New York] origin). Casirivimab and imdevimab, individually and together, retained neutralization activity against the L452R substitution found in the B.1.427/B.1.429 lineages (Epsilon; USA [California] origin).

Casirivimab and imdevimab, individually and together, retained neutralization activity against pseudotyped VLP expressing L452R+T478K substitutions found in the B.1.617.2 and AY.3 lineages (Delta; India origin). Casirivimab and imdevimab together retained neutralization activity against pseudotyped VLP expressing L452R+E484Q substitutions, found in the B.1.617.1/B.1.617.3 lineages (Kappa/no designation; India origin), although casirivimab alone, but not imdevimab, had reduced activity against pseudotyped VLP expressing L452R+E484Q (7-fold). Casirivimab and imdevimab together retained activity against pseudotyped VLP expressing R346K+E484K+N501Y found in the B.1.621/B.1.621.1 (Mu; Colombia origin) lineage although casirivimab alone, but not imdevimab, had reduced activity against pseudotyped VLP expressing R346K+E484K+N501Y (23-fold).

Casirivimab and imdevimab, individually (>1732-fold and >754-fold, respectively) and together (>1013-fold), demonstrated reduced neutralization activity against VLP pseudotyped with the full spike protein sequence of the B.1.1.529/BA.1 (Omicron; South Africa origin) lineage.

Table 9: Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variant Substitutions with Casirivimab and Imdevimab Together

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y[a]	no change[d]
B.1.351	South Africa	Beta	K417N+E484K+N501Y[b]	no change[d]
P.1	Brazil	Gamma	K417T+E484K+N501Y[c]	no change[d]
B.1.617.2/AY.3	India	Delta	L452R+T478K	no change[d]
B.1.427/B.1.429	USA (California)	Epsilon	L452R	no change[d]
B.1.526[e]	USA (New York)	Iota	E484K	no change[d]
B.1.617.1/B.1.617.3	India	Kappa/no designation	L452R+E484Q	no change[d]
B.1.621/B.1.621.1	Colombia	Mu	R346K+E484K+N501Y	no change[d]
B.1.1.529/BA.1	South Africa	Omicron	G339D+S371L+S373P+ S375F+K417N+N440K, G446S+S477N+T478K+ E484A+Q493R+G496S+ Q498R+N501Y+Y505H[f]	>1013-fold[g]

[a] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: del69-70, del145, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H.

[b] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: D80Y, D215Y, del241-243, K417N, E484K, N501Y, D614G, A701V.

[c] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F.

[d] No change: ≤2-fold reduction in susceptibility.

[e] Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

[f] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: A67V, del69-70, T95I, G142D/del143-145, del211/L212I, ins214EPE, G339D, S371L, S373P,

S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F

[g] Casirivimab and imdevimab together are unlikely to be active against variants from this lineage

Abbreviations: del, deletion; ins, insertion

Due to the large reduction of pseudotyped VLP neutralization activity against spike protein from the B.1.1.529/BA.1 (Omicron;South Africa origin) variant, it is unlikely that casirivimab and imdevimab together will be active against this variant.

Casirivimab and imdevimab together retained activity against authentic SARS-CoV-2 variants of B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.617.1 (Kappa) lineages (Table 10), although casirivimab alone, but not imdevimab, had reduced activity against B.1.351 (5-fold), P.1 (>371-fold) and B.1.617.1 (6-fold) variants.

It is not known how pseudotyped VLP or authentic SARS-CoV-2 data correlate with clinical outcomes.

Table 10: Authentic SARS-CoV-2 Neutralization Data for Casirivimab and Imdevimab Together

SARS-CoV-2 Lineage	Country First Identified	WHO Nomenclature	Key Substitutions[a]	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y	no change[b]
B.1.351	South Africa	Beta	K417N+E484K+N501Y	no change[b]
P.1	Brazil	Gamma	K417T+E484K+N501Y	no change[b]
B.1.617.2	India	Delta	L452R+T478K	no change[b]
B.1.617.1	India	Kappa	L452R+E484Q	no change[b]

[a] Key substitutions occurring in receptor binding domain of spike protein which are associated with each lineage

[b] No change: ≤2-fold reduction in susceptibility.

In clinical trial COV-2067, interim data indicated only one variant (G446V) occurring at an allele fraction ≥15%, which was detected in 3/66 subjects who had nucleotide sequencing data, each at a single time point (two at baseline in subjects from placebo and 2,400 mg casirivimab and imdevimab groups, and one at Day 25 in a subject from the 8,000 mg casirivimab and imdevimab group). The G446V variant had reduced susceptibility to imdevimab of 135-fold compared to wild-type in a pseudotyped VSV VLP neutralization assay but retained susceptibility to casirivimab alone and casirivimab and imdevimab together.

It is possible that resistance-associated variants to casirivimab and imdevimab together could have cross-resistance to other mAbs targeting the receptor binding domain of SARS-CoV-2. The clinical impact is not known.

Immune Response Attenuation

There is a theoretical risk that antibody administration may attenuate the endogenous immune response to SARS-CoV-2 and make patients more susceptible to re-infection.

16 NONCLINICAL TOXICOLOGY

Carcinogenicity, genotoxicity, and reproductive toxicology studies have not been conducted with casirivimab and imdevimab.

In a toxicology study in cynomolgus monkeys, casirivimab and imdevimab had no adverse effects when administered intravenously or subcutaneously. Non-adverse liver findings (minor transient increases in AST and ALT) were observed.

In tissue cross-reactivity studies with casirivimab and imdevimab using human adult and fetal tissues, no binding of clinical concern was detected.

17 ANIMAL PHARMACOLOGIC AND EFFICACY DATA

Casirivimab and imdevimab administered together has been assessed in rhesus macaque and Syrian golden hamster treatment models of SARS-CoV-2 infection. Therapeutic administration of casirivimab and imdevimab together at 25 mg/kg or 150 mg/kg into rhesus macaques (n=4 for each dosing group) 1-day post infection resulted in approximately 1-2 $\log_{10}$ reductions in genomic and sub-genomic viral RNA in nasopharyngeal swabs and oral swabs at Day 4 post-challenge in most animals, and reduced lung pathology relative to placebo-treated animals. Therapeutic administration of casirivimab and imdevimab together at 5 mg/kg and 50 mg/kg doses to hamsters 1-day post infection resulted in reduced weight loss relative to placebo treated animals. In the prophylactic setting in rhesus macaques, administration of 50 mg/kg casirivimab and imdevimab together prior to challenge with SARS-CoV-2 demonstrated reduction in viral RNA via nasopharyngeal, oral swabs and bronchioalveolar lavage fluid, as well as a reduction in lung inflammation. In the prophylactic setting in hamsters, administration of 0.5 mg/kg, 5 mg/kg, or 50 mg/kg casirivimab and imdevimab together prior to challenge with SARS-CoV-2 protected against weight loss, and reduced percentage of lung area showing pneumonia pathology and severity of lung inflammation, indicative of reduced morbidity in this model. The applicability of these findings to a clinical setting is not known.

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

18.1 Treatment of Mild to Moderate COVID-19 (COV-2067)

The data supporting this EUA are based on the analysis of Phase 1/2/3 from trial, COV-2067 (NCT04425629). This is a randomized, double-blinded, placebo-controlled clinical trial evaluating REGEN-COV (casirivimab and imdevimab) for the treatment of subjects with mild to moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized). Cohort 1 enrolled adult subjects who were not hospitalized and had 1 or more COVID-19 symptoms that were at least mild in severity. Treatment was initiated within 3 days of obtaining a positive

SARS-CoV-2 viral infection determination. Subjects in the Phase 3 primary efficacy analysis met the criteria for high risk for progression to severe COVID-19, as shown in Section 2.

In the Phase 3 trial, 4,567 subjects with at least one risk factor for severe COVID-19 were randomized to a single intravenous infusion of 600 mg of casirivimab and 600 mg of imdevimab (n=838), 1,200 mg of casirivimab and 1,200 mg of imdevimab (n=1,529), 4,000 mg of casirivimab and 4,000 mg of imdevimab (n=700), or placebo (n=1,500) groups. The two REGEN-COV doses at the start of Phase 3 were 4,000 mg and 1,200 mg of each component; however, based on Phase 1/2 efficacy analyses showing that the 4,000 mg and 1,200 mg doses of each component were similar, the Phase 3 portion of the protocol was amended to compare 1,200 mg dose of each component vs. placebo and 600 mg dose of each component vs. placebo. Comparisons were between subjects randomized to the specific REGEN-COV dose and subjects who were concurrently randomized to placebo.

At baseline, in all randomized subjects with at least one risk factor, the median age was 50 years (with 13% of subjects ages 65 years or older), 52% of the subjects were female, 84% were White, 36% were Hispanic or Latino, and 5% were Black or African American. In subjects with available baseline symptom data, 15% had mild symptoms, 42% had moderate, 42% had severe symptoms, and 2% reported no symptoms at baseline; the median duration of symptoms was 3 days; mean viral load was 6.2 $\log_{10}$ copies/mL at baseline. The baseline demographics and disease characteristics were well balanced across the casirivimab and imdevimab and placebo treatment groups.

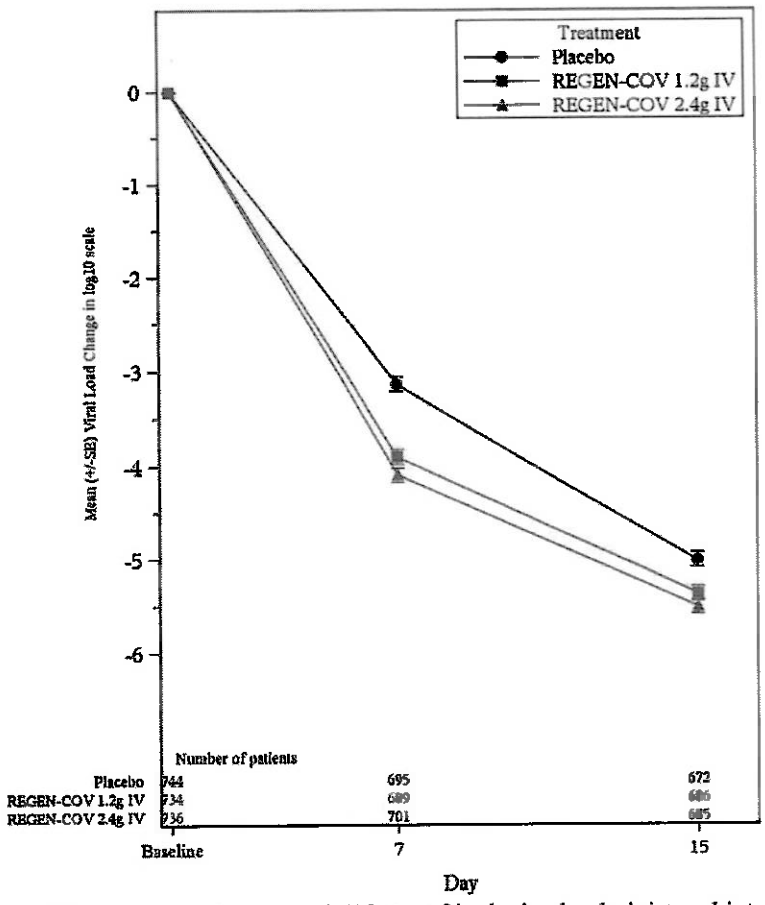
The primary endpoint was the proportion of subjects with ≥1 COVID-19-related hospitalization or all-cause death through Day 29, in subjects with a positive SARS-CoV-2 RT-qPCR result from nasopharyngeal (NP) swab at randomization, and with at least one risk factor for severe COVID-19, i.e., the modified full analysis set (mFAS). In the mFAS, events (COVID-19-related hospitalization or all-cause death through Day 29) occurred in 7 (1.0%) subjects treated with 600 mg of casirivimab and 600 mg of imdevimab compared to 24 (3%) subjects concurrently randomized to placebo, demonstrating a 70% reduction in COVID-19-related hospitalization or all-cause death compared to placebo (p=0.0024). Events occurred in 18 (1.3%) subjects treated with 1,200 mg of casirivimab and 1,200 mg of imdevimab compared to 62 (5%) subjects concurrently randomized to placebo, demonstrating a 71% reduction compared to placebo (REGEN-COV 1% vs placebo 5%, p<0.0001). In the 1,200 mg analysis, there was 1 death each in the REGEN-COV and placebo arm (p=1.0); and in 2,400 mg analysis, there were 1 and 3 deaths, respectively, in the REGEN-COV and placebo arms (p=0.3721). Overall, similar effects were observed for 600 mg of casirivimab and 600 mg of imdevimab and 1,200 mg of casirivimab and 1,200 mg of imdevimab doses, indicating the absence of a dose effect; therefore the 600 mg of casirivimab and 600 mg of imdevimab dose is authorized and the 1,200 mg of casirivimab and 1,200 mg of imdevimab dose is no longer authorized under this EUA (See Table 11). Results were consistent across subgroups of patients defined by nasopharyngeal viral load $>10^6$ copies/mL at baseline or serologic status.

Table 11: Proportion of subjects with ≥1 COVID-19-related hospitalization or all-cause death through day 29 (COV-2067)

	600 mg of casirivimab and 600 mg of imdevimab (intravenous)	**Placebo**	**1,200 mg of casirivimab and 1,200 mg of imdevimab (intravenous)**	**Placebo**
	n=736	n=748	n=1,355	n=1,341
# of subjects with at least 1 event (COVID-19-related hospitalization or all-cause death)	7 (1.0%)	24 (3.2%)	18 (1.3%)	62 (4.6%)
Risk reduction	70% (p=0.0024)		71% (p<0.0001)	

Treatment with REGEN-COV resulted in a statistically significant reduction in the LS mean viral load (log_{10} copies/mL) from baseline to Day 7 compared to placebo (-0.71 log_{10} copies/mL for 600 mg dose of casirivimab and 600 mg of imdevimab and -0.86 log_{10} copies/mL for 2,400 mg; $p<0.0001$). Reductions were observed in the overall mFAS population and in other subgroups, including those with baseline viral load $>10^6$ copies/mL or who were seronegative at baseline. Consistent effects were observed for the individual doses, indicating the absence of a dose effect. Figure 1 shows the mean change from baseline in SARS-COV-2 viral load to Day 15.

Figure 1: Change from Baseline in SARS-COV-2 Viral Load (log_{10} copies/mL) to Day 15 (COV-2067)



REGEN-COV 1.2 g IV = 600 mg of casirivimab and 600 mg of imdevimab administered intravenously
REGEN-COV 2.4 g IV = 1,200 mg of casirivimab and 1,200 mg of imdevimab administered intravenously

The median time to symptom resolution, as recorded in a trial-specific daily symptom diary, was 10 days for REGEN-COV-treated subjects, as compared with 14 days for placebo-treated subjects ($p=0.0001$ for 600 mg of casirivimab and 600 mg of imdevimab vs. placebo; $p<0.0001$ for 1,200 mg of casirivimab and 1,200 mg of imdevimab vs. placebo). Symptoms assessed were fever, chills, sore throat, cough, shortness of breath/difficulty breathing, nausea, vomiting, diarrhea, headache, red/watery eyes, body aches, loss of taste/smell, fatigue, loss of appetite, confusion, dizziness, pressure/tight chest, chest pain, stomachache, rash, sneezing, sputum/phlegm, runny nose. Time to COVID-19 symptom resolution was defined as time from randomization to the first day during which the subject scored 'no symptom' (score of 0) on all of the above symptoms except cough, fatigue, and headache, which could have been 'mild/moderate symptom' (score of 1) or 'no symptom' (score of 0).

18.2 Post-exposure Prophylaxis of COVID-19 (COV-2069)

The data supporting this EUA for post-exposure prophylaxis of COVID-19 are based on the efficacy analysis of data from the Phase 3 COV-2069 trial (NCT04452318). This is a randomized, double-blind, placebo-controlled clinical trial studying REGEN-COV (casirivimab

and imdevimab) for post-exposure prophylaxis of COVID-19 in household contacts of individuals infected with SARS-CoV-2 (index case).

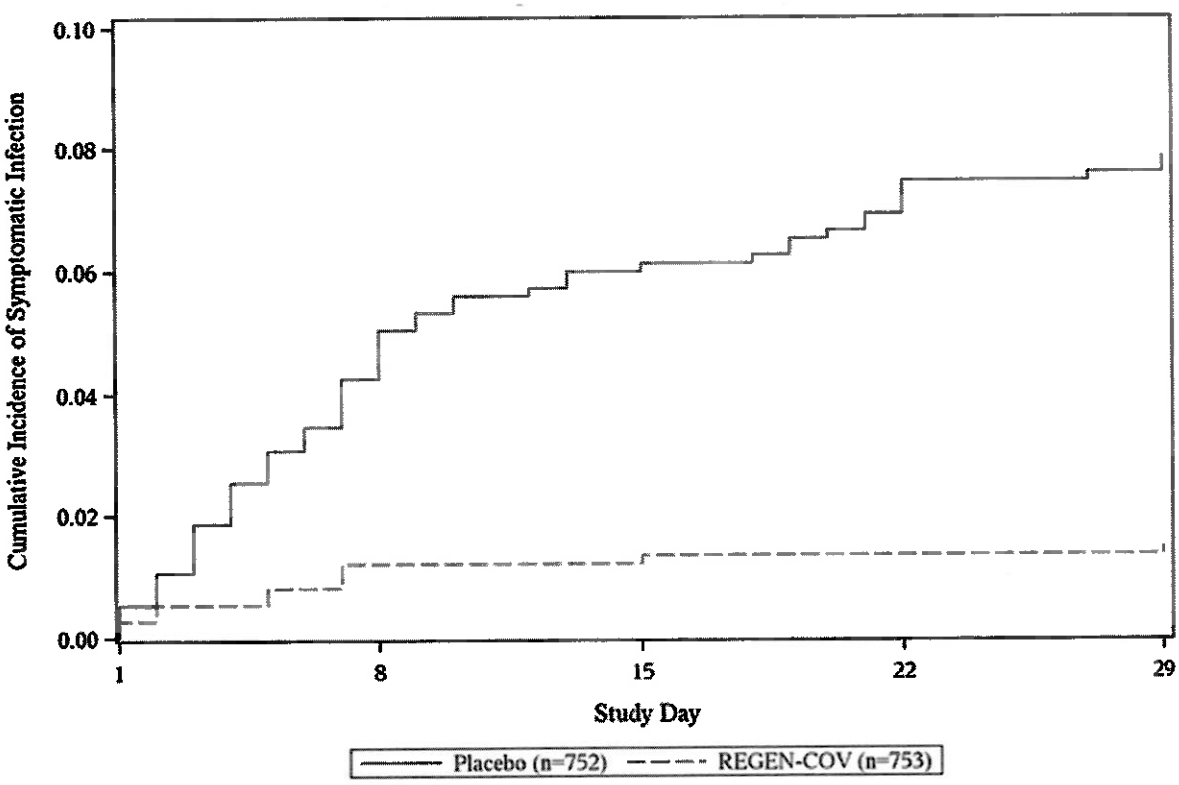
The trial enrolled subjects who were asymptomatic and who lived in the same household with a SARS-CoV-2 infected patient. Subjects were randomized 1:1 to a single dose of 600 mg of casirivimab and 600 mg of imdevimab or placebo administered subcutaneously within 96 hours of collection of the index cases' positive SARS-CoV-2 diagnostic test sample.

Subjects with a negative SARS-CoV-2 RT-qPCR test result at baseline (n=2,067) were enrolled and randomized in Cohort A. The primary analysis population included subjects who were SARS-CoV-2 RT-qPCR negative and seronegative at baseline. Of the 1,505 subjects in the primary analysis population, 753 subjects were randomized to receive REGEN-COV and 752 subjects were randomized to placebo. Following randomization and dosing, subjects had SARS-CoV-2 RT-qPCR testing via a nasopharyngeal swab every 7 days as well as weekly interviews with the investigator for assessment of COVID-19 symptoms during the 28-day efficacy assessment period. No data were collected on the type or extent of exposure to the index case.

For the primary analysis population at baseline, the median age was 44 years (with 9% of subjects ages 65 years or older), 54% of the subjects were female, 86% were White, 41% were Hispanic or Latino, and 9% were Black. The baseline demographics and disease characteristics were well balanced across the casirivimab and imdevimab and placebo treatment groups.

The primary efficacy endpoint was the proportion of subjects who developed RT qPCR-confirmed COVID-19 through Day 29. In the primary analysis population (RT-qPCR negative and seronegative at baseline), there was an 81% risk reduction in the development of COVID-19 with REGEN-COV treatment versus placebo [11/753 (1%) and 59/752 (8%); adjusted odds ratio 0.17; $p<0.0001$]. Figure 2 shows the cumulative incidence of COVID-19 through Day 29. Similar results were obtained in a sensitivity analysis that included RT-qPCR negative subjects at baseline, regardless of baseline serological status, where there was an 82% risk reduction in RT-qPCR-confirmed COVID-19 with REGEN-COV treatment versus placebo. There was a 66% risk reduction in the proportion of participants with any RT-qPCR-confirmed SARS-CoV-2 infection (symptomatic or asymptomatic) with REGEN-COV treatment versus placebo [36/753 (5%) and 107/752 (14%); adjusted odds ratio 0.31; $p<0.0001$].

Figure 2: Cumulative Incidence of Symptomatic COVID-19 (COV-2069 Cohort A)



In a post-hoc analysis in the subgroup of subjects who met the criteria for high risk for progression to severe COVID-19 (as shown in Section 2), there was a 76% risk reduction in COVID-19 with REGEN-COV treatment versus placebo [10/570 (2%) vs 42/567 (7%); adjusted odds ratio 0.22; p<0.0001].

In Cohort B, asymptomatic subjects with a positive SARS-CoV-2 RT-qPCR test result at baseline (n=311) were enrolled and randomized 1:1 to REGEN-COV or placebo. In a post-hoc analysis of the overall combined Cohort A and Cohort B (regardless of serology status at baseline), there was a 62% risk reduction in COVID-19 with REGEN-COV treatment versus placebo [46/1201 (4%) vs 119/1177 (10%); adjusted odds ratio 0.35; p<0.0001].

19 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Co-formulated casirivimab and imdevimab injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution supplied in a vial. Refer to Table 12.

Casirivimab injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution supplied in a vial. Refer to Table 13.

Imdevimab injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution supplied in a vial. Refer to Table 13.

REGEN-COV (casirivimab and imdevimab) injection is available as:

1. **A single vial which contains two antibodies co-formulated in a 1:1 ratio of casirivimab and imdevimab** (Table 12).
2. **Individual antibody solutions in separate vials, which may be supplied in separate cartons** (Table 13) **or together in a single carton (also referred to as a co-packaged carton)** (Table 14), **or in a dose pack** (Table 15).

Table 12: Co-Formulated Casirivimab and Imdevimab

Antibody	Concentration	Package Size	NDC Number
REGEN-COV (casirivimab and imdevimab)	600 mg/600 mg per 10 mL (60 mg/60 mg per mL)	1 vial per carton	61755-039-01

INDIVIDUAL CASIRIVIMAB AND IMDEVIMAB SOLUTIONS MUST BE ADMINISTERED TOGETHER.

Table 13: Individual Package Size

Antibody	Concentration	Package Size	NDC Number
Casirivimab REGN10933	1,332 mg/11.1 mL (120 mg/mL)	1 vial per carton	61755-024-01
	300 mg/2.5 mL (120 mg/mL)	1 vial per carton	61755-026-01
Imdevimab REGN10987	1,332 mg/11.1 mL (120 mg/mL)	1 vial per carton	61755-025-01
	300 mg/2.5 mL (120 mg/mL)	1 vial per carton	61755-027-01

Each co-packaged carton contains 1 vial of casirivimab and 1 vial of imdevimab. Refer to Table 14.

Table 14: Casirivimab and Imdevimab Co-Packaged Carton

Co-Packaged Carton Contents	Co-Packaged Components	Concentration	Co-Packaged Carton NDC Number
2 Vials	**1 vial of casirivimab** (NDC 61755-024-00)	1,332 mg/11.1 mL (120 mg/mL)	61755-042-02
	1 vial of imdevimab (NDC 61755-025-00)	1,332 mg/11.1 mL (120 mg/mL)	

2 Vials	**1 vial of casirivimab** (NDC 61755-026-00)	300 mg/2.5 mL (120 mg/mL)	61755-045-02
	1 vial of imdevimab (NDC 61755-027-00)	300 mg/2.5 mL (120 mg/mL)	

Each REGEN-COV dose pack contains sufficient number of vials of casirivimab [REGN10933] and imdevimab [REGN10987] to prepare up to two treatment doses (600 mg of casirivimab and 600 mg of imdevimab). Refer to Table 15.

Table 15: Dose Pack Providing 1,200 mg Casirivimab and 1,200 mg Imdevimab

REGEN-COV Dose Pack Size	REGEN-COV Dose Pack Components	Concentration	REGEN-COV Dose Pack NDC Number
2 Cartons	**1 vial of casirivimab REGN10933** (NDC 61755-024-01)	1,332 mg/11.1 mL (120 mg/mL)	61755-035-02
	1 vial of imdevimab REGN10987 (NDC 61755-025-01)	1,332 mg/11.1 mL (120 mg/mL)	
8 Cartons	**4 vials of casirivimab REGN10933** (NDC 61755-026-01)	300 mg/2.5 mL (120 mg/mL)	61755-036-08
	4 vials of imdevimab REGN10987 (NDC 61755-027-01)	300 mg/2.5 mL (120 mg/mL)	
5 Cartons	**1 vial of casirivimab REGN10933** (NDC 61755-024-01)	1,332 mg/11.1 mL (120 mg/mL)	61755-037-05
	4 vials of imdevimab REGN10987 (NDC 61755-027-01)	300 mg/2.5 mL (120 mg/mL)	
5 Cartons	**4 vials of casirivimab REGN10933** (NDC 61755-026-01)	300 mg/2.5 mL (120 mg/mL)	61755-038-05
	1 vial of imdevimab REGN10987 (NDC 61755-025-01)	1,332 mg/11.1 mL (120 mg/mL)	

Storage and Handling

Casirivimab is preservative-free. Discard any unused portion.
Imdevimab is preservative-free. Discard any unused portion.

Store unopened casirivimab and imdevimab vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Unopened vials may be stored in the original carton at room temperature [up to 25°C (77°F)] and must be used within 30 days. If not used in the 30 days, discard vials.

DO NOT FREEZE. DO NOT SHAKE. DO NOT EXPOSE TO DIRECT LIGHT.

Solution in vial requires dilution prior to intravenous administration. The prepared infusion solution is intended to be used immediately. If immediate administration is not possible, store diluted casirivimab and imdevimab infusion solution in the refrigerator at 2°C to 8°C (36°F to 46°F) for no more than 36 hours or at room temperature up to 25°C (77°F) for no more than 4 hours. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.

The prepared syringes should be administered immediately. If immediate administration is not possible, store the prepared casirivimab and imdevimab syringes in the refrigerator between 2°C to 8°C (36°F to 46°F) for no more than 24 hours, or at room temperature up to 25°C (77°F) for no more than 8 hours. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 20 minutes prior to administration.

20 PATIENT COUNSELING INFORMATION

Patients treated with REGEN-COV (casirivimab and imdevimab) should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect "high touch" surfaces, and frequent handwashing) according to CDC guidelines. Also see Fact Sheet for Patients, Parents and Caregivers.

21 CONTACT INFORMATION

For additional information visit www.REGENCOV.com
If you have questions, please contact Regeneron at 1-844-734-6643.

REGENERON

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Revised: 12/2021

FDA U.S. FOOD & DRUG ADMINISTRATION

April 16, 2021

Susan Warner, Pharm.D.
Advisor
Global Regulatory Affairs - US
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

RE: Emergency Use Authorization 090

Dear Dr. Warner:

This letter is in response to your request, dated April 15, 2021, that the Food and Drug Administration (FDA) revoke the Emergency Use Authorization (EUA) for emergency use of bamlanivimab for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe Coronavirus Disease 2019 (COVID-19) and/or hospitalization. The EUA (EUA 090) was originally issued on November 9, 2020 and reissued on February 9, 2021 and March 2, 2021.

The authorization of a product for emergency use under section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3) may, pursuant to section 564(g)(2) of the Act, be revised or revoked when the criteria under section 564(b)(1) of the Act no longer exist, the criteria under section 564(c) of the Act for issuance of such authorization are no longer met, or other circumstances make such revision or revocation appropriate to protect the public health or safety.

As part of the Agency's ongoing review of the circumstances and appropriateness of EUA 090, FDA has continually reviewed new data and additional new information to assess whether the criteria for issuance of EUA 090 continue to be met. Under section 564(c)(2) of the Act, an EUA may be issued only if FDA concludes, among other things, "that, based on the totality of scientific evidence available to the Secretary, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that: (A) the product may be effective in diagnosing, treating, or preventing—(i) such disease or condition [....]; and (B) the known and potential benefits of the product, when used to diagnose, prevent, or treat such disease or condition, outweigh the known and potential risks of the product [...]."

Since the initial authorization of bamlanivimab for emergency use, there has been a sustained increase in SARS-CoV-2 viral variants across the U.S. that are resistant to bamlanivimab administered alone. As part of the Agency's ongoing review of the circumstances and appropriateness of EUA 090, we reviewed emerging information and assessed whether, based on the totality of scientific evidence available, the criteria for issuance of the EUA continue to be met.

A summary of these new data and new information includes the following:

- Vesicular stomatitis virus-based pseudovirus expressing spike protein with variant substitutions, specifically E484K and L452R, exhibit large reductions (>1,000 fold) in susceptibility to bamlanivimab alone in neutralization assays.

- The Center for Disease Control (CDC) national genomic surveillance program has reported an increasing frequency of SARS-CoV-2 variants that are expected to be resistant to bamlanivimab alone.
    - As of mid-March 2021, approximately 20% of isolates sequenced in the U.S. were reported as lineages expected to be resistant to bamlanivimab alone, increasing from approximately 5% in mid-January 2021.
    - The CDC national genomic surveillance program has published detailed data regarding variants of the B.1.427 and B.1.429 lineages, first detected in California, which harbor the L452R substitution. These variants have now been identified at frequencies exceeding 20% in eight states and frequencies exceeding 10% in two additional states.
    - There are recent reports that variants with the E484K substitution are circulating at rates exceeding 10% in the New York City metropolitan area including northern New Jersey.

- Testing technologies that enable health care providers to test individual patients for SARS-CoV-2 viral variants prior to initiation of treatment with monoclonal antibodies are not available and frequencies are changing rapidly. Therefore, empiric treatment with monoclonal antibody therapies that are expected to retain activity broadly across the U.S. is needed to reduce the likelihood of treatment failure.

- On April 8, 2021, the National Institutes of Health updated its treatment guidelines for COVID-19 recommending against the use of bamlanivimab alone.

Given the above, we have concluded that the known and potential benefits of bamlanivimab alone no longer outweigh the known and potential risks for the product. As such, FDA has determined that the criteria under section 564(c) of the Act for issuance of EUA 090 referenced above are no longer met.

In your letter requesting that FDA revoke EUA 090, you state that you do not intend to request the return of bamlanivimab that has been distributed prior to this revocation, as the distributed product continues to be authorized for use together with etesevimab under EUA 094. FDA concurs with this approach toward disposition of the previously distributed bamlanivimab authorized for emergency use under EUA 090. Stakeholders may order etesevimab alone to pair with existing supply of bamlanivimab that may be on hand.

Accordingly, FDA revokes the EUA for emergency use of bamlanivimab administered alone for the treatment of mild to moderate COVID-19, pursuant to section 564(g)(2) of the Act.

Notice of this revocation will be published in the *Federal Register*, pursuant to section 564(h)(1) of the Act.

Sincerely,

--/S/--

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

U.S. FOOD & DRUG ADMINISTRATION

Frequently Asked Questions on the Emergency Use Authorization for Bamlanivimab

Q. What is an Emergency Use Authorization (EUA)?

A: Under section 564 of the Federal Food, Drug & Cosmetic Act, the FDA may, pursuant to a declaration by the HHS Secretary based on one of four types of determinations, authorize an unapproved product or unapproved uses of an approved product for emergency use. In issuing an EUA, the FDA must determine, among other things, that the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by a chemical, biological, radiological, or nuclear agent; that the known and potential benefits, when used to treat, diagnose or prevent such disease or condition, outweigh the known and potential risks for the product; and that there are no adequate, approved, and available alternatives. Emergency use authorization is NOT the same as FDA approval or licensure.

Q. What does this EUA authorize?

A. The EUA authorizes bamlanivimab, manufactured by Eli Lilly and Company (Lilly), for emergency use for the treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

Q. How is high risk defined under the EUA?

A. High risk for progressing to severe COVID-19 and/or hospitalization is defined as patients who meet at least one of the following criteria:

- Have a body mass index (BMI) ≥35
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are ≥65 years of age
- Are ≥55 years of age AND have
  - cardiovascular disease, or
  - hypertension, or
  - chronic obstructive pulmonary disease/other chronic respiratory disease.
- Are 12 – 17 years of age AND have
  - BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm, or
  - sickle cell disease, or
  - congenital or acquired heart disease, or
  - neurodevelopmental disorders, for example, cerebral palsy, or
  - a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), or
  - asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

Q. Are there limitations of the authorized use under this EUA?

A. Yes. Bamlanivimab is not authorized for use in patients:

- who are hospitalized due to COVID-19, or
- who require oxygen therapy due to COVID-19, or

- who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

A benefit of treatment with bamlanivimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

Q. Is bamlanivimab a monoclonal antibody? What is a monoclonal antibody?
A. Yes, bamlanivimab is a monoclonal antibody. Monoclonal antibodies are laboratory-produced molecules engineered to serve as substitute antibodies that can restore, enhance or mimic the immune system's attack on pathogens. Bamlanivimab is designed to block viral attachment and entry into human cells, thus neutralizing the virus.

Q. When should bamlanivimab be administered to a patient?
A. It is recommended that bamlanivimab be administered as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset. Bamlanivimab is administered as a single dose of 700 mg via IV infusion. More information about administration is available in the Health Care Provider Fact Sheet.

Q. Where are infusions of bamlanivimab available?
A. The following websites contain information regarding access to monoclonal antibody treatments for COVID-19:

- HHS Protect Public Data Hub – Therapeutics Distribution: https://protect-public.hhs.gov/pages/therapeutics-distribution
- National Infusion Center Association (NICA): https://covid.infusioncenter.org/

Bamlanivimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and have the ability to activate the emergency medical system (EMS), if necessary. Please speak with your doctor or contact your local or state public health department for more information.

Q. Is bamlanivimab approved by the FDA to treat COVID-19?
A. No. Bamlanivimab is an investigational drug. It is not currently FDA-approved to treat any diseases or conditions, including COVID-19.

However, upon issuance of the EUA, bamlanivimab is authorized for emergency use for the treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

Q. Does the EUA permit the use of bamlanivimab as authorized in patients hospitalized *for reasons other* than COVID-19?
A: Bamlanivimab is authorized for emergency use for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization. If a patient is hospitalized *for reasons other* than COVID-19, such as for an elective

orthopedic procedure, and the patient reports mild to moderate symptoms of COVID-19, confirmed with positive results of a direct SARS-CoV-2 viral test, then it may be appropriate for treatment with bamlanivimab, if the patient is also at high risk for progressing to severe COVID-19 and/or hospitalization and the terms and conditions of the authorization are met, as detailed in the Fact Sheet for Health Care Providers.

Bamlanivimab is not authorized for use in patients:

- who are hospitalized *due to* COVID-19, or
- who require oxygen therapy *due to* COVID-19, or
  who require an increase in baseline oxygen flow rate *due to* COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

Q. Are there data showing bamlanivimab might benefit patients with COVID-19?
A. The data supporting this EUA are based on an interim analysis from Part A of the BLAZE-1 clinical trial that occurred after all enrolled patients completed at least Day 29 of the trial.

BLAZE-1 Part A was a randomized, double-blind, placebo-controlled clinical trial studying bamlanivimab for the treatment of ambulatory patients with mild to moderate COVID-19. BLAZE-1 enrolled adult patients who were not hospitalized and had 1 or more mild or moderate COVID-19 symptoms. Treatment was initiated within 3 days of obtaining the first positive clinical sample for SARS-CoV-2 viral infection determination. Patients were treated with a single infusion of bamlanivimab (at doses of 700 mg [N=101], 2800 mg [N=107], or 7000 mg [N=101]) or placebo [N=156]).

The most important evidence that bamlanivimab may be effective came from the predefined secondary endpoint of COVID-19-related hospitalizations or emergency room visits within 28 days after treatment. Among patients who were at high risk for disease progression, hospitalizations and emergency room visits occurred in 3% of bamlanivimab-treated patients compared to 10% in placebo-treated patients. The primary endpoint was change in viral load from baseline to Day 11 for bamlanivimab versus placebo. Most patients, including those receiving placebo, effectively cleared the virus by Day 11. The effects on viral load and on reduction in hospitalizations and ER visits, and the safety profile, were similar in patients receiving any of the three bamlanivimab doses.

Based on the totality of the scientific evidence available, FDA determined that it is reasonable to believe that bamlanivimab may be effective for the treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

Q. Why was the EUA issued for bamlanivimab 700mg dose, and not a higher dose (2800 mg)?
A. A Phase 2 trial (BLAZE-1) evaluated bamlanivimab over a dose range of 1 to 10 times the authorized dose (700 to 7000 mg) of bamlanivimab in patients with mild to moderate COVID-19. A flat exposure-response relationship for efficacy was identified for bamlanivimab within this dose range, based on viral load and clinical outcomes. This means that no meaningful differences were seen between doses with respect to key endpoints. The effects on viral load and on reduction in hospitalizations and ER visits, and the safety profile, were similar in patients receiving any of the three bamlanivimab doses.

See Sections 14.2 and 18.1 of bamlanivimab's Health Care Provider Fact Sheet for additional information.

Q. Are there clinical trials underway evaluating bamlanivimab for COVID-19?
A. Yes. Clinical trials remain ongoing to study bamlanivimab for investigational uses.

Q. Was the bamlanivimab arm of a clinical trial (ACTIV-3) terminated?
A. Yes. The National Institute of Allergy and Infectious Diseases (NIAID)-sponsored ACTIV-3 clinical trial is a platform trial designed to test the safety and efficacy of various investigational agents, including bamlanivimab, for the treatment of patients ***hospitalized*** with COVID-19. The trial was paused on October 13, 2020, by the independent Data Safety Monitoring Board (DSMB). On October 26, 2020, it was announced that no additional patients in ACTIV-3 would receive bamlanivimab. This recommendation was based on trial data suggesting that bamlanivimab is unlikely to help ***hospitalized*** COVID-19 patients recover from a more advanced stage of disease.

The population being studied in the ACTIV-3 trial is different than the population authorized to use bamlanivimab under the EUA. The EUA authorizes emergency use for the treatment of mild to moderate COVID-19 in ***non-hospitalized*** adult and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization, while the ACTIV-3 trial studied ***hospitalized*** patients with COVID-19. This EUA request was based on the interim results from Lilly's BLAZE-1 clinical trial that includes non-hospitalized patients. The EUA limits the authorized use of bamlanivimab. Bamlanivimab is not authorized for use in patients who are hospitalized due to COVID-19, or who require oxygen therapy due to COVID-19, or who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity. Monoclonal antibodies, such as bamlanivimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

Q. Are there side effects of bamlanivimab?
A. Over 850 participants in clinical trials have been treated with a single dose of bamlanivimab 700 mg or higher in clinical trials. Across this total safety database, one anaphylaxis reaction and one serious infusion-related reaction have been reported during infusion of bamlanivimab. The infusions were stopped. Both reactions required treatment, one required epinephrine. Both events resolved.

In BLAZE-1, there were no serious infusion-related reactions. The most commonly reported (in 2-4% of subjects) adverse events during these trials were nausea, diarrhea, dizziness, headache, pruritus, and vomiting. Clinical studies evaluating the safety of bamlanivimab are ongoing, so it is possible all of the risks in using the drug to treat COVID-19 are not known at this time.

Q. How can bamlanivimab be obtained for use under the EUA?
A. HHS will review case counts and severity of outbreaks across the U.S. and make allocations accordingly to state and territorial health departments. State and territorial health departments will allocate to healthcare facilities. AmeriSource Bergen will distribute bamlanivimab for the U.S. Government.

Q. Will there be adequate supply of bamlanivimab for all patients covered under the EUA to receive the drug?
A. HHS recently announced that the Biomedical Advanced Research and Development Authority (BARDA), part of the HHS Office of the Assistant Secretary for Preparedness and Response, collaborated with the DoD Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense and Army Contracting Command to purchase 300,000 doses of bamlanivimab from Lilly over the next two months. Under the agreement, the federal government can purchase up to 650,000 additional doses through the end of June 2021. FDA is closely monitoring Lilly's efforts to increase the supply of bamlanivimab so all patients who need it and are within the scope of the authorization can receive the drug if appropriate.

Q: Bamlanivimab is authorized for the treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization. What does direct SARS-CoV-2 viral testing mean?
A: Direct SARS-CoV-2 viral tests diagnose active COVID-19 infection. Direct SARS-CoV-2 viral tests include two types of diagnostic tests for COVID-19:

- Molecular tests, such as RT-PCR tests, that detect the virus's genetic material
- Antigen tests that detect specific proteins from the virus.

Antibody tests should not be used to diagnose COVID-19 and are not direct SARS-CoV-2 viral tests. Antibody tests look for antibodies made by the immune system in response to the SARS-CoV-2 virus.

Q. Are there reporting requirements for healthcare facilities and providers as part of the EUA?
A. Yes. As part of the EUA, FDA requires health care providers who prescribe bamlanivimab to report all medication errors and serious adverse events considered to be potentially related to bamlanivimab through FDA's MedWatch Adverse Event Reporting program. Providers can complete and submit the report online; or download and complete the form, then submit it via fax at 1-800-FDA-0178. This requirement is outlined in the EUA's health care provider Fact Sheet. FDA MedWatch forms should also be provided to Lilly.

Healthcare facilities and providers must report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services. Such information and data should be reported through HHS Protect, Teletracking or National Healthcare Safety Network (NHSN).

Q. Do patient outcomes need to be reported under the EUA?
A. No, reporting of patient outcomes is not required under the EUA. However, reporting of all medication errors and serious adverse events considered to be potentially related to bamlanivimab occurring during bamlanivimab treatment is required.

Q. Does the EUA authorize bamlanivimab to be used to prevent COVID-19?
A. No. Use of bamlanivimab for the prevention of COVID-19 is not authorized.

Q. Can health care providers share the patient/caregiver Fact Sheet electronically?
A. The letter of authorization for bamlanivimab requires that Fact Sheets be made available to health care providers and to patients/caregivers "through appropriate means." Electronic delivery of the Fact Sheet is an appropriate means. For example, when the patient requests the Fact Sheet electronically, it

can be delivered as a PDF prior to medication administration. Health care providers should confirm receipt of the Fact Sheet with the patient.

Q. Can I receive a COVID-19 vaccine if I was treated with a monoclonal antibody for COVID-19?
A. Currently, there are no data on the safety and effectiveness of either the Pfizer-BioNTech, Moderna, or Janssen COVID-19 vaccines in people who received monoclonal antibodies authorized by FDA for emergency use as part of COVID-19 treatment (bamlanivimab, casirivimab and imdevimab, or bamlanivimab and etesevimab). Under the conditions of the emergency use authorization (EUA) for each monoclonal antibody product, patients treated should have had a documented positive test for COVID-19 infection. Data available to the agency suggests that reinfection with SARS-CoV-2 is uncommon in the 90 days after initial infection. Based upon this low risk of reinfection and the estimated half-life of the monoclonal antibodies, the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) recommends COVID-19 vaccination be deferred for at least 90 days after treatment with a monoclonal antibody for COVID-19. This is a precautionary measure to avoid interference of monoclonal antibody treatment specifically with vaccine-induced immune responses. Updates to this recommendation may be made as additional information on the interaction between prior monoclonal antibody treatment and vaccine response becomes available.

FDA updates Sotrovimab emergency use authorization

Update [4/5/2022] Sotrovimab is no longer authorized to treat COVID-19 in any U.S. region due to increases in the proportion of COVID-19 cases caused by the Omicron BA.2 sub-variant

This statement updates the statements below.

The Centers for Disease Control and Prevention (CDC) Nowcast data (https://covid.cdc.gov/covid-data-tracker/#variant-proportions) from April 5, 2022, estimates that the proportion of COVID-19 cases caused by the Omicron BA.2 variant is above 50% in all Health and Human Services (HHS) U.S. regions. Data included in the health care provider fact sheet (https://www.fda.gov/media/149534/download) show the authorized dose of sotrovimab is unlikely to be effective against the BA.2 sub-variant. Due to these data, sotrovimab is not authorized in any U.S. state or territory at this time.

Health care providers should use other approved or authorized products (https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs) as they choose appropriate treatment options for patients.

FDA will continue to monitor BA.2 in all U.S. regions and will provide follow-up communication when appropriate.

Update [3/30/2022] FDA limits use of Sotrovimab to treat COVID-19 in additional U.S. regions due to the BA.2 Omicron sub-variant

This statement updates the statements below.

The Centers for Disease Control and Prevention (CDC) Nowcast data (https://covid.cdc.gov/covid-data-tracker/#variant-proportions) from March 29, 2022 estimates that the proportion of COVID-19 cases caused by the Omicron BA.2 variant is above 50% in three additional Health and Human Services (HHS) regions (5, 9, and 10). Due to these data, FDA has added these regions to the list of states and territories where sotrovimab is not authorized at this time.

Sotrovimab is not authorized at this time in the following states and territories:

- Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont (Region 1) (as of 3/25/2022)

- New Jersey, New York, Puerto Rico, and the Virgin Islands (Region 2) (as of 3/25/2022)
- Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin (Region 5) (as of 3/30/2022)
- Arizona, California, Hawaii, Nevada, American Samoa, Commonwealth of the Northern Mariana Islands, Federated States of Micronesia, Guam, Marshall Islands, and Republic of Palau (Region 9) (as of 3/30/2022)
- Alaska, Idaho, Oregon, and Washington (Region 10) (as of 3/30/2022)

Sotrovimab remains authorized in U.S. regions where the CDC Nowcast point estimate for the proportion of the Omicron BA.2 variant remains below 50%. FDA will continue to monitor BA.2 in all U.S. regions and may revise the authorization further to ensure that patients with COVID-19 have effective treatments available. Health care providers in regions where sotrovimab remains authorized should strongly consider the use of other approved or authorized products (https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs), and monitor the frequency of BA.2 in their region (https://covid.cdc.gov/covid-data-tracker/#variant-proportions) as they choose appropriate treatment options for patients.

Update [3/25/2022] FDA limits use of Sotrovimab to treat COVID-19 in some U.S. regions due to the BA.2 Omicron sub-variant

This statement updates and replaces the original statement below from 2/25/22.

The U.S. Food and Drug Administration is continually monitoring how authorized and approved treatments for COVID-19 are affected by changing variants—currently Omicron and the Omicron sub-variants, such as BA.2. Today, considering the most recent data available, FDA is announcing that sotrovimab is no longer authorized for use at this time in the following states and territories:

- Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont (Health and Human Services [HHS] Region 1)
- New Jersey, New York, Puerto Rico, and the Virgin Islands (HHS Region 2)

New data included in the health care provider fact sheet (/media/149534/download?attachment) shows that the authorized dose of sotrovimab is unlikely to be effective against the BA.2 sub-variant. Based on Centers for Disease Control and Prevention Nowcast data, the BA.2 sub-variant is estimated to account for more than 50% of cases in the states and territories in Regions 1 and 2 listed above (https://covid.cdc.gov/covid-data-tracker/#variant-proportions) as of March 19, 2022.

There are several other therapies (https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs) – Paxlovid, Veklury (remdesivir), bebtelovimab, and Lagevrio (molnupiravir) – that are expected to be effective against the BA.2 sub-variant, and that are authorized or approved to treat certain patients with mild-to-moderate COVID-19 who are at high risk for progression to severe disease, including hospitalization or death. Health care providers should assess whether these treatments are right for their patients.

We will continue to monitor BA.2 in all U.S. regions and may revise the authorization further to ensure that patients with COVID-19 have effective treatments available. Health care providers should also monitor the frequency of BA.2 in their region (https://covid.cdc.gov/covid-data-tracker/#variant-proportions) as they choose appropriate treatment options for patients.

[2/25/2022] On February 23, 2022, FDA revised the emergency use authorization for sotrovimab to clarify that sotrovimab is not authorized for treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a variant that is not susceptible to this treatment. However, sotrovimab is currently authorized in all U.S. regions until further notice by FDA. For other limitations and conditions, refer to the emergency use authorization (EUA) (https://www.fda.gov/media/149532/download).

FDA will continue to monitor conditions to determine whether use in a geographic region is consistent with the scope of authorization, referring to available information, including information on variant susceptibility and CDC regional variant frequency data (https://covid.cdc.gov/covid-data-tracker/#variant-proportions).

This EUA authorizes sotrovimab for the treatment of mild-to-moderate COVID-19 in adults and certain pediatric patients with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Sotrovimab should be administered by a qualified health care provider as a single intravenous infusion (IV) as soon as possible after positive viral test for COVID-19 and within seven days of symptom onset.

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR SOTROVIMAB

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use SOTROVIMAB under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for SOTROVIMAB.

SOTROVIMAB injection, for intravenous use
Original EUA Authorized Date: 05/2021

----------RECENT MAJOR CHANGES----------

Clinical Pharmacology, Microbiology (12.4)	3/2023
Emergency Use Authorization, Limitations of Authorized Use (1)	2/2022
Dosage and Administration, Recommended Dosage (2.3)	2/2022
Dosage and Administration, Preparation and Administration (2.5)	2/2022

----------EUA FOR SOTROVIMAB----------

- The Secretary of Health and Human Services has issued an EUA for the emergency use of sotrovimab for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

However, sotrovimab is not approved for this use (i.e., sotrovimab has not been demonstrated to be safe and effective for this use).

Limitations of Use:

- Sotrovimab is not authorized for treatment of mild-to-moderate COVID-19 when infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to these drugs and regional variant frequency (1, 12.4).
  - FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.
- Sotrovimab is not authorized for use in patients who:
  - are hospitalized due to COVID-19, OR
  - require oxygen therapy and/or respiratory support due to COVID-19, OR
  - require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 in those patients on chronic oxygen.

See Full Fact Sheet for Healthcare Providers for the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19 (1).

----------DOSAGE AND ADMINISTRATION----------

- The recommended dosage of sotrovimab in patients 12 years of age and older weighing at least 40 kg is 500 mg administered as a single intravenous infusion. (2.2)
- See Full Prescribing Information for instructions on preparation and administration. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 500 mg/8 mL (62.5 mg/mL) single-dose vial. (3)

----------CONTRAINDICATIONS----------

History of anaphylaxis to sotrovimab or to any of the excipients in the formulation. (4)

----------WARNINGS AND PRECAUTIONS----------

Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions: Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of sotrovimab. If clinically significant hypersensitivity reactions or anaphylaxis occur, discontinue and initiate appropriate supportive care. Infusion-related reactions have occurred during the infusion and up to 24 hours post infusion. These reactions may be severe or life threatening. (5.1)

Clinical Worsening After SARS-CoV-2 Monoclonal Antibody Administration: Clinical worsening of COVID-19 after administration of SARS-CoV-2 monoclonal antibody treatment has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, tachycardia, bradycardia), fatigue, and altered mental status. (5.2)

Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19: Benefit of treatment with sotrovimab has not been observed in patients hospitalized due to COVID-19. SARS-CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. (5.3)

----------ADVERSE REACTIONS----------

The most common adverse reactions (incidence ≥1%) included rash, diarrhea, infusion-related reactions, and hypersensitivity adverse reactions. (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to sotrovimab (1) by submitting FDA Form 3500 online, (2) by downloading this form and then submitting by mail or fax, or (3) contacting the FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to GSK, Global Safety: Fax: 919-287-2902; E-mail: WW.GSKAEReportingUS@gsk.com; or call GSK at 1-866-475-2684 to report adverse events. (6.4)

----------DRUG INTERACTIONS----------

Clinical drug-drug interaction studies have not been performed with sotrovimab. Sotrovimab is not renally excreted or metabolized by cytochrome P450 (CYP) enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely. (7)

See PATIENT AND PARENTS/CAREGIVER FACT SHEET.

TABLE OF CONTENTS*

* Sections or subsections omitted from the EUA are not listed

FULL FACT SHEET FOR HEALTHCARE PROVIDERS

1 EMERGENCY USE AUTHORIZATION

The Secretary of Health and Human Services (HHS) has issued an Emergency Use Authorization (EUA) for the emergency use of sotrovimab for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. However, sotrovimab is not approved for this use (i.e., sotrovimab has not been demonstrated to be safe and effective for this use).

LIMITATIONS OF AUTHORIZED USE

- Sotrovimab is not authorized for treatment of mild-to-moderate COVID-19 when infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to these drugs and regional variant frequency *[see Microbiology (12.4)]*.
  - FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.[1]
- Sotrovimab is not authorized for use in patients who:
  - are hospitalized due to COVID-19, OR
  - require oxygen therapy and/or respiratory support due to COVID-19, OR
  - require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 in those patients on chronic oxygen.

Benefit of treatment with sotrovimab has not been observed in patients hospitalized due to COVID-19. SARS-CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation *[see Warnings and Precautions (5.2)]*.

Sotrovimab is not FDA-approved for any use, including for the treatment of COVID-19.

Sotrovimab is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of sotrovimab under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Justification for Emergency Use of Drugs During the COVID-19 Pandemic

There is currently an outbreak of Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2, a novel coronavirus. The Secretary of HHS has declared that:

- A public health emergency related to COVID-19 has existed since January 27, 2020.
- Circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic (March 27, 2020 declaration).

An EUA is a Secretary of HHS authorization for the emergency use of an unapproved product or unapproved use of an approved product (i.e., drug, biological product, or device) in the United States under certain circumstances including, but not limited to, when the Secretary of HHS declares that

[1] FDA will monitor conditions to determine whether the use of sotrovimab is consistent with this scope of authorization, referring to available information, including information on variant susceptibility *[see Microbiology (12.4)]*, and the CDC national and/or regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions.

there is a public health emergency that affects the national security or the health and security of United States citizens living abroad, and that involves biological agent(s) or a disease or condition that may be attributable to such agent(s). Criteria for issuing an EUA include:

- The biological agent(s) can cause a serious or life-threatening disease or condition;
- Based on the totality of the available scientific evidence (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that
  - the product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition; and
  - the known and potential benefits of the product - when used to diagnose, prevent, or treat such disease or condition - outweigh the known and potential risks of the product, taking into consideration the material threat posed by the biological agent(s);
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the serious or life-threatening disease or condition.

Information Regarding Available Alternatives for the EUA Authorized Use

Veklury (remdesivir) is FDA-approved for the treatment of COVID-19 in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) who are hospitalized, or who are not hospitalized, have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death. Veklury is administered via intravenous infusion for a total treatment duration of 3 days in patients who are not hospitalized.

Although Veklury is an approved alternative treatment of mild-to-moderate COVID-19 in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) who are not hospitalized and have mild-to-moderate COVID-19, FDA does not consider Veklury to be an adequate alternative to sotrovimab for this authorized use because it may not be feasible or clinically appropriate for certain patients.

Other therapeutics are currently authorized under Emergency Use Authorization for the same use as sotrovimab. For additional information on all products authorized for treatment or prevention of COVID-19, please see https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

For information on clinical studies of sotrovimab and other therapies for the treatment of COVID-19, see www.clinicaltrials.gov.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Sotrovimab is authorized for the use in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death *[see Clinical Studies (14)]*.

Medical conditions or other factors that may place individual patients at higher risk for progression to severe COVID-19 are listed on the following CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html.

2.2 Important Administration Information

Sotrovimab should be administered intravenously within 7 days of symptom onset.

Sotrovimab should be administered by a qualified healthcare professional and administered only in settings which have immediate access to medications to treat a severe infusion reaction, such as

anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary *[see Warnings and Precautions (5.1)]*.

Sotrovimab is available as a concentrated solution and **must be diluted** prior to IV infusion.

Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

2.3 Recommended Dosage

The recommended dosage for emergency use of sotrovimab authorized under this EUA is 500 mg administered as a single IV infusion over 15 minutes for 50-mL infusion bag or 30 minutes for 100-mL infusion bag.

2.4 Dosage Adjustment in Special Populations

No dosage adjustment is recommended in pregnant or lactating women, in elderly patients, or in patients with renal impairment *[see Use in Specific Populations (8)]*.

Pediatric Use

No dosage adjustment is recommended in pediatric patients who weigh at least 40 kg and are 12 years of age and older.

Sotrovimab is not authorized for patients under 12 years of age or in pediatric patients weighing less than 40 kg *[see Use in Specific Populations (8.4)]*.

2.5 Preparation and Administration

Preparation

Sotrovimab is supplied in a single-dose vial and **must be diluted** prior to IV infusion.

Sotrovimab concentrate for solution for infusion should be prepared by a qualified healthcare professional using aseptic technique.

- Gather a polyvinyl chloride (PVC) or polyolefin (PO), sterile, prefilled 50-mL or 100-mL infusion bag containing 0.9% Sodium Chloride Injection or 5% Dextrose Injection.
- Remove one vial of sotrovimab (500 mg/8 mL) from refrigerated storage and allow to equilibrate to room temperature, protected from light, for approximately 15 minutes.
- Inspect the vial of sotrovimab visually for particulate matter and discoloration prior to administration. Should either be observed, the solution must be discarded, and fresh solution prepared. Sotrovimab is a clear, colorless or yellow to brown solution.
- Gently swirl the vial several times before use without creating air bubbles. **Do not shake the vial.**
- Withdraw 8 mL of sotrovimab from the vial and inject into the prefilled infusion bag.
- Discard vial (even if some product remains).
- Prior to the infusion, gently rock the infusion bag back and forth by hand 3 to 5 times. **Do not invert the infusion bag.** Avoid forming air bubbles.
- This product is preservative-free; therefore, the diluted infusion solution should be administered immediately. If immediate administration is not possible, store the diluted solution of sotrovimab up to 6 hours at room temperature (up to 25°C [77°F]) or refrigerated up to 24 hours (2°C to 8°C [36°F to 46°F]).

Administration

Sotrovimab infusion solution should be administered by a qualified healthcare professional *[see*

Warnings and Precautions (5.1)].

Sotrovimab may only be administered in settings in which healthcare providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary *[see Warnings and Precautions (5.1)]*.

- Gather the materials for IV infusion via infusion pump or gravity:
  - Polyvinyl chloride (PVC) or polyolefin (PO) infusion set, and
  - Use of a 0.2 micron polyethersulfone (PES) filter is strongly recommended.
- Attach the infusion set to the IV bag using standard bore tubing.
- Prime the infusion set.
- Administer the entire infusion over 15 minutes for 50-mL infusion bag or 30 minutes for 100-mL infusion bag. Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.
- Do not administer as an IV push or bolus.
- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of sotrovimab with IV solutions and medications other than 0.9% Sodium Chloride Injection and 5% Dextrose Injection is not known.
- Once infusion is complete, **flush the tubing** with 0.9% Sodium Chloride or 5% Dextrose to ensure delivery of the required dose.
- If the infusion must be discontinued due to an infusion reaction, discard unused product.
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

3 DOSAGE FORMS AND STRENGTHS

Sotrovimab is a sterile, preservative-free, clear, colorless or yellow to brown solution for IV infusion only available as:

- Injection: 500-mg/8-mL (62.5-mg/mL) solution in a single-dose vial

4 CONTRAINDICATIONS

Sotrovimab is contraindicated in patients who have a history of anaphylaxis to sotrovimab or to any of the excipients in the formulation.

5 WARNINGS AND PRECAUTIONS

There are limited clinical data available for sotrovimab. Serious and unexpected adverse events may occur that have not been previously reported with sotrovimab use.

5.1 Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of sotrovimab *[see Adverse Reactions (6.1)]*. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related reactions, occurring during the infusion and up to 24 hours after the infusion, have

been observed with administration of sotrovimab. These reactions may be severe or life threatening.

Signs and symptoms of infusion-related reactions may include *[see Adverse Reactions (6.1)]*:

- fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vaso-vagal reactions (e.g., pre-syncope, syncope), dizziness, and diaphoresis.

If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care. Clinically monitor patients for at least 1 hour after completion of the infusion for signs and symptoms of hypersensitivity.

Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of SARS-CoV-2 monoclonal antibodies under Emergency Use Authorization.

5.2 Clinical Worsening after SARS-CoV-2 Monoclonal Antibody Administration

Clinical worsening of COVID-19 after administration of SARS-CoV-2 monoclonal antibody treatment has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to SARS-CoV-2 monoclonal antibody use or were due to progression of COVID-19.

5.3 Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19

Benefit of treatment with sotrovimab has not been observed in patients hospitalized due to COVID-19. SARS-CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Therefore, sotrovimab is not authorized for use in the following patient populations *[see Limitations of Authorized Use (1)]*:

- Patients who are hospitalized due to COVID-19, OR
- Patients who require oxygen therapy and/or respiratory support due to COVID-19, OR
- Patients who require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 in those patients on chronic oxygen.

6 ADVERSE REACTIONS

The following serious adverse reaction is described in more detail in the *Warnings and Precautions* section of the labeling:

- Hypersensitivity including anaphylaxis and infusion related reactions *[see Warnings and Precautions (5.1)]*.

6.1 Adverse Reactions from Clinical Studies

The following adverse reactions have been observed in the clinical studies of sotrovimab that supported EUA. The adverse reaction rates observed in these clinical studies cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice. Additional adverse events associated with sotrovimab may become apparent with more widespread use.

The safety of sotrovimab in subjects with mild-to-moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized) is based on analyses from COMET-ICE and COMET-TAIL *[see Clinical Studies (14)]*.

In COMET-ICE, subjects received a single 500-mg IV infusion of sotrovimab (n = 523) or placebo (n = 526). In COMET-TAIL, subjects received a single 500-mg IV infusion of sotrovimab (n = 393).

Infusion-Related Reactions Including Hypersensitivity

Infusion-related reactions, including immediate hypersensitivity reactions, were observed in 1% of subjects treated with sotrovimab and 1% of subjects treated with placebo in COMET-ICE and in <1% of subjects treated with IV sotrovimab in COMET-TAIL. Reported events that started within 24 hours of study treatment were pyrexia, chills, dizziness, dyspnea, pruritus, rash, and infusion-related reactions; all events were Grade 1 (mild) or Grade 2 (moderate).

One case of anaphylaxis was reported following sotrovimab infusion in a separate study evaluating sotrovimab in hospitalized subjects; the infusion was immediately discontinued, and the subject received epinephrine. The event resolved but recurred within 2 hours; the subject received another dose of epinephrine and improved with no additional symptoms. Other serious infusion-related reactions (including immediate hypersensitivity reactions) reported following sotrovimab infusion in the hospitalized study included Grade 3 (serious) or Grade 4 (life-threatening) bronchospasm and shortness of breath. These events were also reported following infusion of placebo. Sotrovimab is not authorized for use in subjects hospitalized due to COVID-19 *[see Warnings and Precautions (5.3)]*.

Hypersensitivity adverse reactions (i.e., adverse events assessed as causally related) were observed in 2% of subjects treated with sotrovimab and 1% of subjects treated with placebo in COMET-ICE and in <1% of subjects treated with sotrovimab in COMET-TAIL. All were Grade 1 (mild) or Grade 2 (moderate), and none of the reactions in either trial led to permanent discontinuation of the infusions. One reaction led to pausing of the infusion *[see Warnings and Precautions (5.1)]*.

Common Adverse Events

The most common treatment-emergent adverse events observed in the sotrovimab treatment group in COMET-ICE were rash (1%) and diarrhea (2%), all of which were Grade 1 (mild) or Grade 2 (moderate). No other treatment-emergent adverse events were reported at a higher rate with sotrovimab compared to placebo.

6.2 Adverse Reactions from Spontaneous Reports

The following adverse reactions have been identified during post-authorization use of sotrovimab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders

Anaphylaxis *[see Contraindications (4), Warnings and Precautions (5.1)]*.

6.4 Required Reporting for Serious Adverse Events and Medication Errors

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events* and medication errors potentially related to sotrovimab within 7 calendar days from the healthcare provider's awareness of the event, using FDA Form 3500 (for information on how to access this form, see below). The FDA requires that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race)
- A statement "Sotrovimab use for COVID-19 under Emergency Use Authorization (EUA)" under the **"Describe Event, Problem, or Product Use/Medication Error"** heading
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the

event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes)

- Patient's preexisting medical conditions and use of concomitant products
- Information about the product (e.g., dosage, route of administration, NDC #)

Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online at www.fda.gov/medwatch/report.htm, or
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax to 1-800-FDA-0178, or
- Call 1-800-FDA-1088 to request a reporting form.
- In addition, please provide a copy of all FDA MedWatch forms to:

  GlaxoSmithKline, Global Safety
  Fax: 919-287-2902
  Email: WW.GSKAEReportingUS@gsk.com
  Or call GSK at 1-866-475-2684 to report adverse events.

The prescribing health care provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of sotrovimab.

*Serious adverse events are defined as:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- Other important medical event, which may require a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

7 DRUG INTERACTIONS

Clinical drug-drug interaction studies have not been performed with sotrovimab. Sotrovimab is not renally excreted or metabolized by cytochrome P450 (CYP) enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to sotrovimab during pregnancy. Pregnant and recently pregnant individuals can go to https://covid-pr.pregistry.com to enroll or call 1-800-616-3791 to obtain information about the registry.

Risk Summary

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcome. Sotrovimab should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy *(see Clinical Considerations)*.

Nonclinical reproductive toxicity studies have not been conducted with sotrovimab. In a cross-reactive binding assay using a protein array enriched for human embryofetal proteins, no off-target binding was detected for sotrovimab. Since sotrovimab is a recombinant human immunoglobulin G (IgG) containing the LS modification in the Fc domain, it has the potential for placental transfer from the mother to the developing fetus. The potential treatment benefit or risk of placental transfer of sotrovimab to the developing fetus is not known.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk

COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

8.2 Lactation

Risk Summary

There are no available data on the presence of sotrovimab in human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for sotrovimab and any potential adverse effects on the breastfed infant from sotrovimab or from the underlying maternal condition. Individuals with COVID-19 who are breastfeeding should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

8.4 Pediatric Use

Sotrovimab is not authorized for use in pediatric patients under 12 years of age or weighing less than 40 kg. The safety and effectiveness of sotrovimab have not been assessed in pediatric patients. The recommended dosing regimen in patients 12 years to less than 18 years of age, weighing at least 40 kg, is expected to result in comparable serum exposures of sotrovimab as those observed in adults.

8.5 Geriatric Use

Of the 528 subjects randomized to receive sotrovimab 500 mg in COMET-ICE, 20% were 65 years of age and older and 11% were over 70 years of age. Of the 378 subjects in the primary analysis

population receiving sotrovimab 500 mg in COMET-TAIL, 25% were 65 years of age or older and 8% were over 75 years of age. In these trials, no notable differences in PK or safety were observed in geriatric subjects as compared to subjects less than 65 years of age.

8.6 Renal Impairment

No clinical trials have been conducted to evaluate the effects of renal impairment on the PK of sotrovimab. Sotrovimab is not eliminated intact in the urine, thus renal impairment is not expected to affect the exposure of sotrovimab.

8.7 Hepatic Impairment

No clinical trials have been conducted to evaluate the effects of hepatic impairment on the PK of sotrovimab. The impact of hepatic impairment on the PK of sotrovimab is unknown.

10 OVERDOSAGE

There is no human experience of acute overdosage with sotrovimab.

There is no specific treatment for an overdose with sotrovimab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

11 DESCRIPTION

Sotrovimab is a human immunoglobulin G-1 (IgG1-kappa) monoclonal antibody consisting of 2 identical light chain (LC) polypeptides composed of 214 amino acids each and 2 identical heavy chain (HC) polypeptides, each composed of 457 amino acids. Sotrovimab is produced by a Chinese Hamster Ovary cell line and has a molecular weight of approximately 149 kDa.

Sotrovimab injection is a sterile, preservative-free, clear, colorless or yellow to brown solution supplied in a single-dose vial for IV infusion after dilution.

Each mL contains sotrovimab (62.5 mg), L-histidine (1.51 mg), L-histidine monohydrochloride (2.15 mg), L-methionine (0.75 mg), polysorbate 80 (0.4 mg), and sucrose (70 mg). The solution of sotrovimab has a pH of 6.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sotrovimab is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antiviral drug ***[see Microbiology (12.4)]***.

12.3 Pharmacokinetics

A summary of pharmacokinetic parameters following a single 500-mg IV infusion is presented in Table 1 based on population pharmacokinetic analyses:

Table 1. Summary of IV Sotrovimab Serum Pharmacokinetic Exposure Parameters

Parameter[a]	Sotrovimab (500 mg IV)
C_{max}, mcg/mL	170.1 (53.4)
C_{D28}, mcg/mL	39.7 (37.6)
AUC_{D0-28}[b], day*mcg/mL	1564 (34.4)

[a] Parameters are reported as geometric mean (Geometric %CV).

[b] Based on a population pharmacokinetic analysis using data from a total of 1984 subjects across 5 clinical trials.

The primary analysis in the clinical efficacy study COMET-ICE was conducted when the ancestral Wuhan-Hu-1 virus was predominant, with the most common SARS-CoV-2 variants being Alpha and Epsilon among participants in the study population, which was enrolled prior to the emergence of the Delta and Omicron variants (Table 3).

Specific Populations

Based on available population pharmacokinetic analyses of sotrovimab dosages of 500 mg or less, the pharmacokinetics of sotrovimab administered intravenously were not affected by age or sex; body weight was identified as a significant covariate on the pharmacokinetics of sotrovimab, but the impact is not anticipated to be clinically relevant.

Renal impairment is not expected to impact the pharmacokinetics of sotrovimab since mAbs with molecular weight >69 kDa do not undergo renal elimination. Similarly, dialysis is not expected to impact the pharmacokinetics of sotrovimab.

12.4 Microbiology

Mechanism of Action

Sotrovimab is a recombinant human IgG1-kappa mAb that binds to a conserved epitope on the spike protein receptor binding domain of SARS-CoV-2 with a dissociation constant of K_D = 0.21 nM but does not compete with human ACE2 receptor binding (IC_{50} value >33.6 nM [5 µg/mL]). Sotrovimab inhibits an undefined step that occurs after virus attachment and prior to fusion of the viral and cell membranes. The Fc domain of sotrovimab includes M428L and N434S amino acid substitutions (LS modification) that extend antibody half-life, but do not impact wild-type Fc-mediated effector functions in cell culture.

Antiviral Activity

The neutralization activity of sotrovimab against SARS-CoV-2 (isolate WA1/2020) was measured in a concentration response model using cultured Vero E6 cells. Sotrovimab neutralized SARS-CoV-2 with an average EC_{50} value of 0.67 nM (100.1 ng/mL).

Sotrovimab demonstrated cell culture FcγR activation using Jurkat reporter cells expressing FcγRIIa (low-affinity R131 and high affinity H131 alleles), FcγRIIIa (low-affinity F158 and high-affinity V158 alleles), and FcγRIIb. Sotrovimab exhibited antibody-dependent cell-mediated cytotoxicity (ADCC) in cell culture using isolated human natural killer (NK) cells following engagement with target cells expressing spike protein. Sotrovimab also elicited antibody-dependent cellular phagocytosis (ADCP) in cell-based assays using $CD14^+$ monocytes targeting cells expressing spike protein.

Antibody Dependent Enhancement (ADE) of Infection

The risk that sotrovimab could mediate viral uptake and replication by immune cells was studied in U937 cells, primary human monocytic dendritic cells, and peripheral blood mononuclear cells. This

experiment did not demonstrate productive viral infection in immune cells exposed to SARS-CoV-2 in the presence of concentrations of sotrovimab from 1-fold down to 1000-fold below the EC_{50} value.

The potential for ADE was also evaluated in a hamster model of SARS-CoV-2 using sotrovimab. Intraperitoneal administration prior to inoculation resulted in a dose-dependent improvement in all measured outcomes (body weight, total viral RNA in the lungs, or infectious virus levels based on $TCID_{50}$ measurements). No evidence of enhancement of disease was observed at any dose evaluated, including sub-neutralizing doses down to 0.05 mg/kg.

Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to sotrovimab.

Cell Culture Studies: Spike protein amino acid substitution E340A emerged in cell culture selection of resistant virus and had a >100-fold reduction in activity in a pseudotyped virus-like particle (VLP) assay. This substitution is in the conserved epitope of sotrovimab, which is comprised of 23 amino acids. Pseudotyped VLP assessments in cell culture were performed using Wuhan-Hu-1, Omicron BA.1, and Omicron BA.2 spike proteins. The epitope amino acid substitutions P337H/K/L/N/R/T, E340A/I/K/G/Q/S/V, T345P, K356T, and L441N in the Wuhan-Hu-1 spike, conferred reduced susceptibility to sotrovimab based on observed fold-increase in EC_{50} value shown in parentheses: P337H (5.1), P337K (>304), P337L (>192), P337N (5.6), P337R (>192), P337T (10.6), E340A (>100), E340G (18.2), E340I (>190), E340K (>297), E340Q (>50), E340S (68), E340V (>200), T345P (225), K356T (5.9), and L441N (72). Epitope substitutions P337H (>631), K356T (>631), P337S (>609), E340D (>609), and V341F (5.9) in the Omicron BA.1 spike variant, and P337H (>117), P337S (>117), P337T (>117), E340D (>117), E340G (>117), K356T (>117), and K440D (5.1) in the Omicron BA.2 spike variant conferred reduced susceptibility to sotrovimab based on the observed fold-increase in EC_{50} value shown in parenthesis relative to each spike viral variant.

Table 2 provides cell culture neutralization data for SARS-CoV-2 variants. The clinical relevance of the fold reductions in susceptibility >5 is unknown. There are no data evaluating variants with fold reductions >5 in randomized controlled clinical studies.

Table 2. Sotrovimab Neutralization Data for SARS-CoV-2

SARS-CoV-2 Variant		Key Substitutions Tested[a]	Fold Reduction in Susceptibility[b]	
Lineage	WHO Nomenclature		Pseudotyped VLP	Authentic Virus
B.1.1.7	Alpha	N501Y	No change	No change
B.1.351	Beta	K417N+E484K+N501Y	No change	No change
P.1	Gamma	K417T+E484K+N501Y	No change	No change
B.1.617.2	Delta	L452R+T478K	No change	No change
AY.1 and AY.2	Delta [+K417N]	K417N+L452R+T478K	No change	Not tested
AY.4.2	Delta [+]	L452R+T478K	No change	Not tested
B.1.427/B.1.429	Epsilon	L452R	No change	Not tested
B.1.526	Iota	E484K	No change	Not tested
B.1.617.1	Kappa	L452R+E484Q	No change	No change
C.37	Lambda	L452Q+F490S	No change	Not tested
B.1.621	Mu	R346K+E484K+N501Y	No change	Not tested

B.1.1.529/BA.1	Omicron	G339D+S371L+S373P+ S375F+K417N+N440K+ G446S+S477N+T478K+ E484A+Q493R+G496S+ Q498R+N501Y+Y505H	No change	No change
BA.1.1	Omicron	G339D+R346K+S371L+ S373P+S375F+K417N+ N440K+G446S+S477N+ T478K+E484A+Q493R+ G496S+Q498R+N501Y+ Y505H	No change	No change
BA.2	Omicron	G339D+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ S477N+T478K+E484A+ Q493R+Q498R+N501Y+ Y505H	16	15.7[c]
BA.2.12.1	Omicron	G339D+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ L452Q+S477N+T478K+ E484A+Q493R+Q498R+ N501Y+Y505H	16.6	25.1[c]
BA.2.75	Omicron	G339H+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ G446S+N460K+S477N+ T478K+E484A+Q498R+ N501Y+Y505H	8.3	Not tested
BA.2.75.2	Omicron	G339H+R346T+S371F+ S373P+S375F+T376A+ D405N+R408S+K417N+ N440K+G446S+N460K+ S477N+T478K+E484A+ F486S+Q498R+N501Y+ Y505H	10	Not tested
BA.3	Omicron	G339D+S371F+S373P+ S375F+D405N+K417N+ N440K+G446S+S477N+ T478K+E484A+Q493R+ Q498R+N501Y+Y505H	7.3	Not tested
BA.4	Omicron	G339D+S371F+S373P+ S375F+T376A+D405N+	21.3	48.4[c]

		R408S+K417N+N440K+ L452R+S477N+T478K+ E484A+F486V+Q498R+ N501Y+Y505H		
BA.4.6	Omicron	G339D+R346T+S371F+ S373P+S375F+T376A+ D405N+R408S+K417N+ N440K+L452R+S477N+ T478K+E484A+F486V+ Q498R+N501Y+Y505H	57.9	Not tested
BA.5	Omicron	G339D+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ L452R+S477N+T478K+ E484A+F486V+Q498R+ N501Y+Y505H	22.6	21.6[c]
BF.7/BA.5.2.6	Omicron	G339D+R346T+S371F+ S373P+S375F+T376A+ D405N+R408S+K417N+ N440K+L452R+S477N+ T478K+E484A+F486V+ Q498R+N501Y+Y505H	74.2	Not tested
BN.1	Omicron	G339H+R346T+K356T+ S371F+S373P+S375F+ T376A+D405N+R408S+ K417N+N440K+G446S+ N460K+S477N+T478K+ E484A+F490S+Q498R+ N501Y+Y505H	778	Not tested
BQ.1	Omicron	G339D+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ K444T+L452R+N460K+ S477N+T478K+E484A+ F486V+Q498R+N501Y+ Y505H	28.5	Not tested
BQ.1.1	Omicron	G339D+R346T+S371F+ S373P+S375F+T376A+ D405N+R408S+K417N+ N440K+K444T+L452R+ N460K+S477N+T478K+ E484A+F486V+Q498R+ N501Y+Y505H	94	Not tested

XBB/XBB.1	Omicron	G339H+R346T+L368I+ S371F+S373P+S375F+ T376A+D405N+R408S+ K417N+N440K+V445P+ G446S+N460K+S477N+ T478K+E484A+F486S+ F490S+Q498R+N501Y+ Y505H	6.5	Not tested
XBB.1.5	Omicron	G339H+R346T+L368I+ S371F+S373P+S375F+ T376A+D405N+R408S+ K417N+N440K+V445P+ G446S+N460K+S477N+ T478K+E484A+F486P+ F490S+Q498R+N501Y+ Y505H	11.3	33.3[c]
XD	None[d]	G339D+S371L+S373P+ S375F+K417N+N440K+ G446S+S477N+T478K+ E484A+Q493R+G496S+ Q498R+N501Y+Y505H	Not tested	No change

[a] Substitutions in the spike receptor binding domain relative to wild-type are listed.

[b] Based on EC_{50} fold change compared to wild-type. No change: ≤5-fold change in EC_{50} value compared to wild-type.

[c] Sotrovimab inhibited authentic virus isolates of Omicron BA.2, BA.2.12.1, BA.4, BA.5, and XBB.1.5 lineages with maximum percentage inhibition in the range of 80% to 100%.

[d] Variant has not been named by the WHO.

Clinical Studies: SARS-CoV-2 variants of concern or variants of interest (VOC/VOI) were detected in participants enrolled in COMET-ICE (Table 3).

Table 3. SARS-CoV-2 VOC/VOI Detected at ≥2% Prevalence in Sotrovimab-Treated Participants

Clinical Study	VOC/VOI	Prevalence, % (n/N)[a]	Participants Meeting Primary Clinical Endpoint[b]
COMET-ICE	Alpha (B.1.1.7)	10% (35/338)	1
	Epsilon (B.1.427/B.1.429)	5% (16/338)	1
	Gamma (P.1)	3% (9/338)	0

[a] n = number of sotrovimab-treated participants with the designated VOC/VOI; N = total number of sotrovimab-treated participants with SARS-CoV-2 spike sequence results.

[b] The primary clinical endpoint for progression was defined as hospitalization for >24 hours for acute management of any illness or death from any cause through Day 29.

SARS-CoV-2 viruses with baseline and treatment-emergent substitutions at amino acid positions associated with reduced susceptibility to sotrovimab in cell culture were observed in COMET-ICE

(Table 4). Of the 32 sotrovimab-treated participants with a substitution detected at amino acid positions 337 and/or 340 at any visit baseline or post-baseline, only 1 met the primary endpoint for progression of hospitalization for >24 hours for acute management of any illness or death from any cause through Day 29. This participant had E340K detected post-baseline and was infected with the Epsilon variant of SARS-CoV-2.

Table 4. Baseline and Treatment-Emergent Substitutions Detected in Sotrovimab-Treated Participants at Amino Acid Positions Associated with Reduced Susceptibility to Sotrovimab

	Baseline[a]		Treatment-Emergent[b]	
Clinical Study	Substitutions	Frequency, % (n/N)	Substitutions	Frequency, % (n/N)
COMET-ICE	P337H, E340A	1% (4/307)	P337L/R, E340A/K/V	14% (24/170)[c]

[a] n = number of sotrovimab-treated participants with a baseline substitution detected at spike amino acid positions 337 or 340; N = total number of sotrovimab-treated participants with baseline sequence results.

[b] n = number of sotrovimab-treated participants with treatment-emergent substitutions detected at spike amino acid positions 337 or 340; N = total number of sotrovimab-treated participants with paired baseline and post-baseline sequence results.

[c] Four participants with a post-baseline substitution at P337 or E340 and lacking a baseline sequence are not included.

Immune Response Attenuation

There is a theoretical risk that antibody administration may attenuate the endogenous immune response to SARS-CoV-2 and make patients more susceptible to re-infection.

12.6 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies may be misleading.

Treatment-emergent anti-drug antibodies (ADAs) to sotrovimab were detected in 13% (65/513) of participants, through week 24, in the COMET-ICE study. None of the participants with confirmed treatment-emergent ADAs had neutralizing antibodies against sotrovimab.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis, mutagenesis, and reproductive toxicology studies with sotrovimab have not been conducted.

In a toxicology study in monkeys, sotrovimab had no adverse effects when administered intravenously.

In tissue cross reactivity studies using human and monkey adult tissues, no binding of clinical concern was detected for sotrovimab.

13.2 Animal Toxicology and/or Pharmacology

In a Syrian Golden hamster model of SARS-CoV-2 infection, antiviral activity was demonstrated using a single dose of sotrovimab which was administered intraperitoneally at 24- or 48-hours prior to infection. Animals receiving 5 mg/kg or more of the antibody showed a significant improvement in body weight loss and significantly decreased total lung SARS-CoV-2 viral RNA compared to vehicle only and control antibody-treated animals. Levels of virus in the lung (as measured by $TCID_{50}$) were significantly decreased versus controls in hamsters receiving 0.5 mg/kg or more of the antibody.

Protection was also observed in the Syrian Golden hamster model using the SARS-CoV-2 B.1.351 (Beta, South Africa origin) variant. Significant reductions in total and replication competent virus were observed on Day 4 post-infection in animals receiving a single intraperitoneal dose of 0.5, 2, 5, or 15 mg/kg sotrovimab compared to isotype control antibody-treated animals.

14 CLINICAL STUDIES

The clinical data supporting this EUA are based on the analysis of the Phase 1/2/3 COMET-ICE trial (NCT04545060) with supporting data from the Phase 3 COMET-TAIL trial (NCT04913675).

COMET-ICE (Study 214367)

COMET-ICE was a randomized, multi-center, double-blind, placebo-controlled trial studying sotrovimab for the treatment of subjects with mild-to-moderate COVID-19 (subjects with COVID-19 symptoms who were not hospitalized). Eligible subjects were 18 years of age and older with at least one of the following comorbidities: diabetes, obesity (BMI >30), chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, or moderate to severe asthma; or were 55 years of age and older regardless of comorbidities. The trial included symptomatic subjects with SARS-CoV-2 infection as confirmed by local laboratory tests and/or point of care tests and symptom onset within 5 days of enrollment. The study was conducted when the wild-type Wuhan-Hu-1 virus was predominant, with the highest frequency of variants being Alpha and Epsilon *[see Microbiology (12.4)]*. Subjects with severe COVID-19 requiring supplemental oxygen or hospitalization and severely immunocompromised subjects were excluded from the trial.

A total of 1,057 eligible subjects were randomized to receive a single 500-mg infusion of sotrovimab (n = 528) or placebo (n = 529) over 1 hour (Intent to Treat [ITT] population at Day 29). At baseline, the median age was 53 years (range:17 to 96); 20% of subjects were 65 years of age or older and 11% were over 70 years of age; 46% of subjects were male; 87% were White, 8% Black or African American, 4% Asian, 65% Hispanic or Latino. Fifty-nine percent of subjects received sotrovimab or placebo within 3 days of COVID-19 symptom onset and 41% within 4 to 5 days. The four most common pre-defined risk factors or comorbidities were obesity (63%), 55 years of age or older (47%), diabetes requiring medication (22%), and moderate-to-severe asthma (17%). Overall, baseline demographic and disease characteristics were well balanced between the treatment arms.

The primary endpoint, progression of COVID-19 at Day 29, was reduced by 79% (adjusted relative risk reduction) in recipients of sotrovimab versus placebo. Table 5 provides the results for the primary and key secondary endpoint of COMET-ICE.

Table 5. Efficacy Results in Adults with Mild-to-Moderate COVID-19 in COMET-ICE at Day 29

	Sotrovimab 500 mg n = 528	Placebo n = 529
Progression of COVID-19 (defined as hospitalization for >24 hours for acute management of any illness or death from any cause) (Day 29)[a]		
Proportion (n, %)	6 (1.1%)	30 (5.7%)
Adjusted Relative Risk Reduction (95% CI)	79% (50%, 91%)	
All-cause mortality (up to Day 29)		
Proportion (n, %)	0	2 (<1%)

[a] The determination of primary efficacy was based on a planned interim analysis of 583 subjects, which had similar findings to those seen in the full population above. The adjusted relative risk reduction was 85% with a 97.24% CI of (44%, 96%) and p-value = 0.002.

Within the subset of the ITT population who had a central laboratory confirmed, virologically quantifiable nasopharyngeal swab at Day 1 and Day 8 (n = 639), the mean decline in viral RNA levels from baseline to Day 8 was greater in subjects treated with sotrovimab (-2.610 $\log_{10}$ copies/mL) compared to that in subjects treated with placebo (-2.358); mean difference = -0.251, 95% CI: (-0.415, -0.087).

COMET-TAIL (Study 217114)

COMET-TAIL was a randomized, multi-center, open label trial which evaluated the efficacy, safety, and tolerability of sotrovimab for the treatment of subjects with mild-to-moderate COVID-19 (subjects with COVID-19 symptoms who were not hospitalized). Eligible subjects were 12 years of age or older with at least one of the following comorbidities: diabetes, obesity (BMI ≥85th percentile for age/gender based on Centers for Disease Control and Prevention [CDC] growth charts for adolescents or BMI ≥30 for subjects ≥18 years old), chronic kidney disease, congenital heart disease, congestive heart failure (for subjects ≥18 years old), chronic lung diseases, sickle cell disease, neurodevelopmental disorders, immunosuppressive disease or receiving immunosuppressive medications, or chronic liver disease; or were 55 years of age or older regardless of comorbidities. The trial included symptomatic subjects with SARS-CoV-2 infection as confirmed by local laboratory tests and/or point of care tests and symptom onset within 7 days of enrollment. Subjects with severe COVID-19 requiring supplemental oxygen or hospitalization were excluded from the trial.

The ITT population consisted of 385 subjects randomized to receive a single 500-mg IV infusion of sotrovimab over 15 minutes. The primary analysis population, which excluded 7 subjects because they were fully vaccinated and immunocompetent (key inclusion/exclusion violation), consisted of 378 subjects.

In the primary analysis population at baseline, the median age was 51 years (range:15 to 90, including 2 subjects under 18 years); 25% of subjects were 65 years of age or older and 8% were over 75 years of age; 42% of subjects were male; 96% were White and 4% were Black or African American; 83% were Hispanic or Latino. Forty-eight percent (48%) of subjects received sotrovimab within 3 days of COVID-19 symptom onset, 37% within 4 to 5 days, and 14% within 6 to 7 days. The four most common pre-defined risk factors or comorbidities were obesity (63%), 55 years of age or older (42%), chronic lung disease (16%), and diabetes requiring medication (13%).

In the primary analysis population, 5 (1.3%) of 378 subjects had progression to COVID-19 defined as hospitalization for >24 hours for acute management of any illness or death due to any cause through Day 29. No deaths were reported through Day 29.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Sotrovimab injection 500 mg (62.5 mg/mL) is a sterile, preservative-free, clear, colorless or yellow to brown solution supplied in a carton containing one single-dose glass vial with a rubber vial stopper (not made with natural rubber latex) and a flip-off cap (NDC 0173-0901-86).

Storage and Handling

Sotrovimab is preservative-free. Discard unused portion.

Store unopened vials refrigerated at 2°C to 8°C (36°F to 46°F) in original carton. Do not freeze or shake. Protect from light.

The concentrate for solution of sotrovimab in the vial is preservative-free and requires dilution prior to IV administration. The diluted infusion solution of sotrovimab should be administered immediately. If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) or up to 6 hours at room temperature (up to 25°C [up to 77°F]) including transportation and infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 15 minutes prior to administration.

17 PATIENT COUNSELING INFORMATION

As a healthcare practitioner, you must communicate to the patient and/or caregiver information consistent with the "FACT SHEET FOR PATIENTS AND CAREGIVERS" and provide them with a copy of this Fact Sheet prior to administration of sotrovimab. However, if providing this information will delay the administration of sotrovimab to a degree that would endanger the life of a patient, the information must be provided to the parent and/or caregiver as soon as feasible after sotrovimab administration.

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of sotrovimab. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, advise patients to alert healthcare provider immediately. Inform patients that hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of SARS-CoV-2 monoclonal antibodies and to alert their healthcare provider immediately if signs and symptoms of hypersensitivity occur *[see Warnings and Precautions (5.1)]*.

Pregnancy Registry

Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in individuals exposed to sotrovimab during pregnancy *[see Use in Specific Populations (8.1)]*.

18 MANUFACTURER INFORMATION

Trademark is owned by or licensed to the GSK group of companies.

Manufactured by **GlaxoSmithKline LLC**

Philadelphia, PA 19104, U.S. License No. 1727

Distributed by **GlaxoSmithKline**

Durham, NC 27701

STR:9FS-HCP

Revised: March 2023

FDA U.S. FOOD & DRUG ADMINISTRATION

May 25, 2023

Pfizer, Inc.
Attention: Karen Baker
Director, Global Regulatory Affairs
235 East 42nd Street
New York, NY 10017-5755

RE: Emergency Use Authorization 105

Dear Ms. Baker:

This letter is in response to Pfizer, Inc.'s (Pfizer) request that the Food and Drug Administration (FDA or Agency) issue an Emergency Use Authorization (EUA) for the emergency use of PAXLOVID (nirmatrelvir co-packaged with ritonavir) for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in certain adults and pediatric patients pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §360bbb-3).

On February 4, 2020, as amended on March 15, 2023, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency, or a significant potential for a public health emergency, that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19).[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[2]

On December 22, 2021, the FDA issued an EUA for emergency use of PAXLOVID for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and

[1] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3.* February 4, 2020; U.S. Department of Health and Human Services, *Amended Determination of a Public Health Emergency or Significant Potential for a Public Health Emergency Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3(b).* March 15, 2023. 88 FR 16644 (March 20, 2023) ("Amended Determination").

[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020). *See* Amended Determination ("The declarations issued pursuant to section 564(b)(1) of the FD&C Act that circumstances exist justifying the authorization of emergency use of certain in vitro diagnostics, personal respiratory protective devices, other medical devices and drugs and biological products, as set forth in those declarations, and that are based on the February 4, 2020 determination, remain in effect until those declarations are terminated in accordance with section 564 of the FD&C Act.").

older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. At that time, PAXLOVID was not FDA-approved for any indication.

PAXLOVID is comprised of nirmatrelvir, a SARS-CoV-2 main protease inhibitor (M^{pro}: also referred to as $3CL^{pro}$ or nsp5 protease), co-packaged with ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor. Ritonavir, which has no activity against SARS-CoV-2 on its own, is included to inhibit the CYP3A-mediated metabolism of nirmatrelvir and consequently increase nirmatrelvir plasma concentrations to levels anticipated to inhibit SARS-CoV-2 replication.

FDA subsequently reissued the Letter of Authorization (LOA) on March 17, 2022[3], April 14, 2022[4], July 6, 2022[5], August 5, 2022[6], October 27, 2022[7], and February 1, 2023.[8]

On May 25, 2023, FDA approved NDA 217188 for PAXLOVID, which is indicated for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.

On May 25, 2023, having concluded that revising this EUA is appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA is reissuing the February 1, 2023 letter in its entirety, to incorporate revisions to the authorized use for PAXLOVID under this EUA, to revise condition L on the monitoring and analysis of SARS-CoV-2 variants, and to remove certain post-authorization requirements from this LOA that are adequately addressed as post-market requirements or post-market commitments associated with the approval of NDA 217188.

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[3] In its March 17, 2022 revision, FDA revised the LOA to add a new condition of authorization regarding registration and listing. Condition H in the LOA was also revised to require Pfizer to recall distributed product, upon request by FDA, in the event a significant quality problem is identified that impacts already distributed PAXLOVID.

[4] In its April 14, 2022 revision, FDA revised the LOA to authorize an additional dose pack presentation of PAXLOVID with appropriate dosing for patients within the scope of this authorization with moderate renal impairment. Corresponding revisions were also incorporated into the "How Supplied" section of the Fact Sheet for Healthcare Providers.

[5] In its July 6, 2022 revision, FDA authorized state-licensed pharmacists to prescribe PAXLOVID subject to certain conditions detailed in Section II (Scope of Authorization) of this LOA. Corresponding revisions were also incorporated into the Fact Sheet for Healthcare Providers. Updates were also incorporated to certain post-authorization requirements detailed in Condition O of this letter.

[6] In its August 5, 2022 revision, FDA revised the LOA to add new post-authorization requirements in Condition O of this letter for Pfizer to conduct a clinical trial in patients with "COVID-19 rebound" and a clinical trial evaluating different durations of treatment in immunocompromised patients with mild-to-moderate COVID-19. The Fact Sheet for Patients, Parents, and Caregivers was also revised to include additional clarifying information on how to take PAXLOVID, which included pictures of packaging and tablets for both dosing presentations.

[7] In its October 27, 2022 revision, FDA incorporated clarifying revisions to Condition X of this letter. Condition W was also revised to require that all printed matter, advertising and promotional materials relating to the use of PAXLOVID under this authorization be submitted to FDA for consideration at least 14 calendar days prior to initial dissemination or first use.

[8] In its February 1, 2023 revision, FDA revised the scope of authorization to no longer require positive results of direct SARS-CoV-2 viral testing. As revised, the scope of authorization required, in addition to other requirements, that adults and pediatric patients (12 years of age and older weighing at least 40 kg) have a current diagnosis of mild-to-moderate COVID-19. Corresponding changes were also made to the authorized Fact Sheets. Condition O in this letter was also revised based on the completion of a post-authorization requirement. The Fact Sheet for Healthcare Providers was also revised to reflect the current indication for Veklury, an approved alternative to Paxlovid, and to include new information on drug-drug interactions.

Corresponding revisions, when appropriate, were incorporated into the authorized Fact Sheets. The authorized Fact Sheet for Healthcare Providers was also revised to include a boxed warning on the identification of and assessment for drug-drug interactions with PAXLOVID. Relevant information on drug-drug interactions was also incorporated in the Fact Sheet for Patients, Parents and Caregivers.

Based on the totality of scientific evidence available to FDA, including data from the clinical trial EPIC-HR (NCT04960202), a Phase 2/3 randomized, double blind, placebo-controlled clinical trial, it is reasonable to believe that PAXLOVID may be effective for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (Section II), and when used under the conditions described in this authorization, the known and potential benefits of PAXLOVID outweigh the known and potential risks of such product.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of PAXLOVID for the treatment of mild-to-moderate COVID-19 in certain adults and pediatric patients (12 years of age and older weighing at least 40 kg), as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of PAXLOVID for the treatment of COVID-19, when administered as described in the Scope of Authorization (Section II), meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

1. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that PAXLOVID may be effective for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (Section II), and that, when used under the conditions described in this authorization, the known and potential benefits of PAXLOVID outweigh the known and potential risks of such product; and

3. There is no adequate, approved, and available alternative to the emergency use of PAXLOVID for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death.[9,10]

[9] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.
[10] Veklury (remdesivir) is an FDA-approved alternative to PAXLOVID when used for the treatment of mild-to-

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Distribution of the authorized PAXLOVID will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Pfizer will supply PAXLOVID to authorized distributor(s)[11], who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed;

- PAXLOVID may only be used by healthcare providers for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death;

  Limitations on Authorized Use

  - PAXLOVID is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.[12]
  - PAXLOVID is not authorized for use as pre-exposure or as post-exposure prophylaxis for prevention of COVID-19.
  - PAXLOVID is not authorized for use for longer than 5 consecutive days.

- PAXLOVID may be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs.[13]

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moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death. Veklury is administered via intravenous infusion for a total treatment duration of 3 days. Although Veklury is an FDA-approved alternative to PAXLOVID as described above, FDA does not consider Veklury to be an adequate alternative to PAXLOVID for this authorized use because it may not be feasible or practical for certain patients (e.g., it requires an intravenous infusion daily for 3 days). Additionally, although different presentations of PAXLOVID are now FDA-approved for the treatment of mild-to-moderate COVID-19 in certain adults, there are not sufficient quantities of the approved PAXLOVID available for distribution to this population in its entirety at the time of reissuance of the EUA, and PAXLOVID is not FDA-approved for individuals younger than 18 years of age. Apart from the previous sentence, all reference to the term "PAXLOVID" in this LOA refer to product that is labeled in accordance with this EUA. See "Product Description" in this LOA for more information.

[11] "Authorized Distributor(s)" are identified by Pfizer as an entity or entities allowed to distribute authorized PAXLOVID.

[12] Patients requiring hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID may complete the full 5-day treatment course per the healthcare provider's discretion.

[13] The term "State" includes any State or Territory of the United States, the District of Columbia, and the Commonwealth of Puerto Rico. See Section 201(a)(1) of the Act.

- PAXLOVID may also be prescribed for an individual patient by a state-licensed pharmacist under the following conditions:

    - Sufficient information is available, such as through access to health records less than 12 months old or consultation with a health care provider in an established provider-patient relationship with the individual patient, to assess renal and hepatic function; and
    - Sufficient information is available, such as through access to health records, patient reporting of medical history, or consultation with a health care provider in an established provider-patient relationship with the individual patient, to obtain a comprehensive list of medications (prescribed and non-prescribed) that the patient is taking to assess for potential drug interaction.

- The use of PAXLOVID covered by this authorization must be in accordance with the authorized Fact Sheets.

Product Description

PAXLOVID consists of 150 mg tablets of nirmatrelvir that are co-packaged with 100 mg tablet ritonavir.

PAXLOVID is authorized to be distributed in the following presentations, which are distinguishable by the specific amount of active ingredient per treatment course:

- *300 mg nirmatrelvir;100 mg ritonavir*: Each carton contains 30 tablets divided in 5 daily-dose blister cards. Each blister card contains 4 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each). Nirmatrelvir tablets and ritonavir tablets are supplied in separate blister cavities within the same child-resistant blister card. Each carton and individual blister card include the following statement: "For use under Emergency Use Authorization."
- *150 mg nirmatrelvir; 100 mg ritonavir*[14]: Each carton contains 20 tablets divided in 5 daily-dose blister cards. Each blister card contains 2 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each). Nirmatrelvir tablets and ritonavir tablets are supplied in separate blister cavities within the same child-resistant blister card. Each carton and individual blister card include the following statement: "For use under Emergency Use Authorization."

The authorized storage and handling information for PAXLOVID is included in the authorized Fact Sheet for Healthcare Providers.

PAXLOVID is authorized for emergency use with the following product-specific information required to be made available to healthcare providers and to patients, parents, and caregivers,

[14] The 150 mg nirmatrelvir;100 mg ritonavir presentation is designed to provide appropriate dosing for patients within the scope of this authorization with moderate renal impairment. See section 2.2 of the Fact Sheet for Healthcare Providers for more information.

respectively, through Pfizer's website www.COVID19oralRX.com (referred to as the "authorized labeling"):

- Fact Sheet for Healthcare Providers: Emergency Use Authorization (EUA) for PAXLOVID
- Fact Sheet for Patients, Parents and Caregivers: Emergency Use Authorization (EUA) of PAXLOVID for Coronavirus Disease 2019 (COVID-19)

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of PAXLOVID, when used for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg), and used in accordance with this Scope of Authorization (Section II), outweigh the known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that PAXLOVID may be effective for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that PAXLOVID (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of PAXLOVID under this EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), PAXLOVID is authorized for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

Pfizer and Authorized Distributors[15]

A. Pfizer and authorized distributor(s) will ensure that PAXLOVID is distributed and the authorized labeling (i.e., Fact Sheets) will be made available to healthcare facilities and/or healthcare providers as described in Section II of this Letter of Authorization.

[15] Supra at Note 11.

B. Pfizer and authorized distributor(s) will ensure that appropriate storage is maintained until the product is delivered to healthcare facilities and/or healthcare providers.

C. Pfizer and authorized distributor(s) will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., U.S. government agencies, state and local government authorities, authorized distributors, healthcare facilities, healthcare providers) involved in distributing or receiving PAXLOVID. Pfizer will provide to all relevant stakeholders a copy of this Letter of Authorization and communicate any subsequent amendments that might be made to this Letter of Authorization and its authorized accompanying materials (i.e., Fact Sheets).

D. Pfizer may request changes to this authorization, including to the authorized Fact Sheets for PAXLOVID. Any request for changes to this EUA must be submitted to the Office of Infectious Diseases/Office of New Drugs/Center for Drug Evaluation and Research. Such changes require appropriate authorization prior to implementation.[16]

E. Pfizer may develop and disseminate instructional and educational materials (e.g., materials providing information on product administration and/or patient monitoring) that are consistent with the authorized emergency use of PAXLOVID as described in this Letter of Authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs. Any instructional and educational materials that are inconsistent with the authorized labeling for PAXLOVID are prohibited. If the Agency notifies Pfizer that any instructional and educational materials are inconsistent with the authorized labeling, Pfizer must cease distribution of such instructional and educational materials. Furthermore, as part of its notification, the Agency may also require Pfizer to issue corrective communication(s).

F. Pfizer will report to FDA all serious adverse events and medication errors potentially related to PAXLOVID use that are reported to Pfizer using either of the following options.

   Option 1: Submit reports through the Safety Reporting Portal (SRP) as described on the FDA SRP web page.

   Option 2: Submit reports directly through the Electronic Submissions Gateway (ESG) as described on the FAERS electronic submissions web page.

[16] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study; (8) new strengths of the authorized product, new product sources (e.g., of active pharmaceutical ingredient) or of product components. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), (7), or (8), review and concurrence is required from the Counter-Terrorism and Emergency Coordination Staff/Office of the Center Director/CDER and the Office of Counterterrorism and Emerging Threats/Office of the Chief Scientist.

Submitted reports under both options must state: "PAXLOVID use for COVID-19 under Emergency Use Authorization (EUA)." For reports submitted under Option 1, include this language at the beginning of the question "Describe Event" for further analysis. For reports submitted under Option 2, include this language at the beginning of the "Case Narrative" field.

G. All manufacturing, packaging, and testing sites for both drug substance and drug product will comply with current good manufacturing practice requirements of Section 501(a)(2)(B) of the Act.

H. Pfizer will submit information to the Agency within three working days of receipt of any information concerning significant quality problems with distributed drug product of PAXLOVID that includes the following:

- Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or
- Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the product to meet the established specifications.

If a significant quality problem affects unreleased product and may also impact product(s) previously released and distributed, then information must be submitted for all potentially impacted lots.

Pfizer will include in its notification to the Agency whether the batch, or batches, in question will be recalled. If FDA requests that these, or any other batches, at any time, be recalled, Pfizer must recall them.

If not included in its initial notification, Pfizer must submit information confirming that Pfizer has identified the root cause of the significant quality problems, taken corrective action, and provide a justification confirming that the corrective action is appropriate and effective. Pfizer must submit this information as soon as possible but no later than 45 calendar days from the initial notification.

I. Pfizer will manufacture PAXLOVID to meet all quality standards and per the manufacturing process and control strategy as detailed in Pfizer's EUA request. Pfizer will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product, without notification to and concurrence by the Agency as described under Condition D.

J. Pfizer will list each presentation of PAXLOVID with a unique product NDC under the marketing category of Emergency Use Authorization. Further, the listing will include each establishment where manufacturing is performed for the drug and the type of operation performed at each such establishment.

K. Through a process of inventory control, Pfizer and authorized distributor(s) will maintain records regarding distribution of PAXLOVID (i.e., lot numbers, quantity, receiving site, receipt date).

L. Pfizer must provide the following information to the Agency:

1. Pfizer will conduct a study to monitor genomic database(s) for the emergence of SARS-CoV-2 variants with amino acid polymorphisms in M^{pro} or M^{pro} cleavage sites. Pfizer will conduct these surveillance activities on at least a monthly basis and submit reports to FDA on these surveillance activities on a quarterly basis. In these reports, Pfizer will provide monthly counts of M^{pro} and M^{pro} cleavage site polymorphisms (minimum 0.1% frequency) globally, in the U.S., and in individual countries (any countries with a minimum of 1,000 sequences in at least one month).
2. Pfizer will also provide ad-hoc reports (between quarterly reports) whenever a novel M^{pro} or M^{pro} cleavage site polymorphism is detected at a monthly frequency $\geq$1% either globally, in the U.S., or in an individual country with a minimum of 1,000 sequences. Pfizer will conduct phenotypic analysis for any M^{pro} or M^{pro} cleavage site polymorphisms that are detected at a frequency $\geq$1% either globally or in the U.S. for any single month.

M. Pfizer shall provide samples as requested of the authorized nirmatrelvir to HHS for evaluation of activity against emerging global viral variants of SARS-CoV-2, including specific amino acid substitution(s) of interest (e.g., variants that are highly prevalent or that harbor substitutions in the target protein(s) or target cleavage sites) within 5 business days of any request made by HHS. Analyses performed with the supplied quantity of authorized nirmatrelvir may include, but are not limited to, cell culture potency assays, biochemical assays, and in vivo efficacy assays.

N. Pfizer and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

Healthcare Facilities to Whom PAXLOVID Is Distributed and Healthcare Providers Administering PAXLOVID

O. Healthcare facilities and healthcare providers will ensure that they are aware of the Letter of Authorization, and the terms herein, and that the authorized Fact Sheets are made available to healthcare providers and to patients, parents, and caregivers, respectively, through appropriate means, prior to administration of PAXLOVID.

P. Healthcare facilities and healthcare providers receiving PAXLOVID will track all serious adverse events and medication errors that are considered to be potentially related to PAXLOVID use and must report these to FDA in accordance with the Fact Sheet for Healthcare Providers. Complete and submit a MedWatch form (www.fda.gov/medwatch/report.htm), or complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178) (these forms can be found via link above). Call 1-

800-FDA-1088 for questions. Submitted reports must state, "PAXLOVID use for COVID-19 under Emergency Use Authorization" at the beginning of the question "Describe Event" for further analysis. A copy of the completed FDA Form 3500 must also be provided to Pfizer per the instructions in the authorized labeling.

Q. Healthcare facilities and healthcare providers will ensure that appropriate storage is maintained until the product is administered consistent with the terms of this letter and the authorized labeling.

R. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensing and administration of PAXLOVID for the use authorized in this letter (i.e., lot numbers, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered).

S. Healthcare facilities will ensure that any records associated with this EUA are maintained until notified by Pfizer and/or FDA. Such records will be made available to Pfizer, HHS, and FDA for inspection upon request.

T. Healthcare facilities and providers will report therapeutics information and utilization data as directed by HHS.

Conditions Related to Printed Matter, Advertising, and Promotion

U. All descriptive printed matter, advertising, and promotional materials relating to the use of PAXLOVID under this authorization shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in Section 502(a) and (n) of the Act, as applicable, and FDA implementing regulations. References to "approved labeling", "permitted labeling", or similar terms in these requirements shall be understood to refer to the authorized labeling for the use of PAXLOVID under this authorization. In addition, such materials shall:

- Be tailored to the intended audience.
- Not take the form of reminder advertisements, as that term is described in 21 CFR 202.1(e)(2)(i), 21 CFR 200.200 and 21 CFR 201.100(f).
- Present the same risk information relating to the major side effects and contraindications concurrently in the audio and visual parts of the presentation for advertising and promotional materials in audio-visual format.
- Be accompanied by the authorized labeling, if the promotional materials are not subject to Section 502(n) of the Act.
- Be submitted to FDA accompanied by Form FDA-2253 for consideration at least 14 calendar days prior to initial dissemination or first use.

V. Pfizer may disseminate descriptive printed matter, advertising, and promotional materials relating to the emergency use of PAXLOVID that provide accurate descriptions of safety results and efficacy results on a clinical endpoint(s) from the clinical trial(s) summarized

in the authorized labeling. Such materials must include any limitations of the clinical trial data as described in the authorized labeling. Pfizer may not imply that PAXLOVID is FDA-approved for its authorized use in the pediatric patient population as detailed in the Scope of Authorization (Section II) by making statements such as "PAXLOVID is safe and effective for the treatment of COVID-19 in pediatric patients."

W. All descriptive printed matter, advertising, and promotional material, relating to the use of PAXLOVID under this authorization clearly and conspicuously shall state that:

- PAXLOVID has not been approved, but has been authorized for emergency use by FDA under an EUA, for the treatment of mild-to-moderate COVID-19 in pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death; and
- The emergency use of PAXLOVID is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

If the Agency notifies Pfizer that any descriptive printed matter, advertising, or promotional materials do not meet the terms set forth in Conditions U through W of this EUA, Pfizer must cease distribution of such descriptive printed matter, advertising, or promotional materials in accordance with the Agency's notification. Furthermore, as part of its notification, the Agency may also require Pfizer to issue corrective communication(s).

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR PAXLOVID™

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use PAXLOVID™ under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for PAXLOVID.

PAXLOVID (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use
Original EUA Authorized Date: 12/2021
Revised EUA Authorized Date: 05/2023

WARNING: SIGNIFICANT DRUG INTERACTIONS WITH PAXLOVID
See full prescribing information for complete boxed warning.

- **PAXLOVID includes ritonavir, a strong CYP3A inhibitor, which may lead to greater exposure of certain concomitant medications, resulting in potentially severe, life-threatening, or fatal events.** ***(4, 5.1, 7)***
- **Prior to prescribing PAXLOVID: 1) Review all medications taken by the patient to assess potential drug-drug interactions with a strong CYP3A inhibitor like PAXLOVID and 2) Determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring.** ***(7)***
- **Consider the benefit of PAXLOVID treatment in reducing hospitalization and death, and whether the risk of potential drug-drug interactions for an individual patient can be appropriately managed.** ***(5.1, 7, 14)***

----------RECENT MAJOR CHANGES----------

Boxed Warning: added	05/2023
Limitations of Authorized Use (1): updated	05/2023
Contraindications (4): add rifapentine	05/2023
Warnings and Precautions (5.1, 5.2): updated	05/2023
Adverse Reactions (6.1, 6.2): updated	05/2023
Drug Interactions (7.1, 7.3): updated	05/2023
Use in Specific Populations (8.1, 8.2, 8.5, 8.6): updated	05/2023
Clinical Pharmacology (12.1, 12.2, 12.3, 12.4): updated	05/2023
Nonclinical Toxicology (13.1, 13.2): updated	05/2023
Clinical Studies (14.1, 14.2, 14.3): updated	05/2023
Emergency Use Authorization (1): removal of requirement of SARS-CoV-2 viral testing	02/2023
Warnings and Precautions (5.2, 17): revision to hypersensitivity reactions to PAXLOVID including anaphylaxis	09/2022
Adverse Reactions (6.2): addition of new adverse reactions	09/2022
Microbiology (12.4): addition of Omicron sub-variants, *in vivo*, and resistance data	09/2022
Drug Interactions (7.3): addition of new drug interactions	08/2022
Emergency Use Authorization (1): addition of pharmacist prescribing guidance	07/2022
Contraindications (4): addition of new contraindicated drugs	06/2022
Microbiology (12.4): addition of viral RNA rebound	06/2022

----------EUA FOR PAXLOVID----------

The U.S. Food and Drug Administration has issued an EUA for the emergency use of PAXLOVID which includes nirmatrelvir, a SARS-CoV-2 main protease (M^{pro}: also referred to as 3CLpro or nsp5 protease) inhibitor, and ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor, for the treatment of adults and pediatric patients (12 years of age and older weighing at least 40 kg) with mild-to-moderate coronavirus disease 2019 (COVID-19) and who are at high risk for progression to severe COVID-19, including hospitalization or death.

LIMITATIONS OF AUTHORIZED USE

- PAXLOVID is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.
- PAXLOVID is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
- PAXLOVID is not authorized for use longer than 5 consecutive days.

PAXLOVID may be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs.

PAXLOVID may also be prescribed for an individual patient by a state-licensed pharmacist under the following conditions:

- Sufficient information is available, such as through access to health records less than 12 months old or consultation with a health care provider in an established provider-patient relationship with the individual patient, to assess renal and hepatic function; and
- Sufficient information is available, such as through access to health records, patient reporting of medical history, or consultation with a health care provider in an established provider-patient relationship with the individual patient, to obtain a comprehensive list of medications (prescribed and non-prescribed) that the patient is taking to assess for potential drug interaction.

The state-licensed pharmacist should refer an individual patient for clinical evaluation (e.g., telehealth, in-person visit) with a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs, if any of the following apply:

- Sufficient information is not available to assess renal and hepatic function.
- Sufficient information is not available to assess for a potential drug interaction.
- Modification of other medications is needed due to a potential drug interaction.
- PAXLOVID is not an appropriate therapeutic option based on the authorized Fact Sheet for Healthcare Providers or due to potential drug interactions for which recommended monitoring would not be feasible.

PAXLOVID is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of PAXLOVID under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

See Full Fact Sheet for Healthcare Providers for the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19.

----------DOSAGE AND ADMINISTRATION----------

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. (2.1)
Nirmatrelvir must be co-administered with ritonavir. (2.1)

- Initiate PAXLOVID treatment as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset. (2.1)
- Administer orally with or without food. (2.1)
- Dosage: 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together twice daily for 5 days. (2.1, 2.2)
- **Dose reduction for moderate renal impairment (eGFR ≥30 to <60 mL/min)**: 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet), with both tablets taken together twice daily for 5 days. (2.3)
- PAXLOVID is not recommended in patients with severe renal impairment (eGFR <30 mL/min). (2.3, 8.6)
- PAXLOVID is not recommend in patients with severe hepatic impairment (Child-Pugh Class C). (2.4, 8.7)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: nirmatrelvir 150 mg (3)
- Tablets: ritonavir 100 mg (3)

----------CONTRAINDICATIONS----------

- History of clinically significant hypersensitivity reactions to the active ingredients (nirmatrelvir or ritonavir) or any other components. (4)

- Co-administration with drugs highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions. (4, 7.3)
- Co-administration with potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- The concomitant use of PAXLOVID and certain other drugs may result in potentially significant drug interactions. Consult the full prescribing information prior to and during treatment for potential drug interactions. (5.1, 7)
- Hypersensitivity Reactions: Anaphylaxis, serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome), and other hypersensitivity reactions have been reported with PAXLOVID. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue PAXLOVID and initiate appropriate medications and/or supportive care. (5.2)
- Hepatotoxicity: Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir. (5.3)
- HIV-1 Drug Resistance: PAXLOVID use may lead to a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection. (5.4)

---------- ADVERSE REACTIONS ----------

Adverse events (incidence ≥1% and greater incidence than in the placebo group) were dysgeusia and diarrhea. (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to PAXLOVID (1) by submitting FDA Form 3500 online, (2) by downloading this form and then submitting by mail or fax, or (3) contacting the FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to Pfizer Inc. at fax number: 1-866-635-8337. (6.4)

----------DRUG INTERACTIONS----------

Co-administration of PAXLOVID can alter the plasma concentrations of other drugs and other drugs may alter the plasma concentrations of PAXLOVID. Consider the potential for drug interactions prior to and during PAXLOVID therapy and review concomitant medications during PAXLOVID therapy. (4, 5.1, 7, 12.3)

See FACT SHEET FOR PATIENTS, PARENTS, AND CAREGIVERS.

TABLE OF CONTENTS*

* Sections or subsections omitted from the EUA are not listed.

FULL FACT SHEET FOR HEALTHCARE PROVIDERS

WARNING: SIGNIFICANT DRUG INTERACTIONS WITH PAXLOVID

- **PAXLOVID includes ritonavir, a strong CYP3A inhibitor, which may lead to greater exposure of certain concomitant medications, resulting in potentially severe, life-threatening, or fatal events *[see Contraindications (4), Warnings and Precautions (5.1), and Drug Interactions (7)]*.**
- **Prior to prescribing PAXLOVID: 1) Review all medications taken by the patient to assess potential drug-drug interactions with a strong CYP3A inhibitor like PAXLOVID and 2) Determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring *[see Drug Interactions (7)]*.**
- **Consider the benefit of PAXLOVID treatment in reducing hospitalization and death, and whether the risk of potential drug-drug interactions for an individual patient can be appropriately managed *[see Warnings and Precautions (5.1), Drug Interactions (7), and Clinical Studies (14)]*.**

1 EMERGENCY USE AUTHORIZATION

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of PAXLOVID for the treatment of adults and pediatric patients (12 years of age and older weighing at least 40 kg) with mild-to-moderate coronavirus disease 2019 (COVID-19) and who are at high risk[1] for progression to severe COVID-19, including hospitalization or death.

LIMITATIONS OF AUTHORIZED USE

- PAXLOVID is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19 [see Dosage and Administration (2.1)].[2]
- PAXLOVID is not authorized for use as pre-exposure or post-exposure prophylaxis for prevention of COVID-19 *[see Clinical Studies (14.3)]*.
- PAXLOVID is not authorized for use for longer than 5 consecutive days.

PAXLOVID may be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs.

PAXLOVID may also be prescribed for an individual patient by a state-licensed pharmacist under the following conditions:

- Sufficient information is available, such as through access to health records less than 12 months old or consultation with a health care provider in an established provider-patient relationship with the individual patient, to assess renal and hepatic function; and
- Sufficient information is available, such as through access to health records, patient reporting of medical history, or consultation with a health care provider in an established provider-patient

[1] Determining whether a patient is at high risk for progression to severe COVID-19, including hospitalization or death, is based on the provider's assessment of the individual patient being considered for treatment of COVID-19 and that patient's medical history. For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html.

[2] Patients requiring hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID may complete the full 5-day treatment course per the healthcare provider's discretion.

relationship with the individual patient, to obtain a comprehensive list of medications (prescribed and non-prescribed) that the patient is taking to assess for potential drug interaction.

The state-licensed pharmacist should refer an individual patient for clinical evaluation (e.g., telehealth, in-person visit) with a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs, if any of the following apply:

- Sufficient information is not available to assess renal and hepatic function.
- Sufficient information is not available to assess for a potential drug interaction.
- Modification of other medications is needed due to a potential drug interaction.
- PAXLOVID is not an appropriate therapeutic option based on the authorized Fact Sheet for Healthcare Providers or due to potential drug interactions for which recommended monitoring would not be feasible.

PAXLOVID is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of PAXLOVID under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Justification for Emergency Use of Drugs During the COVID-19 Pandemic

There is currently an outbreak of COVID-19 caused by SARS-CoV-2, a novel coronavirus. The Secretary of Health and Human Services (HHS) has:

- Determined that there is a public health emergency, or significant potential for a public health emergency.[3]
- Declared that circumstances exist justifying the authorization of emergency use of drugs and biological products for the prevention or treatment of COVID-19.[4]

An EUA is a U.S. Food and Drug Administration authorization for the emergency use of an unapproved product or unapproved use of an approved product (i.e., drug, biological product, or device) in the United States under certain circumstances including, but not limited to, when the Secretary of HHS declares that there is a public health emergency that affects the national security or the health and security of United States citizens living abroad, and that involves biological agent(s) or a disease or condition that may be attributable to such agent(s). Criteria for issuing an EUA include:

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[3] *See* U.S. Department of Health and Human Services, Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3. February 4, 2020; https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency. *See also* U.S. Department of Health and Human Services, Amended Determination of a Public Health Emergency or Significant Potential for a Public Health Emergency Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3(b). March 15, 2023 ("Amended Determination"); https://www.federalregister.gov/documents/2023/03/20/2023-05609/covid-19-emergency-use-authorization-declaration.

[4] *See* U.S. Department of Health and Human Services, Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3, 85 FR 18250 (April 1, 2020); https://www.federalregister.gov/documents/2020/04/01/2020-06905/emergency-use-authorization-declaration. *See also* Amended Determination ("The declarations issued pursuant to section 564(b)(1) of the FD&C Act that circumstances exist justifying the authorization of emergency use of certain in vitro diagnostics, personal respiratory protective devices, other medical devices and drugs and biological products, as set forth in those declarations, and that are based on the February 4, 2020 determination, remain in effect until those declarations are terminated in accordance with section 564 of the FD&C Act.").

- The biological agent(s) can cause a serious or life-threatening disease or condition;
- Based on the totality of the available scientific evidence (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that
    - the product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition; and
    - the known and potential benefits of the product—when used to diagnose, prevent, or treat such disease or condition—outweigh the known and potential risks of the product, taking into consideration the material threat posed by the biological agent(s);
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the serious or life-threatening disease or condition.

Information Regarding Approved Alternatives for the EUA Authorized Use[5]

PAXLOVID is FDA-approved for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. Although different presentations of PAXLOVID are now FDA-approved for the treatment of mild-to-moderate COVID-19 in certain adults, there are not currently sufficient supplies of the approved PAXLOVID available for distribution to this patient population in its entirety; therefore, this EUA continues to authorize the emergency use of PAXLOVID[6] for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death, at this time. Apart from this paragraph, all references to the term "PAXLOVID" in this Fact Sheet refer to product that is labelled in accordance with this EUA.

Veklury (remdesivir) is an FDA-approved alternative to PAXLOVID when used for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death. Veklury is administered via intravenous infusion for a total treatment duration of 3 days. Although Veklury is an FDA-approved alternative to PAXLOVID as described above, FDA does not consider Veklury to be an adequate alternative to PAXLOVID for this authorized use because it may not be feasible or practical for certain patients (e.g., it requires an intravenous infusion daily for 3 days).

Other therapeutics are currently authorized for the same use as PAXLOVID. For additional information on all products authorized for treatment or prevention of COVID-19, please see https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

For information on clinical studies that are testing the use of PAXLOVID in COVID-19, please see www.clinicaltrials.gov.

[5] This section only describes the uses for which an FDA-approved drug is considered to be an alternative to PAXLOVID. For additional information, including the full indications for the FDA-approved drugs referenced within this section, please refer to the relevant Prescribing Information at: Drugs@FDA: FDA-Approved Drugs. As stated in the Letter of Authorization, the emergency use of PAXLOVID must be consistent with the terms and conditions of its authorization.

[6] See the Letter of Authorization and section 16 (HOW SUPPLIED/STORAGE AND HANDLING) in this Fact Sheet for the specific presentations of PAXLOVID authorized under this EUA.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Information for Emergency Use of PAXLOVID

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. There are two different dose packs available:

- PAXLOVID (nirmatrelvir; ritonavir) co-packaged for oral use 300 mg;100 mg *[see Dosage and Administration (2.2)]*.
- PAXLOVID (nirmatrelvir; ritonavir) co-packaged for oral use 150 mg;100 mg for patients with moderate renal impairment *[see Dosage and Administration (2.3)]*.

Nirmatrelvir must be co-administered with ritonavir. Failure to correctly co-administer nirmatrelvir with ritonavir may result in plasma levels of nirmatrelvir that are insufficient to achieve the desired therapeutic effect.

Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID [see Dosage and Administration (2.2, 2.3)]. Completion of the full 5-day treatment course and continued isolation in accordance with public health recommendations are important to maximize viral clearance and minimize transmission of SARS-CoV-2.

The 5-day treatment course of PAXLOVID should be initiated as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset even if baseline COVID-19 symptoms are mild. Should a patient require hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID, the patient should complete the full 5-day treatment course per the healthcare provider's discretion.

If the patient misses a dose of PAXLOVID within 8 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 8 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose.

PAXLOVID (both nirmatrelvir and ritonavir tablets) can be taken with or without food *[see Clinical Pharmacology (12.3)]*. The tablets should be swallowed whole and not chewed, broken, or crushed.

2.2 Recommended Dosage

The recommended dosage for PAXLOVID is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) with all 3 tablets taken together orally twice daily for 5 days.

2.3 Dosage in Patients with Renal Impairment

No dosage adjustment is recommended in patients with mild renal impairment (eGFR ≥60 to <90 mL/min).

In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), the dosage of PAXLOVID is 150 mg nirmatrelvir (one 150 mg tablet) and 100 mg ritonavir (one 100 mg tablet) with both tablets taken together twice daily for 5 days *[see How Supplied/Storage and Handling (16)]. Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID.* Providers should counsel patients about renal dosing instructions *[see Patient Counseling Information (17)]*.

PAXLOVID is not recommended in patients with severe renal impairment (eGFR <30 mL/min) until more data are available; the appropriate dosage for patients with severe renal impairment has not been determined *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

2.4 Use in Patients with Hepatic Impairment

No dosage adjustment is needed in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in subjects with severe (Child-Pugh Class C) hepatic impairment; therefore, PAXLOVID is not recommended for use in patients with severe hepatic impairment *[see Use in Specific Populations (8.7)]*.

3 DOSAGE FORMS AND STRENGTHS

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets.

- Nirmatrelvir is supplied as oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Each tablet contains 150 mg of nirmatrelvir.

- Ritonavir is supplied as white or white to off-white film-coated tablets uniquely identified by the color, shape, and debossing *[see How Supplied/Storage and Handling (16)]*. Each tablet contains 100 mg of ritonavir.

4 CONTRAINDICATIONS

PAXLOVID is contraindicated in patients with a history of clinically significant hypersensitivity reactions [e.g., toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome] to its active ingredients (nirmatrelvir or ritonavir) or any other components of the product.

PAXLOVID is contraindicated with drugs that are primarily metabolized by CYP3A and for which elevated concentrations are associated with serious and/or life-threatening reactions and drugs that are strong CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. There are certain other drugs for which concomitant use with PAXLOVID should be avoided and/or dose adjustment, interruption, or therapeutic monitoring is recommended. Drugs listed in this section are a guide and not considered a comprehensive list of all drugs that may be contraindicated with PAXLOVID. The healthcare provider should consult other appropriate resources such as the prescribing information for the interacting drug for comprehensive information on dosing or monitoring with concomitant use of a strong CYP3A inhibitor like PAXLOVID *[see Drug Interactions (7.3)]*:

- Drugs that are primarily metabolized by CYP3A for which elevated concentrations are associated with serious and/or life-threatening reactions *[see Drug Interactions (7.3)]*:

  - Alpha 1-adrenoreceptor antagonist: alfuzosin
  - Antianginal: ranolazine
  - Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
  - Anti-gout: colchicine (in patients with renal and/or hepatic impairment *[see Table 1, Drug Interactions (7.3)]*)
  - Antipsychotics: lurasidone, pimozide

- Benign prostatic hyperplasia agents: silodosin
- Cardiovascular agents: eplerenone, ivabradine
- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
- HMG-CoA reductase inhibitors: lovastatin, simvastatin (these drugs can be temporarily discontinued to allow PAXLOVID use *[see Table 1, Drug Interactions (7.3)]*)
- Immunosuppressants: voclosporin
- Microsomal triglyceride transfer protein inhibitor: lomitapide
- Migraine medications: eletriptan, ubrogepant
- Mineralocorticoid receptor antagonists: finerenone
- Opioid antagonists: naloxegol
- PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)
- Sedative/hypnotics: triazolam, oral midazolam
- Serotonin receptor 1A agonist/serotonin receptor 2A antagonist: flibanserin
- Vasopressin receptor antagonists: tolvaptan

➢ Drugs that are strong CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. PAXLOVID cannot be started immediately after discontinuation of any of the following medications due to the delayed offset of the recently discontinued CYP3A inducer *[see Drug Interactions (7.3)]*:

- Anticancer drugs: apalutamide
- Anticonvulsant: carbamazepine, phenobarbital, primidone, phenytoin
- Antimycobacterials: rifampin, rifapentine
- Cystic fibrosis transmembrane conductance regulator potentiators: lumacaftor/ivacaftor
- Herbal products: St. John's Wort (*hypericum perforatum*)

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Adverse Reactions Due to Drug Interactions

Initiation of PAXLOVID, which contains ritonavir, a strong CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving PAXLOVID, may increase plasma concentrations of medications metabolized by CYP3A. Medications that induce CYP3A may decrease concentrations of PAXLOVID. These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications.
- Loss of therapeutic effect of PAXLOVID and possible development of viral resistance.

Severe, life-threatening, and/or fatal adverse reactions due to drug interactions have been reported in patients treated with PAXLOVID. The most commonly reported concomitant medications resulting in serious adverse reactions were calcineurin inhibitors (e.g., tacrolimus, cyclosporine), followed by calcium channel blockers.

Prior to prescribing PAXLOVID, review all medications taken by the patient to assess potential drug-drug interactions and determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring (e.g., calcineurin inhibitors) *[see Contraindications (4) and Drug Interactions (7)]*. See Table 1 for clinically significant drug interactions, including contraindicated

drugs. Drugs listed in Table 1 are a guide and not considered a comprehensive list of all possible drugs that may interact with PAXLOVID.

Consider the benefit of PAXLOVID treatment in reducing hospitalization and death, and whether the risk of potential drug-drug interactions for an individual patient can be appropriately managed *[see Drug Interactions (7) and Clinical Studies (14)]*.

5.2 Hypersensitivity Reactions

Anaphylaxis, serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome), and other hypersensitivity reactions have been reported with PAXLOVID *[see Adverse Reactions (6.2)]*. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue PAXLOVID and initiate appropriate medications and/or supportive care.

5.3 Hepatotoxicity

Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering PAXLOVID to patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis.

5.4 Risk of HIV-1 Resistance Development

Because nirmatrelvir is co-administered with ritonavir, there may be a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection *[see Contraindications (4), and Drug Interactions (7)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity reactions *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of PAXLOVID is based on two Phase 2/3 randomized, placebo-controlled trials in symptomatic adult subjects 18 years of age and older with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Subjects in both studies received PAXLOVID (nirmatrelvir/ritonavir 300 mg/100 mg) or placebo every 12 hours for 5 days for the treatment of mild-to-moderate COVID-19 within 5 days of symptom onset *[see Clinical Studies (14)]*:

- Trial C4671005 (EPIC-HR) enrolled subjects who were at high risk for progression to severe disease.
- Trial C4671002 (EPIC-SR) enrolled subjects who were at standard risk for progression to severe disease (previously unvaccinated subjects at standard risk or fully vaccinated subjects with at least 1 risk factor for progression to severe disease).

Adverse reactions were those reported while subjects were on study medication and through 28 days after the last dose of study treatment.

In Trial C4671005 (EPIC-HR), 1,038 subjects received PAXLOVID and 1,053 subjects received placebo. The most common adverse reactions (≥1% incidence in the PAXLOVID group and occurring at a greater frequency than in the placebo group) were dysgeusia (5% and <1%, respectively) and diarrhea (3% and 2%, respectively).

Among vaccinated or unvaccinated subjects at standard risk or fully vaccinated subjects with at least 1 risk factor for progression to severe disease in Trial C4671002 (EPIC-SR), 540 subjects received PAXLOVID and 528 subjects received placebo. The adverse reactions observed were consistent with those observed in EPIC-HR.

6.2 Post-Authorization Experience

The following adverse reactions have been identified during post-authorization use of PAXLOVID.

Immune System Disorders: Anaphylaxis, hypersensitivity reactions *[see Warnings and Precautions (5.2)]*
Skin and Subcutaneous Tissue Disorders: Toxic epidermal necrolysis, Stevens-Johnson syndrome *[see Warnings and Precautions (5.2)]*
Nervous System Disorders: Headache
Vascular Disorders: Hypertension
Gastrointestinal Disorders: Abdominal pain, nausea, vomiting
General Disorders and Administration Site Conditions: Malaise

6.4 Required Reporting for Serious Adverse Events and Medication Errors

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events* and medication errors potentially related to PAXLOVID within 7 calendar days from the healthcare provider's awareness of the event, using FDA Form 3500 (for information on how to access this form, see below). The FDA requires that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race).
- A statement " PAXLOVID use for COVID-19 under Emergency Use Authorization (EUA)" under the "**Describe Event, Problem, or Product Use/Medication Error**" heading.
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes).
- Patient's pre-existing medical conditions and use of concomitant products.
- Information about the product (e.g., dosage, route of administration, NDC #).

Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online: https://www.fda.gov/medwatch/report.htm
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax to 1-800-FDA-0178, or
- Call 1-800-FDA-1088 to request a reporting form

In addition, please provide a copy of all FDA MedWatch forms to:

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of PAXLOVID.

*Serious adverse events are defined as:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- Other important medical event, which may require a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

6.5 Other Reporting Requirements

Healthcare facilities and providers will report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

7 DRUG INTERACTIONS

7.1 Potential for PAXLOVID to Affect Other Drugs

PAXLOVID (nirmatrelvir co-packaged with ritonavir) is a strong inhibitor of CYP3A, and an inhibitor of CYP2D6, P-gp and OATP1B1. Co-administration of PAXLOVID with drugs that are primarily metabolized by CYP3A and CYP2D6 or are transported by P-gp or OATP1B1 may result in increased plasma concentrations of such drugs and increase the risk of adverse events. Co-administration of PAXLOVID with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated *[see Contraindications (4) and Drug Interactions (7.3) Table 1]*. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring as shown in Table 1.

7.2 Potential for Other Drugs to Affect PAXLOVID

Nirmatrelvir and ritonavir are CYP3A substrates; therefore, drugs that induce CYP3A may decrease nirmatrelvir and ritonavir plasma concentrations and reduce PAXLOVID therapeutic effect *[see Contraindications (4) and Drug Interactions (7.3) Table 1]*.

7.3 Established and Other Potentially Significant Drug Interactions

Table 1 provides a listing of clinically significant drug interactions, including contraindicated drugs *[see Contraindications (4) and Warnings and Precautions (5.1)]*. Drugs listed in Table 1 are a guide and not considered a comprehensive list of all possible drugs that may interact with PAXLOVID. The healthcare provider should consult other appropriate resources such as the prescribing information for the interacting drug for comprehensive information on dosing or monitoring with concomitant use of a strong CYP3A inhibitor such as ritonavir.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Alpha 1-adrenoreceptor antagonist	alfuzosin	↑ alfuzosin	Co-administration contraindicated due to potential hypotension *[see Contraindications (4)]*.
Alpha 1-adrenoreceptor antagonist	tamsulosin	↑ tamsulosin	Avoid concomitant use with PAXLOVID.
Antianginal	ranolazine	↑ ranolazine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions *[see Contraindications (4)]*.
Antiarrhythmics	amiodarone, dronedarone, flecainide, propafenone, quinidine	↑ antiarrhythmic	Co-administration contraindicated due to potential for cardiac arrhythmias *[see Contraindications (4)]*.
Antiarrhythmics	lidocaine (systemic), disopyramide	↑ antiarrhythmic	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics if available.
Anticancer drugs	apalutamide	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Anticancer drugs	abemaciclib, ceritinib, dasatinib, encorafenib, ibrutinib, ivosidenib, neratinib, nilotinib, venetoclax, vinblastine, vincristine	↑ anticancer drugs	Avoid co-administration of encorafenib or ivosidenib due to potential risk of serious adverse events such as QT interval prolongation. Avoid use of neratinib, venetoclax or ibrutinib. Co-administration of vincristine and vinblastine may lead to significant hematologic or gastrointestinal side effects. For further information, refer to individual product label for anticancer drug.
Anticoagulants	warfarin	↑↓ warfarin	Closely monitor international normalized ratio (INR) if co-administration with warfarin is necessary.
	rivaroxaban	↑ rivaroxaban	Increased bleeding risk with rivaroxaban. Avoid concomitant use.
	dabigatran[a]	↑ dabigatran	Increased bleeding risk with dabigatran. Depending on dabigatran indication and renal function, reduce dose of dabigatran or avoid concomitant use. Refer to the dabigatran product label for further information.
	apixaban	↑ apixaban	Combined P-gp and strong CYP3A inhibitors increase blood levels of apixaban and increase the risk of bleeding. Dosing recommendations for co-administration of apixaban with PAXLOVID depend on the apixaban dose. Refer to the apixaban product label for more information.
Anticonvulsants	carbamazepine[a], phenobarbital, primidone, phenytoin	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.
Anticonvulsants	clonazepam	↑ anticonvulsant	A dose decrease may be needed for clonazepam when co-administered with PAXLOVID and clinical monitoring is recommended.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Antidepressants	bupropion	↓ bupropion and active metabolite hydroxy-bupropion	Monitor for an adequate clinical response to bupropion.
	trazodone	↑ trazodone	Adverse reactions of nausea, dizziness, hypotension, and syncope have been observed following co-administration of trazodone and ritonavir. A lower dose of trazodone should be considered. Refer to trazadone product label for further information.
Antifungals	voriconazole	↓ voriconazole	Avoid concomitant use of voriconazole.
	ketoconazole, isavuconazonium sulfate, itraconazole[a]	↑ ketoconazole ↑ isavuconazonium sulfate ↑ itraconazole	Refer to ketoconazole, isavuconazonium sulfate, and itraconazole product labels for further information.
		↑ nirmatrelvir/ritonavir	A nirmatrelvir/ritonavir dose reduction is not needed.
Anti-gout	colchicine	↑ colchicine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment *[see Contraindications (4)]*.
Anti-HIV protease inhibitors	atazanavir, darunavir, tipranavir	↑ protease inhibitor	For further information, refer to the respective protease inhibitors' prescribing information. Patients on ritonavir- or cobicistat-containing HIV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or protease inhibitor adverse events.
Anti-HIV	efavirenz, maraviroc, nevirapine, zidovudine, bictegravir/ emtricitabine/ tenofovir	↑ efavirenz ↑ maraviroc ↑ nevirapine ↓ zidovudine ↑ bictegravir ↔ emtricitabine ↑ tenofovir	For further information, refer to the respective anti-HIV drugs prescribing information.
Anti-infective	clarithromycin, erythromycin	↑ clarithromycin ↑ erythromycin	Refer to the respective prescribing information for anti-infective dose adjustment.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Antimycobacterial	rifampin, rifapentine	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance. Alternate antimycobacterial drugs such as rifabutin should be considered *[see Contraindications (4)]*.
Antimycobacterial	bedaquiline	↑ bedaquiline	Refer to the bedaquiline product label for further information.
	rifabutin	↑ rifabutin	Refer to rifabutin product label for further information on rifabutin dose reduction.
Antipsychotics	lurasidone, pimozide	↑ lurasidone ↑ pimozide	Co-administration contraindicated due to serious and/or life-threatening reactions such as cardiac arrhythmias *[see Contraindications (4)]*.
Antipsychotics	quetiapine	↑ quetiapine	If co-administration is necessary, reduce quetiapine dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations.
	clozapine	↑ clozapine	If co-administration is necessary, consider reducing the clozapine dose and monitor for adverse reactions.
Benign prostatic hyperplasia agents	silodosin	↑ silodosin	Co-administration contraindicated due to potential for postural hypotension *[see Contraindications (4)]*.
Calcium channel blockers	amlodipine, diltiazem, felodipine, nicardipine, nifedipine, verapamil	↑ calcium channel blocker	Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with PAXLOVID. If co-administered, refer to individual product label for calcium channel blocker for further information.
Cardiac glycosides	digoxin	↑ digoxin	Caution should be exercised when co-administering PAXLOVID with digoxin, with appropriate monitoring of serum digoxin levels. Refer to the digoxin product label for further information.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Cardiovascular agents	eplerenone	↑ eplerenone	Co-administration with eplerenone is contraindicated due to potential for hyperkalemia *[see Contraindications (4)]*.
	ivabradine	↑ ivabradine	Co-administration with ivabradine is contraindicated due to potential for bradycardia or conduction disturbances *[see Contraindications (4)]*.
Cardiovascular agents	aliskiren, ticagrelor, vorapaxar	↑ aliskiren ↑ ticagrelor ↑ vorapaxar	Avoid concomitant use with PAXLOVID.
	clopidogrel	↓ clopidogrel active metabolite	
	cilostazol	↑ cilostazol	Dosage adjustment of cilostazol is recommended. Refer to the cilostazol product label for more information.
Corticosteroids primarily metabolized by CYP3A	betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone, mometasone, triamcinolone	↑ corticosteroid	Co-administration with corticosteroids (all routes of administration) of which exposures are significantly increased by strong CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression. However, the risk of Cushing's syndrome and adrenal suppression associated with short-term use of a strong CYP3A inhibitor is low. Alternative corticosteroids including beclomethasone, prednisone, and prednisolone should be considered.
Cystic fibrosis transmembrane conductance regulator potentiators	lumacaftor/ivacaftor	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.
Cystic fibrosis transmembrane conductance regulator potentiators	ivacaftor	↑ ivacaftor	Reduce dosage when co-administered with PAXLOVID. Refer to individual product labels for more information.
	elexacaftor/tezacaftor/ ivacaftor	↑elexacaftor/tezacaftor /ivacaftor	
	tezacaftor/ivacaftor	↑ tezacaftor/ivacaftor	
Dipeptidyl peptidase 4 (DPP4) inhibitors	saxagliptin	↑ saxagliptin	Dosage adjustment of saxagliptin is recommended. Refer to the saxagliptin product label for more information.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Endothelin receptor antagonists	bosentan	↑ bosentan ↓ nirmatrelvir/ritonavir	Discontinue use of bosentan at least 36 hours prior to initiation of PAXLOVID. Refer to the bosentan product label for further information.
Ergot derivatives	dihydroergotamine, ergotamine, methylergonovine	↑ dihydroergotamine ↑ ergotamine ↑ methylergonovine	Co-administration contraindicated due to potential for acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system *[see Contraindications (4)]*.
Hepatitis C direct acting antivirals	elbasvir/grazoprevir glecaprevir/ pibrentasvir ombitasvir/paritaprevir /ritonavir and dasabuvir sofosbuvir/velpatasvir/ voxilaprevir	↑ antiviral	Increased grazoprevir concentrations can result in alanine transaminase (ALT) elevations. Avoid concomitant use of glecaprevir/pibrentasvir with PAXLOVID. Refer to the ombitasvir/paritaprevir/ritonavir and dasabuvir label for further information. Refer to the sofosbuvir/velpatasvir/voxilaprevir product label for further information. Patients on ritonavir-containing HCV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or HCV drug adverse events with concomitant use.
Herbal products	St. John's Wort (*hypericum perforatum*)	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
HMG-CoA reductase inhibitors	lovastatin, simvastatin	↑ lovastatin ↑ simvastatin	Co-administration contraindicated due to potential for myopathy including rhabdomyolysis *[see Contraindications (4)]*. If treatment with PAXLOVID is considered medically necessary, discontinue use of lovastatin and simvastatin at least 12 hours prior to initiation of PAXLOVID, during the 5 days of PAXLOVID treatment and for 5 days after completing PAXLOVID.
HMG-CoA reductase inhibitors	atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Consider temporary discontinuation of atorvastatin and rosuvastatin during treatment with PAXLOVID. Atorvastatin and rosuvastatin do not need to be withheld prior to or after completing PAXLOVID.
Hormonal contraceptive	ethinyl estradiol	↓ ethinyl estradiol	An additional, non-hormonal method of contraception should be considered during the 5 days of PAXLOVID treatment and until one menstrual cycle after stopping PAXLOVID.
Immunosuppressants	voclosporin	↑ voclosporin	Co-administration contraindicated due to potential for acute and/or chronic nephrotoxicity *[see Contraindications (4)]*.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Immunosuppressants	calcineurin inhibitors: cyclosporine, tacrolimus	↑ cyclosporine ↑ tacrolimus	Avoid concomitant use of calcineurin inhibitors with PAXLOVID when close monitoring of immunosuppressant concentrations is not feasible. If co-administered, dose adjustment of the immunosuppressant and close and regular monitoring for immunosuppressant concentrations and adverse reactions are recommended during and after treatment with PAXLOVID. Obtain expert consultation to appropriately manage the complexity of this co-administration *[see Warnings and Precautions (5.1)]*.
	mTOR inhibitors: everolimus, sirolimus	↑ everolimus ↑ sirolimus	Avoid concomitant use of everolimus and sirolimus and PAXLOVID. Refer to the individual immunosuppressant product label and latest guidelines for further information.
Janus kinase (JAK) inhibitors	tofacitinib, upadacitinib	↑ tofacitinib	Dosage adjustment of tofacitinib is recommended. Refer to the tofacitinib product label for more information.
		↑ upadacitinib	Dosing recommendations for co-administration of upadacitinib with PAXLOVID depends on the upadacitinib indication. Refer to the upadacitinib product label for more information.
Long-acting beta-adrenoceptor agonist	salmeterol	↑ salmeterol	Avoid concomitant use with PAXLOVID. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Microsomal triglyceride transfer protein (MTTP) inhibitor	lomitapide	↑ lomitapide	Co-administration contraindicated due to potential for hepatotoxicity and gastrointestinal adverse reactions *[see Contraindications (4)]*.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Migraine medications	eletriptan	↑ eletriptan	Co-administration of eletriptan within at least 72 hours of PAXLOVID is contraindicated due to potential for serious adverse reactions including cardiovascular and cerebrovascular events *[see Contraindications (4)]*.
	ubrogepant	↑ ubrogepant	Co-administration of ubrogepant with PAXLOVID is contraindicated due to potential for serious adverse reactions *[see Contraindications (4)]*.
Migraine medications	rimegepant	↑ rimegepant	Avoid concomitant use with PAXLOVID.
Mineralocorticoid receptor antagonists	finerenone	↑ finerenone	Co-administration contraindicated due to potential for serious adverse reactions including hyperkalemia, hypotension, and hyponatremia *[see Contraindications (4)]*.
Muscarinic receptor antagonists	darifenacin	↑ darifenacin	The darifenacin daily dose should not exceed 7.5 mg when co-administered with PAXLOVID. Refer to the darifenacin product label for more information.
Narcotic analgesics	fentanyl, hydrocodone, oxycodone, meperidine	↑ fentanyl ↑ hydrocodone ↑ oxycodone ↑ meperidine	Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl, hydrocodone, oxycodone, or meperidine is concomitantly administered with PAXLOVID. If concomitant use with PAXLOVID is necessary, consider a dosage reduction of the narcotic analgesic and monitor patients closely at frequent intervals. Refer to the individual product label for more information.
	methadone	↓ methadone	Monitor methadone-maintained patients closely for evidence of withdrawal effects and adjust the methadone dose accordingly.
Neuropsychiatric agents	suvorexant	↑ suvorexant	Avoid concomitant use of suvorexant with PAXLOVID.
	aripiprazole, brexpiprazole, cariprazine, iloperidone, lumateperone, pimavanserin	↑ aripiprazole ↑ brexpiprazole ↑ cariprazine ↑ iloperidone ↑ lumateperone ↑ pimavanserin	Dosage adjustment of aripiprazole, brexpiprazole, cariprazine, iloperidone, lumateperone, and pimavanserin is recommended. Refer to individual product label for more information.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Opioid antagonists	naloxegol	↑ naloxegol	Co-administration contraindicated due to the potential for opioid withdrawal symptoms *[see Contraindications (4)]*.
Pulmonary hypertension agents (PDE5 inhibitors)	sildenafil (Revatio®)	↑ sildenafil	Co-administration of sildenafil with PAXLOVID is contraindicated for use in pulmonary hypertension due to the potential for sildenafil associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope *[see Contraindications (4)]*.
Pulmonary hypertension agents (PDE5 inhibitors)	tadalafil (Adcirca®)	↑ tadalafil	Avoid concomitant use of tadalafil with PAXLOVID for pulmonary hypertension.
Pulmonary hypertension agents (sGC stimulators)	riociguat	↑ riociguat	Dosage adjustment is recommended for riociguat when used for pulmonary hypertension. Refer to the riociguat product label for more information.
Erectile dysfunction agents (PDE5 inhibitors)	avanafil	↑ avanafil	Do not use PAXLOVID with avanafil because a safe and effective avanafil dosage regimen has not been established.
	sildenafil, tadalafil, vardenafil	↑ sildenafil ↑ tadalafil ↑ vardenafil	Dosage adjustment is recommended for use of sildenafil, tadalafil or vardenafil with PAXLOVID when used for erectile dysfunction. Refer to individual product label for more information.
Sedative/hypnotics	triazolam, oral midazolam[a]	↑ triazolam ↑ midazolam	Co-administration contraindicated due to potential for extreme sedation and respiratory depression *[see Contraindications (4)]*.
Sedative/hypnotics	buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem	↑ sedative/hypnotic	A dose decrease may be needed for these drugs when co-administered with PAXLOVID and monitoring for adverse events.
	midazolam (administered parenterally)	↑ midazolam	Co-administration of midazolam (parenteral) should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered,

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
			especially if more than a single dose of midazolam is administered. Refer to the midazolam product label for further information.
Serotonin receptor 1A agonist/ serotonin receptor 2A antagonist	flibanserin	↑ flibanserin	Co-administration contraindicated due to potential for hypotension, syncope, and CNS depression *[see Contraindications (4)]*.
Vasopressin receptor antagonists	tolvaptan	↑ tolvaptan	Co-administration contraindicated due to potential for dehydration, hypovolemia and hyperkalemia *[see Contraindications (4)]*.

a. See Pharmacokinetics, Drug Interaction Studies Conducted with Nirmatrelvir and Ritonavir (12.3).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data on the use of nirmatrelvir during pregnancy are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Published observational studies on ritonavir use in pregnant women have not identified an increase in the risk of major birth defects. Published studies with ritonavir are insufficient to identify a drug-associated risk of miscarriage *(see Data)*. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy *(see Clinical Considerations)*.

In an embryo-fetal development study with nirmatrelvir, reduced fetal body weights following oral administration of nirmatrelvir to pregnant rabbits were observed at systemic exposures (AUC) approximately 11 times higher than clinical exposure at the authorized human dose of PAXLOVID. No other adverse developmental outcomes were observed in animal reproduction studies with nirmatrelvir at systemic exposures (AUC) greater than or equal to 3 times higher than clinical exposure at the authorized human dose of PAXLOVID *(see Data)*.

In embryo-fetal developmental studies with ritonavir, no evidence of adverse developmental outcomes was observed following oral administration of ritonavir to pregnant rats and rabbits at systemic exposures (AUC) 5 (rat) or 8 (rabbits) times higher than clinical exposure at the authorized human dose of PAXLOVID *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the authorized population is unknown. All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryo-fetal Risk
COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

Data

Human Data

Ritonavir
Based on prospective reports to the antiretroviral pregnancy registry of live births following exposure to ritonavir-containing regimens (including over 3,500 live births exposed in the first-trimester and over 3,500 live births exposed in the second and third trimesters), there was no difference in the rate of overall birth defects for ritonavir compared with the background birth defect rate of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The prevalence of birth defects in live births was 2.4% [95% confidence interval (CI): 1.9%-2.9%] following first-trimester exposure to ritonavir-containing regimens and 2.9% (95% CI: 2.4%-3.5%) following second and third trimester exposure to ritonavir-containing regimens. While placental transfer of ritonavir and fetal ritonavir concentrations are generally low, detectable levels have been observed in cord blood samples and neonate hair.

Animal Data

Nirmatrelvir
Embryo-fetal developmental (EFD) toxicity studies were conducted in pregnant rats and rabbits administered oral nirmatrelvir doses of up to 1,000 mg/kg/day during organogenesis [on Gestation Days (GD) 6 through 17 in rats and GD 7 through 19 in rabbits]. No biologically significant developmental effects were observed in the rat EFD study. At the highest dose of 1,000 mg/kg/day, the systemic nirmatrelvir exposure (AUC_{24}) in rats was approximately 9 times higher than clinical exposures at the authorized human dose of PAXLOVID. In the rabbit EFD study, lower fetal body weights (9% decrease) were observed at 1,000 mg/kg/day in the absence of significant maternal toxicity findings. At 1,000 mg/kg/day, the systemic exposure (AUC_{24}) in rabbits was approximately 11 times higher than clinical exposures at the authorized human dose of PAXLOVID. No other significant developmental toxicities (malformations and embryo-fetal lethality) were observed up to the highest dose tested, 1,000 mg/kg/day. No developmental effects were observed in rabbits at 300 mg/kg/day resulting in systemic exposure (AUC_{24}) approximately 3 times higher than clinical exposures at the authorized human dose of PAXLOVID. A pre- and postnatal developmental (PPND) study in pregnant rats administered oral nirmatrelvir doses of up to 1,000 mg/kg/day from GD 6 through Lactation Day (LD) 20 showed no adverse findings. Although no difference in body weight was noted at birth when comparing offspring born to nirmatrelvir treated versus control animals, a decrease in the body weight of offspring was observed on Postnatal Day (PND) 17 (8% decrease) and PND 21 (up to 7% decrease) in the absence of maternal toxicity. No significant differences in offspring body weight were observed from PND 28 to PND 56. The maternal systemic exposure (AUC_{24}) at 1,000 mg/kg/day was approximately 9 times higher than clinical exposures at the authorized human dose of PAXLOVID. No body weight changes in the offspring were noted at 300 mg/kg/day, where maternal systemic exposure (AUC_{24}) was approximately 6 times higher than clinical exposures at the authorized human dose of PAXLOVID.

Ritonavir
Ritonavir was administered orally to pregnant rats (at 0, 15, 35, and 75 mg/kg/day) and rabbits (at 0, 25, 50, and 110 mg/kg/day) during organogenesis (on GD 6 through 17 in rats and GD 6 through 19 in rabbits). No evidence of teratogenicity due to ritonavir was observed in rats and rabbits at systemic exposures (AUC) 5 (rats) or 8 (rabbits) times higher than exposure at the authorized human dose of PAXLOVID. Increased incidences of early resorptions, ossification delays, and developmental variations, as well as decreased fetal body weights were observed in rats in the presence of maternal toxicity, at systemic exposures (AUC) approximately 10 times higher than exposure at the authorized human dose of PAXLOVID. In rabbits, resorptions, decreased litter size, and decreased fetal weights were observed at maternally toxic doses, at systemic exposures greater than 8 times higher than exposure at the authorized human dose of PAXLOVID. In a PPND study in rats, administration of 0, 15, 35, and 60 mg/kg/day ritonavir from GD 6 through PND 20 resulted in no developmental toxicity, at ritonavir systemic exposures greater than 10 times the exposure at the authorized human dose of PAXLOVID.

8.2 Lactation

Risk Summary

There are no available data on the presence of nirmatrelvir in human or animal milk, the effects on the breastfed infant, or the effects on milk production. A transient decrease in body weight was observed in the nursing offspring of rats administered nirmatrelvir *(see Data)*. Limited published data reports that ritonavir is present in human milk. There is no information on the effects of ritonavir on the breastfed infant or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PAXLOVID and any potential adverse effects on the breastfed infant from PAXLOVID or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

Data
In the PPND study, transiently lower body weight (up to 8%) was observed in the offspring of pregnant rats administered nirmatrelvir at maternal systemic exposure (AUC_{24}) approximately 9 times higher than clinical exposures at the authorized human dose of PAXLOVID. No body weight changes in the offspring were noted at maternal systemic exposure (AUC_{24}) approximately 6 times higher than clinical exposures at the authorized human dose of PAXLOVID.

8.3 Females and Males of Reproductive Potential

Contraception

Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Advise patients using combined hormonal contraceptives to use an effective alternative contraceptive method or an additional barrier method of contraception *[see Drug Interactions (7.3)]*.

8.4 Pediatric Use

PAXLOVID is not authorized for use in pediatric patients younger than 12 years of age or weighing less than 40 kg. The safety and effectiveness of PAXLOVID have not been established in pediatric patients. The authorized adult dosing regimen is expected to result in comparable serum exposures of nirmatrelvir and ritonavir in patients 12 years of age and older and weighing at least 40 kg as

observed in adults, and adults with similar body weight were included in the trial EPIC-HR *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

8.5 Geriatric Use

Clinical studies of PAXLOVID include subjects 65 years of age and older and their data contributes to the overall assessment of safety and efficacy *[see Adverse Reactions (6.1) and Clinical Studies (14.1)]*. Of the total number of subjects in the integrated dataset consisting of EPIC-HR and EPIC-SR who were randomized to and received PAXLOVID (N=1,578), 165 (10%) were 65 years of age and older and 39 (2%) were 75 years of age and older. No overall differences in safety were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in safety between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

Renal impairment increases nirmatrelvir exposure, which may increase the risk of PAXLOVID adverse reactions. No dosage adjustment is recommended in patients with mild renal impairment (eGFR ≥60 to <90 mL/min). Reduce the PAXLOVID dosage in patients with moderate renal impairment (eGFR ≥30 to <60 mL/min). PAXLOVID is not recommended for use in patients with severe renal impairment (eGFR <30 mL/min) or patients with end stage renal disease (eGFR <15 mL/min) receiving dialysis until more data are available. The appropriate dosage for patients with severe renal impairment has not been determined *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]. Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID*. Providers should counsel patients about renal dosing instructions *[see Patient Counseling Information (17)]*.

8.7 Hepatic Impairment

No dosage adjustment of PAXLOVID is recommended for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in subjects with severe (Child-Pugh Class C) hepatic impairment, therefore, PAXLOVID is not recommended for use in patients with severe (Child-Pugh Class C) hepatic impairment *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Treatment of overdose with PAXLOVID should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with PAXLOVID.

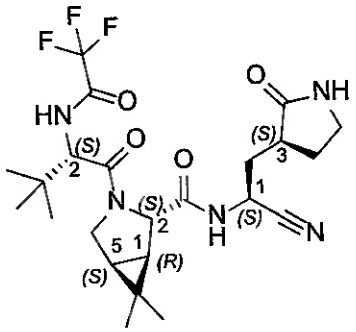
11 DESCRIPTION

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. Nirmatrelvir is a SARS-CoV-2 main protease (M^{pro}) inhibitor, and ritonavir is an HIV-1 protease inhibitor and CYP3A inhibitor.

Nirmatrelvir

The chemical name of active ingredient of nirmatrelvir is (1*R*,2*S*,5*S*)-*N*-((1*S*)-1-Cyano-2-((3*S*)-2-oxopyrrolidin-3-yl)ethyl)-3-((2*S*)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3-

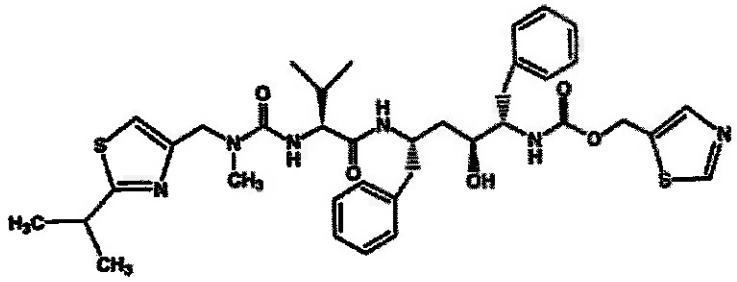
azabicyclo[3.1.0]hexane-2-carboxamide]. It has a molecular formula of $C_{23}H_{32}F_3N_5O_4$ and a molecular weight of 499.54. Nirmatrelvir has the following structural formula:



Nirmatrelvir is available as immediate-release, film-coated tablets. Each tablet contains 150 mg nirmatrelvir with the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, and sodium stearyl fumarate. The following are the ingredients in the film coating: hydroxy propyl methylcellulose, iron oxide red, polyethylene glycol, and titanium dioxide.

Ritonavir

Ritonavir is chemically designated as 10-Hydroxy-2-methyl-5-(1-methylethyl)-1- [2-(1 methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12- tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]. Its molecular formula is $C_{37}H_{48}N_6O_5S_2$, and its molecular weight is 720.95. Ritonavir has the following structural formula:



Ritonavir is available as film-coated tablets. Each tablet contains 100 mg ritonavir with the following inactive ingredients: anhydrous dibasic calcium phosphate, colloidal silicon dioxide, copovidone, sodium stearyl fumarate, and sorbitan monolaurate. The film coating may include the following ingredients: colloidal anhydrous silica, colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, polyethylene glycol, polysorbate 80, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nirmatrelvir is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antiviral drug *[see Microbiology (12.4)]*.

Ritonavir is an HIV-1 protease inhibitor but is not active against SARS-CoV-2 M^{pro}. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At 3 times the steady state peak plasma concentration (C_{max}) at the recommended dose, nirmatrelvir does not prolong the QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

The pharmacokinetics of nirmatrelvir/ritonavir were similar in healthy subjects and in subjects with mild-to-moderate COVID-19.

Nirmatrelvir AUC increased in a less than dose proportional manner over a single dose range from 250 mg to 750 mg (0.83 to 2.5 times the authorized recommended dose) and multiple dose range from 75 mg to 500 mg (0.25 to 1.67 times the authorized recommended dose), when administered in combination with 100 mg ritonavir. Nirmatrelvir steady state was achieved on Day 2 following administration of the authorized recommended dosage and the mean accumulation ratio was approximately 2-fold.

The pharmacokinetic properties of nirmatrelvir/ritonavir are displayed in Table 2.

Table 2: Pharmacokinetic Properties of Nirmatrelvir and Ritonavir in Healthy Subjects

	Nirmatrelvir (When Given With Ritonavir)	Ritonavir
Absorption		
T_{max} (hr), median	3.00[a]	3.98[a]
Food effect	Test/reference (fed/fasted) ratios of adjusted geometric means (90% CI) AUC_{inf} and C_{max} for nirmatrelvir were 119.67 (108.75, 131.68) and 161.01 (139.05, 186.44), respectively.[b]	
Distribution		
% bound to human plasma proteins	69%	98-99%
Blood-to-plasma ratio	0.60	0.14[d]
V_z/F (L), mean	104.7[c]	112.4[c]
Elimination		
Major route of elimination	Renal elimination[d]	Hepatic metabolism
Half-life ($T_{1/2}$) (hr), mean	6.05[a]	6.15[a]
Oral clearance (CL/F) (L/hr), mean	8.99[c]	13.92[c]
Metabolism		
Metabolic pathways	Nirmatrelvir is a CYP3A substrate but when dosed with ritonavir, metabolic clearance is minimal.	Major CYP3A, Minor CYP2D6
Excretion		
% drug-related material in feces	35.3%[e]	86.4%[f]
% of dose excreted as total (unchanged drug) in feces	27.5%[e]	33.8%[f]
% drug-related material in urine	49.6%[e]	11.3%[f]
% of dose excreted as total (unchanged drug) in urine	55.0%[e]	3.5%[f]

Abbreviations: CL/F=apparent clearance; hr=hour; L/hr=liters per hour; $T_{½}$=terminal elimination half-life; T_{max}=the time to reach C_{max}; V_z/F=apparent volume of distribution.

a. Represents data after a single dose of 300 mg nirmatrelvir (2 x 150 mg tablet formulation) administered together with 100 mg ritonavir tablet in healthy subjects.
b. Following a single oral dose of nirmatrelvir 300 mg boosted ritonavir 100 mg at -12 hours, 0 hours and 12 hours, administered under fed (high fat and high calorie meal) or fasted conditions.
c. 300 mg nirmatrelvir (oral suspension formulation) co-administered with 100 mg ritonavir (tablet formulation) twice daily for 3 days.
d. Red blood cell to plasma ratio.
e. Determined by ^{19}F-NMR analysis following 300 mg nirmatrelvir oral suspension administered at 0 hr enhanced with 100 mg ritonavir at -12 hours, 0 hours, 12 hours, and 24 hours.
f. Determined by ^{14}C analysis following 600 mg ^{14}C-ritonavir oral solution (6 times the authorized ritonavir dose).

The predicted Day 5 nirmatrelvir exposure parameters in adult subjects with mild-to-moderate COVID-19 who were treated with PAXLOVID in EPIC-HR are presented in Table 3.

Table 3: Predicted Day 5 Nirmatrelvir Exposure Parameters Following Administration of Nirmatrelvir/Ritonavir 300 mg/100 mg Twice Daily in Subjects with Mild-to-Moderate COVID-19

Pharmacokinetic Parameter (units)[a]	Nirmatrelvir[b]
C_{max} (µg/mL)	3.43 (2.59, 4.52)
AUC_{tau} (µg*hr/mL)[c]	30.4 (22.9, 39.8)
C_{min} (µg/mL)	1.57 (1.16, 2.10)

Abbreviations: C_{max}=predicted maximal concentration; C_{min}=predicted minimal concentration (C_{trough}).

a. Data presented as geometric mean (10^{th} and 90^{th} percentile).
b. Based on 1,016 subjects with their post hoc PK parameters.
c. AUC_{tau}=predicted area under the plasma concentration-time profile from time 0 to 12 hours for twice-daily dosing.

Effect of Food

No clinically significant differences in the pharmacokinetics of nirmatrelvir were observed following administration of a high fat meal (800-1000 calories; 50% fat) to healthy subjects.

Specific Populations

There were no clinically significant differences in the pharmacokinetics of nirmatrelvir based on age (18 to 86 years), sex, or race/ethnicity.

Pediatric Patients

The pharmacokinetics of nirmatrelvir/ritonavir in patients less than 18 years of age have not been established.

Patients with Renal Impairment

The pharmacokinetics of nirmatrelvir in patients with renal impairment following administration of a single oral dose of nirmatrelvir 100 mg (0.33 times the authorized recommended dose) co-administered with ritonavir 100 mg are presented in Table 4. Compared to healthy controls with no renal impairment, the C_{max} and AUC of nirmatrelvir in patients with mild renal impairment was 30% and 24% higher, in patients with moderate renal impairment was 38% and 87% higher, and in patients with severe renal impairment was 48% and 204% higher, respectively.

Table 4: Impact of Renal Impairment on Nirmatrelvir/Ritonavir Pharmacokinetics

	Normal Renal Function (n=8)	Mild Renal Impairment (n=8)	Moderate Renal Impairment (n=8)	Severe Renal Impairment (n=8)
C_{max} (µg/mL)	1.60 (31)	2.08 (29)	2.21 (17)	2.37 (38)
AUC_{inf} (µg*hr/mL)	14.46 (20)	17.91 (30)	27.11 (27)	44.04 (33)
T_{max} (hr)	2.0 (1.0 - 4.0)	2.0 (1.0 – 3.0)	2.50 (1.0 – 6.0)	3.0 (1.0 - 6.1)
$T_{1/2}$ (hr)	7.73 ± 1.82	6.60 ± 1.53	9.95 ± 3.42	13.37 ± 3.32

Abbreviations: AUC_{inf}=area under the plasma concentration-time profile from time zero extrapolated to infinite time; C_{max}=the observed maximum concentration; CV=coefficient of variation; SD=standard deviation; $T_{½}$=terminal elimination half-life; T_{max}=the time to reach C_{max}.
Values are presented as geometric mean (geometric % CV) except median (range) for T_{max} and arithmetic mean ± SD for $T_{1/2}$.

Patients with Hepatic Impairment
The pharmacokinetics of nirmatrelvir were similar in patients with moderate (Child-Pugh Class B) hepatic impairment compared to healthy subjects following administration of a single oral dose of nirmatrelvir 100 mg (0.33 times the authorized recommended dose) co-administered with ritonavir 100 mg. The impact of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of nirmatrelvir or ritonavir has not been studied.

Clinical Drug Interaction Studies

Table 5 describes the effect of other drugs on the C_{max} and AUC of nirmatrelvir.

Table 5: The Effect of Other Drugs on the Pharmacokinetic Parameters of Nirmatrelvir

Co-administered Drug	Dose (Schedule)		N	Percent Ratio (in combination with co-administered drug/alone) of Nirmatrelvir Pharmacokinetic Parameters (90% CI); No Effect=100	
	Co-administered Drug	Nirmatrelvir/ Ritonavir		C_{max}	AUC[a]
Carbamazepine[b]	300 mg twice daily (16 doses)	300 mg/100 mg once daily (2 doses)	10	56.82 (47.04, 68.62)	44.50 (33.77, 58.65)
Itraconazole	200 mg once daily (8 doses)	300 mg/100 mg twice daily (5 doses)	11	118.57 (112.50, 124.97)	138.82 (129.25, 149.11)

Abbreviations: AUC=area under the plasma concentration-time curve; AUC_{inf}=area under the plasma concentration-time profile from time zero extrapolated to infinite time; AUC_{tau}=area under the plasma concentration-time profile from time zero to time tau (τ), the dosing interval. CI=confidence interval; C_{max}=observed maximum plasma concentrations.

a. For carbamazepine, AUC=AUC_{inf}; for itraconazole, AUC=AUC_{tau}.

b. Carbamazepine titrated up to 300 mg twice daily on Day 8 through Day 15 (e.g., 100 mg twice daily on Day 1 through Day 3 and 200 mg twice daily on Day 4 through Day 7).

Table 6 describes the effect of nirmatrelvir/ritonavir on the C_{max} and AUC of other drugs.

Table 6: Effect of Nirmatrelvir/Ritonavir on Pharmacokinetics of Other Drugs

Co-administered Drug	Dose (Schedule)		N	Percent Ratio of Test/Reference of Geometric Means (90% CI); No Effect=100	
	Co-administered Drug	Nirmatrelvir/ Ritonavir		C_{max}	AUC[a]
Midazolam[b]	2 mg (1 dose)	300 mg/100 mg twice daily (9 doses)	10	368.33 (318.91, 425.41)	1430.02 (1204.54, 1697.71)
Dabigatran[b]	75 mg (1 dose)	300 mg/100 mg twice daily (4 doses)[b]	24	233.06 (172.14, 315.54)	194.47 (155.29, 243.55)

Abbreviations: AUC=area under the plasma concentration-time curve; CI=confidence interval; C_{max}=observed maximum plasma concentrations; P-gp=p-glycoprotein.

a. AUC=AUC_{inf} for both midazolam and dabigatran.

b. For midazolam, Test=nirmatrelvir/ritonavir plus midazolam, Reference=Midazolam. Midazolam is an index substrate for CYP3A. For dabigatran, Test=nirmatrelvir/ritonavir plus dabigatran, Reference=Dabigatran. Dabigatran is an index substrate for P-gp.

In Vitro Studies
Cytochrome P450 (CYP) Enzymes:

- Nirmatrelvir is a reversible and time-dependent inhibitor of CYP3A, but not an inhibitor CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Nirmatrelvir is an inducer of CYP2B6, 2C8, 2C9, and 3A4, but there is minimal risk for pharmacokinetic interactions arising from induction of these CYP enzymes at the proposed therapeutic dose.
- Ritonavir is a substrate of CYP2D6 and CYP3A. Ritonavir is an inducer of CYP1A2, CYP2C9, CYP2C19, CYP2B6, and CYP3A.

Transporter Systems: Nirmatrelvir is an inhibitor of P-gp and OATP1B1. Nirmatrelvir is a substrate for P-gp, but not BCRP, MATE1, MATE2K, NTCP, OAT1, OAT2, OAT3, OCT1, OCT2, PEPT1, OATP1B1, OATP1B3, OATP2B1, or OATP4C1.

12.4 Microbiology

Mechanism of Action

Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (M^{pro}), also referred to as 3C-like protease ($3CL^{pro}$) or nonstructural protein 5 (nsp5) protease. Inhibition of SARS-CoV-2 M^{pro} renders it incapable of processing the viral polyproteins pp1a and pp1ab, preventing viral replication. Nirmatrelvir inhibited the activity of recombinant SARS-CoV-2 M^{pro} in a biochemical assay with a K_i value of 3.1 nM and an IC_{50} value of 19.2 nM. Nirmatrelvir was found to bind directly to the SARS-CoV-2 M^{pro} active site by X-ray crystallography.

Antiviral Activity

Cell Culture Antiviral Activity
Nirmatrelvir exhibited antiviral activity against SARS-CoV-2 (USA-WA1/2020 isolate) infection of differentiated normal human bronchial epithelial (dNHBE) cells with EC_{50} and EC_{90} values of 62 nM (31 ng/mL) and 181 nM (90 ng/mL), respectively, after 3 days of drug exposure.

The antiviral activity of nirmatrelvir against the Omicron sub-variants BA.2, BA.2.12.1, BA.4, BA.4.6, BA.5, BF.7, BQ.1, BQ.1.11, and XBB.1.5 was assessed in Vero E6-TMPRSS2 cells in the presence of a P-gp inhibitor. Nirmatrelvir had a median EC_{50} value of 83 nM (range: 39-146 nM) against the Omicron sub-variants, reflecting EC_{50} value fold-changes ≤1.5 relative to the USA-WA1/2020 isolate.

In addition, the antiviral activity of nirmatrelvir against the SARS-CoV-2 Alpha, Beta, Gamma, Delta, Lambda, Mu, and Omicron BA.1 variants was assessed in Vero E6 P-gp knockout cells. Nirmatrelvir had a median EC_{50} value of 25 nM (range: 16-141 nM). The Beta variant was the least susceptible variant tested, with an EC_{50} value fold-change of 3.7 relative to USA-WA1/2020. The other variants had EC_{50} value fold-changes ≤1.1 relative to USA-WA1/2020.

Clinical Antiviral Activity
In clinical trial EPIC-HR, which enrolled subjects who were primarily infected with the SARS-CoV-2 Delta variant, PAXLOVID treatment was associated with a 0.83 log_{10} copies/mL greater median decline in viral RNA shedding levels in nasopharyngeal samples through Day 5 (mITT1 analysis set, all treated subjects with onset of symptoms ≤5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment); similar results were observed in the mITT2 analysis set (all treated subjects with onset of symptoms ≤5 days). In the EPIC-SR trial, which included subjects who were infected with SARS-CoV-2 Delta (79%) or Omicron (19%) variants,

PAXLOVID treatment was associated with a 1.05 log_{10} copies/mL greater median decline in viral RNA shedding levels in nasopharyngeal samples through Day 5, with similar declines observed in subjects infected with Delta or Omicron variants. The degree of reduction in viral RNA levels relative to placebo following 5 days of PAXLOVID treatment was similar between unvaccinated high-risk subjects in EPIC-HR and vaccinated high-risk subjects in EPIC-SR.

Antiviral Resistance

In Cell Culture and Biochemical Assays
SARS-CoV-2 M^{pro} residues potentially associated with nirmatrelvir resistance have been identified using a variety of methods, including SARS-CoV-2 resistance selection, testing of recombinant SARS-CoV-2 viruses with M^{pro} substitutions, and biochemical assays with recombinant SARS-CoV-2 M^{pro} containing amino acid substitutions. Table 7 indicates M^{pro} substitutions and combinations of M^{pro} substitutions that have been observed in nirmatrelvir-selected SARS-CoV-2 in cell culture. Individual M^{pro} substitutions are listed regardless of whether they occurred alone or in combination with other M^{pro} substitutions. Note that the M^{pro} S301P and T304I substitutions overlap the P6 and P3 positions of the nsp5/nsp6 cleavage site located at the C-terminus of M^{pro}. Substitutions at other M^{pro} cleavage sites have not been associated with nirmatrelvir resistance in cell culture. The clinical significance of these substitutions is unknown.

Table 7: SARS-CoV-2 M^{pro} Amino Acid Substitutions Selected by Nirmatrelvir in Cell Culture

Single Substitutions (EC_{50} value fold-change)	T21I (1.1-4.6), L50F (1.5-4.2), P108S (ND), T135I (ND), F140L (4.1), S144A (2.2-5.3), C160F (ND), E166A (3.3), E166V (25-288), L167F (ND), T169I (ND), H172Y (ND), A173V (0.9-1.7), V186A (ND), R188G (ND), A191V (ND), A193P (ND), P252L (5.9), S301P (ND), and T304I (1.4-5.5).
≥2 Substitutions (EC_{50} value fold-change)	T21I+S144A (9.4), T21I+E166V (83), T21I+A173V (3.1), T21I+T304I (3.0-7.9), L50F+E166V (34-175), L50F+T304I (5.9), T135I+T304I (3.8), F140L+A173V (10.1), H172Y+P252L (ND), A173V+T304I (20.2), T21I+L50F+A193P+S301P (28.8), T21I+S144A+T304I (27.8), T21I+C160F+A173V+V186A+T304I (28.5), T21I+A173V+T304I (15), and L50F+F140L+L167F+T304I (54.7).

Abbreviation: ND=no data.

In a biochemical assay using recombinant SARS-CoV-2 M^{pro} containing amino acid substitutions, the following SARS-CoV-2 M^{pro} substitutions led to ≥3-fold reduced nirmatrelvir activity (fold-change based on K_i values): Y54A (25), F140A (21), F140L (7.6), F140S (260), G143S (3.6), S144A (46), S144E (480), S144T (170), H164N (6.7), E166A (35), E166G (6.2), E166V (7,700), H172Y (250), A173S (4.1), A173V (16), R188G (38), Q192L (29), Q192P (7.8), and V297A (3.0). In addition, the following combinations of M^{pro} substitutions led to ≥3-fold reduced nirmatrelvir activity: T21I+S144A (20), T21I+E166V (11,000), T21I+A173V (15), L50F+E166V (4,500), T135I+T304I (5.1), F140L+A173V (95), H172Y+P252L (180), A173V+T304I (28), T21I+S144A+T304I (51), T21I+A173V+T304I (55), L50F+E166A+L167F (210), T21I+L50F+A193P+S301P (7.3), L50F+F140L+L167F+T304I (190), and T21I+C160F+A173V+V186A+T304I (28). The following substitutions and substitution combinations emerged in cell culture but conferred <3-fold reduced nirmatrelvir activity in biochemical assays: T21I (1.6), L50F (0.2), P108S (2.9), T135I (2.2), C160F (0.6), L167F (0.9), T169I (1.4), V186A (0.8), A191V (0.8), A193P (0.9), P252L (0.9), S301P (0.2), T304I (1.0), T21I+T304I (1.8), and L50F+T304I (1.3). The clinical significance of these substitutions is unknown.

In Clinical Trials

Treatment-emergent substitutions were evaluated among subjects in clinical trials EPIC-HR/SR with sequence data available at both baseline and a post-baseline visit (n=907 PAXLOVID-treated subjects, n=946 placebo-treated subjects). SARS-CoV-2 M^{pro} amino acid changes were classified as PAXLOVID treatment-emergent substitutions if they occurred at the same amino acid position in 3 or more PAXLOVID-treated subjects and were ≥2.5-fold more common in PAXLOVID-treated subjects than placebo-treated subjects. The following PAXLOVID treatment-emergent M^{pro} substitutions were observed: T98I/R/del(n=4), E166V (n=3), and W207L/R/del (n=4). Within the M^{pro} cleavage sites, the following PAXLOVID treatment-emergent substitutions were observed: A5328S/V(n=7) and S6799A/P/Y (n=4). These cleavage site substitutions were not associated with the co-occurrence of any specific M^{pro} substitutions.

None of the treatment-emergent substitutions listed above in M^{pro} or M^{pro} cleavage sites occurred in PAXLOVID-treated subjects who experienced hospitalization. Thus, the clinical significance of these substitutions is unknown.

Viral RNA Rebound (With and Without COVID-19 Symptoms) and Treatment-Emergent Substitutions

EPIC-HR and EPIC-SR were not designed to evaluate COVID-19 rebound; exploratory analyses were conducted to assess the relationship between PAXLOVID use and rebound in viral RNA shedding levels or self-reported COVID-19 symptoms.

Post-treatment increases in SARS-CoV-2 RNA shedding levels in nasopharyngeal samples were observed on Day 10 and/or Day 14 in a subset of PAXLOVID and placebo recipients in EPIC-HR and EPIC-SR, irrespective of COVID-19 symptoms. The frequency of detection of post-treatment viral RNA rebound varied according to analysis parameters, but was generally similar among PAXLOVID and placebo recipients. A similar or smaller percentage of placebo recipients compared to PAXLOVID recipients had nasopharyngeal viral RNA results <lower limit of quantitation (LLOQ) at all study timepoints in both the treatment and post-treatment periods.

In EPIC-HR, of 59 PAXLOVID-treated subjects identified with post-treatment viral RNA rebound and with available viral sequence data, treatment-emergent substitutions in M^{pro} potentially reducing nirmatrelvir activity were detected in 2 (3%) subjects, including E166V in 1 subject and T304I in 1 subject. Both subjects had viral RNA shedding levels <LLOQ by Day 14.

Post-treatment viral RNA rebound was not associated with the primary clinical outcome of COVID-19-related hospitalization or death from any cause through Day 28 following the single 5-day course of PAXLOVID treatment. The clinical relevance of post-treatment increases in viral RNA following PAXLOVID or placebo treatment is unknown.

The frequency of symptom rebound through Day 28, irrespective of viral RNA results, was similar among PAXLOVID and placebo recipients. The frequency of combined viral RNA rebound plus symptom rebound could not be fully assessed as most episodes of symptom rebound occurred after Day 14 (the last day SARS-CoV-2 RNA levels were routinely assessed).

Cross-Resistance

Cross-resistance is not expected between nirmatrelvir and remdesivir or any other anti-SARS-CoV-2 agents with different mechanisms of action (i.e., agents that are not M^{pro} inhibitors).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Nirmatrelvir

Carcinogenicity studies have not been conducted with nirmatrelvir.

Nirmatrelvir was negative for mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the *in vitro* micronucleus assay using human lymphoblastoid TK6 cells, and the *in vivo* rat micronucleus assays.

In a fertility and early embryonic development study, nirmatrelvir was administered orally to male and female rats at doses of 60, 200, or 1,000 mg/kg/day once daily beginning 14 days prior to mating, throughout the mating phase, and continued through GD 6 for females and for a total of 32 doses for males. There were no effects on fertility, reproductive performance, or early embryonic development at doses up to 1,000 mg/kg/day, resulting in systemic exposure (AUC_{24}) approximately 5 times higher than exposure at the authorized human dose of PAXLOVID.

Ritonavir

Carcinogenicity studies in mice and rats have been conducted on ritonavir. In male mice, at levels of 50, 100, or 200 mg/kg/day, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 25 times higher than the exposure in humans at the authorized human dose of PAXLOVID. No carcinogenic effects were observed in females at up to the highest dose tested, resulting in systemic exposure (AUC_{24}) approximately 25 times higher than the exposure in humans at the authorized human dose of PAXLOVID. In rats dosed at levels of 7, 15, or 30 mg/kg/day, there were no carcinogenic effects. In this study, the exposure at the high dose was approximately 5 times higher than the exposure in humans at the authorized human dose of PAXLOVID.

Ritonavir was found to be negative for mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Ritonavir produced no effects on fertility in rats at drug exposures approximately 18 (male) and 27 (female) times higher than the exposure in humans at the authorized human dose of PAXLOVID.

14 CLINICAL STUDIES

14.1 Efficacy in Subjects at High Risk of Progression to Severe COVID-19 (EPIC-HR)

EPIC-HR (NCT04960202) was a Phase 2/3, randomized, double-blind, placebo-controlled trial in non-hospitalized symptomatic adult subjects with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Eligible subjects were 18 years of age and older with at least 1 of the following risk factors for progression to severe disease: diabetes, overweight (BMI >25), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, sickle cell disease,

neurodevelopmental disorders, active cancer, medically-related technological dependence, or were 60 years of age and older regardless of comorbidities. Subjects with COVID-19 symptom onset of ≤5 days were included in the study. Subjects were randomized (1:1) to receive PAXLOVID (nirmatrelvir/ritonavir 300 mg/100 mg) or placebo orally every 12 hours for 5 days. The trial excluded individuals with a history of prior COVID-19 infection or vaccination and excluded individuals taking any medications with clinically significant drug interactions with PAXLOVID. The primary efficacy endpoint was the proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28. The analysis was conducted in the modified intent-to-treat (mITT) analysis set [all treated subjects with onset of symptoms ≤3 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic monoclonal antibody (mAb) treatment], the mITT1 analysis set (all treated subjects with onset of symptoms ≤5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment), and the mITT2 analysis set (all treated subjects with onset of symptoms ≤5 days).

A total of 2,113 subjects were randomized to receive either PAXLOVID or placebo. At baseline, mean age was 45 years; 51% were male; 71% were White, 15% were Asian, 9% were American Indian or Alaska Native, 4% were Black or African American, and 1% was missing or unknown; 41% were Hispanic or Latino; 67% of subjects had onset of symptoms ≤3 days before initiation of study treatment; 49% of subjects were serological negative at baseline; the mean (SD) baseline viral RNA in nasopharyngeal samples was 4.71 $\log_{10}$ copies/mL (2.89); 27% of subjects had a baseline viral RNA of ≥10^7 ($\log_{10}$ copies/mL); 6% of subjects either received or were expected to receive COVID-19 therapeutic monoclonal antibody treatment at the time of randomization and were excluded from the mITT and mITT1 analyses.

The baseline demographic and disease characteristics were balanced between the PAXLOVID and placebo groups.

The proportions of subjects who discontinued treatment due to an adverse event were 2.0% in the PAXLOVID group and 4.2% in the placebo group.

Table 8 provides results of the primary endpoint in mITT1 analysis population. For the primary endpoint, the relative risk reduction in the mITT1 analysis population for PAXLOVID compared to placebo was 86% (95% CI: 72%, 93%).

Table 8: COVID-19 Related Hospitalization or Death from Any Cause Through Day 28 in Non-Hospitalized Adults with COVID-19 (mITT1 Analysis Set): EPIC-HR

	PAXLOVID (N=977)	Placebo (N=989)
COVID-19 Related Hospitalization or Death from Any Cause Through Day 28		
n (%) Reduction Relative to Placebo[a] (95% CI), %	9 (0.9%) -5.6 (-7.3, -4.0)	64 (6.5%)
COVID-19 Related Hospitalization Through Day 28, %	9 (0.9%)	63 (6.4%)
All-cause Mortality Through Day 28[b], %	0	12 (1.2%)

Abbreviations: CI=confidence interval; COVID-19=coronavirus disease 2019; mAb=monoclonal antibody; mITT1=modified intent-to-treat 1 (all treated subjects with onset of symptoms ≤5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment).

The determination of primary efficacy was based on a planned interim analysis of 754 subjects in mITT population. The estimated risk reduction was -6.5% with a 95% CI of (-9.3%, -3.7%) and 2-sided p-value <0.0001.

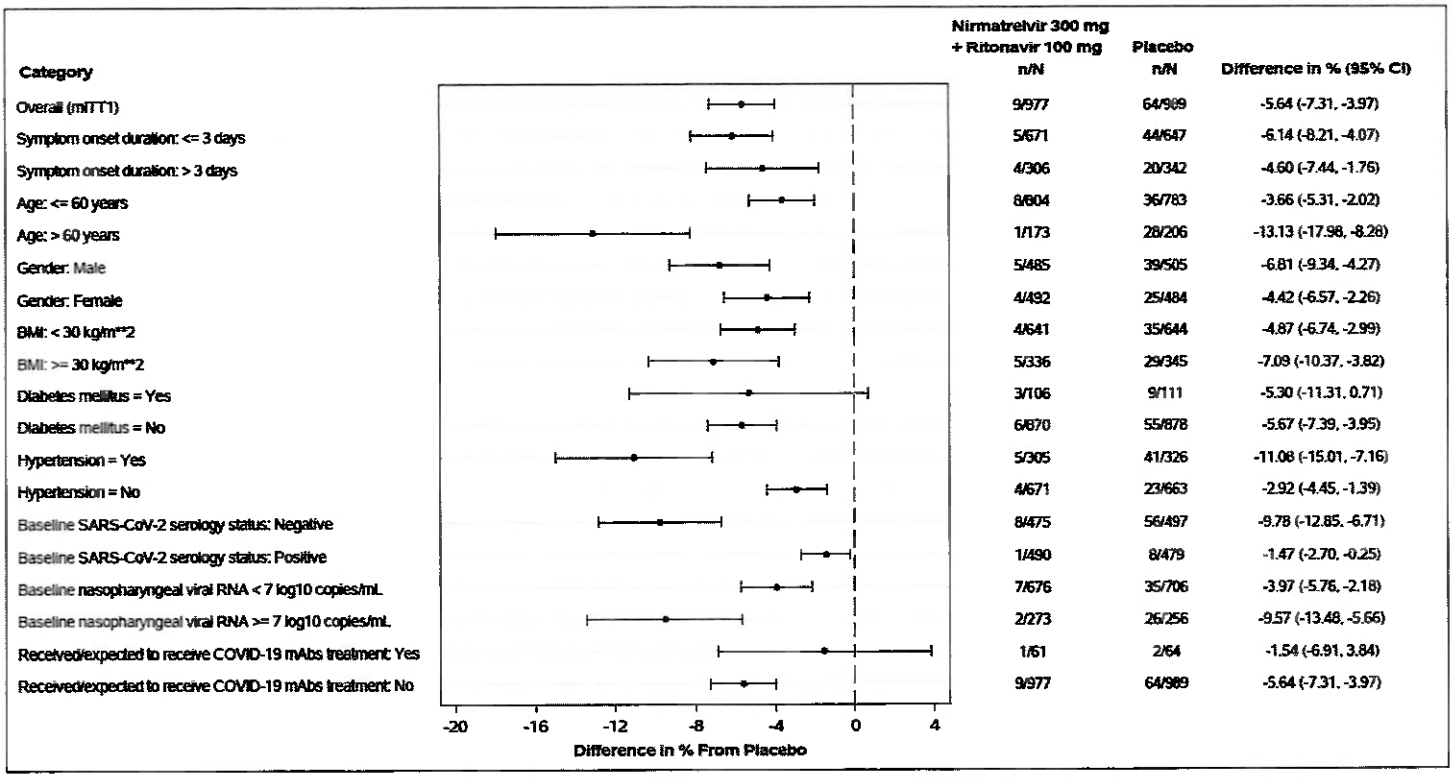
a. The estimated cumulative proportion of subjects hospitalized or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.

b. For the secondary endpoint of all-cause mortality through Week 24, there were 0 and 15 (1%) events in the PAXLOVID arm and placebo arm, respectively.

Consistent results were observed in the mITT and mITT2 analysis populations.

Similar trends have been observed across subgroups of subjects *(see Figure 1)*.

Figure 1: Subgroup Analysis of Adults with COVID-19 Dosed within 5 Days of Symptom Onset with COVID-19 Related Hospitalization or Death from Any Cause Through Day 28: EPIC-HR



Abbreviations: BMI=body mass index; COVID-19=coronavirus disease 2019; mAb=monoclonal antibody; mITT=modified intent-to-treat; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.
N=number of subjects in the category of the analysis set.
All categories are based on mITT1 population except for COVID-19 mAb treatment which is based on mITT2 population.
Seropositivity was defined if results were positive in either Elecsys anti-SARS-CoV-2 S or Elecsys anti-SARS-CoV-2 (N) assay.
The difference of the proportions in the 2 treatment groups and its 95% confidence interval based on normal approximation of the data are presented.

Among subjects who were SARS-CoV-2 seropositive at baseline, 1/490 (0.2%) PAXLOVID recipients versus 8/479 (1.7%) placebo recipients met the primary endpoint of COVID-19 related hospitalization or death from any cause through Day 28 [reduction relative to placebo -1.47% (-2.70%, -0.25%)].

14.2 Trial in Unvaccinated Subjects Without a Risk Factor for Progression to Severe COVID-19 or Subjects Fully Vaccinated Against COVID-19 With at Least One Factor for Progression to Severe COVID-19 (EPIC-SR)

PAXLOVID is not authorized for the treatment of COVID-19 in patients without a risk factor for progression to severe COVID-19.

EPIC-SR (NCT05011513) was a Phase 2/3, randomized, double-blind, placebo-controlled trial in non-hospitalized symptomatic adult subjects with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Eligible subjects were 18 years of age or older with COVID-19 symptom onset of ≤5 days who were at standard risk for progression to severe disease. The trial included previously unvaccinated subjects with no risk factors for progression to severe disease or subjects fully vaccinated against COVID-19 (i.e., completed a primary vaccination series) with at least 1 of the risk factors for progression to severe disease as defined in EPIC-HR. Through the December 19, 2021, data cutoff, a total of 1,075 subjects were randomized (1:1) to receive PAXLOVID or placebo orally every 12 hours for 5 days; of these, 59% were fully vaccinated high-risk subjects.

The primary endpoint in this trial, the difference in time to sustained alleviation of all targeted COVID-19 signs and symptoms through Day 28 among PAXLOVID versus placebo recipients, was not met.

In an exploratory analysis of the subgroup of fully vaccinated subjects with at least 1 risk factor for progression to severe disease, a non-statistically significant numerical reduction relative to placebo for the secondary endpoint of COVID-19 related hospitalization or death from any cause through Day 28 was observed.

14.3 Post-Exposure Prophylaxis Trial

PAXLOVID is not authorized for the post-exposure prophylaxis of COVID-19.

In a double-blind, double-dummy, placebo-controlled trial, the efficacy of PAXLOVID when administered for 5 or 10 days as post-exposure prophylaxis of COVID-19 was evaluated. Eligible subjects were asymptomatic adults 18 years of age and older who were SARS-CoV-2 negative at baseline and who lived in the same household with symptomatic individuals with a recent diagnosis of SARS-CoV-2. A total of 2,736 subjects were randomized (1:1:1) to receive PAXLOVID orally every 12 hours for 5 days, PAXLOVID orally every 12 hours for 10 days, or placebo.

The primary endpoint for this trial was not met. The primary endpoint was the risk reduction between the 5-day and 10-day PAXLOVID regimens versus placebo in the proportion of subjects who developed RT-PCR or RAT-confirmed symptomatic SARS-CoV-2 infection through Day 14 who had a negative SARS-CoV-2 RT-PCR result at baseline. The proportion of subjects who had events through Day 14 was 2.6% for the 5-day PAXLOVID regimen, 2.4% for the 10-day PAXLOVID regimen, and 3.9% for placebo. There was not a statistically significant risk reduction versus placebo for either the 5-day or 10-day PAXLOVID regimen.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. It is supplied in two different Dose Packs.

Nirmatrelvir tablets and ritonavir tablets are supplied in separate blister cavities within the same child-resistant blister card.

Dose Pack	Content	NDC	Description
300 mg nirmatrelvir; 100 mg ritonavir	**Each Carton Contains:** 30 tablets divided in 5 daily-dose blister cards	0069-1085-30	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White film-coated ovaloid tablets debossed with the "a" logo and the code NK.
		Or	

		0069-0345-30	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White to off-white, capsule-shaped, film-coated tablets debossed with "H" on one side and "R9" on the other side.
	Each Blister Card[a] Contains: 4 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each)	0069-1085-06	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White film-coated ovaloid tablets debossed with the "a" logo and the code NK.
		Or	
		0069-0345-06	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White to off-white, capsule-shaped, film-coated tablets debossed with "H" on one side and "R9" on the other side.
150 mg nirmatrelvir; 100 mg ritonavir	**Each Carton Contains:** 20 tablets divided in 5 daily-dose blister cards	0069-1101-20	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White film-coated ovaloid tablets debossed with the "a" logo and the code NK.
	Each Blister Card[a] Contains: 2 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each)	0069-1101-04	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White film-coated ovaloid tablets debossed with the "a" logo and the code NK.

a. Indicates which tablets need to be taken in the morning and evening.

Storage and Handling

Store at USP controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

17 PATIENT COUNSELING INFORMATION

As a healthcare practitioner, you must communicate to the patient and/or caregiver information consistent with the "FACT SHEET FOR PATIENTS, PARENTS, AND CAREGIVERS" and provide them with a copy of this Fact Sheet prior to administration of PAXLOVID.

Drug Interactions

Inform patients that PAXLOVID may interact with certain drugs and is contraindicated for use with certain drugs; therefore, advise patients to report to their healthcare provider the use of any prescription, non-prescription medication, or herbal products *[see Boxed Warning, Contraindications (4), Warnings and Precautions (5.1), and Drug Interactions (7)]*.

Hypersensitivity Reactions

Inform patients that anaphylaxis, serious skin reactions, and other hypersensitivity reactions have been reported, even following a single dose of PAXLOVID. Advise them to immediately discontinue the drug and to inform their healthcare provider at the first sign of a skin rash, hives or other skin reactions, difficulty in swallowing or breathing, any swelling suggesting angioedema (for example, swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction *[see Warnings and Precautions (5.2)]*.

Dosage Modification in Patients with Moderate Renal Impairment

To ensure appropriate dosing in patients with moderate renal impairment, instruct such patients that they will be taking one 150 mg nirmatrelvir tablet with one 100 mg ritonavir tablet together twice daily for 5 days *[see Dosage and Administration (2.3)]*.

In the event that the PAXLOVID 150 mg;100 mg dose pack is unavailable: pharmacist should refer to the provided instructions entitled "IMPORTANT PAXLOVID™ EUA DISPENSING INFORMATION FOR PATIENTS WITH MODERATE RENAL IMPAIRMENT" for dispensing of PAXLOVID to patients with moderate renal impairment *[see Dosage and Administration (2.3)]* and patients should be informed that their daily blister card has been altered to ensure they receive the correct dose.

Administration Instructions

Inform patients to take PAXLOVID with or without food as instructed. Advise patients to swallow all tablets for PAXLOVID whole and not to chew, break, or crush the tablets. Alert the patient of the importance of completing the full 5-day treatment course and to continuing isolation in accordance with public health recommendations to maximize viral clearance and minimize transmission of SARS-CoV-2. If the patient misses a dose of PAXLOVID within 8 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 8 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose *[see Dosage and Administration (2.1)]*.

18 MANUFACTURER INFORMATION

For general questions, visit the website or call the telephone number provided below.

Website	Telephone number
www.COVID19oralRx.com	1-877-219-7225 (1-877-C19-PACK)

For Medical Information about PAXLOVID, please visit www.pfizermedinfo.com or call 1-800-438-1985.

Pfizer

Distributed by
Pfizer Labs
Division of Pfizer Inc.
New York, NY 10001

LAB-1492-12.4b
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U.S. FOOD & DRUG ADMINISTRATION

Frequently Asked Questions on the Emergency Use Authorization for Paxlovid for Treatment of COVID-19

Click to jump to each section

U.S. FOOD & DRUG ADMINISTRATION

Questions related to Paxlovid's approval or EUA

Q: Is Paxlovid FDA-approved to treat or prevent COVID-19?

A. On May 25, 2023, FDA approved a New Drug Application (NDA) for Paxlovid for the treatment of mild-to-moderate coronavirus disease (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. FDA has determined Paxlovid is safe and effective when used in accordance with the FDA-approved labeling.

Paxlovid is not FDA-approved for use as pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

Q. Now that Paxlovid is an approved drug, is the EUA continuing, and what does the EUA authorize?

A. Yes. The EUA authorizes the emergency use of Paxlovid for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death.

The EUA continues to authorize Paxlovid for emergency use to treat certain eligible pediatric patients, a patient population that is not covered under the approved NDA for Paxlovid at this time. Paxlovid also remains authorized under EUA to ensure continued access for all eligible patients to the U.S. government's supply of Paxlovid, including adult patients who are the subject of the approved NDA, pending commercial launch of the approved product.

Paxlovid is not authorized:

- for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.
- for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
- for use longer than five consecutive days.

The use of Paxlovid under the EUA must be consistent with the terms and conditions of the authorization.

Q. Does the authorized Paxlovid provide the same clinical benefit as the approved Paxlovid, once the approved Paxlovid is available?

A. Yes. The authorized Paxlovid contains the same tablets (nirmatrelvir tablets and ritonavir tablets) as the Paxlovid that is now FDA-approved. Since Paxlovid was initially authorized for emergency use, Pfizer has also been required, as a condition under the EUA, to comply with the same good manufacturing practices that apply to approved products. Based on these considerations, it is FDA's expectation that patients being treated with Paxlovid for COVID-19 will receive the same clinical benefit as long as the product is used in accordance with the labeling, regardless of whether the authorized or approved Paxlovid is dispensed.

Paxlovid is FDA-approved for the treatment of mild-to-moderate COVID-19 in certain adults. Paxlovid is authorized for emergency use, but not FDA-approved, for the treatment of mild-to-moderate COVID-19 in certain pediatric patients.

Q. Why does the EUA authorize Paxlovid for its approved patient population, specifically for the treatment of mild-to-moderate COVID-19 in high-risk adults?

A. Although different presentations of PAXLOVID are now FDA-approved for the treatment of mild-to-moderate COVID-19 in certain adults, there are not sufficient quantities of the approved PAXLOVID available for distribution to this population in its entirety at the time of reissuance of this EUA. To ensure continued access to the U.S. government's supply for Paxlovid and fully meet the public health need before commercial launch of the approved product, the EUA continues to include the patient population now approved under the NDA for Paxlovid.

The use of Paxlovid under the EUA must be consistent with the terms and conditions of the authorization.

Q. May health care providers prescribe Paxlovid for uses not authorized under EUA?

A. At this time, the U.S. government continues to oversee the distribution of Paxlovid, which consists solely of Paxlovid that is labeled and packaged in accordance with the EUA. The Letter of Authorization for the EUA provides for the use of Paxlovid only when consistent with the terms and conditions of the authorization. Paxlovid is currently authorized for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death. Although Paxlovid has been approved for use in eligible adult patients who are also included in the EUA population, the approved product has not yet commercially launched.

In certain circumstances, Paxlovid labeled and packaged in accordance with the EUA may also be accessed through an Expanded Access Investigational New Drug Application, also referred to as "compassionate use", for uses not within the scope of the EUA for Paxlovid, as appropriate. Expanded access may be considered when **all** of the following apply:

- Patient has a serious or immediately life-threatening disease or condition.
- There is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition.
- Patient enrollment in a clinical trial is not possible.
- Potential patient benefit justifies the potential risks of treatment.
- Providing the investigational medical product will not interfere with investigational trials that could support a medical product's development or marketing approval for the treatment indication.

Health care providers seeking to obtain Paxlovid under expanded access should first contact Pfizer through its website.

Once Pfizer has provided the requisite authorization, health care providers should contact FDA using the information detailed below to complete the process:

- During normal business hours (8:00 a.m. – 4:30 p.m. ET, weekdays):
  - By phone – (301) 796-3400 or (855) 543-3784

- By email – DDI.EIND@fda.hhs.gov
- Outside of normal business hours (After 4:30 p.m. ET weekdays and all day on weekends/federal holidays)
  - By phone – (301) 796-9900
  - By email – CDER-EIND@fda.hhs.gov

General information on expanded access for providers and patients, respectively, can be found on FDA's website.

Q. Paxlovid is approved and authorized only for certain patients at "high risk". What does "high risk" mean?

A. Determining whether a patient is at high risk for progression to severe COVID-19, including hospitalization or death, is based on the provider's assessment of the individual patient being considered for treatment with COVID-19 and that patient's medical history.

Resources providing information on conditions that place a patient with mild-to-moderate COVID-19 at high risk for disease progression, including hospitalization or death, can be found at the Centers for Disease Control and Prevention site: Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals and at NIH's COVID-19 Treatment Guidelines: Clinical Spectrum of SARS-CoV-2 Infection.

Q. Why is pediatric use not approved for Paxlovid and only authorized under the EUA?

A. The clinical development of Paxlovid for pediatric use is ongoing.

Q. How can Paxlovid be obtained for use under the EUA?

A. For questions on how to obtain Paxlovid, please contact COVID19therapeutics@hhs.gov. Information about Paxlovid's distribution can be found here.

Efficacy and Safety Considerations

Q. Are there data showing the benefit of Paxlovid for treatment of mild-to-moderate COVID-19 for certain patients?

A. Yes. The primary data supporting the approval as well as the EUA for Paxlovid are from EPIC-HR, a randomized, double-blind, placebo-controlled clinical trial studying Paxlovid for the treatment of non-hospitalized symptomatic adults with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Patients were adults 18 years of age and older with a prespecified risk factor for progression to severe disease or were 60 years and older regardless of prespecified chronic medical conditions. All patients had not received a COVID-19 vaccine and had not been previously infected with COVID-19. The main outcome measured in the trial was the proportion of people who were hospitalized due to COVID-19 or died due to any cause during 28 days of follow-up. Paxlovid significantly reduced the proportion of people with COVID-19 related hospitalization or death from any cause through 28 days of follow-up by 86% compared to placebo among patients treated within five days of symptom onset and who did not receive COVID-19 therapeutic monoclonal antibody treatment.

In this analysis, 977 patients received Paxlovid, and 989 patients received placebo, and among these patients, 0.9% who received Paxlovid were hospitalized due to COVID-19 or died from any cause during 28 days of follow-up compared to 6.5% of the patients who received placebo. Of the people who received Paxlovid, no patients died through 24 weeks after receipt compared to 15 people who received placebo.

Details on the clinical trial results can be found in Section 14 of the authorized Fact Sheet for Health Care Providers and approved Prescribing Information.

Q. Are there data supporting the benefit of Paxlovid for high-risk patients with mild-moderate COVID-19 regardless of prior/acquired immunity?

A. Benefit of Paxlovid was observed in patients with prior immunity to the virus that causes COVID-19. Among patients in EPIC-HR who were antibody positive at trial enrollment, the risk of COVID-19-related hospitalization or death from any cause during 28 days of follow-up was 0.2% among those treated with Paxlovid compared with 1.7% of those receiving placebo. EPIC-SR was another clinical trial that enrolled vaccinated patients with at least one risk factor for progression to severe COVID-19. Among these vaccinated patients, there was a reduction in the risk of COVID-19 related hospitalization or death from any cause with use of PAXLOVID versus placebo, although not statistically significant.

Q. Does Paxlovid retain activity against currently circulating Omicron variants?

A. Yes. Based on virology data, Paxlovid retains activity against currently circulating Omicron variants.

Q. Does Paxlovid cause COVID-19 rebound?

A. EPIC-HR, described above, and EPIC-SR, another trial that enrolled vaccinated patients with at least one risk factor for progression to severe COVID-19 or unvaccinated patients with no risk factors for progression to severe COVID-19, were both randomized placebo-controlled trials. These trials provide useful data to assess COVID-19 rebound. Data from these two trials showed that rebound in SARS-CoV-2 (RNA or virus) shedding or self-reported COVID-19 symptoms occurred in a subset of patients and happened at similar rates in both the patients receiving Paxlovid and placebo. Based on the data currently available to FDA, there is not a clear association between Paxlovid treatment and COVID-19 rebound.

Q. Are there potential side effects of Paxlovid?

A. Yes. Paxlovid consists of nirmatrelvir and ritonavir, and ritonavir interacts with many other medicines, which may lead to serious or life-threatening adverse reactions. Patients should tell their health care providers all of the medicines they are taking, including over-the-counter medications and herbal supplements, when deciding whether to take Paxlovid.

Because of the importance of reducing the risk of significant drug-drug interactions with Paxlovid, the approved Prescribing Information and authorized Fact Sheet for Health Care Providers for the Paxlovid EUA include a boxed warning with instructions for providers to review all medications taken by the patient to assess for potential drug-drug interactions and determine if other medicines that a patient may be taking require a dose adjustment, interruption and/or additional monitoring.

The most common side effects of taking Paxlovid include impaired sense of taste (for example, a metallic taste in the mouth) and diarrhea.

Liver problems have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering Paxlovid to patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis. Patients should talk with their health care provider if they have a history of liver problems.

Paxlovid is not recommended for patients with severe kidney problems, and a different dose is needed for patients with moderate kidney problems. Patients should talk with their health care provider if they have a history of kidney problems.

See Warnings and Precautions in the FDA-approved Prescribing Information and the Fact Sheet for Health Care Providers for additional information on risks associated with Paxlovid.

Q. Why was a boxed warning included in the Paxlovid prescribing information?

A. Paxlovid includes ritonavir, a strong CYP3A inhibitor, which may lead to greater exposure of certain other medications the patient may be taking, resulting in potentially severe, life-threatening, or fatal events due to drug-drug interactions. Such interactions can be avoided by appropriate handling of the patient's other medications when starting treatment with Paxlovid or, in some situations when adjustments of the patient's other medication may not be feasible, choosing an alternative COVID-19 treatment for the individual patient. Since the authorization of Paxlovid under EUA, FDA has reviewed new data related to the risk of drug-drug interactions. These data were discussed by FDA during the recent Antimicrobial Drugs Advisory Committee on March 16, 2023.

- FDA identified more than 250 cases of serious adverse events assessed as possibly or probably related to Paxlovid drug-drug interactions. Many of these cases reported hospitalization, and a fatal outcome was reported in a few cases.
- FDA determined that greater than 50% of Paxlovid-eligible Medicare and VA patients were taking medications that were identified as having a drug-drug interaction with Paxlovid. FDA noted that most of these potential drug-drug interactions could be prevented or managed with dose modification, interruption, and/or additional monitoring.
- FDA determined that most Paxlovid prescriptions were written by a broad range of health care providers, who may not be familiar with managing potential drug-drug interactions associated with ritonavir, which is more commonly prescribed by infectious disease physicians and other specialists who may have more experience managing ritonavir drug-drug interactions.

Drug-drug interactions are not unique to Paxlovid and are almost always manageable risks. Prior to prescribing Paxlovid, health care providers must: 1) review all medications taken by the patient to assess potential drug-drug interactions with a strong CYP3A inhibitor like Paxlovid and 2) determine if medications require a dose adjustment, interruption, and/or additional monitoring if taken at the same time as Paxlovid.

There are resources for health care providers to identify and manage potential drug-drug interactions with Paxlovid. These include: the approved prescribing information, the Fact Sheet for Health Care Providers and the Prescriber Patient Eligibility Screening Checklist available on the FDA EUA webpage. Other resources include: the NIH COVID-19 Treatment Guidelines, the IDSA COVID-19 Treatment Guidelines and the University of Liverpool COVID-19 Drug Interactions online checker.

U.S. FOOD & DRUG ADMINISTRATION

Provider Considerations When Prescribing Paxlovid

Q. Who may prescribe Paxlovid?

A. Paxlovid may be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs.

Paxlovid may also be prescribed for an individual patient by a state-licensed pharmacist under certain conditions that are listed in the EUA. For more information on this topic, please refer to the section titled Questions for Pharmacist Prescribers below.

Q. When should Paxlovid be administered to a patient?

A. Patients should talk to their health care provider to determine whether, based on their individual circumstances, they are eligible to receive Paxlovid. Paxlovid treatment should be initiated as soon as possible after diagnosis of COVID-19, even if symptoms are mild, and within five days after symptoms start.

More information about administration is available in the in the FDA-approved Prescribing Information and the Fact Sheet for Health Care Providers.

Q: Is a positive result from a direct SARS-CoV-2 viral test required prior to prescribing Paxlovid to a patient who is at high risk for severe COVID-19?

A: No. FDA recognizes that, in rare instances, individuals with a recent known exposure (e.g., a household contact) who develop signs and symptoms consistent with COVID-19 may be diagnosed by their health care provider as having COVID-19 even if they have a negative direct SARS-CoV-2 viral test result. In such instances, their health care provider may determine that treatment with Paxlovid for COVID-19 is appropriate if the patient reports mild-to-moderate symptoms of COVID-19 and is at high-risk for progression to severe COVID-19, including hospitalization or death, and the terms and conditions of the authorization are met, as detailed in the Letter of Authorization for Paxlovid and the authorized Fact Sheet for Healthcare Providers.

The agency continues to recommend that providers use direct SARS-CoV-2 viral testing to help diagnose COVID-19.

Q. I am traveling soon. May I receive Paxlovid under the EUA prior to travel in case I become sick with COVID-19?

A. Individuals being considered for Paxlovid treatment must meet the eligibility requirements under the EUA at the time of prescription. Providers must determine that patients have signs and symptoms consistent with mild-to-moderate COVID-19, assess risk for disease progression, assess renal and hepatic function, and review all medications taken by the patient to assess for potential drug-drug interactions and determine if other medicines that a patient may be taking require a dose adjustment, interruption and/or additional monitoring.

Q. What if I have questions about the expiration date on the Paxlovid carton or container?

A. FDA has authorized an extension to the expiration date (shelf-life) for certain lots of Paxlovid. To find the extended expiration date, enter the lot number found on the side of the carton or bottom of the blister pack at this website or talk with the pharmacist or provider.

Information on the authorized shelf-life extensions for Paxlovid may also be found on FDA's website.

Questions for pharmacist prescribers

Q. Are pharmacists permitted to prescribe Paxlovid?

A. The EUA authorizes state-licensed pharmacists to prescribe Paxlovid for an individual patient, subject to the terms and conditions of the EUA (e.g., eligible patient populations), under the following conditions:

- Sufficient information is available, such as through access to health records less than 12 months old or consultation with a health care provider in an established provider-patient relationship with the individual patient, to assess renal and hepatic function; and
- Sufficient information is available, such as through access to health records, patient reporting of medical history, or consultation with a health care provider in an established provider-patient relationship with the individual patient, to obtain a comprehensive list of medications (prescribed and non-prescribed) that the patient is taking to assess for potential drug interaction.

The state-licensed pharmacist should refer an individual patient for clinical evaluation (e.g., telehealth, in-person visit) with a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs, if any of the following apply:

- Sufficient information is not available to assess renal and hepatic function.
- Sufficient information is not available to assess for a potential drug interaction.
- Modification of other medications is needed due to a potential drug interaction.
- Paxlovid is not an appropriate therapeutic option based on the authorized Fact Sheet for Healthcare Providers or due to potential drug interactions for which recommended monitoring would not be feasible.

Q. What do state-licensed pharmacist prescribers need to do to determine whether a patient may be eligible to receive Paxlovid?

A. State-licensed pharmacist prescribers have the same requirements as all other prescribers to assess an adult or pediatric patient (12 years of age and older weighing at least 40 kg), who is being considered for treatment with Paxlovid, to determine that they have a diagnosis of mild-to-moderate COVID-19 and are at high risk for progression to severe COVID-19, including hospitalization or death.

A review of reported symptoms should be completed to determine that patients have signs and symptoms consistent with mild-to-moderate COVID-19, and not severe COVID-19. Patients reporting

shortness of breath or difficulty breathing should be immediately referred for further medical assessment to determine whether their illness has progressed to the severe stage, which may require hospitalization. Paxlovid is not authorized or approved for the treatment of severe COVID-19.

Definitions for mild and moderate illness are provided in NIH's COVID-19 Treatment Guidelines: Clinical Spectrum of SARS-CoV-2 Infection.

State-licensed pharmacist prescribers may determine whether an individual patient is at high risk for severe COVID-19 by obtaining a medical history from the patient or by accessing the patient's medical records. Resources about conditions that place a patient with mild-to-moderate COVID-19 at increased risk for disease progression or death can be found at the Centers for Disease Control and Prevention site: Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals and at NIH's COVID-19 Treatment Guidelines: Clinical Spectrum of SARS-CoV-2 Infection.

Q. How do state-licensed pharmacist prescribers assess for potential drug interactions?

A. All prescribers are expected to utilize available health records or patient history to obtain a complete list of all medications (prescribed and non-prescribed) that the patient is taking. State-licensed pharmacists may also consult with a health care provider in an established provider-patient relationship with the individual patient to obtain a comprehensive list of medications the patient is taking. Resources to identify potential drug interactions include the approved Prescribing Information, the Fact Sheet for Health Care Providers and the Prescriber Patient Eligibility Screening Checklist available on the FDA EUA webpage. Other resources include: the NIH COVID-19 Treatment Guidelines, the IDSA COVID-19 Treatment Guidelines and the University of Liverpool COVID-19 Drug Interactions.

Should an adjustment to another medication be needed due to a potential drug interaction, the state-licensed pharmacist should refer the individual patient for clinical evaluation with a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs.

Q. How do state-licensed pharmacist prescribers assess renal and hepatic function?

A. State-licensed pharmacist prescribers must have access to sufficient information from health records to assess renal and hepatic function. Health records include access to an electronic health record system containing this information in progress notes or laboratory records, reviewing a printed health record such as a laboratory report provided by the patient, or reviewing information in electronic health records the patient may have access to through a phone app or other means. Health records within the past 12 months are generally acceptable, provided there is no patient self-report or other information suggestive of kidney or liver disease. State-licensed pharmacists may also consult with a health care provider in an established provider-patient relationship with the individual patient to obtain this information. If sufficient information is not available to assess renal and hepatic function, the state-licensed pharmacist should refer the individual patient to a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs.

Physicians, advanced practice registered nurses, and physician assistants may rely on patient history and access to the patient's health records to make an assessment regarding the likelihood of renal

impairment. These providers may consider ordering a serum creatinine or calculating the estimated glomerular filtration rate (eGFR) for certain patients after assessment on a case-by-case basis.

Q. Will state-licensed pharmacists be able to prescribe both the standard and renal doses of Paxlovid?

A. Yes, the EUA authorizes state-licensed pharmacists to prescribe both the standard and renal doses of Paxlovid, subject to the terms and conditions on pharmacist prescribing as detailed in the EUA, provided the pharmacist has adequate information to assess renal function and the patient is otherwise eligible to receive Paxlovid.

General EUA-related questions

Q. What is an emergency use authorization (EUA)?

A. Under section 564 of the Federal Food, Drug & Cosmetic Act, after a declaration by the HHS Secretary based on one of four types of determinations, FDA may authorize an unapproved product or unapproved uses of an approved product for emergency use. In issuing an EUA, FDA must determine, among other things, that based on the totality of scientific evidence available to the agency, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by a chemical, biological, radiological, or nuclear agent; that the known and potential benefits of the product, when used to treat, diagnose or prevent such disease or condition, outweigh the known and potential risks of the product; and that there are no adequate, approved, and available alternatives. Emergency use authorization is NOT the same as FDA approval or licensure.

Q. Are there reporting requirements for health care facilities and providers as part of the EUA?

A. Yes. As part of the EUA, FDA requires health care providers who prescribe Paxlovid to report all medication errors and serious adverse events considered to be potentially related to Paxlovid through FDA's MedWatch Adverse Event Reporting program. Providers can complete and submit the report online; or download and complete the form, then submit it via fax at 1-800-FDA-0178. This requirement is outlined in the EUA's Fact Sheet for Health Care Providers. FDA MedWatch forms should also be provided to Pfizer.

Health care facilities and providers must report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

Q. Do patient outcomes need to be reported under the EUA?

A. No, reporting of patient outcomes is not required under the EUA. However, reporting of all medication errors and serious adverse events considered to be potentially related to Paxlovid occurring during treatment is required.

Q. FDA has issued a number of EUAs including for therapeutics. If state laws impose different or additional requirements on the medical product covered by an EUA, are those state laws preempted?

A. As stated in FDA's Emergency Use Authorization of Medical Products and Related Authorities Guidance, "FDA believes that the terms and conditions of an EUA issued under section 564 preempt state or local law, both legislative requirements and common-law duties, that impose different or additional requirements on the medical product for which the EUA was issued in the context of the emergency declared under section 564." The guidance explains the basis for FDA's views on this subject.

Q. Can health care providers share the patient/caregiver Fact Sheet electronically?

A. Under the authorization, Pfizer must make available the authorized Fact Sheets on its website at: www.COVID19oralRX.com. Health care facilities and health care providers must ensure that fact sheets are made available to patients, parents, and caregivers through "appropriate means" and electronic delivery of the Fact Sheet is an appropriate means.

U.S. FOOD & DRUG ADMINISTRATION

February 1, 2023

Merck Sharp & Dohme LLC
Attention: Sushma Kumar, PhD, PMP
Senior Director, Global Regulatory Affairs and Clinical Safety
1 Merck Drive
PO Box 100
Whitehouse Station, NJ 08889-0100

RE: Emergency Use Authorization 108

Dear Dr. Kumar:

This letter is in response to Merck Sharp & Dohme Corp.'s (Merck) request that the Food and Drug Administration (FDA or Agency) issue an Emergency Use Authorization (EUA) for the emergency use of LAGEVRIO (molnupiravir)[1] for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in certain adults who are at high risk for progression to severe COVID-19, including hospitalization or death, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §360bbb-3).

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19).[2] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[3]

On December 23, 2021 the Food and Drug Administration (FDA) issued an EUA for emergency use of LAGEVRIO as treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing, who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.

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[1] The December 23, 2021, and February 11, 2022 Letters of Authorization (LOA) referred to the authorized drug as "molnupiravir,"; however, Merck subsequently requested, and FDA concurred, that the Fact Sheets be revised to add references to molnupiravir's trade name, "LAGEVRIO." "LAGEVRIO" is used in this March 23, 2022 reissued letter.

[2] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3.* February 4, 2020.

[3] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).

LAGEVRIO capsules contain molnupiravir; a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis. LAGEVRIO is not FDA-approved for any uses, including use as treatment for COVID-19.

FDA subsequently reissued the LOA on February 11, 2022[4], March 23, 2022[5], and August 5, 2022[6], and October 27, 2022.[7]

On February 1, 2023, again having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the October 27, 2022 letter in its entirety, to revise the scope of authorization to no longer require positive results of direct SARS-CoV-2 viral testing. As revised, the scope of authorization now requires, in addition to other requirements, that adults have a current diagnosis of mild-to-moderate COVID-19. Corresponding changes have also been made to the authorized Fact Sheets. Conditions P and U in this letter and the Fact Sheets have been revised to include updated information on the collection of pregnancy exposure and outcomes data through a pregnancy registry. The Fact Sheets have also been revised to include information on administering LAGEVRIO via nasogastric and orogastric tubes. The Fact Sheet for Healthcare Providers was also revised to reflect the current indication for Veklury, an approved alternative to Paxlovid, and to include additional carcinogenicity and virology information.

Based on the review of the data from the MOVe-OUT clinical trial (NCT04575597), a Phase III randomized, double-blind, placebo-controlled clinical trial studying LAGEVRIO for the treatment of non-hospitalized patients with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, it is reasonable to believe that LAGEVRIO may be effective for the treatment of adults with a current diagnosis of mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate, as described in the Scope of Authorization (Section II), and when used under the conditions described in this authorization, the known and potential benefits of LAGEVRIO outweigh the known and potential risks of such product.

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[4] In its February 11, 2022 revision, FDA revised the scope of this LOA to account for the FDA approval of Veklury (remdesivir) for the treatment of COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, who are not hospitalized and have mild-to-moderate COVID-19, and who are at high risk for progression to severe COVID-19, including hospitalization or death. The letter of authorization was also revised to include a new condition regarding registration and listing. The authorized Fact Sheets were also revised to reflect the revision to the scope of authorization for LAGEVRIO as described above and include information on post-authorization reports of hypersensitivity reactions and rashes.

[5] In its March 23, 2022 revision, FDA revised this LOA to add references to molnupiravir's trade name, "LAGEVRIO". Corresponding revisions were also made to the authorized Fact Sheets. The Fact Sheet for Healthcare Providers was also revised to include updated antiviral activity and resistance information.

[6] In its August 5, 2022 revision, FDA revised this LOA to update certain post-authorization requirements as detailed in Condition O of this letter. The Fact Sheet for Healthcare Providers was also revised to include additional virology information and to identify Veklury (remdesivir) as an approved alternative to Lagevrio.

[7] In its October 27, 2022 revision, FDA incorporated clarifying revisions to Condition BB of this letter. Condition AA was also revised to require that all printed matter, advertising and promotional materials relating to the use of LAGEVRIO under this authorization be submitted to FDA for consideration at least 14 calendar days prior to initial dissemination or first use.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of LAGEVRIO for the treatment of adults with a current diagnosis of mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of LAGEVRIO for treatment of mild-to-moderate COVID-19, when administered as described in the Scope of Authorization (Section II), meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

1. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that LAGEVRIO may be effective for the treatment of adults with a current diagnosis of mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (section II), and that, when used under the conditions described in this authorization, the known and potential benefits of LAGEVRIO outweigh the known and potential risks of such product; and

3. There is no adequate, approved, and available alternative[8] to the emergency use of LAGEVRIO for the treatment of adults with a current diagnosis of mild-to-moderate COVID-19 as further described in the Scope of Authorization (section II).[9]

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Distribution of the authorized LAGEVRIO will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Merck will supply LAGEVRIO to authorized distributor(s)[10], who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed;

- LAGEVRIO may only be used for the treatment of adults with a current diagnosis of mild-to-moderate COVID-19:

[8] Although Veklury (remdesivir) is an approved alternative to treat COVID-19 in adults within the scope of this authorization, FDA does not consider it to be an adequate alternative for certain patients for whom it may not be feasible or practical (e.g., it requires a 3-day treatment duration).
[9] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.
[10] "Authorized Distributor(s)" are identified by Merck as an entity or entities allowed to distribute authorized molnupiravir.

- Who are at high risk[11] for progression to severe COVID, including hospitalization or death, and for
- Whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

Limitations on Authorized Use

- LAGEVRIO is not authorized for use in patients who are less than 18 years of age.
- LAGEVRIO is not authorized for initiation of treatment in patients requiring hospitalization due to COVID-19.[12] Benefit of treatment with LAGEVRIO has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19.
- LAGEVRIO is not authorized for use for longer than 5 consecutive days.
- LAGEVRIO is not authorized for use as pre-exposure or as post-exposure prophylaxis for prevention of COVID-19.

- LAGEVRIO may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state[13] law to prescribe drugs in the therapeutic class to which LAGEVRIO belongs (i.e., anti-infectives).

- The use of LAGEVRIO covered by this authorization must be in accordance with the authorized Fact Sheets.

Product Description

The authorized LAGEVRIO is supplied as a bottle (NDC-0006-5055-06, NDC-0006-5055-07, NDC-0006-5055-09) containing a sufficient quantity of LAGEVRIO 200 mg capsules to complete a full treatment course (i.e., 40 capsules). LAGEVRIO is manufactured as a Swedish Orange, opaque capsule containing the Merck corporate logo and "82" printed in white ink.

The authorized storage and handling information is included in the authorized Fact Sheet for Healthcare Providers.

LAGEVRIO is authorized for emergency use with the following product-specific information required to be made available to healthcare providers and to patients and caregivers, respectively, through Merck's website www.molnupiravir.com (referred to as the "authorized labeling"):

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[11] For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html.

[12] Patients requiring hospitalization after starting treatment with molnupiravir may complete the full 5-day treatment course per the healthcare provider's discretion.

[13] The term "State" includes any State or Territory of the United States, the District of Columbia, and the Commonwealth of Puerto Rico. See section 201(a)(1) of the Act.

- Fact Sheet for Healthcare Providers: Emergency Use Authorization (EUA) for LAGEVRIO
- Fact Sheet for Patients and Caregivers: Emergency Use Authorization (EUA) of LAGEVRIO for Coronavirus Disease 2019 (COVID-19)

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of LAGEVRIO, when used for the treatment of adults with a current diagnosis of mild-to-moderate COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh the known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that LAGEVRIO may be effective for the treatment of adults with a current diagnosis of mild-to-moderate COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that LAGEVRIO (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of LAGEVRIO product under this EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), LAGEVRIO is authorized for the treatment of adults with a current diagnosis of mild-to-moderate COVID-19 as described in this Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

Merck and Authorized Distributors[14]

A. Merck and authorized distributor(s) will ensure that LAGEVRIO is distributed and the authorized labeling (i.e., Fact Sheets) will be made available to healthcare facilities and/or healthcare providers as described in Section II of this Letter of Authorization.

B. Merck and authorized distributor(s) will ensure that appropriate storage is maintained until the product is delivered to healthcare facilities and/or healthcare providers.

C. Merck and authorized distributor(s) will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., U.S. government agencies, state and local

[14] Supra at Note 10.

government authorities, authorized distributors, healthcare facilities, healthcare providers) involved in distributing or receiving LAGEVRIO. Merck will provide to all relevant stakeholders a copy of this Letter of Authorization and communicate any subsequent amendments that might be made to this Letter of Authorization and its authorized accompanying materials (i.e., Fact Sheets).

D. Merck may request changes to this authorization, including to the authorized Fact Sheets for LAGEVRIO. Any request for changes to this EUA must be submitted to the Office of Infectious Diseases/Office of New Drugs/Center for Drug Evaluation and Research. Such changes require appropriate authorization prior to implementation.[15]

E. Merck may develop and disseminate instructional and educational materials (e.g., materials providing information on product administration and/or patient monitoring) that are consistent with the authorized emergency use of LAGEVRIO as described in this Letter of Authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs. Any instructional and educational materials that are inconsistent with the authorized labeling for LAGEVRIO are prohibited. If the Agency notifies Merck that any instructional and educational materials are inconsistent with the authorized labeling, Merck must cease distribution of such instructional and educational materials. Furthermore, as part of its notification, the Agency may also require Merck to issue corrective communication(s).

F. Merck will report to FDA all serious adverse events and medication errors potentially related to LAGEVRIO use that are reported to Merck using either of the following options.

   Option 1: Submit reports through the Safety Reporting Portal (SRP) as described on the FDA SRP web page.

   Option 2: Submit reports directly through the Electronic Submissions Gateway (ESG) as described on the FAERS electronic submissions web page.

   Submitted reports under both options must state: "LAGEVRIO use for COVID-19 under Emergency Use Authorization (EUA)." For reports submitted under Option 1, include this language at the beginning of the question "Describe Event" for further analysis. For reports submitted under Option 2, include this language at the beginning of the "Case Narrative" field.

[15] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study; (8) new strengths of the authorized product, new product sources (e.g., of active pharmaceutical ingredient) or of product components. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), (7), or (8), review and concurrence is required from the Counter-Terrorism and Emergency Coordination Staff/Office of the Center Director/CDER and the Office of Counterterrorism and Emerging Threats/Office of the Chief Scientist.

G. All manufacturing, packaging, and testing sites for both drug substance and drug product used for EUA supply will comply with current good manufacturing practice requirements of Section 501(a)(2)(B) of the Act.

H. Merck will submit information to the Agency within three working days of receipt of any information concerning significant quality problems with distributed drug product of LAGEVRIO that includes the following:

- Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or
- Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the product to meet the established specifications.

If a significant quality problem affects unreleased product and may also impact product(s) previously released and distributed, then information must be submitted for all potentially impacted lots.

Merck will include in its notification to the Agency whether the batch, or batches, in question will be recalled. If FDA requests that these, or any other batches, at any time, be recalled, Merck must recall them.

If not included in its initial notification, Merck must submit information confirming that Merck has identified the root cause of the significant quality problems, taken corrective action, and provide a justification confirming that the corrective action is appropriate and effective. Merck must submit this information as soon as possible but no later than 45 calendar days from the initial notification.

I. Merck will manufacture LAGEVRIO to meet all quality standards and per the manufacturing process and control strategy as detailed in Merck's EUA request. Merck will also test the active pharmaceutical ingredient (API) starting material for additional quality attributes agreed upon by Merck and the Agency. Merck will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product, without notification to and concurrence by the Agency as described under condition D.

J. Merck will list LAGEVRIO with a unique product NDC under the marketing category of Emergency Use Authorization. Further, the listing will include each establishment where manufacturing is performed for the drug and the type of operation performed at each such establishment.

K. Through a process of inventory control, Merck and authorized distributor(s) will maintain records regarding distribution of LAGEVRIO (i.e., lot numbers, quantity, receiving site, receipt date).

L. Merck will establish a process for monitoring genomic database(s) for the emergence of global viral variants of SARS-CoV-2. Merck will provide reports to the Agency on a monthly basis summarizing any findings as a result of its monitoring activities and, as needed, any follow-up assessments planned or conducted.

M. FDA may require Merck to assess the activity of the authorized LAGEVRIO against any global SARS-CoV-2 variant(s) of interest (e.g., variants that are prevalent or becoming prevalent that harbor substitutions in the target protein or in protein(s) that interact with the target protein). Merck will perform the required assessment in a manner and timeframe agreed upon by Merck and the Agency. Merck will submit to FDA a preliminary summary report immediately upon completion of its assessment followed by a detailed study report within 30 calendar days of study completion. Merck will submit any relevant proposal(s) to revise the authorized labeling based on the results of its assessment, as may be necessary or appropriate based on the foregoing assessment.

N. Merck shall provide samples as requested of LAGEVRIO to the U.S. Department of Health and Human Services (HHS) for evaluation of activity against emerging global viral variants of SARS-CoV-2, including specific amino acid substitution(s) of interest (e.g., variants that are highly prevalent or that harbor substitutions in the target protein) within 5 business days of any request made by HHS. Analyses performed with the supplied quantity of LAGEVRIO may include, but are not limited to, cell culture potency assays, biochemical assays, and in vivo efficacy assays.

O. Merck must provide the following information to the Agency:

1. Merck will conduct a thorough investigation into the differences in efficacy observed in the first and second half of Part 2 of trial MK-4482-002. This assessment should involve the synthesis of data, including, but not limited to, additional baseline serology testing, a detailed comparison of baseline characteristics (including demographic, clinical disease, and virologic characteristics), and an exploration of potential differences in standard of care by region and over time. Merck will submit a final report, including available serology results, to the Agency no later than September 30, 2022.
2. Merck will conduct a pharmacokinetic (PK) study in wild type Fisher 344 rats to establish if NHC or NHC-TP is detected in testes. The study should include plasma exposure levels that meet/exceed the human exposure for NHC. Merck will submit the results of the PK study no later than March 31, 2022.

    - If the results of the PK study demonstrate NHC or NHC-TP distribution to testes, Merck will also conduct a male germ cell mutation assay in the Big Blue rat model. Merck must submit a protocol for the Big Blue rat assay no later than 30 days after the PK results are submitted to FDA, or by April 30, 2022. Results from the Big Blue rat assay will be submitted no later than July 31, 2023.

P. Merck must participate in a pregnancy registry to collect information through telephone and online reporting of pregnancies and collect outcomes for individuals who are exposed to LAGEVRIO during pregnancy. Merck must submit to the Agency reports detailing any available exposure information and outcome(s) data on a monthly basis unless otherwise notified by FDA.

Q. Merck and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

Healthcare Facilities to Whom LAGEVRIO Is Distributed and Healthcare Providers Administering LAGEVRIO

R. Healthcare facilities and healthcare providers will ensure that they are aware of the Letter of Authorization, and the terms herein. Healthcare providers must provide and document that a copy of the authorized Fact Sheet for Patients and Caregivers has been provided, either through electronic means or hardcopy, to the patient or caregiver prior to prescribing LAGEVRIO.

S. Healthcare providers must inform patients or caregivers of the information detailed in the section *Mandatory Requirements for Administration of LAGEVRIO Under Emergency Use Authorization* in the Fact Sheet for Healthcare Providers.

T. LAGEVRIO may only be prescribed to a pregnant individual after the prescribing healthcare provider has completed the mandatory requirements on patient assessment, patient counseling, and documentation as described in the Fact Sheet for Healthcare Providers. See *Mandatory Requirements for Administration of LAGEVRIO Under Emergency Use Authorization* in the Fact Sheet for Healthcare Providers.

U. Healthcare providers must inform and document that pregnant individuals who are prescribed LAGEVRIO have been made aware of the pregnancy registry at https://covid-pr.pregistry.com or 1-800-616-3791.

V. Healthcare facilities and healthcare providers receiving LAGEVRIO will track all serious adverse events and medication errors that are considered to be potentially related to LAGEVRIO use and must report these to FDA in accordance with the Fact Sheet for Healthcare Providers. Complete and submit a MedWatch form (www.fda.gov/medwatch/report.htm), or complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178) (these forms can be found via link above). Call 1-800-FDA-1088 for questions. Submitted reports must state, "LAGEVRIO use for COVID-19 under Emergency Use Authorization" at the beginning of the question "Describe Event" for further analysis.

W. Healthcare facilities and healthcare providers will ensure that appropriate storage is maintained until the product is administered consistent with the terms of this letter and the authorized labeling.

X. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensing and administration of LAGEVRIO for the use authorized in this letter (i.e., lot numbers, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered).

Y. Healthcare facilities will ensure that any records associated with this EUA are maintained until notified by Merck and/or FDA. Such records will be made available to Merck, HHS, and FDA for inspection upon request.

Z. Healthcare facilities and providers will report therapeutics information and utilization data as directed by HHS.

Conditions Related to Printed Matter, Advertising, and Promotion

AA. All descriptive printed matter, advertising, and promotional materials relating to the use of LAGEVRIO under this authorization shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in Section 502(a) and (n) of the Act, as applicable, and FDA implementing regulations. References to "approved labeling", "permitted labeling" or similar terms in these requirements shall be understood to refer to the authorized labeling for the use of LAGEVRIO under this authorization. In addition, such materials shall:

- Be tailored to the intended audience.
- Not take the form of reminder advertisements, as that term is described in 21 CFR 202.1(e)(2)(i), 21 CFR 200.200 and 21 CFR 201.100(f).
- Present the same risk information relating to the major side effects and contraindications concurrently in the audio and visual parts of the presentation for advertising and promotional materials in audio-visual format.
- Be accompanied by the authorized labeling, if the promotional materials are not subject to Section 502(n) of the Act.
- Be submitted to FDA accompanied by Form FDA-2253 for consideration at least 14 calendar days prior to initial dissemination or first use.

BB. Merck may disseminate descriptive printed matter, advertising, and promotional materials relating to the emergency use of LAGEVRIO that provide accurate descriptions of safety results and efficacy results on a clinical endpoint(s) from the clinical trial(s) summarized in the authorized labeling. Such materials must include any limitations of the clinical trial data as described in the authorized labeling. Merck may not imply that LAGEVRIO is FDA-approved for its authorized use by making statements such as "LAGEVRIO is safe and effective for the treatment of COVID-19."

CC. All descriptive printed matter, advertising, and promotional material, relating to the use of LAGEVRIO under this authorization clearly and conspicuously shall state that:

- LAGEVRIO has not been approved, but has been authorized for emergency use by FDA under an EUA, for the treatment of adults with a current diagnosis of mild-to-moderate COVID-19, who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate; and

- The emergency use of LAGEVRIO is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

If the Agency notifies Merck that any descriptive printed matter, advertising or promotional materials do not meet the terms set forth in conditions AA through CC of this EUA, Merck must cease distribution of such descriptive printed matter, advertising, or promotional materials in accordance with the Agency's notification. Furthermore, as part of its notification, the Agency may also require Merck to issue corrective communication(s).

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

--/S/--

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR LAGEVRIO™ (molnupiravir) CAPSULES

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use LAGEVRIO under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for LAGEVRIO.

LAGEVRIO™ (molnupiravir) capsules, for oral use
Original EUA Authorized Date: 12/23/2021
Revised EUA Authorized Date: 07/2023

MANDATORY REQUIREMENTS FOR ADMINISTRATION OF LAGEVRIO UNDER EMERGENCY USE AUTHORIZATION

Refer to FULL FACTSHEET for details.

----------RECENT MAJOR CHANGES----------

Adverse Reactions (Section 6.2): update to post-authorization experience section	07/2023
Mandatory Requirements Box, Use in Specific Populations (Section 8.1): Updates to pregnancy registry information	02/2023
Emergency Use Authorization (Section 1): Removal of requirement of SARS-CoV-2 viral testing	02/2023
Dosage and Administration (Section 2.3): Addition of preparation and administration instructions via nasogastric and orogastric tube.	02/2023
Microbiology (Section 12.4): Addition of Omicron subvariants	02/2023
Nonclinical Toxicology (Section 13.1): Updated carcinogenicity data	02/2023
Microbiology (Section 12.4): addition of viral RNA rebound	08/2022
Mandatory Requirements Box: Revised requirements pertaining to other therapeutics	02/2022
Emergency Use Authorization (Section 1): Updates on available alternatives to LAGEVRIO	02/2022
Warnings and Precautions (Sections 5.2 and 17): addition of hypersensitivity including anaphylaxis	02/2022
Adverse Reactions (Section 6.2): addition of post-authorization experience section	02/2022

----------EUA FOR LAGEVRIO----------

The U.S. Food and Drug Administration (FDA) has issued an EUA for the emergency use of the unapproved LAGEVRIO, a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis for the treatment of adults with a current diagnosis of mild-to-moderate coronavirus disease 2019 (COVID-19):

- who are at high risk for progression to severe COVID-19, including hospitalization or death, and for
- whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

LAGEVRIO is not FDA-approved for any use including for use for the treatment of COVID-19. Prior to initiating treatment with LAGEVRIO, carefully consider the known and potential risks and benefits. (1)

LIMITATIONS OF AUTHORIZED USE (1)

- LAGEVRIO is not authorized
  - for use in patients less than 18 years of age (5.3)
  - for initiation of treatment in patients requiring hospitalization due to COVID-19. Benefit of treatment with LAGEVRIO has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19. (2.1)
  - for use for longer than 5 consecutive days.
  - for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

LAGEVRIO may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which LAGEVRIO belongs (i.e., anti-infectives).

LAGEVRIO is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of LAGEVRIO under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

See the box in the beginning of the Full Fact Sheet for details on mandatory requirements for administration of LAGEVRIO under emergency use authorization.

See Full Fact Sheet for Healthcare Providers for the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19.

----------DOSAGE AND ADMINISTRATION----------

- 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food. (2.1, 2.3)
- Take LAGEVRIO as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset. (2.1)
- Completion of the full 5-day treatment course and continued isolation in accordance with public health recommendations are important to maximize viral clearance and minimize transmission of SARS-CoV-2. (2.1)
- LAGEVRIO is not authorized for use for longer than 5 consecutive days because the safety and efficacy have not been established. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 200 mg (3)

----------CONTRAINDICATIONS----------

No contraindications have been identified based on the limited available data on the emergency use of LAGEVRIO authorized under this EUA. (4)

----------WARNINGS AND PRECAUTIONS----------

- Embryo-Fetal Toxicity: LAGEVRIO is not recommended for use during pregnancy. (5.1, 8.1, 8.3)
- Hypersensitivity reactions, including anaphylaxis have been reported with LAGEVRIO. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue LAGEVRIO. (5.2)
- Bone and Cartilage Toxicity: LAGEVRIO is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth. (5.3, 8.4, 13.2)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥ 1%) are diarrhea, nausea, and dizziness. (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to LAGEVRIO (1) by submitting FDA Form 3500 online, (2) by downloading this form and then submitting by mail or fax, or (3) contacting the FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to Merck Sharp & Dohme LLC, Rahway, NJ USA at 1-800-672-6372 or Fax 215-616-5677 (6.4)

----------DRUG INTERACTIONS----------

No drug interactions have been identified based on the limited available data on the emergency use of LAGEVRIO authorized under this EUA. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: The use of LAGEVRIO is not recommended during pregnancy. Advise individuals of childbearing potential to use effective contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of LAGEVRIO. (8.1, 8.3)
- Lactation: Breastfeeding is not recommended during treatment and for 4 days after the last dose of LAGEVRIO. A lactating individual

may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for 4 days after the last dose of LAGEVRIO. (8.2)

See FACT SHEET FOR PATIENTS AND CAREGIVERS.

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* Sections or subsections omitted from the EUA are not listed

FULL FACT SHEET FOR HEALTHCARE PROVIDERS

MANDATORY REQUIREMENTS FOR ADMINISTRATION OF LAGEVRIO UNDER EMERGENCY USE AUTHORIZATION

In order to mitigate the risks of using this unapproved product under the EUA and to optimize the potential benefit of LAGEVRIO, the following steps are required. Use of LAGEVRIO under this EUA is limited to the following (all requirements must be met):

1. Treatment of adults with a current diagnosis of mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate *[see Limitations of Authorized Use (1)]*.

2. As the prescribing healthcare provider, review the information contained within the "Fact Sheet for Patients and Caregivers" with your patient or caregiver prior to the patient receiving LAGEVRIO. Healthcare providers must provide the patient/caregiver with an electronic or hard copy of the "Fact Sheet for Patients and Caregivers" prior to the patient receiving LAGEVRIO and must document that the patient/caregiver has been given an electronic or hard copy of the "Fact Sheet for Patients and Caregivers".

3. The prescribing healthcare providers must inform the patient/caregiver that:
    i. LAGEVRIO is an unapproved drug that is authorized for use under this Emergency Use Authorization.
    ii. Other therapeutics are currently approved or authorized for the same use as LAGEVRIO *[see Emergency Use Authorization (1) - Information Regarding Available Alternatives for the EUA Authorized Use]*.
    iii. There are benefits and risks of taking LAGEVRIO as outlined in the "Fact Sheet for Patients and Caregivers."
    iv. There is a pregnancy registry.
    v. Females of childbearing potential should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of LAGEVRIO.
    vi. Males of reproductive potential who are sexually active with females of childbearing potential should use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose.

4. The prescribing healthcare provider must assess whether a female of childbearing potential is pregnant or not, if clinically indicated *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.3)]*.

5. Based on findings from animal reproduction studies, LAGEVRIO may cause fetal harm when administered to pregnant individuals. If LAGEVRIO is used during pregnancy, prescribing healthcare providers must communicate to the patient the known and potential benefits and the potential risks of LAGEVRIO use during pregnancy, as outlined in the "Fact Sheet for Patients and Caregivers" *[see Warnings and Precautions (5.1, 5.3), Use in Specific Populations (8.1, 8.3) and Nonclinical Toxicology (13.1)]*.

6. If the decision is made to use LAGEVRIO during pregnancy, the prescriber must document that the known and potential benefits and the potential risks of LAGEVRIO use during pregnancy, as outlined in the "Fact Sheet for Patients and Caregivers," were discussed with the patient.

7. The prescribing healthcare provider must document that a pregnant individual was made aware of the pregnancy registry at https://covid-pr.pregistry.com or 1-800-616-3791.

8. The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all medication errors and serious adverse events potentially related to LAGEVRIO within 7 calendar days from the healthcare provider's awareness of the event *[see Adverse Reactions (6.4)]*.

For information on clinical studies of LAGEVRIO and other therapies for the treatment of COVID-19, see www.clinicaltrials.gov .

1 EMERGENCY USE AUTHORIZATION

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product LAGEVRIO™ for treatment of adults with a current diagnosis of mild-to-moderate coronavirus disease 2019 (COVID-19):

- who are at high risk for progression to severe COVID-19, including hospitalization or death. Refer to CDC website[1] for additional details, and for
- whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

LIMITATIONS OF AUTHORIZED USE

- LAGEVRIO is not authorized for use in patients who are less than 18 years of age *[see Warnings and Precautions (5.3)]*.
- LAGEVRIO is not authorized for initiation of treatment in patients hospitalized due to COVID-19[2]. Benefit of treatment with LAGEVRIO has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19 *[see Dosing and Administration (2.1)]*.
- LAGEVRIO is not authorized for use for longer than 5 consecutive days.
- LAGEVRIO is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

LAGEVRIO may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which LAGEVRIO belongs (i.e., anti-infectives).

LAGEVRIO is not approved for any use, including for use for the treatment of COVID-19.

Prior to initiating treatment with LAGEVRIO, carefully consider the known and potential risks and benefits *[see Warnings and Precautions (5.1, 5.3), Use in Specific Populations (8.1, 8.3) and Nonclinical Toxicology (13.1)]*.

LAGEVRIO is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of LAGEVRIO under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Justification for Emergency Use of Drugs During the COVID-19 Pandemic

There is currently an outbreak of Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2, a novel coronavirus. The Secretary of HHS has declared that:

- A public health emergency related to COVID-19 has existed since January 27, 2020.

[1] https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html . Healthcare providers should consider the benefit-risk for an individual patient.

[2] Should a patient require hospitalization after starting treatment with LAGEVRIO, the patient may complete the full 5 day treatment course per the healthcare provider's discretion.

- Circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic (March 27, 2020 declaration).

An EUA is a FDA authorization for the emergency use of an unapproved product or unapproved use of an approved product (i.e., drug, biological product, or device) in the United States under certain circumstances including, but not limited to, when the Secretary of HHS declares that there is a public health emergency that affects the national security or the health and security of United States citizens living abroad, and that involves biological agent(s) or a disease or condition that may be attributable to such agent(s). Criteria for issuing an EUA include:

- The biological agent(s) can cause a serious or life-threatening disease or condition;
- Based on the totality of the available scientific evidence (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that
  - the product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition; and
  - the known and potential benefits of the product - when used to diagnose, prevent, or treat such disease or condition - outweigh the known and potential risks of the product, taking into consideration the material threat posed by the biological agent(s);
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the serious or life-threatening disease or condition.

APPROVED AVAILABLE ALTERNATIVES

Veklury (remdesivir) is FDA-approved for the treatment of COVID-19 in adults and pediatric patients (at least 28 days old and weighing at least 3 kg) who are not hospitalized and have mild-to-moderate COVID-19, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Veklury is administered via intravenous infusion for a total treatment duration of 3 days.

Although Veklury is an approved alternative treatment of mild-to-moderate COVID-19 in adults and who are at high risk for progression to severe COVID-19, including hospitalization or death, FDA does not consider Veklury to be an adequate alternative to LAGEVRIO for this authorized use because it may not be feasible or clinically appropriate for certain patients.

Other therapeutics are currently authorized for the same use as LAGEVRIO. For additional information on all products authorized for treatment or prevention of COVID-19, please see https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization .

For information on clinical studies of LAGEVRIO and other therapies for the treatment of COVID-19, see www.clinicaltrials.gov.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Emergency Use of LAGEVRIO in Adult Patients

The dosage in adult patients is 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food *[see Clinical Pharmacology (12.3)]*. Take LAGEVRIO as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset *[see Emergency Use Authorization (1) and Clinical Studies (14)]*.

Completion of the full 5-day treatment course and continued isolation in accordance with public health recommendations are important to maximize viral clearance and minimize transmission of SARS-CoV-2 *[see Patient Counseling Information (17)]*.

LAGEVRIO is not authorized for use for longer than 5 consecutive days because the safety and efficacy have not been established.

If the patient misses a dose of LAGEVRIO within 10 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 10 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose.

Should a patient require hospitalization after starting treatment with LAGEVRIO, the patient may complete the full 5 day treatment course per the healthcare provider's discretion.

2.2 Dosage Adjustments in Specific Populations
No dosage adjustment is recommended based on renal or hepatic impairment or in geriatric patients *[see Use in Specific Populations (8.5, 8.6, 8.7)]*.

2.3 Administration via Nasogastric (NG) or Orogastric (OG) Tube (12F or Larger)

1. Open four (4) capsules and transfer contents into a clean container with a lid.
2. Add 40 mL of water to the container.
3. Put the lid on the container and shake to mix the capsule contents and water thoroughly for 3 minutes.
   - **NOTE**: Capsule contents may not dissolve completely.
   - The prepared mixture may have visible undissolved particulates and are acceptable for administration.
4. Flush NG/OG tube with 5 mL of water prior to administration.
5. Using a catheter tip syringe, draw up the entire contents from the container and administer immediately through the NG/OG tube (12F or larger). Do not keep the mixture for future use.
6. If any portion of the capsule contents are left in the container, add 10 mL of water to the container, mix, and using the same syringe draw up the entire contents of the container and administer through the NG/OG (12F or larger). Repeat as needed until no capsule contents are left in the container or syringe.
7. Flush the NG/OG tube with 5 mL of water twice (10 mL total) after administration of the mixture.

3 DOSAGE FORMS AND STRENGTHS
Capsules: 200 mg, Swedish Orange opaque size 0 capsules. The capsules have the corporate logo and "82" printed in white ink.

4 CONTRAINDICATIONS
No contraindications have been identified based on the limited available data on the emergency use of LAGEVRIO authorized under this EUA.

5 WARNINGS AND PRECAUTIONS
There are limited clinical data available for LAGEVRIO. Serious and unexpected adverse events may occur that have not been previously reported with LAGEVRIO use.

5.1 Embryo-Fetal Toxicity
Based on findings from animal reproduction studies, LAGEVRIO may cause fetal harm when administered to pregnant individuals. There are no available human data on the use of LAGEVRIO in pregnant individuals to evaluate the risk of major birth defects, miscarriage or adverse maternal or fetal outcomes; therefore, LAGEVRIO is not recommended for use during pregnancy. When considering LAGEVRIO for a pregnant individual, the prescribing healthcare provider must communicate the known and potential benefits and the potential risks of using LAGEVRIO during pregnancy to the pregnant individual. LAGEVRIO is authorized to be prescribed to a pregnant individual only after the healthcare provider has determined that the benefits would outweigh the risks for that individual patient. If the decision is made to use LAGEVRIO during pregnancy, the prescribing healthcare provider must document that the known

and potential benefits and the potential risks of using LAGEVRIO during pregnancy were communicated to the pregnant individual.

Advise individuals of childbearing potential of the potential risk to a fetus and to use an effective method of contraception correctly and consistently, as applicable, during treatment with LAGEVRIO and for 4 days after the final dose *[see Use in Specific Populations (8.1, 8.3 and Nonclinical Toxicology (13.1)]*.

Prior to initiating treatment with LAGEVRIO, assess whether an individual of childbearing potential is pregnant or not, if clinically indicated. Pregnancy status does not need to be confirmed in patients who have undergone permanent sterilization, are currently using an intrauterine system or contraceptive implant, or in whom pregnancy is not possible. In all other patients, assess whether the patient is pregnant based on the first day of last menstrual period in individuals who have regular menstrual cycles, is using a reliable method of contraception correctly and consistently or have had a negative pregnancy test. A pregnancy test is recommended if the individual has irregular menstrual cycles, is unsure of the first day of last menstrual period or is not using effective contraception correctly and consistently *[see Box]*.

5.2 Hypersensitivity Including Anaphylaxis
Hypersensitivity reactions, including anaphylaxis, have been reported with LAGEVRIO. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue LAGEVRIO and initiate appropriate medications and/or supportive care.

5.3 Bone and Cartilage Toxicity
LAGEVRIO is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth. Bone and cartilage toxicity was observed in rats after repeated dosing *[see Nonclinical Toxicity (13.2)]*. The safety and efficacy of LAGEVRIO have not been established in pediatric patients *[see Use in Specific Populations (8.4)]*.

6 ADVERSE REACTIONS
6.1 Adverse Reactions from Clinical Studies
The following adverse reactions have been observed in the clinical study of LAGEVRIO that supported the EUA. The adverse reaction rates observed in these clinical trials cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Additional adverse events associated with LAGEVRIO may become apparent with more widespread use.

Overall, more than 900 subjects have been exposed to LAGEVRIO 800 mg twice daily in clinical trials. The safety assessment of LAGEVRIO is primarily based on an analysis from subjects followed through Day 29 in the Phase 3 study in non-hospitalized subjects with COVID-19 (MOVe-OUT) *[see Clinical Studies (14)]*.

The safety of LAGEVRIO was evaluated based on an analysis of a Phase 3 double-blind trial (MOVe-OUT) in which 1,411 non-hospitalized subjects with COVID-19 were randomized and treated with LAGEVRIO (N=710) or placebo (N=701) for up to 5 days. Adverse events were those reported while subjects were on study intervention or within 14 days of study intervention completion/discontinuation.

Discontinuation of study intervention due to an adverse event occurred in 1% of subjects receiving LAGEVRIO and 3% of subjects receiving placebo. Serious adverse events occurred in 7% of subjects receiving LAGEVRIO and 10% receiving placebo; most serious adverse events were COVID-19 related. Adverse events leading to death occurred in 2 (<1%) subjects receiving LAGEVRIO and 12 (2%) of subjects receiving placebo.

The most common adverse reactions in the LAGEVRIO treatment group in MOVe-OUT are presented in Table 1, all of which were Grade 1 (mild) or Grade 2 (moderate).

Table 1: Adverse Reactions Occurring in Greater Than or Equal to 1% of Subjects Receiving LAGEVRIO in MOVe-OUT*

	LAGEVRIO N=710	Placebo N=701
Diarrhea	2%	2%
Nausea	1%	1%
Dizziness	1%	1%
*Frequencies of adverse reactions are based on all adverse events attributed to study intervention by the investigator.		

Laboratory Abnormalities
Selected Grade 3 and 4 laboratory abnormalities in chemistry (alanine aminotransferase, aspartate aminotransferase, creatinine, and lipase) and hematology (hemoglobin, platelets, and leukocytes) parameters all occurred at a rate of less than or equal to 2% and occurred at a similar rate across arms in MOVe-OUT.

6.2 Post-Authorization Experience
The following adverse reactions have been identified during post-authorization use of LAGEVRIO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders
vomiting

Immune System Disorders
hypersensitivity, anaphylaxis, angioedema *[see Warnings and Precautions (5.2)]*

Skin and Subcutaneous Tissue Disorders
erythema, pruritus, rash, urticaria

6.4 Required Reporting for Serious Adverse Events and Medication Errors
The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events* and medication errors potentially related to LAGEVRIO within 7 calendar days from the healthcare provider's awareness of the event, using FDA Form 3500 (for information on how to access this form, see below). The FDA requires that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race)
- A statement "*LAGEVRIO* use for COVID-19 under Emergency Use Authorization (EUA)" under the **"Describe Event, Problem, or Product Use/Medication Error"** heading
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes).
- Patient's preexisting medical conditions and use of concomitant products
- Information about the product (e.g., dosage, route of administration, NDC #).

Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax to 1-800-FDA-0178, or
- Call 1-800-FDA-1088 to request a reporting form

In addition, please provide a copy of all FDA MedWatch forms to:
Merck Sharp & Dohme LLC, Rahway, NJ USA
Fax: 215-616-5677
E-mail: dpoc.usa@msd.com

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of LAGEVRIO.

*Serious adverse events are defined as:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- Other important medical event, which may require a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

6.5 Other Reporting Requirements
Healthcare facilities and providers will report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

7 DRUG INTERACTIONS
No drug interactions have been identified based on the limited available data on the emergency use of LAGEVRIO authorized under this EUA. No clinical drug-drug interaction trials of LAGEVRIO with concomitant medications, including other treatments for mild-to-moderate COVID-19, have been conducted *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Registry
There is a pregnancy registry that monitors pregnancy outcomes in individuals exposed to LAGEVRIO during pregnancy. The prescribing healthcare provider must document that a pregnant individual was made aware of the pregnancy registry at https://covid-pr.pregistry.com or 1-800-616-3791. Pregnant individuals exposed to LAGEVRIO or their healthcare providers can also report the exposure by contacting Merck Sharp & Dohme LLC, Rahway, NJ USA at 1-877-888-4231.

Risk Summary
Based on animal data, LAGEVRIO may cause fetal harm when administered to pregnant individuals. There are no available human data on the use of LAGEVRIO in pregnant individuals to evaluate the risk of major birth defects, miscarriage or adverse maternal or fetal outcomes; therefore, LAGEVRIO is not recommended during pregnancy *[see Box and Warnings and Precautions (5.1)]*. In an animal reproduction study, oral administration of molnupiravir to pregnant rats during the period of organogenesis resulted in embryofetal lethality and teratogenicity at 8 times the human NHC (N4-hydroxycytidine) exposures at the recommended

human dose (RHD) and reduced fetal growth at ≥ 3 times the human NHC exposure at the RHD. Oral administration of molnupiravir to pregnant rabbits during the period of organogenesis resulted in reduced fetal body weights at 18 times the human NHC exposure at the RHD (see *Data*). When considering LAGEVRIO for a pregnant individual, the prescribing healthcare provider must communicate the known and potential benefits and the potential risks of using LAGEVRIO during pregnancy to the pregnant individual. LAGEVRIO may only be prescribed to a pregnant individual after the prescribing healthcare provider has determined that the benefits would outweigh the risks for that individual patient. If the decision is made to use LAGEVRIO during pregnancy, the prescribing healthcare provider must document that the known and potential benefits and potential risks of using LAGEVRIO during pregnancy were communicated to the pregnant individual *[see Box]*. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy *(see Clinical Considerations)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

Data

Animal Data

In an embryofetal development (EFD) study in rats, molnupiravir was administered orally to pregnant rats at 0, 100, 250, or 500 mg/kg/day from gestation days (GDs) 6 to 17. Molnupiravir was also administered orally to pregnant rats at up to 1,000 mg/kg/day from GDs 6 to 17 in a preliminary EFD study. Developmental toxicities included post-implantation losses, malformations of the eye, kidney, and axial skeleton, and rib variations at 1,000 mg/kg/day (8 times the human NHC exposure at the RHD) and decreased fetal body weights and delayed ossification at ≥500 mg/kg/day (3 times the human NHC exposure at the RHD). There were no developmental toxicities at ≤250 mg/kg/day (less than the human NHC exposure at the RHD). Maternal toxicities included decreased food consumption and body weight losses, resulting in the early sacrifice of two of sixteen animals at 1,000 mg/kg/day, and decreased body weight gain at 500 mg/kg/day.

In an EFD study in rabbits, molnupiravir was administered orally to pregnant rabbits at 0, 125, 400, or 750 mg/kg/day from GDs 7 to 19. Developmental toxicity was limited to reduced fetal body weights at 750 mg/kg/day (18 times the human NHC exposures at the RHD). There was no developmental toxicity at ≤400 mg/kg/day (7 times the human NHC exposures at the RHD). Maternal toxicities included reduced food consumption and body weight gains, and abnormal fecal output at 750 mg/kg/day.

In a pre- and post-natal developmental study, molnupiravir was administered orally to female rats at doses up to 500 mg/kg/day (similar to the human NHC exposure at the RHD) from GD6 through lactation day 20. No effects were observed in offspring.

8.2 Lactation

Risk Summary

There are no data on the presence of molnupiravir or its metabolites in human milk. NHC was detected in the plasma of nursing pups from lactating rats administered molnupiravir *(see Data)*. It is unknown whether molnupiravir has an effect on the breastfed infant or effects on milk production.

Based on the potential for adverse reactions in the infant from LAGEVRIO, breastfeeding is not recommended during treatment with LAGEVRIO and for 4 days after the final dose. A lactating individual may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for 4 days after the last dose of LAGEVRIO *[see Warnings and Precautions (5.1, 5.3)]*.

Data
When molnupiravir was administered to lactating rats at ≥250 mg/kg/day in the pre- and post-natal development study, NHC was detected in plasma of nursing pups.

8.3 Females and Males of Reproductive Potential
Based on animal studies, LAGEVRIO may cause fetal harm when administered to a pregnant individual.

Pregnancy Testing
Prior to initiating treatment with LAGEVRIO, assess whether an individual of childbearing potential is pregnant or not, if clinically indicated *[see Warnings and Precautions (5.1)]*.

Contraception
Females
Advise individuals of childbearing potential to use a reliable method of contraception correctly and consistently, as applicable for the duration of treatment and for 4 days after the last dose of LAGEVRIO *[see Warnings and Precautions (5.1)]*.

Males
While the risk is regarded as low, nonclinical studies to fully assess the potential for LAGEVRIO to affect offspring of treated males have not been completed. Advise sexually active individuals with partners of childbearing potential to use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose of LAGEVRIO.
The risk beyond three months after the last dose of LAGEVRIO is unknown. Studies to understand the risk beyond three months are ongoing.

Molnupiravir was equivocal (neither clearly positive nor negative) in one *in vivo* mutagenicity assay of reticulocytes and RBCs which are used to reflect prior effects on hematopoietic stem cells in bone marrow. Molnupiravir was not mutagenic when assessed in a second *in vivo* assay of liver (somatic cells) and bone marrow (somatic cells and stem cells) from transgenic rats administered molnupiravir for 28 days. In contrast to somatic cells, germ cells (eggs and sperm) pass genetic information from generation to generation. A planned study of male testicular germ cells from transgenic rats will assess the potential for molnupiravir to affect offspring of treated males *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use
LAGEVRIO is not authorized for use in patients less than 18 years of age.
Bone and cartilage toxicity were observed in a 3-month, repeat-dose toxicology study in rats. The safety and efficacy of LAGEVRIO have not been established in pediatric patients *[see Warnings and Precautions (5.3) and Nonclinical Toxicology (13.2)]*.

8.5 Geriatric Use
In MOVe-OUT, there was no difference in safety and tolerability between patients ≥65 years of age and younger patients who were treated with LAGEVRIO. No dosage adjustment is recommended based on age. The PK of NHC was similar in geriatric patients compared to younger patients *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment
No dosage adjustment in patients with any degree of renal impairment is recommended. Renal clearance is not a meaningful route of elimination for NHC. Mild or moderate renal impairment did

not have a meaningful impact on the PK of NHC. While the PK of NHC has not been evaluated in patients with eGFR less than 30 mL/min/1.73m^2 or on dialysis, severe renal impairment, and end-stage renal disease (ESRD) are not expected to have a significant effect on NHC exposure *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dosage adjustment in patients with hepatic impairment is recommended. Preclinical data indicate that hepatic elimination is not expected to be a major route of NHC elimination therefore, hepatic impairment is unlikely to affect NHC exposure *[see Clinical Pharmacology (12.3)]*.

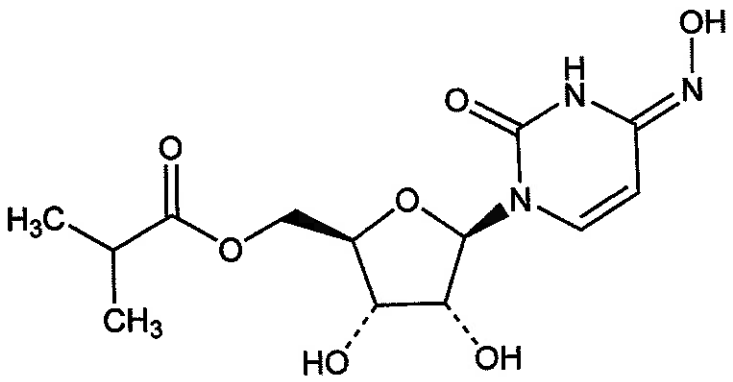
10 OVERDOSAGE

There is no human experience of overdosage with LAGEVRIO. Treatment of overdose with LAGEVRIO should consist of general supportive measures including the monitoring of the clinical status of the patient. Hemodialysis is not expected to result in effective elimination of NHC.

11 DESCRIPTION

LAGEVRIO capsules contain molnupiravir, a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis and is the 5′-isobutyrate ester of the ribonucleoside analog N4-hydroxycytidine (NHC).

The chemical name for molnupiravir is {(2R,3S,4R,5R)-3,4-Dihydroxy-5-[(4Z)-4-(hydroxyimino)-2-oxo-3,4-dihydropyrimidin-1(2H)-yl]oxolan-2-yl}methyl 2-methylpropanoate. It has an empirical formula of $C_{13}H_{19}N_3O_7$ and its molecular weight is 329.31 g/mol. Its structural formula is:



Molnupiravir is a white to off-white powder that is soluble in water.

Each LAGEVRIO capsule, for oral use, contains 200 mg of molnupiravir and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate and microcrystalline cellulose and purified water. The capsule shell is made of hypromellose, red iron oxide and titanium dioxide. The capsule is printed with white ink made of butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac, strong ammonia solution and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Molnupiravir is a prodrug with antiviral activity against SARS-CoV-2. It is metabolized to the cytidine nucleoside analogue, NHC which distributes into cells where NHC is phosphorylated to form the pharmacologically active ribonucleoside triphosphate (NHC-TP). NHC-TP incorporation (as NHC-monophosphate [NHC-MP]) into SARS-CoV-2 RNA by the viral RNA polymerase (nsp12) results in an accumulation of errors in the viral genome leading to inhibition of replication. The mechanism of action (known as viral error catastrophe or viral lethal mutagenesis) is supported by biochemical and cell culture data, studies of SARS-CoV-2

infection in animal models, and analyses of SARS-CoV-2 genome sequences in human subjects treated with LAGEVRIO.

12.2 Pharmacodynamics

The relationship between NHC and intracellular NHC-TP with antiviral efficacy has not been evaluated clinically.

12.3 Pharmacokinetics

Molnupiravir is a 5´-isobutyrate prodrug of NHC that is hydrolyzed during or after absorption. NHC, the primary circulating analyte, is taken up by cells and anabolized to NHC-TP. NHC is eliminated by metabolism to uridine and/or cytidine through the same pathways involved in endogenous pyrimidine metabolism. NHC pharmacokinetics are shown in Table 2.

Plasma NHC concentrations in patients (N=5) following administration of molnupiravir via nasogastric or orogastric tube fell within the range of NHC concentrations following oral molnupiravir capsule administration under the same dosing regimen.

Table 2: Pharmacokinetics of NHC After Multiple Oral Administration of 800 mg LAGEVRIO Every 12 Hours

	NHC Geometric Mean (%CV)
Pharmacokinetics in Patients	
$AUC_{0\text{-}12hr}$ (ng*hr/mL)*	8260 (41.0)
C_{max} (ng/mL)*	2330 (36.9)
C_{12hr} (ng/mL)*	31.1 (124)
Pharmacokinetics in Healthy Subjects	
$AUC_{0\text{-}12hr}$ (ng*hr/mL)	8330 (17.9)
C_{max} (ng/mL)	2970 (16.8)
C_{12hr} (ng/mL)	16.7 (42.8)
AUC Accumulation Ratio	1.09 (11.8)
Absorption	
T_{max} (hr)†	1.50 [1.00 – 2.02]
Effect of Food	35% reduction in C_{max}, no effect on AUC
Distribution	
Plasma Protein Binding (*in vitro*)	0%
Apparent Volume of Distribution (L)*	142
Elimination	
Effective $t_{1/2}$ (hr)	3.3
Apparent Clearance (L/hr)*	76.9
Fraction of dose excreted in urine over the time interval of 0-12 hours	3% (81.6%)

Values were obtained from a Phase 1 study of healthy subjects, unless otherwise indicated.
*Values were obtained from population PK analysis.
†Median [min - max]

Specific Populations

Population PK analysis results indicated that age, sex, race, ethnicity, or disease severity do not meaningfully influence the PK of NHC.

Pediatric Patients

LAGEVRIO has not been studied in pediatric patients.

Patients with Renal Impairment

Renal clearance is not a meaningful route of elimination for NHC. In a population PK analysis, mild or moderate renal impairment did not have a meaningful impact on the PK of NHC. The PK

of molnupiravir and NHC has not been evaluated in patients with eGFR less than 30 mL/min/1.73m^2 or on dialysis.

Patients with Hepatic Impairment
The PK of molnupiravir and NHC has not been evaluated in patients with moderate and severe hepatic impairment. Preclinical data indicate that hepatic elimination is not expected to be a major route of NHC elimination; therefore, hepatic impairment is unlikely to affect NHC exposure.

Drug Interaction Studies
In vitro study results indicated that molnupiravir and NHC are not substrates of CYP enzymes or human P-gp and BCRP transporters. *In vitro* study results also indicated that molnupiravir and NHC are not inhibitors of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 or inhibitors of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2K, MRP2, MDR1 and BCRP or inducers of CYP1A2, 2B6, and 3A4. The interaction between molnupiravir with concomitant medications, including other treatments for mild-to-moderate COVID-19, has not been evaluated.

12.4 Microbiology
Antiviral Activity
NHC, the nucleoside analogue metabolite of molnupiravir, was active in cell culture assays against SARS-CoV-2 (USA-WA1/2020 isolate) with 50% effective concentrations (EC_{50} values) ranging between 0.67 to 2.7 µM in A-549 cells and 0.32 to 2.0 µM in Vero E6 cells. NHC had similar antiviral activity against SARS-CoV-2 variants Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), Lambda (C.37), Mu (B.1.621) and Omicron (B.1.1.529/BA.1, BA.1.1, BA.2, BA.4 and BA.5), with mean EC_{50} values of 0.55-3.0 µM. NHC had non-antagonistic antiviral activity with remdesivir against SARS-CoV-2 in cell culture.

Resistance
No amino acid substitutions in SARS-CoV-2 associated with resistance to NHC have been identified in Phase 2 clinical trials evaluating LAGEVRIO for the treatment of COVID-19. Studies to evaluate selection of resistance to NHC with SARS-CoV-2 in cell culture have not been completed. Resistance selection studies have been conducted with other coronaviruses (MHV and MERS-CoV) and showed a low likelihood of resistance development to NHC. Following 30 passages in cell culture, only a 2-fold decrease in susceptibility was observed and no NHC resistance-associated amino acid substitutions were identified.

In clinical trials, encoded amino acid changes (substitutions, deletions or insertions) were more likely to be detected in viral sequences in subjects treated with LAGEVRIO compared to placebo. In a small number of subjects amino acid changes in the spike protein occurred at positions targeted by monoclonal antibodies and vaccines. The clinical and public health significance of these changes are unknown.

Cross-Resistance
NHC retained activity in cell culture against virus with polymerase (nsp 12) substitutions (e.g., F480L, V557L and E802D) associated with decreased remdesivir susceptibility, indicating a lack of cross-resistance.

Activity against SARS-CoV-2 in animal models
The antiviral activity of molnupiravir has been demonstrated in mouse, hamster, and ferret models of SARS-CoV-2 infection when dosing was administered prior to or within 1-2 days after viral challenge. In SARS-CoV-2 infected ferrets, molnupiravir significantly reduced SARS-CoV-2 viral titers in the upper respiratory tract and completely inhibited viral spread to untreated contact animals. In SARS-CoV-2 infected Syrian hamsters, molnupiravir reduced viral RNA and infectious virus titers in the lungs of animals. Histopathological analysis of lung tissue harvested after infection showed significantly reduced SARS-CoV-2 viral antigen levels and a lower abundance of pulmonary lesions in molnupiravir-treated animals compared with controls.

In Vitro Cytotoxicity
NHC, the nucleoside analogue metabolite of molnupiravir, had variable cytotoxicity against different mammalian cell types with CC_{50} values ranging from 7.5 µM (human lymphoid CEM cell line) to >100 µM, in 3-day exposure assays. Molnupiravir inhibited the proliferation of human bone marrow progenitor cells with CC_{50} values of 24.9 µM and 7.7 µM for erythroid and myeloid progenitor proliferation, respectively, in 14-day colony formation assays.

Viral RNA Rebound
Post-treatment increases in SARS-CoV-2 RNA shedding levels (i.e., viral RNA rebound) in nasopharyngeal samples were observed on Day 10, Day 15, and/or Day 29 in a subset of LAGEVRIO and placebo recipients in the Phase 3 MOVe-OUT trial. Approximately 1% of both LAGEVRIO and placebo recipients had evidence of recurrent COVID-19 symptoms coinciding with a rebound in viral RNA levels in nasopharyngeal samples.

Post-treatment viral RNA rebound was not associated with the primary clinical outcome of hospitalization or death through Day 29 following the single 5-day course of LAGEVRIO treatment. Post-treatment viral RNA rebound also was not associated with the detection of cell culture infectious virus in nasopharyngeal swab samples.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Molnupiravir was not carcinogenic in a 6-month oral carcinogenicity study in RasH2 transgenic (Tg.RasH2) mice at any dose tested (30, 100 or 300 mg/kg/day).

Mutagenesis
Molnupiravir and NHC were positive in the *in vitro* bacterial reverse mutation assay (Ames assay) with and without metabolic activation. Molnupiravir was studied in two *in vivo* rodent mutagenicity models. The *in vivo* Pig-a mutagenicity assay gave equivocal results. Molnupiravir was negative in the *in vivo* Big Blue® (cII Locus) transgenic rodent mutagenicity assay. Molnupiravir was negative for induction of chromosomal damage in *in vitro* micronucleus (with and without metabolic activation) and *in vivo* rat micronucleus assays. To assess effects on germ cells, a transgenic rodent male germ cell mutagenicity assay is planned.

Based on the totality of the available genotoxicity data and the duration of treatment (5 days), molnupiravir is low risk for genotoxicity.

Impairment of Fertility
There were no effects on fertility, mating performance or early embryonic development when molnupiravir was administered to female or male rats at NHC exposures approximately 2 and 6 times, respectively, the human NHC exposure at the RHD.

13.2 Animal Toxicology and/or Pharmacology

Bone and cartilage toxicity changes resulting in impaired transformation of growth cartilage into new bone were observed in the femur and tibia of rats in a 3-month toxicity study at ≥ 500 mg/kg/day (5 times the human NHC exposure at the RHD). There was no bone or cartilage toxicity in a 1-month toxicity study in rats up to 500 mg/kg/day (4 and 8 times the human NHC exposure at the RHD in females and males, respectively), in dogs dosed for 14 days up to 50 mg/kg/day (similar to the human NHC exposure at the RHD), or in a 1-month toxicity study in mice up to 2,000 mg/kg/day (19 times the human NHC exposure at the RHD).

Growth cartilage is not present in mature skeletons, therefore the bone and cartilage findings are not relevant for adult humans but may be relevant for pediatric patients *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.4)]*.

Reversible, dose-related bone marrow toxicity affecting all hematopoietic cell lines was observed in dogs at ≥17 mg/kg/day (less than the human NHC exposure at the RHD). Mild decreases in peripheral blood cell and platelet counts were seen after 7 days of molnupiravir treatment progressing to more severe hematological changes after 14 days of treatment. Neither bone marrow nor hematological toxicity was observed in a 1-month toxicity study in mice up to 2,000 mg/kg/day (19 times the human NHC exposure at the RHD) and a 3-month toxicity study in rats up to 1,000 mg/kg/day (9 and 15 times the human NHC exposure at the RHD in females and males, respectively).

14 CLINICAL STUDIES

Clinical data supporting this EUA are based on data from 1,433 randomized subjects in the Phase 3 MOVe-OUT trial (NCT04575597). MOVe-OUT is a randomized, placebo-controlled, double-blind clinical trial studying LAGEVRIO for the treatment of non-hospitalized patients with mild-to-moderate COVID-19 who are at risk for progressing to severe COVID-19 and/or hospitalization. Eligible subjects were 18 years of age and older and had one or more pre-defined risk factors for disease progression: over 60 years of age, diabetes, obesity (BMI ≥30), chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease, or active cancer. The study included symptomatic subjects not vaccinated against SARS-CoV-2 and who had laboratory confirmed SARS-CoV-2 infection and symptom onset within 5 days of randomization. Subjects were randomized 1:1 to receive 800 mg of LAGEVRIO or placebo orally twice daily for 5 days.

At baseline, in all randomized subjects, the median age was 43 years (range:18 to 90); 17% of subjects were over 60 years of age and 3% were 75 years of age or older; 49% of subjects were male; 57% were White, 5% Black or African American, 3% Asian, 50% Hispanic or Latino. The majority of subjects were enrolled from sites in Latin America (46%) and Europe (33%); 12% were enrolled in Africa, 6% were enrolled in North America and 3% were enrolled in Asia. Forty-eight percent of subjects received LAGEVRIO or placebo within 3 days of COVID-19 symptom onset. The most common risk factors were obesity (74%), over 60 years of age (17%), and diabetes (16%). Among 792 subjects (55% of total randomized population) with available baseline SARS-CoV-2 variant/clade identification results, 58% were infected with Delta (B.1.617.2 and AY lineages), 20% were infected with Mu (B.1.621), 11% were infected with Gamma (P.1), and the remainder were infected with other variants/clades. Overall, baseline demographic and disease characteristics were well balanced between the treatment arms.

Table 3 provides the results of the primary endpoint (the percentage of subjects who were hospitalized or died through Day 29 due to any cause). The efficacy results are based on unvaccinated adults who were 18 years of age and older and had one or more pre-defined risk factors for disease progression: over 60 years of age, diabetes, obesity (BMI ≥30), chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease, or active cancer. Please refer to Figure 1 for results by certain subgroups. These subgroup analyses are considered exploratory. Data are not available in certain subgroups of subjects who are at high risk for progression to severe COVID-19 as defined by CDC.

Table 3. Efficacy Results in Non-Hospitalized Adults with COVID-19*

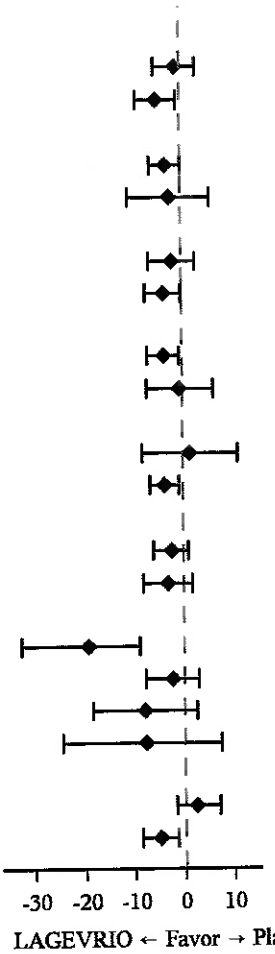
LAGEVRIO (N=709) n (%)	Placebo (N=699) n (%)	Adjusted Risk Difference % (95% CI)
All-cause hospitalization ≥24 hours for acute care or death through Day 29		
48 (6.8%)	68 (9.7%)	-3.0% (-5.9%, -0.1%)
All-cause mortality through Day 29		
1 (0.1%)	9 (1.3%)	

*The determination of primary efficacy was based on a planned interim analysis of 762 subjects. At the interim analysis, 7.3% of patients who received LAGEVRIO were either hospitalized or died through Day 29 (28/385), compared with 14.1% of placebo-treated patients (53/377). The adjusted risk difference was -6.8% with a 95% CI of (-11.3%, -2.4%) and 2-sided p-value = 0.0024.

Adjusted relative risk reduction of LAGEVRIO compared to placebo for all randomized subjects was 30% (95% CI: 1%, 51%).

Analyses are adjusted by the stratification factor of time of COVID-19 symptom onset (≤3 days vs. >3 [4-5] days).

Figure 1. Subgroup Efficacy Results in Non-Hospitalized Adults with COVID-19 - All-Randomized Subjects



	Difference (%)	# Events/Subjects LAGEVRIO	# Events/Subjects Placebo	Risk Difference % (95% CI)
Time from Symptom Onset to Randomization				
≤ 3 days		25/339	28/335	-1.0 (-5.2, 3.2)
> 3 days		23/370	40/364	-4.8 (-9.0, -0.7)
Age				
≤ 60 years		36/591	52/572	-3.0 (-6.1, 0.0)
> 60 years		12/118	16/127	-2.4 (-10.6, 5.8)
Sex				
Male		32/330	41/355	-1.9 (-6.5, 2.8)
Female		16/379	27/344	-3.6 (-7.4, -0.2)
Obesity (BMI ≥ 30)				
Yes		29/535	46/507	-3.7 (-6.9, -0.5)
No		19/174	22/192	-0.5 (-7.1, 6.2)
Diabetes Mellitus				
Yes		17/107	17/117	1.4 (-8.2, 11.1)
No		31/602	51/582	-3.6 (-6.6, -0.7)
Baseline COVID Severity				
Mild		19/395	27/376	-2.4 (-5.9, 1.0)
Moderate		29/311	40/321	-3.1 (-8.1, 1.8)
Most Common Baseline Clades				
20J (Gamma)		0/37	9/47	-19.1 (-32.6, -8.9)
21A, 21I, 21J (Delta)		18/237	22/221	-2.4 (-7.8, 2.9)
21H (Mu)		6/75	13/82	-7.9 (-18.5, 2.6)
Other		5/47	7/38	-7.8 (-24.4, 7.4)
Baseline Antibody Status				
Positive		5/136	2/146	2.3 (-1.7, 7.1)
Negative		39/541	64/520	-5.1 (-8.8, -1.6)

The corresponding confidence interval is based on Miettinen & Nurminen method.
The modified intent-to-treat population is the efficacy analysis population.
Baseline serum samples were evaluated with the Roche Elecsys anti-N assay to test for the presence of antibodies (IgM, IgG and IgA) against the SARS-CoV-2 nucleocapsid protein.
The findings of these subgroup analyses are considered exploratory.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

LAGEVRIO capsules are supplied as follows:

Contents	Description	How Supplied	NDC

200 mg molnupiravir	Swedish Orange opaque capsules with corporate logo and "82" printed in white ink	40 count bottles	NDC-0006-5055-06 NDC-0006-5055-07 NDC-0006-5055-09

Storage and Handling
Store LAGEVRIO capsules at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION
As a prescribing healthcare practitioner, you must communicate to the patient and/or caregiver information consistent with the "FACT SHEET FOR PATIENTS AND CAREGIVERS" and document that information was provided. A copy of this Fact Sheet should be provided to the patient and/or caregiver prior to receiving LAGEVRIO *[see Box]*.

Hypersensitivity Reactions
Inform patients that hypersensitivity reactions have been reported, even following a single dose of LAGEVRIO, and to discontinue the drug and to inform their healthcare provider at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema (for example, swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction *[see Warnings and Precautions (5.2)]*.

Risk of Fetal Toxicity
Advise patients that LAGEVRIO is not recommended for use in pregnancy because it may cause fetal harm. Advise individuals of childbearing potential to inform their healthcare provider of a known or suspected pregnancy *[see Box, Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*.

Advise individuals of childbearing potential to use effective contraception correctly and consistently while taking LAGEVRIO and for 4 days after the last dose.

While the risk is regarded as low, nonclinical studies to fully assess the potential for LAGEVRIO to affect offspring of treated males have not been completed. Advise sexually active individuals with partners of childbearing potential to use a reliable method of contraception consistently and correctly while taking LAGEVRIO and for at least 3 months after the last dose of LAGEVRIO. The risk beyond 3 months after the last dose of LAGEVRIO is unknown. Studies to understand the risk beyond three months are ongoing *[see Use in Specific Populations (8.3)]*.

Risk of Bone and Cartilage Toxicity
LAGEVRIO is not authorized for use in patients less than 18 year of age as it may affect bone growth and cartilage formation *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.4)]*.

Pregnancy Registry
There is a pregnancy registry that monitors pregnancy outcomes in individuals exposed to LAGEVRIO during pregnancy. Encourage participation and advise patients about how they may enroll in the pregnancy registry at https://covid-pr.pregistry.com or 1-800-616-3791 *[see Use in Specific Populations (8.1)]*.

Lactation
Breastfeeding is not recommended while taking LAGEVRIO and for 4 days after the last dose of LAGEVRIO. Advise lactating individuals to consider interrupting breastfeeding and to consider

pumping and discarding breast milk during treatment and for 4 days after the last dose of LAGEVRIO *[see Use in Specific Populations (8.2)]*.

Administration Instructions
Inform patients to take LAGEVRIO with or without food. Advise patients to swallow LAGEVRIO capsules whole, and to not open, break, or crush the capsules. Instruct patients that if they miss a dose of LAGEVRIO and it is within 10 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 10 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. Advise the patient to not double the dose to make up for a missed dose *[see Dosage and Administration (2.2)]*.

LAGEVRIO capsule contents can be mixed with water and given via NG/OG tube. Inform patients to follow the instructions as described in the fact sheet for patients and caregivers *[see Dosage and Administration (2.3)]*.

Alert the patient of the importance of completing the full 5-day treatment course and to continuing isolation in accordance with public health recommendations to maximize viral clearance and minimize transmission of SARS-CoV-2 *[see Dosage and Administration (2.1)]*.

18 MANUFACTURER INFORMATION
For additional information visit: www.molnupiravir.com

If you have questions, please contact
1-800-672-6372

Manuf. for: Merck Sharp & Dohme LLC
Rahway, NJ 07065, USA

For patent information: www.msd.com/research/patent

usfshcp-mk4482-c-2307r008

U.S. FOOD & DRUG ADMINISTRATION

Frequently Asked Questions on the Emergency Use Authorization for Lagevrio (molnupiravir) for Treatment of COVID-19

Q: What is an emergency use authorization (EUA)?
A: Under section 564 of the Federal Food, Drug & Cosmetic Act, after a declaration by the HHS Secretary based on one of four types of determinations, FDA may authorize an unapproved product or unapproved uses of an approved product for emergency use. In issuing an EUA, FDA must determine, among other things, that based on the totality of scientific evidence available to the agency, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by a chemical, biological, radiological, or nuclear agent; that the known and potential benefits of the product, when used to treat, diagnose or prevent such disease or condition, outweigh the known and potential risks for the product; and that there are no adequate, approved, and available alternatives. Emergency use authorization is NOT the same as FDA approval or licensure.

Q: What does this EUA authorize? What are the limitations of authorized use?
A: FDA has issued an EUA for the emergency use of the unapproved product Lagevrio (molnupiravir) for the treatment of adults with a current diagnosis of mild-to-moderate coronavirus disease 2019 (COVID-19), who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate. Lagevrio is not FDA-approved for any use including for the treatment of COVID-19. Prior to initiating treatment with Lagevrio, carefully consider the known and potential risks and benefits.

Lagevrio is not authorized:

- for use in patients less than 18 years of age.
- for initiation of treatment in patients requiring hospitalization due to COVID-19. Benefit of treatment with Lagevrio has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19.
- for use for longer than five consecutive days.
- for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

Q: How is high risk defined under the EUA?
A: Information about conditions that place a patient with mild-to-moderate COVID-19 at increased risk for disease progression or death can be found at the Centers for Disease Control and Prevention's People with Certain Medical Conditions website. Health care providers should consider the benefit-risk for an individual patient.

Q: Does the EUA require a positive result from a direct SARS-CoV-2 viral test prior to prescribing Lagevrio to a patient who is at high risk for severe COVID-19?"
A: No. Although the Agency continues to recommend that authorized prescribers use direct SARS-CoV-2 viral testing to help diagnose COVID-19, the Agency removed the requirement for positive test results effective February 1, 2023. FDA recognizes that, in rare instances, individuals with a recent known exposure (e.g., a household contact with a positive direct SARS-CoV-2 viral test) who develop signs and symptoms consistent with COVID-19 may be diagnosed by an authorized prescriber as having COVID-19 even if they have a negative direct SARS-CoV-2 viral test result. In such instances, the authorized prescriber may determine that treatment with Lagevrio for COVID-19 is appropriate if the patient

reports mild-to-moderate symptoms of COVID-19 and is at high-risk for progression to severe COVID-19, including hospitalization or death, and the terms and conditions of the authorization are met, as detailed in the Fact Sheet for Healthcare Providers.

Q: What does direct SARS-CoV-2 viral testing mean?
A: Direct SARS-CoV-2 viral tests diagnose current COVID-19 infection. Direct SARS-CoV-2 viral tests include two types of diagnostic tests for COVID-19:

- Molecular tests, such as reverse transcription polymerase chain reaction (RT-PCR) tests, that detect the virus's genetic material.
- Antigen tests that detect specific proteins from the virus.

Antibody tests should not be used to diagnose COVID-19 and are not direct SARS-CoV-2 viral tests. Antibody tests look for antibodies that the immune system makes in response to the SARS-CoV-2 virus.

Q: Are there any warnings or precautions that should be taken when administering Lagevrio?
A: Yes, health care providers and patients must be aware of the following warnings and precautions:

- Pregnancy
  Lagevrio may cause fetal harm when administered to pregnant individuals. Therefore, **Lagevrio is not recommended for use during pregnancy.** Prior to initiating treatment with Lagevrio, health care providers should assess whether an individual of childbearing potential is pregnant or not, if clinically indicated. Lagevrio is authorized to be prescribed to a pregnant individual only after the health care provider has determined that the benefits would outweigh the risks for that individual patient and the known and potential benefits and potential risks of using Lagevrio during pregnancy are communicated to the pregnant individual.

- Lactation
  Breastfeeding is not recommended during treatment with Lagevrio and for four days after the final dose. A lactating individual may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for 4 days after the last dose of Lagevrio.

- Females of Reproductive Potential
  Females of childbearing potential are advised to use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for four days after the last dose of Lagevrio.

- Males of Reproductive Potential
  While the risk is regarded as low, studies to fully assess the potential for Lagevrio to affect offspring of treated males have not been completed. Sexually active individuals with partners of childbearing potential are advised to use a reliable method of contraception correctly and consistently during treatment and for at least three months after the last dose of Lagevrio. The risk beyond three months after the last dose of Lagevrio is unknown. Studies to understand the risk beyond three months are ongoing.

- Hypersensitivity Including Anaphylaxis

Hypersensitivity reactions, including anaphylaxis, have been reported with Lagevrio. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue Lagevrio and initiate appropriate medications and/or supportive care.

Q: Are there potential side effects of Lagevrio?
A: Possible side effects of Lagevrio include diarrhea, nausea, and dizziness. Lagevrio is not recommended for use during pregnancy because findings from animal reproduction studies showed that Lagevrio may cause fetal harm when administered to pregnant individuals.

Hypersensitivity, anaphylaxis, angioedema, erythema, rash, and urticaria adverse reactions have been identified during post-authorization use of Lagevrio.

Q: Why is Lagevrio only authorized in adults?
A: Lagevrio is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth.

Q: Is Lagevrio approved by the FDA to prevent or treat COVID-19?
A: No. Lagevrio is not FDA-approved to prevent or treat any diseases or conditions, including COVID-19. Lagevrio is an investigational drug.

Q: How can Lagevrio be obtained for use under the EUA?
A: For questions on how to obtain Lagevrio, please contact COVID19therapeutics@hhs.gov.

Q. Who may prescribe Lagevrio under the EUA?
A. Under the authorization, Lagevrio may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which Lagevrio belongs (i.e., anti-infectives).

Q: When should Lagevrio be administered to a patient?
A: Patients should talk to their healthcare provider to determine whether, based on their individual circumstances and whether alternative COVID-19 treatment options approved or authorized by FDA are accessible or clinically appropriate, they are eligible to receive Lagevrio. Patients should take Lagevrio as soon as possible after a diagnosis of COVID-19 has been made, and within five days of symptom onset.

More information about administration is available in the Fact Sheet for Health Care Providers.

Q: Does the EUA permit the use of Lagevrio as authorized in patients hospitalized *for reasons other* than COVID-19?
A: If a patient is hospitalized *for reasons other* than COVID-19, such as for an elective orthopedic procedure, and the patient has a current diagnosis of mild-to-moderate COVID-19, then treatment with Lagevrio is authorized if the patient is also at high risk for progression to severe COVID-19, including hospitalization or death, and the terms and conditions of the authorization are met as detailed in the Fact Sheet for Health Care Providers.

Lagevrio is also authorized for patients who require hospitalization after starting treatment with Lagevrio. These patients may complete the full five-day treatment course per the health care provider's discretion.

Q: Are there data showing treatment with Lagevrio may benefit adults with mild-to-moderate COVID-19 who are at high risk for progressing to severe COVID-19 and/or hospitalization?
A: Yes. The most important scientific evidence supporting the authorization of Lagevrio is from MOVe-OUT, a randomized, placebo-controlled, double-blind clinical trial studying Lagevrio for the treatment of non-hospitalized patients with mild-to-moderate COVID-19 who are at risk for progressing to severe COVID-19 and/or hospitalization. Eligible subjects were 18 years of age and older and had one or more pre-defined risk factors for disease progression: over 60 years of age, diabetes, obesity (BMI ≥30), chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease, or active cancer. The study included symptomatic subjects not vaccinated against SARS CoV-2 and who had laboratory confirmed SARS-CoV-2 infection and symptom onset within five days of randomization.

The main outcome measured in the trial was the percentage of people who were hospitalized or died due to any cause during 29 days of follow-up. Of the 709 people who received Lagevrio, 6.8% were hospitalized or died within this time period compared to 9.7% of the 699 people who received a placebo. This represented an adjusted relative risk reduction of Lagevrio compared to placebo of approximately 30% for all those randomized. Of the people who received Lagevrio, one died within this time period compared to nine people who received a placebo. The safety and effectiveness of Lagevrio for the treatment of COVID-10 continue to be evaluated.

Q: Are there requirements for health care facilities and prescribing health care providers as part of the EUA?
A: Yes.

- As part of the EUA, FDA requires health care providers who prescribe Lagevrio to report all medication errors and serious adverse events considered to be potentially related to Lagevrio through FDA's MedWatch Adverse Event Reporting program. Providers can complete and submit the report online; or download and complete the form, then submit it via fax at 1-800-FDA-0178. This requirement is outlined in the EUA's Fact Sheet for Health Care Providers. FDA MedWatch forms should also be provided to Merck Sharp & Dohme Corp.
- Health care facilities and providers must report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.
- Healthcare providers must provide an electronic or hard copy of the "Fact Sheet for Patients, and Caregivers" prior to the patient receiving Lagevrio and must document that the patient has been given an electronic or hard copy of the "Fact Sheet for Patients and Caregivers".
- Healthcare providers must inform the patient or caregiver that:
    - Lagevrio is an unapproved drug that is authorized for use under this Emergency Use Authorization.
    - Other therapeutics are currently approved or authorized for the same use as Lagevrio [see Emergency Use Authorization (1) - Information Regarding Available Alternatives for the EUA Authorized Use].
    - There are benefits and risks of taking Lagevrio as outlined in the "Fact Sheet for Patients and Caregivers."
    - There is a pregnancy registry for patients exposed to Lagevrio.

  - Females of childbearing potential should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for four days after the last dose of Lagevrio.
  - Males of reproductive potential who are sexually active with females of childbearing potential should use a reliable method of contraception correctly and consistently during treatment and for at least three months after the last dose.
- The prescribing health care provider must assess whether an individual of childbearing potential is pregnant or not, if clinically indicated.
- Based on findings from animal reproduction studies, Lagevrio may cause fetal harm when administered to pregnant individuals. If Lagevrio is used during pregnancy, prescribing healthcare providers must communicate to the patient the known and potential benefits and the potential risks of Lagevrio use during pregnancy, as outlined in the "Fact Sheet for Patients and Caregivers".
- If the decision is made to use Lagevrio during pregnancy, the prescriber must document that the known and potential benefits and the potential risks of Lagevrio use during pregnancy, as outlined in the "Fact Sheet for Patients and Caregivers," were discussed with the patient.
- There is a pregnancy registry that monitors pregnancy outcomes in individuals exposed to Lagevrio during pregnancy. The prescribing healthcare provider must document that a pregnant individual was made aware of the pregnancy registry at https://covid-pr.pregistry.com or 1-800-616-3791. Pregnant individuals exposed to Lagevrio or their healthcare providers can also report the exposure by contacting Merck Sharp & Dohme LLC, Rahway, NJ USA at 1-877-888-4231.

Q: Do patient outcomes need to be reported under the EUA?
A: No, reporting of patient outcomes is not required under the EUA. However, reporting of all medication errors and serious adverse events considered to be potentially related to Lagevrio occurring during treatment is required.

Q: FDA has issued a number of EUAs, including for therapeutics. If state laws impose different or additional requirements on the medical product covered by an EUA, are those state laws preempted?
A: As stated in FDA's Emergency Use Authorization of Medical Products and Related Authorities; Guidance for Industry and Other Stakeholders, "FDA believes that the terms and conditions of an EUA issued under section 564 preempt state or local law, both legislative requirements and common-law duties, that impose different or additional requirements on the medical product for which the EUA was issued in the context of the emergency declared under section 564." The guidance explains the basis for FDA's views on this subject.

Q: Can health care providers share the patient/caregiver fact sheet electronically?
A: Yes. The letter of authorization for Lagevrio authorizes healthcare providers to share the patient/caregiver fact sheet electronically.

U.S. Food and Drug Administration

Center for Drug Evaluation and Research

Addendum to FDA Briefing Document

Antimicrobial Drugs Advisory Committee Meeting

November 30, 2021

On October 8, 2021, the sponsor (Merck & Co., Inc) submitted a request for Emergency Use Authorization for molnupiravir (MOV) for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death, based on a pre-specified P002 Part 2, interim analysis when approximately 50% of participants enrolled and completed the trial through Day 29. At the planned interim analysis (N=775 for efficacy and N=765 for safety), the external data monitoring committee recommended that due to efficacy on the primary endpoint of reducing hospitalization ≥24 hours for acute care of illness or death due to any cause by Day 29, the study met the criteria for stopping enrollment. The trial stopped enrollment, and all the randomized participants (N=1433) will continue to be followed until their Month 7 visit (end of study) or early withdrawal.

On November 22, 2021 the Agency became aware of the topline safety and efficacy results from all 1433 randomized participants (full population) through Day 29. Please refer to the sponsor's addendum for the updated efficacy and safety analyses. A few key updates include the following:

The number of participants who received MOV 800 mg Q12h for five days in Part 2 of P002 increased from 386 participants (interim population) to 710 participants (full population), bringing the total molnupiravir 800 mg safety database to 917 participants.

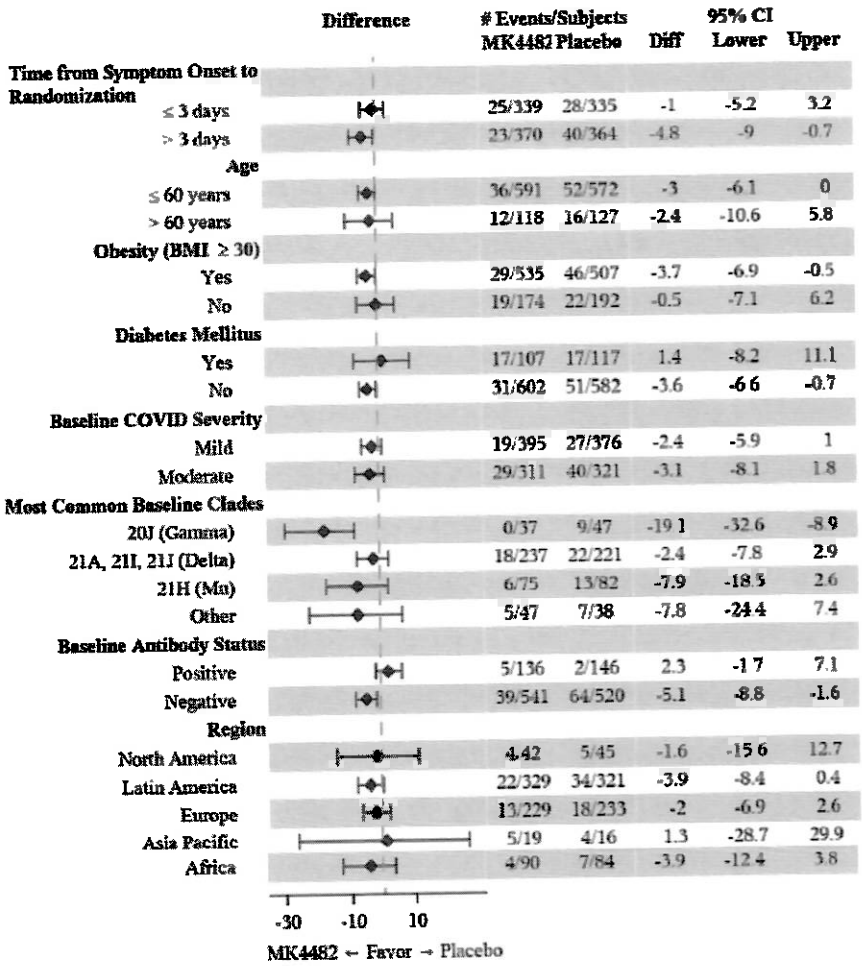
In the analysis submitted with the EUA request (interim population), all cause hospitalization or death through Day 29 was 7.3% (28/385) and 14.1% (53/377) for the MOV and placebo groups, respectively. The risk difference (MOV-Placebo) is -6.8 (95% CI: -11.3, -2.4) based on the Miettinen and Nurminen method stratified by time from COVID-19 symptom onset (≤3 days vs. >3 [4-5] days).

In the updated analysis (full population), all cause hospitalization or death through Day 29 was 6.8% (48/709) and 9.7% (68/699) for the MOV and placebo groups, respectively. For the full population, the risk difference (MOV – Placebo) is -3.0% (95% CI: -5.9%, -0.1%) based on the Miettinen and Nurminen method stratified by time from COVID-19 symptom onset (≤3 days vs. >3 [4-5] days). The risk difference is the pre-specified primary analysis method. Additionally,

the relative risk reduction of MOV compared to placebo was 30% (95% CI: 1%, 51%) based on the Cochran-Mantel-Haenszel method stratified by time from COVID-19 symptom onset (≤3 days versus >3 [4 to 5] days). The incidence of hospitalization or death through Day 29 by subgroup for the full population is shown in Figure 1 (source, sponsor's analyses).

Figure 1

Incidence of Hospitalization or Death Through Day 29 by Subgroup (Protocol 002 – Full Population)



The Agency continues to evaluate the known and potential benefits and risks of MOV considering the results from all randomized participants. During the meeting, the Agency will provide additional key safety and efficacy results based on all 1433 randomized participants (full population). The review issues and benefit/risk assessments may therefore differ from the original assessments provided in the briefing document which was based on the interim analysis.

Additionally, we are providing information from the November 4, 2019 FDA Genetic Toxicology Workshop: How Many Doses of an DNA Reactive (Ames-positive) Drug can be

Safely Administered to Healthy Subjects? The full transcript of the 2019 FDA workshop and other related workshop materials are available to the public at this link: https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/fda-genetic-toxicology-workshop-how-many-doses-dna-reactive-ames-positive-drug-can-be-safely#event-information.

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IMPORTANT PRESCRIBING INFORMATION

Subject: **Inconsistencies between VEKLURY® (remdesivir) Prescribing Information and VEKLURY for injection (supplied as lyophilized powder in vial) container label and carton labeling may lead to medication errors in pediatric patients.**

Dear Healthcare Provider:

Gilead Sciences, Inc., would like to alert providers that the **preparation and storage information on the container label and carton labeling of VEKLURY® (remdesivir) for injection (supplied as lyophilized powder in vial) may be inconsistent** with the US Prescribing Information that was revised on 25 April 2022 to include pediatric patients 28 days and older and weighing 3 kg to less than 40 kg.

To prevent medication errors, **healthcare providers should refer to the Dosage and Administration (Sections 2.6 and 2.7) of the most currently approved US Prescribing Information to prepare doses for pediatric patients** 28 days and older and weighing 3 kg to less than 40 kg. The current US Prescribing Information is available at www.gilead.com/science-and-medicine/medicines.

VEKLURY is available in two injectable dosage forms, a solution and lyophilized powder. **Only the VEKLURY for injection dosage form (supplied as lyophilized powder in vial) is approved for pediatric patients 28 days and older and weighing 3 kg to less than 40 kg.**

Reporting Adverse Events and Medication Errors

Healthcare providers are encouraged to report all adverse events and all medication errors when using VEKLURY to Gilead Sciences at Safety_fc@gilead.com and to FDA online at www.fda.gov/medwatch or by calling 1-800-FDA-1088.

Healthcare providers should direct questions on VEKLURY packaging or use to Gilead Sciences at 1-866-633-4474 or www.askgileadmedical.com.

For additional information about VEKLURY, including the full Prescribing Information, please visit www.vekluryhcp.com. Please also see Important Safety Information at the end of this letter.

Information and reports of suspicious, counterfeit, or unregistered remdesivir can be submitted to Gilead anticounterfeiting@gilead.com and/or www.fraud.org/fakerx.

Fernando Bognar, MD
Vice President, Global Medical Affairs HIV and COVID-19
Gilead Sciences, Inc.

Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
phone 650 574 3000 *facsimile* 650 578 9264

www.gilead.com

U.S. Indication and Important Safety Information for VEKLURY® (remdesivir)

Indication

VEKLURY is indicated for the treatment of COVID-19 in adults and pediatric patients (≥28 days old and weighing ≥3 kg) with positive results of SARS-CoV-2 viral testing, who are:

- Hospitalized, or
- Not hospitalized, have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

Important Safety Information

Contraindication

- VEKLURY is contraindicated in patients with a history of clinically significant hypersensitivity reactions to VEKLURY or any of its components.

Warnings and precautions

- **Hypersensitivity, including infusion-related and anaphylactic reactions:** Hypersensitivity, including infusion-related and anaphylactic reactions, has been observed during and following administration of VEKLURY; most occurred within 1 hour. Monitor patients during infusion and observe for at least 1 hour after infusion is complete for signs and symptoms of hypersensitivity as clinically appropriate. Symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, and shivering. Slower infusion rates (maximum infusion time of up to 120 minutes) can potentially prevent these reactions. If a severe infusion-related hypersensitivity reaction occurs, immediately discontinue VEKLURY and initiate appropriate treatment (see Contraindications).
- **Increased risk of transaminase elevations:** Transaminase elevations have been observed in healthy volunteers and in patients with COVID-19 who received VEKLURY; these elevations have also been reported as a clinical feature of COVID-19. Perform hepatic laboratory testing in all patients (see Dosage and Administration). Consider discontinuing VEKLURY if ALT levels increase to >10x ULN. Discontinue VEKLURY if ALT elevation is accompanied by signs or symptoms of liver inflammation.
- **Risk of reduced antiviral activity when coadministered with chloroquine or hydroxychloroquine:** Coadministration of VEKLURY with chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on data from cell culture experiments, demonstrating potential antagonism, which may lead to a decrease in the antiviral activity of VEKLURY.

Adverse reactions

- The most common adverse reaction (≥5% all grades) was nausea.
- The most common lab abnormalities (≥5% all grades) were increases in ALT and AST.

Drug interactions

- Drug interaction trials of VEKLURY and other concomitant medications have not been conducted in humans.

Dosage and administration

- **Dosage:**
- For adults and pediatric patients weighing ≥40 kg: 200 mg on Day 1, followed by once-daily maintenance doses of 100 mg from Day 2, administered only via intravenous infusion.
- For pediatric patients ≥28 days old and weighing ≥3 kg to <40 kg: 5 mg/kg on Day 1, followed by once-daily maintenance doses of 2.5 mg/kg from Day 2, administered only via intravenous infusion.
- There are two different formulations of VEKLURY: VEKLURY for injection (supplied as 100 mg lyophilized powder in vial) and VEKLURY injection (supplied as 100 mg/20 mL [5 mg/mL] solution in vial). The only approved dosage form for pediatric patients weighing 3 kg to <40 kg is the lyophilized powder formulation; See full Prescribing Information.
- **Treatment duration:**
- For patients who are hospitalized and require invasive mechanical ventilation and/or ECMO, the recommended total treatment duration is 10 days. VEKLURY should be initiated as soon as possible after diagnosis of symptomatic COVID-19.
- For patients who are hospitalized and do not require invasive mechanical ventilation and/or ECMO, the recommended treatment duration is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days, for a total treatment duration of up to 10 days.
- For patients who are not hospitalized, diagnosed with mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death, the recommended total treatment duration is 3 days. VEKLURY should be initiated as soon as possible after diagnosis of symptomatic COVID-19 and within 7 days of symptom onset.
- **Testing prior to and during treatment:** Perform eGFR, hepatic laboratory, and prothrombin time testing prior to initiating VEKLURY and during use as clinically appropriate.
- **Renal impairment:** VEKLURY is not recommended in individuals with eGFR <30 mL/min.
- **Dose preparation and administration:**
- There are two different formulations of VEKLURY: VEKLURY for injection (supplied as 100 mg lyophilized powder in vial), the only approved dosage form of VEKLURY for pediatric patients weighing 3 kg to <40 kg; and VEKLURY injection (supplied as 100 mg/20 mL [5 mg/mL] solution in vial). See full Prescribing Information.
- Administration should be under conditions where management of severe hypersensitivity reactions, such as anaphylaxis, is possible.

Pregnancy and lactation

- **Pregnancy:** A pregnancy registry has been established. There are insufficient

human data on the use of VEKLURY during pregnancy. COVID-19 is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

- **Lactation:** It is not known whether VEKLURY can pass into breast milk. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

Please see full Prescribing Information for VEKLURY, available at www.gilead.com.

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Why You Should Not Use Ivermectin to Treat or Prevent COVID-19

Español (/consumers/articulos-en-espanol/por-que-no-debe-utilizar-ivermectina-para-tratar-o-prevenir-el-covid-19)

Português (/consumers/consumer-updates/por-que-voce-nao-deve-usar-ivermectina-para-tratar-ou-prevenir-covid-19)

中文 (/consumers/consumer-updates/weishenmebuyinggaishiyongyiweijunsuzhiliaohuoyufang2019xinguanfeiyan)

Tagalog (/consumers/consumer-updates/bakit-hindi-ka-dapat-gumamit-ng-ivermectin-upang-gamutin-o-maiwasan-ang-covid-19)

Tiếng Việt (/consumers/consumer-updates/tai-sao-ban-khong-nen-su-dung-ivermectin-de-dieu-tri-hoac-ngan-ngua-covid-19)

한국어 (/consumers/consumer-updates/kobideu-19-covid-19leul-chilyohago-yebanghagi-wihayeo-ibeomegtineul-sayonghaji-malaya-haneun-iyu)

COVID-19. We've been living with it for what sometimes seems like forever. Given the number of deaths that have occurred from the disease, it's perhaps not surprising that some consumers are turning to drugs not approved or authorized by the Food and Drug Administration (FDA).

One of the FDA's jobs is to carefully evaluate the scientific data on a drug to be sure that it is both safe and effective for a particular use. In some instances, it can be highly dangerous to use a medicine for the prevention or treatment of COVID-19 that has not been approved by or has not received emergency use authorization from the FDA.

There seems to be a growing interest in a drug called ivermectin for the prevention or treatment of COVID-19 in humans. Certain animal formulations of ivermectin such as pour-on, injectable, paste, and "drench," are approved in the U.S. to treat or prevent parasites in animals. For humans, ivermectin tablets are approved at very specific doses to treat some parasitic worms, and there are topical (on the skin) formulations for head lice and skin conditions like rosacea.

However, the FDA has received multiple reports of patients who have required medical attention, including hospitalization, after self-medicating with ivermectin intended for livestock.

Here's What You Need to Know about Ivermectin

- The FDA has not authorized or approved ivermectin for use in preventing or treating COVID-19 in humans or animals. Ivermectin is approved for human use to treat infections caused by some parasitic worms and head lice and skin conditions like rosacea.
- Currently available data do not show ivermectin is effective against COVID-19. Clinical trials (https://www.clinicaltrials.gov/ct2/results?cond=COVID-19&term=ivermectin&cntry=&state=&city=&dist=&Search=Search) assessing ivermectin tablets for the prevention or treatment of COVID-19 in people are ongoing.
- Taking large doses of ivermectin is dangerous.
- If your health care provider writes you an ivermectin prescription, fill it through a legitimate source such as a pharmacy, and take it *exactly* as prescribed.
- Never use medications intended for animals on yourself or other people. Animal ivermectin products are very different from those approved for humans. Use of animal ivermectin for the prevention or treatment of COVID-19 in humans is dangerous.

What is Ivermectin and How is it Used?

Ivermectin tablets are approved by the FDA to treat people with intestinal strongyloidiasis and onchocerciasis, two conditions caused by parasitic worms. In addition, some topical forms of ivermectin are approved to treat external parasites like head lice and for skin conditions such as rosacea.

Some forms of animal ivermectin are approved to prevent heartworm disease and treat certain internal and external parasites. It's important to note that these products are different from the ones for people, and safe only when used in animals as prescribed.

When Can Taking Ivermectin Be Unsafe?

The FDA has not authorized or approved ivermectin for the treatment or prevention of COVID-19 in people or animals. Ivermectin has not been shown to be safe or effective for these indications.

There's a lot of misinformation around, and you may have heard that it's okay to take large doses of ivermectin. It is not okay.

Even the levels of ivermectin for approved human uses can interact with other medications, like blood-thinners. You can also overdose on ivermectin, which can cause nausea, vomiting, diarrhea, hypotension (low blood pressure), allergic reactions (itching and hives), dizziness, ataxia (problems with balance), seizures, coma and even death.

Ivermectin Products for Animals Are Different from Ivermectin Products for People

For one thing, animal drugs are often highly concentrated because they are used for large animals like horses and cows, which weigh a lot more than we do— up to a ton or more. Such high doses can be highly toxic in humans. Moreover, the FDA reviews drugs not just for safety and effectiveness of the active ingredients, but also for the inactive ingredients. Many inactive ingredients found in products for animals aren't evaluated for use in people. Or they are included in much greater quantity than those used in people. In some cases, we don't know how those inactive ingredients will affect how ivermectin is absorbed in the human body.

Options for Preventing and Treating COVID-19

The most effective ways to limit the spread of COVID-19 (https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html) include getting a COVID-19 vaccine when it is available to you and following current CDC guidance.

Talk to your health care provider about available COVID-19 vaccines and treatment options. Your provider can help determine the best option for you, based on your health history.

ORIGINAL ARTICLE

Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19

The RECOVERY Collaborative Group*

ABSTRACT

BACKGROUND

Hydroxychloroquine and chloroquine have been proposed as treatments for coronavirus disease 2019 (Covid-19) on the basis of in vitro activity and data from uncontrolled studies and small, randomized trials.

METHODS

In this randomized, controlled, open-label platform trial comparing a range of possible treatments with usual care in patients hospitalized with Covid-19, we randomly assigned 1561 patients to receive hydroxychloroquine and 3155 to receive usual care. The primary outcome was 28-day mortality.

RESULTS

The enrollment of patients in the hydroxychloroquine group was closed on June 5, 2020, after an interim analysis determined that there was a lack of efficacy. Death within 28 days occurred in 421 patients (27.0%) in the hydroxychloroquine group and in 790 (25.0%) in the usual-care group (rate ratio, 1.09; 95% confidence interval [CI], 0.97 to 1.23; P=0.15). Consistent results were seen in all prespecified subgroups of patients. The results suggest that patients in the hydroxychloroquine group were less likely to be discharged from the hospital alive within 28 days than those in the usual-care group (59.6% vs. 62.9%; rate ratio, 0.90; 95% CI, 0.83 to 0.98). Among the patients who were not undergoing mechanical ventilation at baseline, those in the hydroxychloroquine group had a higher frequency of invasive mechanical ventilation or death (30.7% vs. 26.9%; risk ratio, 1.14; 95% CI, 1.03 to 1.27). There was a small numerical excess of cardiac deaths (0.4 percentage points) but no difference in the incidence of new major cardiac arrhythmia among the patients who received hydroxychloroquine.

CONCLUSIONS

Among patients hospitalized with Covid-19, those who received hydroxychloroquine did not have a lower incidence of death at 28 days than those who received usual care. (Funded by UK Research and Innovation and National Institute for Health Research and others; RECOVERY ISRCTN number, ISRCTN50189673; ClinicalTrials.gov number, NCT04381936.)

The members of the writing committee (Peter Horby, F.R.C.P., Marion Mafham, M.D., Louise Linsell, D.Phil., Jennifer L. Bell, M.Sc., Natalie Staplin, Ph.D., Jonathan R. Emberson, Ph.D., Martin Wiselka, Ph.D., Andrew Ustianowski, Ph.D., Einas Elmahi, M.Phil., Benjamin Prudon, F.R.C.P., Tony Whitehouse, F.R.C.A., Timothy Felton, Ph.D., John Williams, M.R.C.P., Jakki Faccenda, M.D., Jonathan Underwood, Ph.D., J. Kenneth Baillie, M.D., Ph.D., Lucy C. Chappell, Ph.D., Saul N. Faust, F.R.C.P.C.H., Thomas Jaki, Ph.D., Katie Jeffery, Ph.D., Wei Shen Lim, F.R.C.P., Alan Montgomery, Ph.D., Kathryn Rowan, Ph.D., Joel Tarning, Ph.D., James A. Watson, D.Phil., Nicholas J. White, F.R.S., Edmund Juszczak, M.Sc., Richard Haynes, D.M., and Martin J. Landray, Ph.D.) assume responsibility for the overall content and integrity of this article.

The affiliations of the members of the writing committee are listed in the Appendix. Address reprint requests to Dr. Horby or Dr. Landray at the RECOVERY Central Coordinating Office, Richard Doll Bldg., Old Road Campus, Roosevelt Dr., Oxford OX3 7LF, United Kingdom, or at recoverytrial@ndph.ox.ac.uk.

*A complete list of collaborators in the RECOVERY trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Horby, Mafham, and Linsell and Prof. Juszczak, Dr. Haynes, and Dr. Landray contributed equally to this article.

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (Covid-19), emerged in China in late 2019 from a zoonotic source.[1] The majority of Covid-19 infections are either asymptomatic or result in only mild disease. However, in a substantial proportion of infected persons, the infection leads to a respiratory illness requiring hospital care,[2] which can progress to critical illness with hypoxemic respiratory failure and lead to prolonged ventilatory support.[3-6] Among the patients with Covid-19 who have been admitted to hospitals in the United Kingdom, the case fatality rate is approximately 30%.[7]

Hydroxychloroquine and chloroquine, two 4-aminoquinoline drugs that were developed more than 70 years ago and have been used to treat malaria and rheumatologic conditions, have been proposed as treatments for Covid-19. Chloroquine has been shown to have in vitro activity against a variety of viruses, including SARS-CoV-2 and the related SARS-CoV-1.[8-13] The exact mechanism of antiviral action is uncertain, but these drugs increase the pH of endosomes that the virus uses for cell entry and also interfere with the glycosylation of angiotensin-converting–enzyme 2 (ACE2), which is the cellular receptor of SARS-CoV, and of associated gangliosides.[10,14] The 4-aminoquinoline levels that are required to inhibit SARS-CoV-2 replication in vitro are higher than the free plasma levels that have been observed in the prevention and treatment of malaria.[15] These drugs generally have an acceptable side-effect profile and are inexpensive and widely available. After oral administration, they are rapidly absorbed, even in severely ill patients. Therapeutic hydroxychloroquine levels could be expected to be reached in human lung tissue shortly after an initial loading dose.

In small preclinical studies of SARS-CoV-2 infection in animals, prophylaxis or treatment with hydroxychloroquine had no beneficial effect on clinical disease or viral replication.[16] A clinical benefit and an antiviral effect from the administration of these drugs alone or in combination with azithromycin in patients with Covid-19 have been reported in some observational studies[17-21] but not in others.[22-24] The results of a few small trials of hydroxychloroquine or chloroquine for the treatment of Covid-19 have been inconclusive, whereas one larger randomized, controlled trial involving patients who were hospitalized with mild-to-moderate Covid-19 showed that hydroxychloroquine (at a dose of 400 mg twice daily, with or without azithromycin) did not improve clinical status at day 15, as compared with usual care.[25-29] Here, as part of the controlled, open-label Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial, we report the results of a comparison between hydroxychloroquine and usual care involving patients hospitalized with Covid-19.

METHODS

TRIAL DESIGN AND OVERSIGHT

The RECOVERY trial is an investigator-initiated platform trial to evaluate the effects of potential treatments in patients hospitalized with Covid-19. The trial is being conducted at 176 hospitals in the United Kingdom. (Details are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.) The investigators were assisted by the National Institute for Health Research Clinical Research Network, and the trial is coordinated by the Nuffield Department of Population Health at the University of Oxford, the trial sponsor. Although patients are no longer being enrolled in the hydroxychloroquine, dexamethasone, and lopinavir–ritonavir groups, the trial continues to study the effects of azithromycin, tocilizumab, convalescent plasma, and REGN-COV2 (a combination of two monoclonal antibodies directed against the SARS-CoV-2 spike protein). Other treatments may be studied in the future. The hydroxychloroquine that was used in this phase of the trial was supplied by the U.K. National Health Service (NHS).

Hospitalized patients were eligible for the trial if they had clinically-suspected or laboratory-confirmed SARS-CoV-2 infection and no medical history that might, in the opinion of the attending clinician, put patients at substantial risk if they were to participate in the trial. Initially, recruitment was limited to patients who were at least 18 years of age, but the age limit was removed as of May 9, 2020.

Written informed consent was obtained from all the patients or from a legal representative if they were too unwell or unable to provide consent. The trial was conducted in accordance with Good Clinical Practice guidelines of the International Conference on Harmonisation and was approved by the U.K. Medicines and Healthcare

Products Regulatory Agency (MHRA) and the Cambridge East Research Ethics Committee. The protocol with its statistical analysis plan are available at NEJM.org, with additional information in the Supplementary Appendix and on the trial website at www.recoverytrial.net.

The initial version of the manuscript was drafted by the first and last authors, developed by the writing committee, and approved by all members of the trial steering committee. The funders had no role in the analysis of the data, in the preparation or approval of the manuscript, or in the decision to submit the manuscript for publication. The first and last members of the writing committee vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol and statistical analysis plan.

RANDOMIZATION AND TREATMENT

We collected baseline data using a Web-based case-report form that included demographic data, level of respiratory support, major coexisting illnesses, the suitability of the trial treatment for a particular patient, and treatment availability at the trial site. Using a Web-based unstratified randomization method with the concealment of trial group, we assigned patients to receive either the usual standard of care or the usual standard of care plus hydroxychloroquine or one of the other available treatments that were being evaluated. The number of patients who were assigned to receive usual care was twice the number who were assigned to any of the active treatments for which the patient was eligible (e.g., 2:1 ratio in favor of usual care if the patient was eligible for only one active treatment group, 2:1:1 if the patient was eligible for two active treatments, etc.).

For some patients, hydroxychloroquine was unavailable at the hospital at the time of enrollment or was considered by the managing physician to be either definitely indicated or definitely contraindicated. Patients with a known prolonged corrected QT interval on electrocardiography were ineligible to receive hydroxychloroquine. (Coadministration with medications that prolong the QT interval was not an absolute contraindication, but attending clinicians were advised to check the QT interval by performing electrocardiography.) These patients were excluded from entry in the randomized comparison between hydroxychloroquine and usual care.

In the hydroxychloroquine group, patients received hydroxychloroquine sulfate (in the form of a 200-mg tablet containing a 155-mg base equivalent) in a loading dose of four tablets (total dose, 800 mg) at baseline and at 6 hours, which was followed by two tablets (total dose, 400 mg) starting at 12 hours after the initial dose and then every 12 hours for the next 9 days or until discharge, whichever occurred earlier (see the Supplementary Appendix).[15] The assigned treatment was prescribed by the attending clinician. The patients and local trial staff members were aware of the assigned trial groups.

PROCEDURES

A single online follow-up form was to be completed by the local trial staff members when each trial patient was discharged, at 28 days after randomization, or at the time of death, whichever occurred first. Information was recorded regarding the adherence to the assigned treatment, receipt of other treatments for Covid-19, duration of admission, receipt of respiratory support (with duration and type), receipt of renal dialysis or hemofiltration, and vital status (including cause of death). Starting on May 12, 2020, extra information was recorded on the occurrence of new major cardiac arrhythmia. In addition, we obtained routine health care and registry data that included information on vital status (with date and cause of death) and discharge from the hospital.

OUTCOME MEASURES

The primary outcome was all-cause mortality within 28 days after randomization; further analyses were specified at 6 months. Secondary outcomes were the time until discharge from the hospital and a composite of the initiation of invasive mechanical ventilation including extracorporeal membrane oxygenation or death among patients who were not receiving invasive mechanical ventilation at the time of randomization. Decisions to initiate invasive mechanical ventilation were made by the attending clinicians, who were informed by guidance from NHS England and the National Institute for Health and Care Excellence. Subsidiary clinical outcomes included cause-specific mortality (which was recorded in all patients) and major cardiac arrhythmia (which was recorded in a subgroup of patients). All information presented in this report is based on a

data cutoff of September 21, 2020. Information regarding the primary outcome is complete for all the trial patients.

STATISTICAL ANALYSIS

For the primary outcome of 28-day mortality, we used the log-rank observed-minus-expected statistic and its variance both to test the null hypothesis of equal survival curves and to calculate the one-step estimate of the average mortality rate ratio in the comparison between the hydroxychloroquine group and the usual-care group. Kaplan–Meier survival curves were constructed to show cumulative mortality over the 28-day period. The same methods were used to analyze the time until hospital discharge, with censoring of data on day 29 for patients who had died in the hospital. We used the Kaplan–Meier estimates to calculate the median time until hospital discharge. For the prespecified composite secondary outcome of invasive mechanical ventilation or death within 28 days (among patients who had not been receiving invasive mechanical ventilation at randomization), the precise date of the initiation of invasive mechanical ventilation was not available, so the risk ratio was estimated instead. Estimates of the between-group difference in absolute risk were also calculated.

All the analyses were performed according to the intention-to-treat principle. Prespecified analyses of the primary outcome were performed in six subgroups, as defined by characteristics at randomization: age, sex, race, level of respiratory support, days since symptom onset, and predicted 28-day risk of death. (Details are provided in the Supplementary Appendix.)

Estimates of rate and risk ratios are shown with 95% confidence intervals without adjustment for multiple testing. The P value for the assessment of the primary outcome is two-sided. The full database is held by the trial team, which collected the data from the trial sites and performed the analyses, at the Nuffield Department of Population Health at the University of Oxford.

The independent data monitoring committee was asked to review unblinded analyses of the trial data and any other information that was considered to be relevant at intervals of approximately 2 weeks. The committee was then charged with determining whether the randomized comparisons in the trial provided evidence with respect to mortality that was strong enough (with a range of uncertainty around the results that was narrow enough) to affect national and global treatment strategies. In such a circumstance, the committee would inform the members of the trial steering committee, who would make the results available to the public and amend the trial accordingly. Unless that happened, the steering committee, investigators, and all others involved in the trial would remain unaware of the interim results until 28 days after the last patient had been randomly assigned to a particular treatment group.

On June 4, 2020, in response to a request from the MHRA, the independent data monitoring committee conducted a review of the data and recommended that the chief investigators review the unblinded data for the hydroxychloroquine group. The chief investigators and steering committee members concluded that the data showed no beneficial effect of hydroxychloroquine in patients hospitalized with Covid-19. Therefore, the enrollment of patients in the hydroxychloroquine group was closed on June 5, 2020, and the preliminary result for the primary outcome was made public. Investigators were advised that any patients who were receiving hydroxychloroquine as part of the trial should discontinue the treatment.

RESULTS

PATIENTS

From March 25 to June 5, 2020, a total of 11,197 patients underwent randomization; of these patients, 7513 (67%) were eligible to receive hydroxychloroquine (i.e., the patient had no known indication for or contraindication to hydroxychloroquine, and the drug was available in the hospital at the time) (Fig. 1). Of the eligible patients, 1561 were assigned to receive hydroxychloroquine and 3155 were assigned to receive usual care; the remainder of the patients were randomly assigned to one of the other treatment groups.

The mean (±SD) age of the patients in this trial was 65.4±15.3 years (Table 1 and Table S1 in the Supplementary Appendix). A total of 38% of the patients were female; 18% were Black or Asian or had a minority ethnic background. No children were enrolled. A history of diabetes was present in 27% of patients, heart disease in 26%, and chronic lung disease in 22%, with 57% hav-

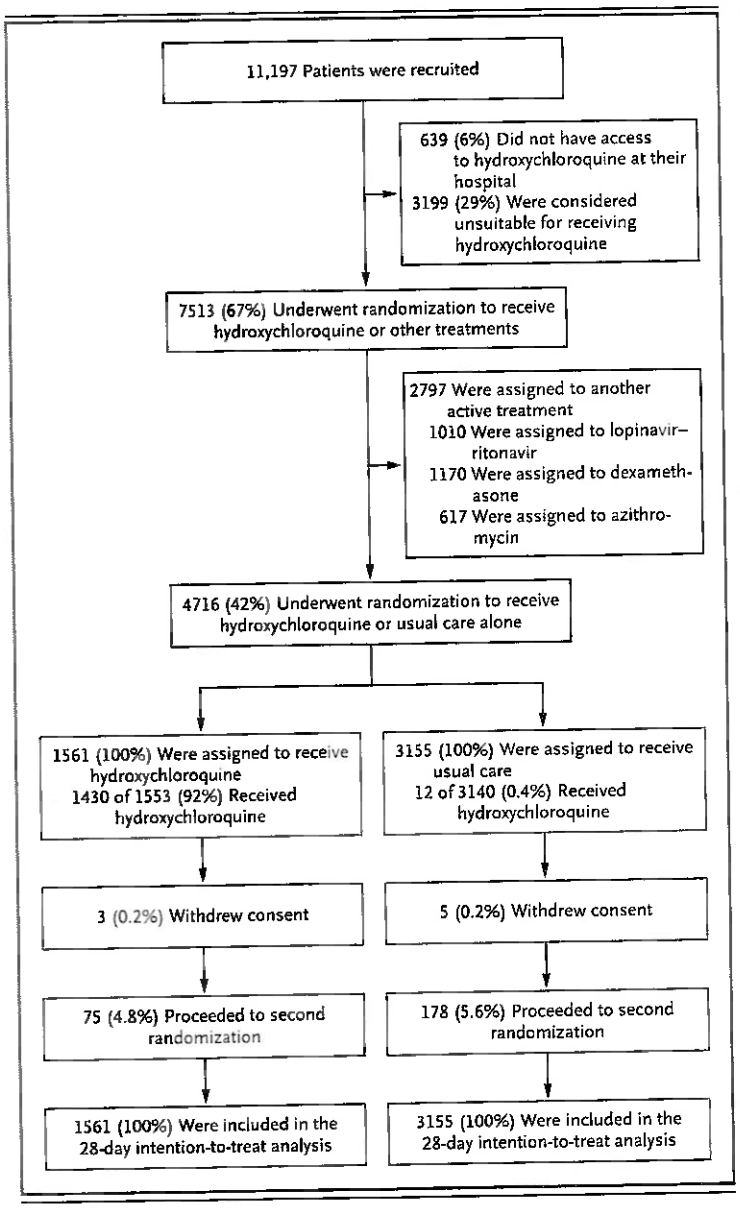

Figure 1. Enrollment and Outcomes in the RECOVERY Trial.

The enrollment number that is shown is the total number of patients in the RECOVERY platform trial during the period in which adult patients could be recruited for the comparison between hydroxychloroquine and usual care. Patients could have more than one reason for not participating in the hydroxychloroquine trial. At the time of this analysis, data from the trial follow-up form were available for 1553 of 1561 patients (99.5%) in the hydroxychloroquine group and for 3140 of 3155 patients (99.5%) in the usual-care group. The subgroup of patients who later underwent a second randomization to tocilizumab versus usual care in the RECOVERY trial included 37 of 1561 patients (2.4%) in the hydroxychloroquine group and 89 of 3155 patients (2.8%) in the usual care group. In addition, 6 patients were randomly assigned to receive either convalescent plasma or usual care alone (1 patient [0.1%] in the hydroxychloroquine group and 5 patients [0.2%] in the usual-care group) in accordance with protocol version 6.0. Among the 167 sites at which at least 1 patient was assigned to receive hydroxychloroquine, the median number of patients who underwent randomization was 20 (interquartile range, 11 to 41).

ing at least one major coexisting illness that was recorded. In this analysis, 90% of the patients had laboratory-confirmed SARS-CoV-2 infection, with the result not known for less than 1%. At randomization, 17% were receiving invasive mechanical ventilation including extracorporeal membrane oxygenation, 60% were receiving oxygen only (with or without noninvasive ventilation), and 24% were receiving neither.

A total of 1430 patients in the hydroxychloroquine group (92%) received at least one dose (Table S2). The median duration of treatment was 6 days (interquartile range, 3 to 10 days). In addition, 12 patients (0.4%) in the usual-care group received hydroxychloroquine. The frequency of use of azithromycin or other macrolide drug during the follow-up period was similar in the hydroxychloroquine group and the usual-care group (18.6% vs. 20.3%), as was the use of dexamethasone (9.1% vs. 9.2%). Remdesivir was administered to less than 0.1% of the patients in each group.

PRIMARY OUTCOME

Death at 28 days occurred in 421 of 1561 patients (27.0%) in the hydroxychloroquine group and in 790 of 3155 patients (25.0%) in the usual-care group (rate ratio, 1.09; 95% confidence interval [CI], 0.97 to 1.23; P=0.15) (Fig. 2). Similar results were seen across all six prespecified subgroups (Fig. 3). In a post hoc exploratory analysis that was restricted to the 4266 patients (90.5%) with a positive SARS-CoV-2 test result, the result was similar to the overall result (rate ratio, 1.09; 95% CI, 0.96 to 1.23).

SECONDARY OUTCOMES

Patients in the hydroxychloroquine group had a longer duration of hospitalization than those in the usual-care group (median, 16 days vs. 13 days) and a lower probability of discharge alive within 28 days (59.6% vs. 62.9%; rate ratio, 0.90; 95% CI, 0.83 to 0.98) (Table 2). Among the patients

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Hydroxychloroquine (N=1561)	Usual Care (N=3155)
Age		
Mean ±SD	65.2±15.2	65.4±15.4
Distribution — no. (%)		
<70 yr	925 (59.3)	1873 (59.4)
≥70 to <80 yr	342 (21.9)	630 (20.0)
≥80 yr	294 (18.8)	652 (20.7)
Sex — no. (%)		
Male	960 (61.5)	1974 (62.6)
Female†	601 (38.5)	1181 (37.4)
Race or ethnic group — no. (%)‡		
White	1181 (75.7)	2298 (72.8)
Black, Asian, or minority ethnic group	264 (16.9)	593 (18.8)
Unknown	116 (7.4)	264 (8.4)
Median no. of days since symptom onset (IQR)§	9 (5–14)	9 (5–13)
Median no. of days since hospitalization (IQR)	3 (1–6)	3 (1–5)
Respiratory support — no. (%)		
No oxygen received	362 (23.2)	750 (23.8)
Oxygen only	938 (60.1)	1873 (59.4)
Invasive mechanical ventilation	261 (16.7)	532 (16.9)
Previous disease — no. (%)		
Any of the listed conditions	882 (56.5)	1807 (57.3)
Diabetes	427 (27.4)	856 (27.1)
Heart disease	422 (27.0)	789 (25.0)
Chronic lung disease	334 (21.4)	712 (22.6)
Tuberculosis	4 (0.3)	9 (0.3)
HIV infection	8 (0.5)	13 (0.4)
Severe liver disease¶	18 (1.2)	46 (1.5)
Severe kidney impairment‖	111 (7.1)	261 (8.3)
SARS-CoV-2 test result — no. (%)		
Positive	1399 (89.6)	2867 (90.9)
Negative	156 (10.0)	275 (8.7)
Unknown	6 (0.4)	13 (0.4)

* Percentages may not total 100 because of rounding. HIV denotes human immunodeficiency virus, IQR interquartile range, and SD standard deviation.
† Among the women, 2 in the hydroxychloroquine group and 4 in the usual-care group were pregnant.
‡ Race or ethnic group is reported as it was recorded in the patient's electronic health record.
§ Data regarding the number of days since symptom onset were missing for 9 patients in the hydroxychloroquine group and 9 patients in the usual-care group.
¶ Severe liver disease was defined as a diagnosis that resulted in ongoing specialist care.
‖ Severe kidney impairment was defined as an estimated glomerular filtration rate of less than 30 ml per minute per 1.73 m^2 of body-surface area.

who were not undergoing invasive mechanical ventilation at baseline, the number of patients who had progression to the prespecified composite secondary outcome of invasive mechanical ventilation or death was higher among those in the hydroxychloroquine group than among

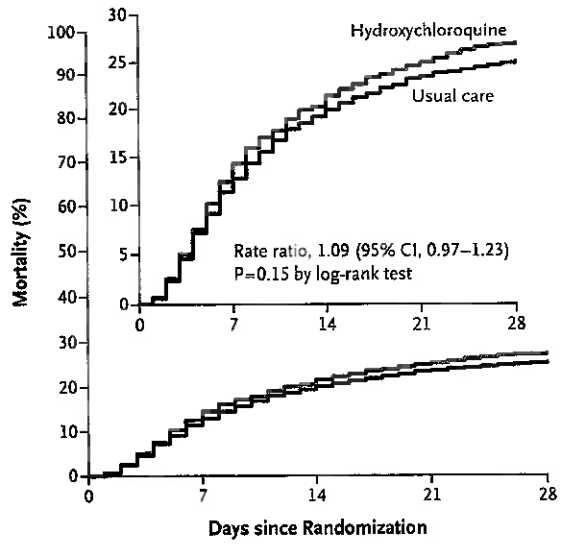

Figure 2. Mortality at 28 Days.

Death at 28 days (the primary outcome) occurred in 421 patients (27.0%) in the hydroxychloroquine group and in 790 (25.0%) in the usual-care group. The inset shows the same data on an expanded y axis.

those in the usual-care group (risk ratio, 1.14; 95% CI, 1.03 to 1.27).

OTHER PRESPECIFIED OUTCOMES

There was no difference between the hydroxychloroquine group and the usual-care group in 28-day mortality that was ascribed to Covid-19 (24.0% vs. 23.5%). However, patients in the hydroxychloroquine group had a greater risk of death from cardiac causes (mean [±SE] excess, 0.4±0.2 percentage points) and from non–SARS-CoV-2 infection (mean excess, 0.4±0.2 percentage points) (Table S3). Data regarding the occurrence of new major cardiac arrhythmia were collected for 735 of 1561 patients (47.1%) in the hydroxychloroquine group and 1421 of 3155 patients (45.0%) in the usual-care group, after collection of this information was added to the follow-up form on May 12, 2020. Among these patients, there were no significant differences between the hydroxychloroquine group and the usual-care group in the frequency of supraventricular tachycardia (7.6% vs. 6.0%), ventricular tachycardia or fibrillation (0.7% vs. 0.4%), or atrioventricular block requiring intervention (0.1% vs. 0.1%) (Table S4). There was one report of a serious adverse reaction that was deemed by investigators to be related to hydroxychloroquine: a case of torsades de pointes, from which the patient recovered without undergoing intervention. Among the patients who were not receiving renal dialysis or hemofiltration at randomization, the percentage who went on to receive such treatment during the follow-up period was the same in the hydroxychloroquine group and the usual-care group (7.9% vs. 7.9%) (Table S5).

DISCUSSION

In this analysis of the RECOVERY trial, we determined that hydroxychloroquine was not an effective treatment for patients hospitalized with Covid-19. The lower boundary of the confidence limit for the primary outcome ruled out any reasonable possibility of a meaningful mortality benefit. The results were consistent across subgroups according to age, sex, race, time since illness onset, level of respiratory support, and baseline-predicted risk. In addition, the results suggest that the patients who received hydroxychloroquine had a longer duration of hospitalization and, among those who were not undergoing mechanical ventilation at baseline, a higher risk of invasive mechanical ventilation or death than those who received usual care.

The RECOVERY trial is a large, pragmatic, randomized, controlled platform trial designed to assess the effect of potential treatments for Covid-19 on 28-day mortality. Approximately 15% of the patients who were hospitalized with Covid-19 in the United Kingdom during the trial period were enrolled, and the percentage of patients in the usual-care group who died was consistent with the hospitalized case fatality rate among hospitalized patients in the United Kingdom and elsewhere.[7,30,31] Only essential data were collected at hospital sites, with additional information (including long-term mortality) ascertained through linkage with routine data sources. We did not collect information on physiologic, electrocardiographic, laboratory, or virologic measurements.

Hydroxychloroquine has been proposed as a treatment for Covid-19 largely on the basis of its

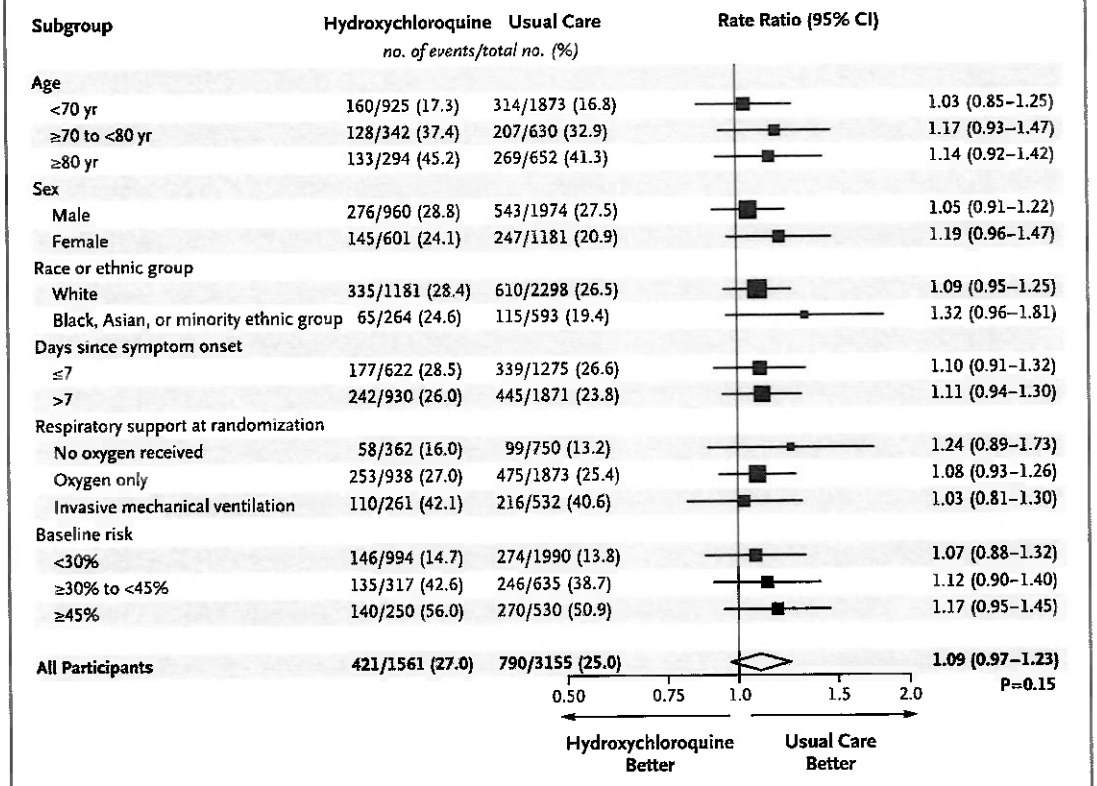

Figure 3. Mortality at 28 Days, According to Subgroup.

The size of the squares representing rate ratios is proportional to the amount of statistical information that was available for each comparison. The method that was used for calculating the baseline-predicted risk in each subgroup is described in the Supplementary Appendix. Race or ethnic group was recorded in the patient's electronic health record.

Table 2. Primary and Secondary Outcomes.

Outcome	Hydroxychloroquine (N=1561)	Usual Care (N=3155)	Rate or Risk Ratio (95% CI)
	no./total no. (%)		
Primary outcome: 28-day mortality	421/1561 (27.0)	790/3155 (25.0)	1.09 (0.97–1.23)*
Secondary outcomes			
Discharge from hospital in ≤28 days	931/1561 (59.6)	1983/3155 (62.9)	0.90 (0.83–0.98)*
Invasive mechanical ventilation or death†	399/1300 (30.7)	705/2623 (26.9)	1.14 (1.03–1.27)‡
Invasive mechanical ventilation	128/1300 (9.8)	225/2623 (8.6)	1.15 (0.93–1.41)
Death	311/1300 (23.9)	574/2623 (21.9)	1.09 (0.97–1.23)

* The between-group difference was calculated as a rate ratio.
† Patients who were receiving invasive mechanical ventilation at randomization were excluded from this analysis.
‡ The between-group difference was calculated as a risk ratio.

in vitro SARS-CoV-2 antiviral activity and on data from observational studies reporting effective reduction in viral loads. However, the 4-aminoquinoline drugs are relatively weak antiviral agents.[15] The demonstration of therapeutic efficacy of hydroxychloroquine in severe Covid-19 would require rapid attainment of efficacious levels of free drug in the blood and respiratory epithelium.[32] Thus, to provide the greatest chance of providing benefit in life-threatening Covid-19, the dose regimen in our trial was designed to result in rapid attainment and maintenance of plasma levels that were as high as safely possible.[15] These levels were predicted to be at the upper end of those observed during steady-state treatment of rheumatoid arthritis with hydroxychloroquine.[33] Our dosing schedule was based on pharmacokinetic modeling of hydroxychloroquine that referenced a SARS-CoV-2 50% effective concentration of 0.72 μM, as scaled to whole-blood levels and on the assumption that cytosolic levels in the respiratory epithelium are in dynamic equilibrium with blood levels.[8,15,34]

The primary concern with short-term, high-dose 4-aminoquinoline regimens is cardiovascular toxicity. Hydroxychloroquine causes predictable prolongation of the corrected QT interval on electrocardiography, which is exacerbated by coadministration with azithromycin, as widely prescribed in Covid-19 treatment.[16-18] Although torsades de pointes has been described, serious cardiovascular toxicity has been infrequently reported, despite the high prevalence of cardiovascular disease in hospitalized patients, the common occurrence of myocarditis in Covid-19, and the extensive use of hydroxychloroquine and azithromycin together. The exception is a Brazilian study that was stopped early because of cardiotoxicity. However, in that study, chloroquine was administered at a base dose of 600 mg twice daily for 10 days, a higher total dose than those that were used in other trials, including the RECOVERY trial.[35,36] Pharmacokinetic modeling in combination with information regarding blood levels and mortality from a case series involving 302 patients with chloroquine overdose predicts that a chloroquine regimen that was equivalent to the hydroxychloroquine regimen used in our trial should have an acceptable safety profile.[36] There was a small absolute excess of cardiac mortality of 0.4 percentage points in the hydroxychloroquine group on the basis of very few events, but we did not observe excess mortality in the first 2 days of treatment with hydroxychloroquine, the time when early effects of dose-dependent toxicity might be expected. Furthermore, the data presented here did not show any excess in ventricular tachycardia or ventricular fibrillation in the hydroxychloroquine group.

These findings indicate that hydroxychloroquine is not an effective treatment for hospitalized patients with Covid-19 but do not address its use as prophylaxis or in patients with less severe SARS-CoV-2 infection managed in the community. A review of Covid-19 treatment guidelines that was produced early in the pandemic showed that chloroquine or hydroxychloroquine was recommended in China, France, Italy, the Netherlands, and South Korea.[37] In the United States, the use of chloroquine and hydroxychloroquine was permitted in certain hospitalized patients under an Emergency Use Authorization (EUA) of the Food and Drug Administration (FDA). A retrospective cohort study involving 1376 patients with Covid-19 who were admitted to the hospital in New York City in March and April 2020 showed that 59% of the patients received hydroxychloroquine.[22,38] Since our preliminary results were made public on June 5, 2020, the FDA has revoked the EUA for chloroquine and hydroxychloroquine,[39] and the World Health Organization (WHO) and the National Institutes of Health have ceased trials of its use in hospitalized patients on the grounds of a lack of benefit. The WHO has released preliminary results from the SOLIDARITY trial on the effectiveness of hydroxychloroquine in hospitalized patients with Covid-19 that are consistent with the results from the RECOVERY trial.[40]

The views expressed in this article are those of the authors and not necessarily those of the National Health Service (NHS), the National Institute for Health Research (NIHR), or the Department of Health and Social Care.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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Court Orders Halt to Sale of Silver Product fraudulently Touted as COVID-19 Cure

Department of Justice

FOR IMMEDIATE RELEASE
Wednesday, April 29, 2020

A federal court in Utah has entered an injunction halting the sale of a fraudulent coronavirus (COVID-19) treatment, the Department of Justice announced today.

In response to a civil complaint and accompanying court papers filed on April 27, 2020, in Salt Lake City, the U.S. District Court for the District of Utah issued a temporary restraining order against defendants Gordon Pedersen of Cedar Hills, Utah, and his companies, My Doctor Suggests LLC and GP Silver LLC. The civil complaint alleges that the defendants are fraudulently promoting and selling various silver products for the treatment and prevention of COVID-19. The court's order temporarily enjoins the defendants from continuing to sell or distribute their silver products for the diagnosis, cure, mitigation, treatment, or prevention of any disease, including COVID-19. A separate court order temporarily freezes defendants' assets in order to preserve the court's ability to grant effective final relief and to maintain the status quo. A hearing on the government's request for a preliminary injunction is set for May 12, 2020.

"The Department of Justice will take swift action to protect consumers from those who would recklessly exploit this public health crisis by offering phony cure-alls for the treatment and prevention of COVID-19," said Assistant Attorney General Jody Hunt of the Department of Justice's Civil Division. "We work closely with our partners at the Food and Drug Administration and will move quickly to shut down schemes that promote and sell unlawful products during this pandemic."

"Even in a time of great uncertainty, there are at least two unchanging realities. There are those who would unlawfully exploit our vulnerabilities, and there are those who will hold such parties accountable," said U.S. Attorney John W. Huber for the District of Utah. "COVID-19 is a dangerous disease, and American consumers must have accurate and reliable information as they make important health decisions."

The complaint alleges that, beginning in early 2020, the defendants conducted a scheme to defraud consumers throughout the United States, promoting and selling silver products based on fraudulent claims of protection against, and treatment for, COVID-19. According to the

complaint, the defendants have made a wide variety of false and misleading claims touting silver products as a preventative for COVID-19, including that having silver in the bloodstream will "usher" any coronavirus out of the body and that "it has been proven that Alkaline Structured Silver will destroy all forms of viruses, it will protect people from the Coronavirus." Additionally, the defendants assert that once in the blood stream, silver nanoparticles can block the virus from attaching to their cells, and thus "prevent [] the disease totally and completely."

"The FDA will continue to help ensure those who place profits above the public health during the COVID-19 pandemic are stopped," said Judy McMeekin, Pharm.D., Associate Commissioner for Regulatory Affairs, U.S. Food and Drug Administration. "We are fully committed to working with the Department of Justice to take appropriate action against those jeopardizing the health of Americans by offering and distributing products with unproven claims to prevent or treat COVID-19."

The enforcement action filed today is being prosecuted by Trial Attorneys Speare I. Hodges and Sarah Williams of the Department of Justice, Civil Division's Consumer Protection Branch and Assistant U.S. Attorney Joel A. Ferre of the U.S. Attorney's Office for the District of Utah, with support from FDA's Office of Criminal Investigations and Office of the Chief Counsel.

The claims made in the complaint are allegations that, if the case were to proceed to trial, the government must prove to receive a permanent injunction against the defendants.

Additional information about the Consumer Protection Branch and its enforcement efforts may be found at www.justice.gov/civil/consumer-protection-branch (http://www.justice.gov/civil/consumer-protection-branch). For more information about the U.S. Attorney's Office for the District of Utah, visit its website at https://www.justice.gov/usao-ut (https://www.justice.gov/usao-ut). For information about the Department of Justice's efforts to stop illegal COVID-19-related activity, visit www.justice.gov/coronavirus (http://www.justice.gov/coronavirus). For the most up-to-date information on COVID-19, consumers may visit the Centers for Disease Control and Prevention (CDC) and WHO websites.

The public is urged to report suspected fraud schemes related to COVID-19 (the Coronavirus) by calling the National Center for Disaster Fraud (NCDF) hotline (1-866-720-5721) or by e-mailing the NCDF at disaster@leo.gov (mailto:disaster@leo.gov).

Topic(s):
Coronavirus
Component(s):
Civil Division
USAO - Utah
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October 27, 2022

Eli Lilly and Company
Attention: Jillian Venci Fuhs, JD, PharmD
Advisor, Global Regulatory Affairs – North America
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

RE: Emergency Use Authorization 092

Dear Dr. Fuhs:

This letter is in response to Eli Lilly and Company's ("Lilly") request that the Food and Drug Administration (FDA or Agency) issue an Emergency Use Authorization (EUA) for the emergency use of baricitinib for the treatment of COVID-19 in certain hospitalized patients, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §360bbb-3).

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19).[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[2]

On November 19, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of baricitinib (Olumiant), in combination with remdesivir (Veklury), for the treatment of suspected or laboratory confirmed COVID-19 in certain hospitalized patients requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). Baricitinib is a Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Baricitinib (Olumiant tablets 1 mg and 2 mg) is approved by FDA for

[1] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3.* February 4, 2020.
[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).

the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor antagonist therapies. At that time, baricitinib was not approved by FDA for the treatment of COVID-19.

FDA subsequently reissued the Letter of Authorization (LOA) on July 28, 2021[3], December 20, 2021[4], and May 10, 2022.[5]

On October 27, 2022, having concluded that revising this EUA is appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA is reissuing the May 10, 2022 letter in its entirety, to incorporate clarifying revisions to Condition S of this letter. Condition R was also revised to require that all printed matter, advertising and promotional materials relating to the use of baricitinib under this authorization be submitted to FDA for consideration at least 14 calendar days prior to initial dissemination or first use.

Based on the review of data from the clinical trial ACTT-2 (NCT04401579), a randomized, double-blind, placebo-controlled trial conducted by the National Institute of Allergy and Infectious Diseases (NIAID) comparing baricitinib in combination with remdesivir to remdesivir alone; data from COV-BARRIER (NCT04421027), a randomized, double-blind, placebo-controlled clinical trial conducted by the NIAID comparing treatment with baricitinib to placebo in hospitalized adults with confirmed SARS-CoV-2 infection; data for baricitinib that FDA has reviewed for the FDA-approved indication of rheumatoid arthritis (NDA 207924); and data from populations studied for other indications, including pediatric patients, it is reasonable to believe that baricitinib may be effective for treatment of COVID-19 in hospitalized pediatric patients 2 to less than 18 years of age requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO, and that, when used under the conditions described in this authorization, the known and potential benefits of baricitinib when used to treat COVID-19 in such patients, outweigh the known and potential risks of such product.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of baricitinib for treatment of COVID-19, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

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[3] In its July 28, 2021 revision, FDA revised the LOA to no longer require that baricitinib be used in combination with remdesivir. While the LOA authorized the use of baricitinib alone for the uses detailed in the Scope of Authorization (Section II), the Agency noted that the COV-BARRIER trial supporting this authorization did not raise questions about the safety or efficacy of baricitinib used in combination with remdesivir for the treatment of patients hospitalized due to COVID-19 requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO. As such, the use of baricitinib in combination with remdesivir was not contraindicated under the terms and conditions of this authorization.

[4] In its December 20, 2021 revision, FDA revised the LOA to include the authorized use of the baricitinib 4 mg tablets and to reference authorized storage and handling within the authorized Fact Sheet for Healthcare Providers.

[5] In its May 10, 2022 revision, FDA revised the scope of authorization in the LOA to continue authorizing baricitinib for the treatment of COVID-19 in hospitalized pediatric patients 2 to less than 18 years of age requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO and removing the adult population covered under the approved indication.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of baricitinib for the treatment of COVID-19 when administered as described in the Scope of Authorization (Section II) meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

1. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that baricitinib may be effective in treating COVID-19 in hospitalized pediatric patients 2 to less than 18 years of age requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO, and that, when used under the conditions described in this authorization, the known and potential benefits of baricitinib to treat COVID-19 in such patients outweigh the known and potential risks of such product; and

3. There is no adequate, approved, and available alternative to the emergency use of baricitinib for treatment of COVID-19 in hospitalized pediatric patients 2 to less than 18 years of age requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.[6, 7]

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- The baricitinib covered by this authorization will be used only by healthcare providers to treat COVID-19 in hospitalized[8] pediatric patients 2 to less than 18 years of age requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO; and

- The use of baricitinib covered by this authorization must be in accordance with the authorized Fact Sheets.

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[6] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

[7] Veklury (remdesivir) is approved for the treatment of COVID-19 in pediatric patients (28 days of age and older and weighing at least 3 kg) with positive results of direct SARS-CoV-2 viral testing, who are hospitalized, or not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death. Although Veklury is an approved alternative treatment of COVID-19 in pediatric patients (28 days of age and older and weighing at least 3 kg) with positive results of direct SARS-CoV-2 viral testing, who are hospitalized, FDA does not consider Veklury to be an adequate alternative to baricitinib for this authorized use. Veklury is a nucleoside ribonucleic acid polymerase inhibitor that has demonstrated antiviral activity against SARS-COV-2. Baricitinib is a Janus kinase (JAK) inhibitor, a class of drugs that block extracellular signals from multiple cytokines that are involved in inflammatory diseases and thought to contribute to inflammation and worsening of COVID-19. This is distinct from Veklury, which acts as an antiviral agent.

[8] Individuals determined as being appropriate for acute inpatient hospitalization and who are admitted or transferred to an alternate care site (ACS) that is capable of providing acute care that is comparable to general inpatient hospital care are within the terms and conditions of this Letter of Authorization. An ACS is intended to provide additional hospital surge capacity and capability for communities overwhelmed by patients with COVID-19.

Product Description

Baricitinib is a Janus kinase (JAK) inhibitor. Baricitinib is available as debossed, film-coated, immediate-release tablets. Each tablet contains a recessed area on each face of the tablet surface. Baricitinib tablets are to be taken orally or can be crushed, dispersed in water, and given via a gastrostomy tube. The authorized baricitinib is supplied in 30 count bottles as follows:

- commercially available[9] OLUMIANT (baricitinib) tablet 1 mg (NDC 0002-4732-30)
- commercially available OLUMIANT (baricitinib) tablet 2 mg (NDC 0002-4182-30)
- commercially available OLUMIANT (baricitinib) tablet 4 mg (NDC 0002-4479-30)

Baricitinib is authorized for emergency use with the FDA-approved package insert and the following product-specific information required to be made available to healthcare providers and patients/caregivers, respectively, through Lilly's website at *www.baricitinibemergencyuse.com* (referred to as the "authorized labeling"):

- Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of Baricitinib

- Fact Sheet for Patients, Parents and Caregivers: Emergency Use Authorization (EUA) of Baricitinib

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of baricitinib, when used for the treatment of COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh its known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that baricitinib may be effective for the treatment of COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that baricitinib (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of your product under an EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), baricitinib is authorized to treat COVID-19 in hospitalized pediatric patients 2 to less than 18 years of age requiring supplemental

[9] For the purposes of this Letter of Authorization, commercially available Olumiant (baricitinib) tablets refers to product in United States distribution under the approved New Drug Application 207924.

oxygen, non-invasive or invasive mechanical ventilation, or ECMO as described in the Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

Eli Lilly and Company (Lilly) and Authorized Distributors[10]

A. Lilly and authorized distributor(s) will ensure that the authorized baricitinib is distributed and the FDA-approved package insert and authorized labeling (i.e., Fact Sheets) as described in Section II of this Letter of Authorization will be made available to healthcare facilities and/or healthcare providers.

B. Lilly and authorized distributor(s) will ensure that appropriate storage is maintained until the authorized product is delivered to healthcare facilities and/or healthcare providers.

C. Lilly and authorized distributor(s) will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., U.S. government agencies, state and local government authorities, authorized distributors, healthcare facilities, healthcare providers) involved in distributing or receiving authorized baricitinib. Lilly will provide to all relevant stakeholders a copy of this letter of authorization and communicate any subsequent amendments that might be made to this letter of authorization and its authorized accompanying materials (i.e., Fact Sheets).

D. Lilly may request changes to this authorization, including to the authorized Fact Sheets for baricitinib. Any request for changes to this EUA must be submitted to the Division of Rheumatology and Transplant Medicine/Office of Immunology and Inflammation/Office of New Drugs/Center for Drug Evaluation and Research. Such changes require appropriate authorization prior to implementation.[11]

E. Lilly may develop and disseminate instructional and educational materials (e.g., materials providing information on product administration and/or patient monitoring) that are consistent with the authorized emergency use of baricitinib as described in this letter of authorization and authorized labeling, without FDA's review and concurrence, when

[10] "Authorized Distributor(s)" are identified by Lilly as an entity or entities allowed to distribute authorized baricitinib.

[11] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study; (8) new strengths of the authorized product, new product sources (e.g., of active pharmaceutical ingredient) or of product components. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), (7), or (8), review and concurrence is required from the Counter-Terrorism and Emergency Coordination Staff/Office of the Center Director/CDER and the Office of Counterterrorism and Emerging Threats/Office of the Chief Scientist.

necessary to meet public health needs. Any instructional and educational materials that are inconsistent with the authorized labeling for baricitinib are prohibited. Should the Agency become aware of any instructional or educational materials that are inconsistent with the authorized labeling for baricitinib, the Agency will require Lilly to cease distribution of such instructional and educational materials.

F. Lilly will report to FDA all serious adverse events and medication errors potentially related to baricitinib use under this EUA that are reported to Lilly using either of the following options.

Option 1: Submit reports through the Safety Reporting Portal (SRP) as described on the FDA SRP web page.

Option 2: Submit reports directly through the Electronic Submissions Gateway (ESG) as described on the FAERS electronic submissions web page.

Submitted reports under both options should state: "Baricitinib use for COVID-19 under Emergency Use Authorization (EUA)." For reports submitted under Option 1, include this language at the beginning of the question "Describe Event" for further analysis. For reports submitted under Option 2, include this language at the beginning of the "Case Narrative" field.

G. All manufacturing, packaging, and testing sites for both drug substance and drug product will comply with current good manufacturing practice requirements of Section 501(a)(2)(B) of the Act.

H. Lilly will submit information to the Agency within three working days of receipt of any information concerning significant quality problems with drug product distributed under this emergency use authorization for baricitinib that includes the following:

- Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or
- Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the product to meet the established specifications.

If a significant quality problem affects unreleased product and may also impact product(s) previously released and distributed, then information must be submitted for all potentially impacted lots.

Lilly will include in its notification to the Agency whether the batch, or batches, in question will be recalled.

If not included in its initial notification, Lilly must submit information confirming that Lilly has identified the root cause of the significant quality problems, taken corrective action, and

provide a justification confirming that the corrective action is appropriate and effective. Lilly must submit this information as soon as possible but no later than 45 calendar days from the initial notification.

I. Lilly will manufacture baricitinib to meet all quality standards and per the manufacturing process and control strategy as detailed in Lilly's EUA request. Lilly will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product, without notification to and concurrence by the Agency as described under condition D.

J. Through a process of inventory control, Lilly and authorized distributor(s) will maintain records regarding distribution of the authorized baricitinib (i.e., lot numbers, quantity, receiving site, receipt date).

K. Lilly and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

L. Lilly will list baricitinib 4 mg tablets with a unique product NDC under the marketing category of Emergency Use Authorization. Further, the listing will include each establishment where manufacturing is performed for the drug and the type of operation performed at each such establishment.

Healthcare Facilities to Whom the Authorized Baricitinib Is Distributed and Healthcare Providers Administering the Authorized Baricitinib

M. Healthcare facilities and healthcare providers will ensure that they are aware of the letter of authorization, and the terms herein, and that the authorized Fact Sheets are made available to healthcare providers and to patients and caregivers, respectively, through appropriate means, prior to administration of baricitinib for the authorized use.

N. Healthcare facilities and healthcare providers will track all serious adverse events and medication errors potentially related to baricitinib use under this EUA and must report these to FDA in accordance with the Fact Sheet for Healthcare Providers. Complete and submit a MedWatch form (www.fda.gov/medwatch/report.htm), or Complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178) (these forms can be found via link above). Call 1-800-FDA-1088 for questions. Submitted reports should state, "Baricitinib use for COVID-19 under Emergency Use Authorization (EUA)" at the beginning of the question "Describe Event" for further analysis. A copy of the completed FDA Form 3500 should also be provided to Lilly per the instructions in the authorized labeling.

O. Healthcare facilities and healthcare providers will ensure that appropriate storage is maintained until the authorized product is administered consistent with the terms of this letter and the authorized labeling.

P. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensed authorized baricitinib (i.e., lot numbers, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered).

Q. Healthcare facilities will ensure that any records associated with this EUA are maintained until notified by Lilly and/or FDA. Such records will be made available to Lilly, HHS, and FDA for inspection upon request.

Conditions Related to Printed Matter, Advertising and Promotion

R. All descriptive printed matter, advertising, and promotional material, relating to the use of the baricitinib under this authorization shall be consistent with the authorized labeling, as well as the terms set forth in this EUA and meet the requirements set forth in Section 502(a) and (n) of the Act, as applicable, and FDA implementing regulations. References to "approved labeling", "permitted labeling" or similar terms in these requirements shall be understood to refer to the authorized labeling for the use of baricitinib under this authorization. In addition, such materials shall:

- Be tailored to the intended audience.
- Not take the form of reminder advertisements, as that term is described in 21 CFR 202.1(e)(2)(i), 21 CFR 200.200 and 21 CFR 201.100(f).
- Present the same risk information relating to the major side effects and contraindications concurrently in the audio and visual parts of the presentation for advertising and promotional materials in audio-visual format.
- Be accompanied by the authorized labeling, if the promotional materials are not subject to Section 502(n) of the Act.
- Be submitted to FDA accompanied by Form FDA-2253 for consideration at least 14 calendar days prior to initial dissemination or first use.

S. Lilly may disseminate descriptive printed matter, advertising, and promotional materials relating to the emergency use of baricitinib that provide accurate descriptions of safety results and efficacy results on a clinical endpoint(s) from the clinical trial(s) summarized in the authorized labeling. Such materials must include any limitations of the clinical trial data as described in the authorized labeling. Lilly may not imply that baricitinib is FDA-approved for its authorized use by making statements such as "baricitinib is safe and effective for the treatment of COVID-19."

T. All descriptive printed matter, advertising, and promotional material, relating to the use of the baricitinib under this authorization clearly and conspicuously shall state that:

- baricitinib has not been approved, but has been authorized for emergency use by FDA for treatment of COVID-19 in hospitalized pediatric patients 2 to less than 18 years of age requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

- The emergency use of baricitinib is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

If the Agency notifies Lilly that any descriptive printed matter, advertising or promotional materials do not meet the terms set forth in conditions R through T of this EUA, Lilly must cease distribution of such descriptive printed matter, advertising, or promotional materials in accordance with the Agency's notification. Furthermore, as part of its notification, the Agency may also require Lilly to issue corrective communication(s).

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

Patrizia A. Cavazzoni -S

Digitally signed by Patrizia A. Cavazzoni -S
Date: 2022.10.27 14:14:30 -04'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

U.S. FOOD & DRUG ADMINISTRATION

Frequently Asked Questions on Olumiant (Baricitinib) for the Treatment of COVID-19

Q. Is Olumiant (baricitinib) approved by FDA to treat COVID-19?
A. On May 10, 2022, FDA approved Olumiant (baricitinib) for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

Q. Is Olumiant available for use under an emergency use authorization for pediatric patients?
A. Olumiant is authorized under an emergency use authorization (EUA) for the treatment of COVID-19 in hospitalized patients 2 to less than 18 years of age who require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). The EUA for hospitalized adults for the same indication was revoked following FDA approval for this population on May 10, 2022.

For additional information on the authorized use of Olumiant under the EUA, refer to the Fact Sheet for Healthcare Providers.

Clinical trials assessing the safe and effective use of Olumiant in pediatric populations remain ongoing.

Q. What is the difference between an Emergency Use Authorization (EUA) and an FDA approval?
A. Under section 564 of the Federal Food, Drug & Cosmetic Act (FD&C Act), after a declaration by the HHS Secretary based on one of four types of determinations, FDA may authorize an unapproved product or unapproved uses of an approved product for emergency use. In issuing an EUA, the FDA must determine, among other things, that based on the totality of scientific evidence available to the agency, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by a chemical, biological, radiological, or nuclear agent; that the known and potential benefits of the product, when used to diagnose, treat, or prevent such diseases or conditions, outweigh the known and potential risks for the product; and that there are no adequate, approved, and available alternatives. Emergency use authorization is NOT the same as FDA approval or licensure.

Q. Can Olumiant be used outside the hospital (i.e., for non-hospitalized patients with COVID-19)?
A. No, Olumiant is approved by FDA to treat certain hospitalized adults. Under the EUA, Olumiant is authorized for emergency use to treat certain hospitalized pediatric patients with COVID-19. The Letter of Authorization clarifies that individuals determined as being appropriate for acute inpatient hospitalization and who are admitted or transferred to an alternate care site (ACS) that can provide acute care that is comparable to general inpatient hospital care are within the terms and conditions of the EUA. An ACS is intended to provide additional hospital surge capacity and capability for communities overwhelmed by patients with COVID-19.

Q. What data support FDA's determination that Olumiant is safe and effective for use in hospitalized adults for the treatment of COVID-19?

A. The approval of Olumiant for adults on May 10, 2022, was supported by data from two phase 3, randomized, double-blind, placebo-controlled clinical trials (COVID I and COVID II). Approval was also supported by a substudy in mechanically ventilated patients and top-line results from an open-label pragmatic study, Randomised Evaluation of COVID-19 Therapy (RECOVERY).

In the COVID I trial, 1,033 hospitalized adults were randomized to receive Olumiant plus remdesivir (n=515) or placebo plus remdesivir (n=518). In this trial, the primary endpoint was time to recovery (defined as discharged from hospital or hospitalized but not requiring supplemental oxygen or ongoing medical care) within 29 days after randomization. Data from this study demonstrated an improvement in time to recovery, and the median time to recovery was 7 days for Olumiant and remdesivir compared to 8 days for placebo and remdesivir. The proportion of patients who died by Day 29 was 4.7% (24/515) for Olumiant and remdesivir compared to 7.1% (37/518) for placebo and remdesivir.

In the COVID II trial, 1,525 hospitalized adults were randomized to receive Olumiant (n=764) or placebo (n=761). In this trial, the primary endpoint was the proportion of patients who died or progressed to non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation within the first 28-days of the study. The estimated proportion of patients who died or progressed to non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation was lower in patients treated with Olumiant (27.8%) compared to placebo (30.5%), but this effect was not statistically significant. The proportion of patients who died by Day 28 was 8.1% (62/764) for Olumiant compared to 13.3% (101/761) for placebo.

In a separate group of patients requiring invasive mechanical ventilation or ECMO at baseline and enrolled in a substudy of COVID II, a total of 101 patients were randomized to Olumiant (n=51) or placebo (n=50). The proportion who died by Day 28 was 39.2% (20/51) for Olumiant compared to 58.0% (29/50) for placebo.

RECOVERY was a randomized, controlled, open-label, platform trial that evaluated the efficacy of Olumiant in patients with COVID-19 pneumonia. A total of 8,156 hospitalized patients were reported to be randomized, with 4,008 patients randomized to the usual care group and 4,148 patients randomly allocated to the Olumiant group. The primary endpoint evaluated death through 28 days of follow-up. Treatment with Olumiant was reported to reduce deaths, with 513 deaths (12%) reported in patients treated with Olumiant and 546 deaths (14%) in patients treated with usual care group at Day 28.

Q. Are side effects possible with Olumiant?

A. Yes. Possible side effects of Olumiant are:

- Serious venous thrombosis, including pulmonary embolism, and serious infections have been observed in COVID-19 patients treated with Olumiant and are known adverse drug reactions of Olumiant. Olumiant is not recommended for patients with known active tuberculosis infections, who are on dialysis, have end-stage renal disease, or have acute kidney injury.
- See Warnings and Precautions in the FDA-approved full prescribing information for additional information on risks associated with longer-term treatment with Olumiant.

Q: Is Olumiant approved to treat health conditions other than COVID-19?
A: In 2018, FDA approved Olumiant for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor blockers.

Q. How can Olumiant for use under the EUA be obtained?
A. Eli Lilly and Company and its authorized distributors distribute Olumiant to hospitals and health care facilities for its authorized use under the EUA. Licensed health care providers interested in administering Olumiant should contact Lilly.

Q. Is there a requirement for providers to report side effects as part of the EUA?
A. Yes. As part of the EUA for the pediatric population, FDA is requiring health care providers who prescribe Olumiant to treat COVID-19 to report all serious adverse events and medication errors that are considered to be potentially related to Olumiant through FDA's MedWatch Adverse Event Reporting program. Providers can complete and submit the report online; or download and complete the form, then submit it via fax at 1-800-FDA-0178. This requirement is outlined in the EUA's health care provider Fact Sheet. FDA MedWatch forms should also be provided to Lilly.

Q. Are there post-marketing safety reporting requirements for the approved Olumiant?
A. Applicants of NDAs and other responsible parties are subject to regulatory requirements regarding post-marketing safety reporting. For further information, see 21 CFR 314.80 (Postmarketing reporting of adverse drug experiences) or FDA's March 2001 guidance for industry, "Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines."

Q. Do patient outcomes need to be reported under the EUA?
A. No, reporting of patient outcomes is not required under the EUA. However, reporting of all medication errors and adverse events considered to be potentially related to the emergency use of Olumiant occurring during treatment is required under the authorization.

Q. Does the EUA authorize Olumiant to be used to prevent COVID-19?
A. No. The EUA for Olumiant does not authorize the emergency use of Olumiant for the prevention of COVID-19.

Q. Can health care providers share the patient/caregiver Fact Sheet electronically?
A. The letter of authorization for Olumiant requires that Fact Sheets be made available to healthcare providers and to patients/caregivers, "through appropriate means." Electronic delivery of the Fact Sheet is an appropriate means. For example, when the patient requests the Fact Sheet electronically, it can be delivered as a PDF prior to medication administration. Health care providers should confirm receipt of the Fact Sheet with the patient.

FDA NEWS RELEASE

Coronavirus (COVID-19) Update: FDA Authorizes Drug for Treatment of COVID-19

For Immediate Release:

June 24, 2021

Español (/news-events/press-announcements/actualizacion-sobre-el-coronavirus-covid-19-la-fda-autoriza-un-medicamento-para-el-tratamiento-del)

Today, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) (/media/150319/download?attachment) for the drug Actemra (tocilizumab) for the treatment of hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). Actemra is not authorized for use in outpatients with COVID-19.

In clinical trials of hospitalized patients with COVID-19, Actemra in addition to the routine care patients receive for treatment of COVID-19, which included corticosteroid therapy, was shown to reduce the risk of death through 28 days of follow-up and decrease the amount of time patients remained hospitalized. The risk of patients being placed on ventilators or death through 28 days of follow-up was also decreased.

"Today's action demonstrates the FDA's commitment to making new therapies available through every stage of the global COVID-19 pandemic," said Patrizia Cavazzoni, M.D., director of the FDA's Center for Drug Evaluation and Research. "Although vaccines have been successful in decreasing the number of patients with COVID-19 who require hospitalization, providing additional therapies for those who do become hospitalized is an important step in combating this pandemic."

Actemra is a monoclonal antibody that reduces inflammation by blocking the interleukin-6 receptor. In the case of COVID-19 infection, the immune system can become hyperactive, which may result in worsening of disease. Actemra does not directly target SARS-COV-2. Actemra is a prescription medication given by intravenous infusion that is FDA-approved for multiple inflammatory diseases, including rheumatoid arthritis. Under today's EUA, the FDA is authorizing the emergency use of Actemra for the treatment of certain hospitalized patients with COVID-19. Actemra is not approved as a treatment for COVID-19.

The issuance of an EUA is different than an FDA approval. In determining whether to issue an EUA, the FDA evaluates the totality of available scientific evidence and carefully balances any known or potential risks with any known or potential benefits of the product for use during an emergency. Based on the FDA's review of the totality of the scientific evidence available, the agency has determined that it is reasonable to believe that Actemra may be effective in treating COVID-19 for the authorized population. And, when used to treat COVID-19 for the authorized population, the known and potential benefits of Actemra outweigh the known and potential risks for the drug. There are no adequate, approved and available alternative treatments to Actemra for the treatment of COVID-19 in hospitalized adults and pediatric patients (2 years of age or older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

The data supporting this EUA for Actemra are based on four clinical trials. These included one randomized, controlled, open-label, platform trial [Randomised Evaluation of COVID-19 Therapy (RECOVERY)] and three randomized, double-blind, placebo-controlled trials (EMPACTA, COVACTA and REMDACTA). While all four clinical trials contribute to the FDA's understanding of Actemra for the treatment of COVID-19, the most important scientific evidence on the potential benefit of Actemra for its authorized use came from the RECOVERY and EMPACTA trials.

In the RECOVERY trial, 4,116 hospitalized patients with severe COVID-19 pneumonia were randomized to receive either Actemra in addition to usual care (2,022 patients) or usual care alone (2,094 patients). The primary endpoint evaluated death through 28 days of follow-up, and the results of the primary analysis were statistically significant. The probabilities of death by day 28 were estimated to be 30.7% for patients receiving Actemra and 34.9% for patients receiving usual care alone. The median time to hospital discharge was 19 days for patients receiving Actemra and more than 28 days for patients receiving usual care alone.

In the EMPACTA trial, 389 hospitalized patients with COVID-19 pneumonia were randomized to receive Actemra (249 patients) or placebo (128 patients). The primary endpoint evaluated the need for mechanical ventilation or death through 28 days of follow-up. For patients receiving Actemra, there was an observed reduction in progression to mechanical ventilation or death compared to patients who received placebo, with the primary analysis results being statistically significant. The proportion of patients who required mechanical ventilation or died by day 28 was estimated to be 12.0% for patients receiving Actemra and 19.3% for patients receiving placebo.

In the COVACTA trial, 452 hospitalized patients with severe COVID-19 pneumonia were randomized to receive Actemra (294 patients) or placebo (144 patients). The primary endpoint was clinical status through 28 days of follow-up assessed on a 7-category ordinal scale. While

there was no statistically significant difference observed in clinical status on the 7-category ordinal scale at day 28 between treatment groups, the COVACTA trial contributed to the assessment of the safety for Actemra when used for the treatment of COVID-19.

In the REMDACTA trial, 649 hospitalized patients with severe COVID-19 pneumonia were randomized to receive Actemra in combination with remdesivir (430 patients) or placebo in combination with remdesivir (210 patients). The primary endpoint was time to hospital discharge or "ready for discharge" through 28 days of follow-up. Additionally, while there were no statistically significant differences observed between treatment groups with respect to time to hospital discharge or "ready for discharge" through 28 days of follow-up, the REMDACTA trial contributed to the assessment of the safety for Actemra when used for the treatment of COVID-19.

Under the EUA, fact sheets that provide important information about using Actemra in treating COVID-19 as authorized must be made available to health care providers (/media/150321/download?attachment) and to patients, parents, and caregivers (/media/150320/download?attachment). These fact sheets include dosing instructions, potential side effects and drug interactions. Common side effects of Actemra observed in the COVID-19 trials include constipation, anxiety, diarrhea, insomnia, hypertension and nausea.

The EUA was issued to Genentech Inc.

Related Information

- Actemra EUA Letter of Authorization (/media/150319/download?attachment)
- Frequently Asked Questions on the Emergency Use Authorization for Actemra (/media/150345/download?attachment)
- Emergency Use Authorization: Therapeutics (/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization)
- Coronavirus Disease (COVID-19) (/emergency-preparedness-and-response/mcm-issues/coronavirus-disease-2019-covid-19)

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The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

U.S. FOOD & DRUG ADMINISTRATION

Frequently Asked Questions on the Emergency Use Authorization for Actemra (Tocilizumab) for Treatment of COVID-19

Q. What is the difference between an Emergency Use Authorization (EUA) and an FDA approval?

A. Under section 564 of the Federal Food, Drug & Cosmetic Act (FD&C Act), the FDA may, pursuant to a declaration by the HHS Secretary based on one of four types of determinations, authorize an unapproved product or unapproved uses of an approved product for emergency use. In issuing an EUA, the FDA must determine, among other things, that based on the totality of scientific evidence available, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by a chemical, biological, radiological, or nuclear agent; that the known and potential benefits of the product, when used to diagnose, treat, or prevent such diseases or conditions, outweigh the known and potential risks for the product; and that there are no adequate, approved, and available alternatives. Emergency use authorization is NOT the same as FDA approval or licensure.

Q. What does this EUA authorize?

A. Actemra (tocilizumab), manufactured by Genentech, is authorized for emergency use for the treatment of COVID-19 in hospitalized pediatric patients 2 to less than 18 years of age who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

Q. Is Actemra approved by FDA to treat COVID-19?

A. On December 21, 2022, FDA approved Actemra for the treatment of COVID-19 in hospitalized adult patients who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

Actemra is also FDA-approved to treat:

- Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs)
- Adult patients with giant cell arteritis
- Slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD)
- Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis (PJIA)
- Patients 2 years of age and older with active systemic juvenile idiopathic arthritis (SJIA)
- Adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS)

FDA has determined Actemra is safe and effective for these uses when used in accordance with the FDA-approved labeling.

Q. Can Actemra be used outside the hospital (i.e., for non-hospitalized patients)?

A. Actemra is not currently approved or authorized under its EUA for the treatment of non-hospitalized patients with COVID-19.

Q. Are there data showing Actemra might benefit patients with COVID-19?

A. The data supporting Actemra's approval in adults as indicated and the EUA in pediatric patients 2 to less than 18 years of age hospitalized with COVID-19 are from four clinical trials. These include one randomized, controlled, open-label, platform trial (Randomised Evaluation of COVID-19 Therapy [RECOVERY]) and three randomized, double-blind, placebo-controlled trials (EMPACTA, COVACTA, and REMDACTA). The largest trial, RECOVERY, showed a benefit in mortality, and EMPACTA also showed a benefit for treatment with Actemra. While COVACTA and REMDACTA did not show a benefit of treatment with Actemra, these trials contributed to the assessment of safety.

- In the RECOVERY trial, 4,116 hospitalized patients with severe COVID-19 pneumonia were randomized, 2,022 patients received Actemra in addition to standard of care and 2,094 patients received standard of care (the routine care patients receive for treatment of COVID-19) alone. The primary outcome evaluated death through 28 days of follow-up, and results of the primary analysis were statistically significant. The probability of death by day 28 was estimated to be 30.7% for patients receiving Actemra and 34.9% for patients receiving standard of care alone.
- In the EMPACTA trial, 389 hospitalized patients with COVID-19 pneumonia were randomized, 249 patients received Actemra and 128 patients received a placebo. The primary endpoint was the cumulative proportion of patients who required mechanical ventilation or died through 28 days of follow-up. For patients receiving Actemra, there was an observed reduction in progression to mechanical ventilation or death compared to patients who received placebo, with the primary analysis results being statistically significant. The proportion of patients who required mechanical ventilation or died by day 28 was estimated to be 12.0% for Actemra and 19.3% for placebo.
- In the COVACTA trial, 452 hospitalized patients with severe COVID-19 pneumonia were randomized, 294 patients received Actemra and 144 patients received a placebo. The primary efficacy endpoint was clinical status through 28 days of follow-up assessed on a 7-category ordinal scale. While there was no statistically significant difference observed in clinical status on the 7-category ordinal scale between treatment groups, the COVACTA trial contributed to the assessment of the safety for Actemra when used for the treatment of COVID-19.
- In the REMDACTA trial, 649 hospitalized patients with severe COVID-19 pneumonia were randomized, 430 received Actemra in combination with remdesivir and 210 received a placebo in combination with remdesivir. The primary efficacy endpoint was time to hospital discharge or "ready for discharge" through 28 days of follow-up. While there were no statistically significant differences observed between treatment groups with respect to time to hospital discharge or

"ready for discharge" through 28 days of follow-up, the REMDACTA trial contributed to the assessment of the safety for Actemra when used for the treatment of COVID-19.

FDA has authorized the emergency use of Actemra in certain children (2 years and less than 18 years of age) hospitalized with COVID-19 based upon the data in adults from RECOVERY, EMPACTA, COVACTA, and REMDACTA clinical trials that supported Actemra's approval in adults; the similarity of COVID-19 in children to COVID-19 in adults; and extensive safety and dosing information with use of Actemra in pediatric patients for approved indications (i.e., SJIA, PJIA, and CRS).

For additional information, please refer to the Fact Sheet for Health Care Providers and section 14 of the prescribing information.

Q. Are clinical trials underway evaluating Actemra for COVID-19?

A. Yes. Clinical trials remain ongoing to study Actemra for the treatment of COVID-19.

Q. Are side effects possible with Actemra?

A. Yes. Possible side effects of Actemra are:

- Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections have occurred in patients receiving Actemra. In COVID-19 patients, Actemra should not be administered if patients have any other concurrent active infection, including localized infection.
- Increases in levels of liver enzymes. Actemra is not recommended in COVID-19 patients with elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) above 10 times the upper limit of the reference range. When Actemra is used for treatment of COVID-19, ALT and AST should be monitored according to current standard clinical practice.
- Hypersensitivity reactions, including anaphylaxis. Actemra should only be infused by a healthcare professional with appropriate medical support to manage anaphylaxis.
- Common adverse reactions in COVID-19 patients include constipation, anxiety, diarrhea, insomnia, hypertension, and nausea.

See Warnings and Precautions in the FDA-approved full prescribing information for additional information on risks associated with longer-term treatment with Actemra.

Q. How can Actemra for use under the EUA be obtained?

A. Genentech and its authorized distributors distribute Actemra to hospitals for its authorized use under the EUA. Licensed healthcare providers interested in administering Actemra should contact Genentech or visit Genentech's website.

Q. Is there a requirement for providers to report side effects as part of the EUA?

A. Yes. As part of the EUA, FDA is requiring health care providers who prescribe Actemra to treat COVID-19 to report all medication errors and serious adverse events considered to be potentially related to Actemra through FDA's MedWatch Adverse Event Reporting program. Providers can complete and submit the report online; or download and complete the form, then submit it via fax at 1-800-FDA-0178. This requirement is outlined in the EUA's health care provider Fact Sheet. FDA MedWatch forms should also be provided to Genentech.

Q. Do patient outcomes need to be reported under the EUA?

A. No, reporting of patient outcomes is not required under the EUA. However, reporting of all medication errors and serious adverse events considered to be potentially related to the emergency use of Actemra occurring during treatment is required.

Q. Can health care providers share the patient/caregiver fact sheet electronically?

A. The letter of authorization for Actemra requires that fact sheets be made available to health care providers and to patients, parents, and caregivers, "through appropriate means." Electronic delivery of the Fact Sheet is an appropriate means. For example, when the patient requests the Fact Sheet electronically, it can be delivered as a PDF prior to medication administration. Health care providers should confirm receipt of the Fact Sheet with the patient.

Q: Are there clinical data about the use of Actemra in people who are pregnant or breastfeeding?

A. The limited data available with Actemra in people who are pregnant is not sufficient to determine whether there is a drug-associated risk for major birth defects and miscarriage. No information is available on the presence of Actemra in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. The lack of clinical data during lactation prevents a clear determination of the risk of Actemra to an infant during lactation. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Actemra and the potential adverse effects on the breastfed child from Actemra or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

Open Forum Infectious Diseases

MAJOR ARTICLE

Evaluation of Bebtelovimab for Treatment of Covid-19 During the SARS-CoV-2 Omicron Variant Era

Erin K. McCreary,[1] Kevin E. Kip,[2] Kevin Collins,[2] Tami E. Minnier,[3] Graham M. Snyder,[1] Ashley Steiner,[4] Russell Meyers,[4] Tina Borneman,[5] Michelle Adam,[4] Lauren Thurau,[4] Donald M. Yealy,[4] David T. Huang,[4,6] J. Ryan Bariola,[1] Mark Schmidhofer,[7] Richard J. Wadas,[4] Derek C. Angus,[6] Paula L. Kip,[3] and Oscar C. Marroquin[2]

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Background. Monoclonal antibody (mAb) treatment is associated with decreased risk of hospitalization and death in high-risk outpatients with mild to moderate coronavirus disease 2019 (COVID-19) caused by early severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants. Bebtelovimab exhibits in vitro activity against the Omicron variant and its sublineages; however, clinical data are lacking.

Methods. A retrospective cohort study was conducted comparing bebtelovimab-treated patients with propensity score–adjusted and matched nontreated control groups. Participants included high-risk outpatients eligible for bebtelovimab treatment under Emergency Use Authorization with a positive SARS-CoV-2 test from March 30 to May 28, 2022. Treated patients received single-dose intravenous treatment with bebtelovimab. The primary outcome was hospitalization or death over 28 days.

Results. Before matching/statistical adjustment, mAb-treated patients were, on average, 10 years older than nontreated patients (61.6 vs 51.3 years) and had higher prevalence of obstructive sleep apnea, hypertension, chronic kidney disease, cancer, organ or cell transplant, and immunocompromised status (standardized mean differences ≥0.20). The adjusted odds ratio (OR) of hospitalization or death comparing 1006 treated with 2023 nontreated patients was 0.50 (95% CI, 0.31–0.80). Among 930 treated and 930 propensity score–matched nontreated patients, the incidence of hospitalization or death was 3.1% vs 5.5%, respectively (conditional OR, 0.53; 95% CI, 0.32–0.86). The lower odds ratio of hospitalization or death associated with bebtelovimab treatment was most evident in older patients, those with immunocompromised status, and fully vaccinated patients.

Conclusions. Monoclonal antibody treatment with bebtelovimab among COVID-19 outpatients is associated with lower odds of hospitalization or death, particularly among immunocompromised and older patients.

Keywords. bebtelovimab; death; hospitalization; immunosuppression; Omicron SARS-CoV-2 variant; propensity score matching.

Monoclonal antibody (mAb) treatment has demonstrated decreased risk of hospitalization and death in at-risk outpatients with mild to moderate coronavirus disease 2019 (COVID-19) caused by early severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants, as compared with patients who did not receive treatment [1–4]. As SARS-CoV-2 variants evolve and emerge, the US Food and Drug Administration (FDA) Emergency Use Authorizations (EUAs) for mAb products change. Decisions for EUA modifications are often based on in vitro potency of mAbs alone, as randomized controlled trials and real-world clinical data are not available in real time. At the time of this report, bebtelovimab is the only mAb authorized for treatment of COVID-19 and is expected to maintain neutralizing activity against Omicron and its sublineages [5].

There is an absence of clinical data for use of bebtelovimab and for any mAb product for use in patients infected with the Omicron variant and its sublineages. Due to this lack of clinical data, the National Institutes of Health (NIH) positions bebtelovimab as an alternative therapy for nonhospitalized adults with COVID-19 [6]. However, first-line therapies are plagued by drug–drug interactions (nirmaltrevir/ritonavir) and logistical challenges thwarting accessibility (3-day course of intravenous remdesivir); therefore, determining the clinical effectiveness of bebtelovimab is important for public health. Additionally, there is a critical need for ongoing evaluation of individual mAb products as new variants emerge to test clinical effectiveness and determine patient populations who optimally benefit from treatment. Therefore, we assessed the real-world effectiveness of bebtelovimab treatment for outpatients with

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mild to moderate COVID-19 during the Omicron variant era within a large US health care system. We examined the association of bebtelovimab treatment overall with 28-day incidence of hospitalization or death and stratified results by age, body mass index, immunocompromised status, and COVID-19 vaccination status.

METHODS

This was a retrospective cohort study of outpatients with COVID-19 who had at least 1 risk factor for progression to severe disease and were eligible for mAb treatment with bebtelovimab per the EUA. Patients treated with bebtelovimab were compared with nontreated control patients. All treated patients verbally consented to treatment with bebtelovimab and reviewed the FDA EUA Fact Sheet before treatment. Bebtelovimab treatment assignment occurred via a central management system overseen by a multidisciplinary COVID-19 Therapeutics Committee [7].

Patient Consent

The Quality Improvement Review Committee and Institutional Review Board at the University of Pittsburgh provided ethical review and approval of the study as an exempt protocol that did not require patient written consent, and all data remained deidentified for this analysis.

Data Sources

Health-related data captured in the electronic health record (EHR) and ancillary clinical systems were aggregated and harmonized in a Clinical Data Warehouse (CDW) [1, 8]. For treated patients and nontreated control patients, sociodemographic data, medical history, and billing charges were accessed for all outpatient and in-hospital encounters with diagnoses and procedures coded based on the International Classification of Diseases, Ninth and Tenth revisions (ICD-9 and ICD-10, respectively) [9, 10]. Race was self-declared and classified as Black vs all others based on overall low minority prevalence. Death identification at 28-day used hospital discharge disposition of "Ceased to Breathe" sourced from the inpatient Medical Record System along with deaths after discharge identified with the Death Master File from the Social Security Administration 2022 National Technical Information Service [11, 12]. A description of definitions for variables used in the analysis, as captured in the EHR, is provided below and in Supplement Appendix A.

Selection of Patient Cohorts

Treated patients were those 12 years of age or older who received intravenous bebtelovimab (175 mg) during the period from March 30 to May 28, 2022, in an outpatient infusion clinic for treatment of COVID-19. Patients were excluded if they were pregnant, had received mAb treatment in an emergency department or hospital setting, or had received mAb treatment for postexposure prophylaxis (Figure 1). Nontreated patients were identified as any nonpregnant patient 12 years of age or older with a positive SARS-CoV-2 polymerase chain reaction or antigen test within our health system and not treated with any mAb during the same time period. Patients had at least 1 EUA-eligible risk factor for progression to severe disease identified in the EHR on the day of the positive SARS-CoV-2 test

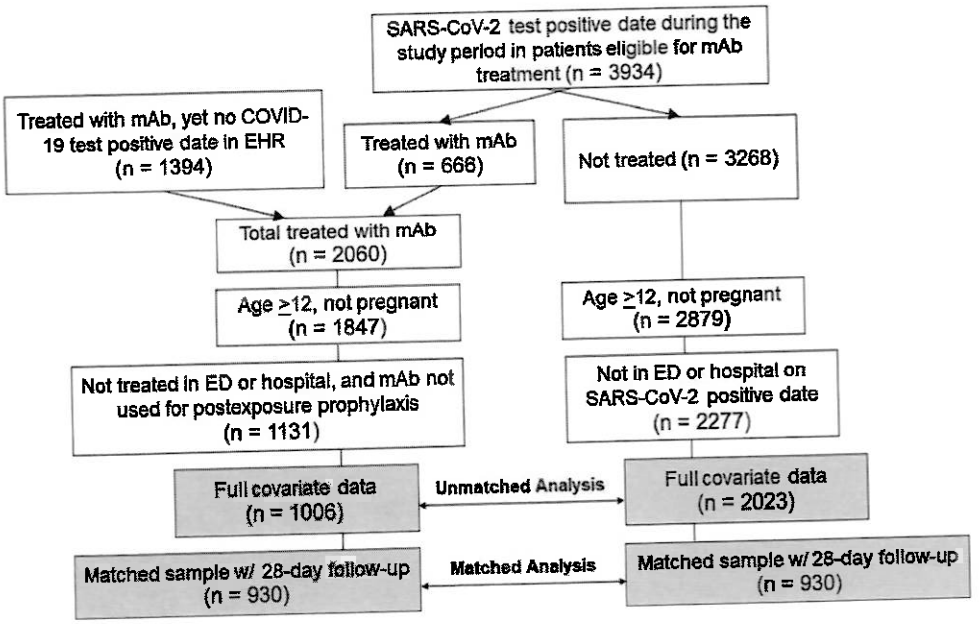

Figure 1. CONSORT diagram of selection of treated and nontreated control patients for analysis. Abbreviations: COVID-19, coronavirus disease 2019; ED, emergency department; EHR, electronic health record; mAb, monoclonal antibody; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

result. Patients were excluded if they were hospitalized or in the emergency department on the day of their positive SARS-CoV-2 test result (Figure 1). After identifying patients with at least 1 health record in the EHR in the past year, both groups had complete covariate data other than for body mass index (509 missing cases, 16.7%).

Outcomes

The primary outcome was the incidence of hospitalization or death at 28 days, with secondary outcomes of 28-day hospitalization, death, emergency department (ED) visit without hospitalization, and the composite outcome ED visit/hospitalization. For treated patients, the 28-day follow-up period started on the day of mAb treatment. For nontreated controls, the 28-day follow-up period started the day after the SARS-CoV-2 test positive date, as the median time from test positive result to mAb treatment (interquartile range) was 1 (1–3) day.

Covariates

In addition to specific variables used in propensity score adjustment/matching (Table 1), key covariates in prespecified subgroup analyses included (i) age (years), classified as <65 vs

Table 1. Comparison of Characteristics in Treated and Nontreated Groups

	Unmatched			Matched		
Characteristic	Treated (n = 1006)	Nontreated (n = 2023)	SMD	Treated (n = 930)	Nontreated (n = 930)	SMD
Age, mean (SD), y	61.6 (17.3)	51.3 (20.6)	0.53	61.2 (17.5)	62.2 (18.3)	0.05
Female sex, No. (%)	620 (61.6)	1298 (64.2)	0.05	575 (61.8)	571 (61.4)	0.01
Black race, No. (%)	46 (4.6)	161 (8.0)	0.13	42 (4.5)	30 (3.2)	0.07
Area deprivation index ≥85, No. (%)	51 (5.1)	156 (7.7)	0.10	47 (5.1)	42 (4.5)	0.03
Body mass index, mean (SD), kg/m^2	31.0 (6.0)	31.3 (7.2)	0.12	31.0 (5.9)	31.6 (6.9)	0.02
History of diabetes, No. (%)	222 (22.1)	304 (15.0)	0.18	198 (21.3)	200 (21.5)	0.01
History of obstructive sleep apnea, No. (%)	232 (23.1)	291 (14.4)	0.22	199 (21.4)	198 (21.3)	0.00
History of hypertension, No. (%)	572 (56.9)	804 (39.7)	0.35	515 (55.4)	499 (53.7)	0.03
History of stroke, No. (%)	88 (8.7)	130 (6.4)	0.09	82 (8.8)	78 (8.4)	0.02
History of valvular heart disease, No. (%)	93 (9.2)	120 (5.9)	0.12	83 (8.9)	86 (9.2)	0.01
History of atrial fibrillation, No. (%)	118 (11.7)	138 (6.8)	0.17	110 (11.8)	104 (11.2)	0.02
History of congestive heart failure, No. (%)	107 (10.6)	121 (6.0)	0.17	90 (9.7)	86 (9.2)	0.01
History of chronic kidney disease, No. (%)	134 (13.3)	146 (7.2)	0.20	108 (11.6)	116 (12.5)	0.03
History of dyspnea, No. (%)	77 (7.7)	129 (6.4)	0.05	71 (7.6)	73 (7.8)	0.01
History of COPD, No. (%)	224 (23.3)	313 (15.5)	0.17	199 (21.4)	187 (20.1)	0.03
History of bronchiectasis, No. (%)	7 (0.7)	5 (0.2)	0.07	6 (0.6)	4 (0.4)	0.03
History of pulmonary hypertension, No. (%)	24 (2.4)	29 (1.4)	0.07	19 (2.0)	15 (1.6)	0.03
History of pulmonary fibrosis, No. (%)	1 (0.1)	6 (0.3)	0.04	1 (0.1)	0 (0.0)	0.05
History of fatty liver disease, No. (%)	46 (4.6)	55 (2.7)	0.10	41 (4.4)	35 (3.8)	0.03
History of cirrhosis, No. (%)	17 (1.7)	14 (0.7)	0.09	13 (1.4)	12 (1.3)	0.01
History of gastrostomy, No. (%)	1 (0.1)	2 (0.1)	0.00	1 (0.1)	1 (0.1)	0.00
History of cancer, No. (%)	207 (20.6)	205 (10.1)	0.29	171 (18.4)	153 (16.5)	0.05
History of chemotherapy, No. (%)	99 (9.8)	47 (2.3)	0.32	76 (8.2)	44 (4.7)	0.14
History of lung cancer, No. (%)	7 (0.7)	11 (0.5)	0.02	6 (0.6)	3 (0.3)	0.05
History of allergic rhinitis, No. (%)	162 (16.1)	301 (14.9)	0.03	151 (16.2)	137 (14.7)	0.04
History of rheumatoid arthritis, No. (%)	62 (6.2)	52 (2.6)	0.18	56 (6.0)	46 (4.9)	0.05
History of sarcoidosis, No. (%)	9 (0.9)	4 (0.2)	0.09	6 (0.6)	4 (0.4)	0.03
History of lupus, No. (%)	24 (2.4)	11 (0.5)	0.15	17 (1.8)	11 (1.2)	0.05
History of viral hepatitis, No. (%)	20 (2.0)	25 (1.2)	0.06	18 (1.9)	18 (1.9)	0.00
History of organ or cell transplant, No. (%)	31 (3.1)	3 (0.1)	0.23	5 (0.5)	3 (0.3)	0.03
History of bone marrow transplant, No. (%)	3 (0.3)	3 (0.1)	0.03	2 (0.2)	1 (0.1)	0.03
History of immunocompromised, No. (%)	301 (29.9)	227 (11.2)	0.48	233 (25.1)	194 (20.9)	0.10
Alpha blocker, No. (%)	21 (2.1)	22 (1.1)	0.08	18 (1.9)	17 (1.8)	0.01
ACE inhibitors, No. (%)	170 (16.9)	279 (13.8)	0.08	158 (17.0)	165 (17.7)	0.02
Angiotensin II receptor blocker, No. (%)	166 (16.5)	191 (9.4)	0.21	151 (16.2)	151 (16.2)	0.00
Beta blockers, No. (%)	320 (31.8)	446 (22.0)	0.22	285 (30.6)	277 (29.8)	0.02
Corticosteroids as a home medication, No. (%)	427 (42.4)	677 (33.5)	0.18	385 (41.4)	378 (40.6)	0.02
Statins, No. (%)	481 (47.8)	631 (31.2)	0.34	435 (46.8)	448 (48.2)	0.03
Antidepressants, No. (%)	346 (34.4)	628 (31.0)	0.07	318 (34.2)	313 (33.7)	0.01

SMD values are presented as absolute values. All variables were used in the propensity score model.

Abbreviations: ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease; SMD, standardized mean difference.

Table 2. Twenty-Eight-Day Outcome Risks and Odds Ratios by Treatment vs Nontreatment With Bebtelovimab (Unmatched Cohort)

	Not Treated		Treated			Adjusted Analyses					
Outcome	N	n (%)	N	n (%)	Unadj. OR	PS Adj. OR	95% CI	*P* Value	IPW OR	95% CI	*P* Value
Hospitalization/death	2023	70 (3.5)	1006	33 (3.3)	0.95	0.50	0.31–0.80	.004	0.57	0.38–0.84	.005
Hospitalization	2023	58 (2.9)	1006	33 (3.3)	1.15	0.66	0.41–1.07	.09	0.72	0.48–1.09	.12
Death	2023	13 (0.6)	1006	1 (0.1)	0.15	0.05	0.01–0.42	.006	0.08	0.01–0.51	.008
ED admission/no hospitalization	2023	65 (3.2)	1006	46 (4.6)	1.44	1.14	0.75–1.74	.53	1.06	0.74–1.53	.74
ED admission/hospitalization	2023	118 (5.8)	1006	76 (7.6)	1.32	0.90	0.65–1.25	.52	0.91	0.68–1.20	.49

Abbreviations: IPW, inverse probability weighting; OR, odds ratio; PS, propensity score adjustment as a continuous variable; Unadj, unadjusted.

≥65; (ii) body mass index (kg/m^2), classified as ≤30 vs >30; (iii) immunocompromised status, classified as no vs yes; and (iv) COVID-19 vaccination status. Immunocompromised was defined from a range of conditions such as selected cancer diagnoses within the past year (eg, leukemia), selected autoimmune disorders in the past year (eg, lupus), and having an encounter in the UPMC health system within the past year and any prior history of transplant (Supplement Appendix B). Patients were classified as fully vaccinated when there was evidence in the EHR of at least 2 doses of an approved COVID-19 mRNA technology vaccine (eg, Pfizer, Moderna) or a single dose of an approved virus-based technology vaccine (eg, Johnson & Johnson). Because many patients may have been vaccinated outside of the system, the subgroup of patients with documented evidence of being fully vaccinated (51.9% of all patients) is reported, as well as all other patients with undetermined vaccination status (many of whom were likely vaccinated). Missing body mass index (16.7% of subjects) was imputed using the mean value for subjects with known values.

Statistical Methods

Sociodemographic and clinical characteristics between mAb-treated and nontreated subjects (before and after matching) were compared using standardized mean differences (SMDs). To calculate a propensity score (for treatment) for each patient [13, 14], we fit a logistic regression model with treatment with bebtelovimab as the response variable and inclusion of explanatory variables measured at baseline (Table 1). For each clinical outcome of interest (eg, hospitalization or death), an indicator variable for treatment (yes/no) was the primary predictor of interest in an unconditional (nonmatched) logistic regression model, with inclusion of the propensity score to adjust for confounding. As a sensitivity analysis. confounding was also adjusted for in the unmatched analyses by use of inverse probability weighting. Results are presented as adjusted odds ratios (ORs). These approaches were used overall and for the prespecified subgroups of interest for the primary outcome of hospitalization or death.

In a matched cohort sensitivity analysis, nontreated control subjects were matched to treated subjects by propensity score methodology [13, 14]. Specifically, 1:1 propensity score greedy nearest neighbor matching within a caliper width of 0.20 was used to construct matched treated and nontreated groups [15]. From the matched groups, the 28-day incidence rates of patient outcomes were calculated with treated vs nontreated comparisons of association estimated by use of conditional ORs and 95% CIs [16]. The Kaplan-Meier method was used to plot survival curves for freedom from hospitalization or death by treatment status over follow-up. A third sensitivity analysis was conducted using a conditional (matched) logistic regression analysis (described above) among patients with nonmissing data on body mass index (BMI). Analyses were conducted using the SAS System (SAS, Cary, NC, USA), version 9.4. Methods and results follow The REporting of studies Conducted using Observational Routinely-Collected Health Data (RECORD) statement (Supplement Appendix C) [17].

RESULTS

Baseline Characteristics

The unmatched analysis cohort consisted of 1006 treated patients and 2023 nontreated controls (Figure 1). Of the 1006 treated patients, 930 were individually matched 1:1 to nontreated control patients. Before 1:1 propensity score matching/adjustment, the mean (SD) age of treated patients was 61.6 (17.3) years compared with 51.3 (20.6) years in nontreated controls (Table 1). Similarly, before matching, the overall risk profile was higher in treated patients compared with nontreated controls, including higher prevalence of obstructive sleep apnea, hypertension, chronic kidney disease, cancer, chemotherapy, and being immunocompromised (all SMDs ≥0.20). After 1:1 propensity score matching, treated patients were similar to nontreated patients on all variables (SMD values ≤0.07) except for a nominally higher prevalence of history of chemotherapy (8.2% vs 4.7%; SMD, 0.14) and immunocompromised status (25.1% vs 20.9%; SMD, 0.10) (Table 1). The mean (SD) propensity score probability (×100) was 39.4 (16.2) in treated patients compared with 38.4 (15.1) in matched nontreated controls.

Outcomes

The crude overall 28-day incidence of hospitalization or death was 3.3% in treated patients compared with 3.5% in nontreated

Table 3. Risks and Conditional Odds Ratios of 28-Day Outcomes by Treatment vs Nontreatment With Bebtelovimab (Matched Cohort)

	Not Treated		Treated			Conditional Matched Analysis[a]			
Outcome	N	n (%)	N	n (%)	OR	Pairs in Analysis	Conditional OR	95% CI	*P* Value
Hospitalization/death	930	51 (5.5)	930	29 (3.1)	0.55	74	0.53	0.32–0.86	.01
Hospitalization	930	41 (4.4)	930	29 (3.1)	0.70	66	0.68	0.41–1.12	.13
Death	930	11 (1.2)	930	1 (0.1)	0.09	12	0.09	0.01–0.70	.02
ED admission/no hospitalization	930	35 (3.8)	930	41 (4.4)	1.18	76	1.24	0.77–2.01	.38
ED admission/hospitalization	930	72 (7.7)	930	67 (7.2)	0.93	127	0.94	0.66–1.35	.75

The number of pairs in the analysis represents the number of matched pairs (treated vs not-treated) with discordant outcomes.

Abbreviation: OR, odds ratio.

[a]The model includes adjustment for immunocompromised status and history of chemotherapy.

controls (Table 2). This corresponded to an unadjusted OR of 0.95. After statistical adjustment for the propensity score (ie, higher risk profile of treated patients), the estimated odds of hospitalization or death were 50% lower in treated patients compared with nontreated controls (OR, 0.50; 95% CI, 0.31–0.80). The corresponding adjusted OR for hospitalization was 0.66 (95% CI, 0.41–1.07), and there was only 1 death (0.1%) in the treated group compared with 13 deaths (0.6%) in the untreated group. Treatment with bebtelovimab was not associated with adjusted odds of ED admission with or without hospitalization. Results across outcomes were similar with the use of inverse probability weighting.

Sensitivity Analyses

In the matched cohort analysis, the incidence of hospitalization or death was 3.1% in treated patients compared with 5.5% in nontreated controls, with a corresponding conditional OR of 0.53 (95% CI, 0.32–0.86) (Table 3). The divergence in freedom from death or hospitalization in the direction favoring the treated group began at about day 4 of follow-up (Supplement Figure 1). The conditional OR for hospitalization was 0.68 (95% CI, 0.41–1.12), and there was 1 death (0.1%) in the treated group compared with 11 deaths (1.2%) in the matched untreated group. Thus, results were similar in the unmatched (adjusted) and matched cohort analyses. Results for the OR of hospitalization or death were also similar for the subgroup of patients with nonmissing BMI data (OR, 0.52; 95% CI, 0.33–0.83).

Subgroup Analyses

There was evidence that the association between treatment with bebtelovimab and odds of hospitalization or death was modified by predefined subgroups (Table 4). Specifically, among patients <65 years of age, there was no association between treatment and odds of hospitalization or death (adjusted OR, 1.03; 95% CI, 0.45–2.36), whereas there was a strong indication of lower odds in patients aged 65 and older (adjusted OR, 0.37; 95% CI, 0.21–0.63). There was no indication that the overall lower odds of hospitalization or death in treated patients was modified by obesity status.

Treatment with bebtelovimab was associated with a particularly low odds of hospitalization or death in patients with immunocompromised status (adjusted OR, 0.24; 95% CI, 0.11–0.50) and those who were fully vaccinated (adjusted OR, 0.26; 95% CI, 0.13–0.51). Results were similar with the use of inverse probability weighting. In post hoc subgroup analyses, there was an indication of substantially lower odds of hospitalization or death in immunocompromised patients who were fully vaccinated (adjusted OR, 0.19; 95% CI, 0.07–0.48), as well as immunocompromised patients with undetermined vaccination status (adjusted OR, 0.39; 95% CI, 0.12–1.29).

The absence of treatment association in patients under the age of 65 years and in those with undetermined vaccination status appeared to be driven by very low rates of hospitalization or death in the control group of nontreated patients (1.4% and 2.8%, respectively). In supplemental analyses, patients with undetermined vaccination status were less likely to have received chemotherapy (1.9% vs 7.5%) or be immunocompromised (11.8% vs 22.6%) than patients who were fully vaccinated (ie, lower overall risk).

DISCUSSION

In this analysis, treatment with bebtelovimab was associated with lower odds of hospitalization or death in propensity score–adjusted and –matched cohorts during a time period when the Omicron variant and its sublineages predominated. Patients aged 65 years and older, those with immunocompromised status, and those who were fully vaccinated had the lowest odds of hospitalization or death associated with bebtelovimab therapy, whereas OR estimates were not modified by body mass index.

Bebtelovimab was authorized for use in February 2022 as in vitro data emerged suggesting that previously approved mAbs would be ineffective at neutralizing certain Omicron sublineages, whereas bebtelovimab retained in vitro activity against all known variants [18]. This in vitro activity has since been confirmed; however, clinical data are lacking [5]. To our knowledge, this study represents the first large observational analysis of bebtelovimab treatment among a heterogeneous group of

Table 4. Subgroup Analyses of 28-Day Risk and Odds Ratios of Hospitalization or Death by Treatment vs Nontreatment With Bebtelovimab (Unmatched Cohort)

	Not Treated		Treated			Adjusted Analyses					
Subgroup	N	n (%)	N	n (%)	Unadj. OR	PS Adj. OR	95% CI	*P* Value	IPW OR	95% CI	*P* Value
Age											
<65 y	1435	20 (1.4)	470	13 (2.8)	2.01	1.03	0.45–2.36	.95	1.09	0.55–2.14	.81
≥65 y	588	50 (8.5)	536	20 (3.7)	0.42	0.37	0.21–0.63	<.001	0.38	0.22–0.62	<.001
Body mass index											
≤30 kg/m^2	877	35 (4.0)	378	16 (4.2)	1.06	0.53	0.27–1.05	.07	0.60	0.34–1.07	.08
>30 kg/m^2	902	32 (3.5)	365	14 (3.8)	1.08	0.56	0.27–1.13	.11	0.69	0.39–1.22	.20
Immunocompromised											
No	1796	43 (2.4)	705	20 (2.8)	1.19	0.85	0.48–1.50	.57	0.92	0.56–1.52	.76
Yes	227	27 (11.9)	301	13 (4.3)	0.33	0.24	0.11–0.50	<.001	0.25	0.12–0.51	<.001
Vaccination status											
Fully vaccinated	957	40 (4.2)	616	15 (2.4)	0.57	0.26	0.13–0.51	<.001	0.29	0.16–0.53	<.001
Not determined	1066	30 (2.8)	390	18 (4.6)	1.67	1.07	0.56–2.06	.84	1.14	0.66–1.96	.63

Abbreviations: IPW, inverse probability weighting; OR, odds ratio; PS, propensity score adjustment as a continuous variable; Unadj, unadjusted.

patients with COVID-19 assumed to be infected with the Omicron variant or an Omicron sublineage [19], and that includes a nontreated matched cohort. A small study of 25 solid organ transplant recipients treated with bebtelovimab suggested a possible treatment benefit with mAb therapy [20], and a larger retrospective cohort study of adult solid organ transplant recipients treated with either bebtelovimab (n = 92) or sotrovimab (n = 269) reported similar 30-day rates of hospitalization (~3%) [21]. Our 28-day rate of hospitalization (3.3%) in bebtelovimab-treated patients is consistent with the latter study. Throughout the pandemic, some therapies with in vitro activity against SARS-CoV-2 have failed to demonstrate clinical benefit; therefore, our data are important for public health because they provide reassurance that current in vitro assessments of mAbs seemingly track with clinical assessments of effectiveness.

This analysis shows evidence of substantially lower 28-day adjusted ORs of hospitalization and death among patients 65 years of age or older and/or immunocompromised patients treated with bebtelovimab compared with no treatment. Patients who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications and/or who may not mount an adequate immune response to COVID-19 vaccination are at high risk of severe SARS-CoV-2 infection and complications. Accordingly, the NIH prioritizes these individuals for mAb treatment during times of scarcity. Our results support continued prioritization of these patients, which occurred intermittently throughout the pandemic at our health system during times of staff or drug shortages (explaining the difference in age and immunocompromised status in the unmatched cohort). Importantly, the lower odds of death or hospitalization among bebtelovimab-treated patients was statistically significant despite a nominally higher prevalence of immunocompromised patients in the treated group after matching and relatively low event rates in the nontreated cohort. These results are consistent with previous data describing an overall lower rate of hospitalization during the Omicron period as compared with the Delta time period [22].

In this study, there was no association between bebtelovimab treatment and 28-day odds of hospitalization or death in patients with unknown vaccination status, which was in contrast to patients known to be fully vaccinated, who had a much lower OR of hospitalization or death with bebtelovimab treatment. Multiple potential explanations exist for this finding. First, the 28-day incidence of hospitalization or death was only 2.8% in nontreated controls with undetermined vaccinated status, and patients with undetermined vaccinated status had a generally lower risk profile than fully vaccinated patients. Thus, the apparent absence of treatment association may simply reflect low overall risk in this subcohort of patients with undetermined vaccination status. Second, "fully vaccinated" was defined as at least 2 mRNA vaccines or a single dose of an approved virus-based technology vaccine. This definition did not consider or require receipt of a third dose of an mRNA vaccine, which is now considered the primary series for an immunocompromised patient, or receipt of vaccine booster shots (consistent with more recent definitions of "fully" vaccinated). There is evidence that vaccination alone may be insufficient to mount protection against SARS-CoV-2 among immunocompromised and/or patients with advanced age; therefore, full vaccination in this population may be less protective against disease than having no comorbidities [23]. Finally, "fully vaccinated" status may be an indicator of patients being more likely to access health care, with overlap with elderly and immunocompromised patients.

Assessment of existing and new mAb products is paramount, including continuous appraisal of selected patient populations most likely to benefit from treatment. Given the speed of SARS-CoV-2 mutations, the conduct of conventional randomized controlled trials may be impractical, thereby necessitating analyses from large observational cohorts. Nonetheless, our observational study has several limitations.

First, matching of nontreated controls used EUA-eligible risk factors only, and we were unable to determine the time from symptom onset to SARS-CoV-2 test positive result or symptom severity (whether symptomatic or asymptomatic) of patients. We postulate that many nontreated patients may have been asymptomatic (ie, due to routine SARS-CoV-2 testing or incidental findings) and thereby at low risk of hospitalization, which would tend to bias results against mAb treatment. Second, as previously stated, we were unable to determine vaccination status (including booster status) in all patients, and the definition of "fully vaccinated" has changed dramatically with updated dosing schedules and authorization of additional vaccines. Third, receipt of tixagevimab/cilgavimab was not assessed, and we were unable to assess other treatments outside of our health system for control (untreated) patients, although, 3-day remdesivir was not offered by UPMC or any other regional hospital. Fourth, Omicron and its sublineages were the dominant SARS-CoV-2 variants during the study period, yet no patient-specific genotype sampling was conducted. Fifth, our definition of "immunocompromised" is broad, with multiple qualifying conditions. Sixth, hospitalizations that may have occurred outside the UPMC system are not captured in the present analyses. Finally, we cannot rule out potential residual confounding of the estimated mAb treatment effects despite our close propensity score matching of treated patients and nontreated "mAb-eligible" controls.

CONCLUSIONS

In this cohort study of outpatients with COVID-19 during an Omicron variant period, treatment with bebtelovimab was associated with significantly lower odds of hospitalization or death. Results indicate that outpatient use of bebtelovimab should be prioritized for older adults and those who are immunocompromised.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. Dr. Kip and Dr. Marroquin take full responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Kip, Marroquin, McCreary. Acquisition of data: Collins, Marroquin, McCreary, Kip. Interpretation of data: all authors. Drafting of the manuscript: Kip, Marroquin. Critical revision of the manuscript for important intellectual content: all authors. Study supervision: Kip, Marroquin, McCreary.

Reproducible research statement. Study protocol: No separate study protocol was required, a priori, as this retrospective analysis was deemed a quality improvement initiative, with ethical review and approval granted by the UPMC Quality Improvement Review Committee and Institutional Review Board.

Availability of data. Selected statistical code may be requested by contacting by Dr. Kip at kipke2@upmc.edu. The data set contains protected health information and will not be available upon request.

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MAJOR ARTICLE

Effectiveness of Casirivimab-Imdevimab Monoclonal Antibody Treatment Among High-Risk Patients With Severe Acute Respiratory Syndrome Coronavirus 2 B.1.617.2 (Delta Variant) Infection

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Background. Real-world data on the effectiveness of neutralizing casirivimab-imdevimab monoclonal antibody (Cas-Imd mAb) against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection among high-risk patients may inform the response to future SARS-CoV-2 variants.

Methods. This study covers an observational retrospective data analysis in Banner Health Care System sites, mainly in Arizona. During the study period, the prevalence of SARS-CoV-2 Delta variant was between 95% and 100%. Of 29 635 patients who tested positive for coronavirus disease 2019 (COVID-19) between 1 August 2021 and 30 October 2021, in the Banner Health Care System, the study cohort was split into 4213 adult patients who received Cas-Imd mAb (1200 mg) treatment compared to a PS-matched 4213 untreated patients. The primary outcomes were the incidence of all-cause hospitalization, intensive care unit (ICU) admission, and mortality within 30 days of Cas-Imd mAb administration or Delta variant infection.

Results. Compared to the PS-matched untreated cohort, the Cas-Imd mAb cohort had significantly lower all-cause hospitalization (4.2% vs 17.6%; difference in percentages, −13.4 [95% confidence interval {CI}, −14.7 to −12.0]; $P < .001$), ICU admission (0.3% vs 2.8%; difference, −2.4 [95% CI, −3.0 to −1.9]; $P < .001$), and mortality (0.2% vs 2.0%; difference, −1.8 [95% CI, −2.3 to −1.3]; $P < .001$) within 30 days. The Cas-Imd mAb treatment was associated with lower rate of hospitalization (hazard ratio [HR], 0.22 [95% CI, .19–.26]; $P < .001$) and mortality (HR, 0.11 [95% CI, .06–.21]; $P < .001$).

Conclusions. Cas-Imd mAb treatment was associated with a lower hospitalization rate, ICU admission, and mortality within 30 days among patients infected with the SARS-CoV-2 Delta variant.

Keywords. all-cause hospitalization; casirivimab-imdevimab monoclonal antibody; Delta variant; mortality; propensity matching; SARS-CoV-2.

The coronavirus disease 2019 (COVID-19) pandemic has caused a significant number of deaths in the United States (US) and globally [1]. With ongoing infections worldwide, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mutations are occurring, and new variants continue to emerge. The SARS-CoV-2 variants of concern, notably the B.1.617.2 (Delta) and most recently B.1.1.529 (Omicron) variants, have reduced antibody neutralization [2].

The COVID-19 vaccines have been instrumental in preventing hospitalizations and deaths [3]. However, there is a risk of breakthrough infections secondary to waning immunity [4–6]

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and reduced response to vaccination, especially among immunosuppressed patients [7]. Therefore, in addition to the vaccine, therapeutic options are essential in the fight against the COVID-19 pandemic. Researchers have been developing therapies for COVID-19 in the outpatient setting. While oral agents have been studied to treat COVID-19, including fluvoxamine [8] and, recently authorized by the US Food and Drug Administration (FDA) under Emergency Use Authorization (EUA), nirmatrelvir-ritonavir [9] and molnupiravir [10], these drugs were not approved during the period of Delta variant spread. During this time, the only available therapeutics for the outpatient management of COVID-19 were neutralizing monoclonal antibodies (mAbs) targeting the SARS-CoV-2 spike protein. The mAbs used to treat mild to moderate COVID-19 and/or to prevent severe disease include casirivimab-imdevimab (Cas-Imd mAb), bamlanivimab-etesevimab, and sotrovimab [11–15]. Data from clinical trials indicate a significant reduction in hospitalization rates of up to 70% with bamlanivimab, 67% with casirivimab-imdevimab, 87% with bamlanivimab-etesevimab, and 85% with sotrovimab in high-risk patients [16–20]. In addition, mAb showed a role in treating COVID-19 breakthrough infections in vaccinated individuals [21]. Also, pre–Delta variant SARS-CoV-2 real-world data showed promise for Cas-Imd mAb in reducing hospitalizations [22]. Recently, it was shown that Cas-Imd mAb decreased the rate of hospitalization among patients with COVID-19 during the early period of the Delta variant [21]. In vitro data showed that Cas-Imd mAb is possibly effective against the Delta variant [23], which presents Cas-Imd mAb as a viable option in treating the Delta variant. The Cas-Imd treatment was initially dosed at 2400 mg under the authorized FDA EUA; it was later changed to 1200 mg in June 2021 [24, 25]. In this study, we aimed to determine the effectiveness of Cas-Imd mAb (1200 mg) in reducing all-cause hospitalization, intensive care unit (ICU) admission, and all-cause mortality within 30 days of administration of Cas-Imd mAb or COVID-19 infection diagnosis.

METHODS

Patient Consent Statement

This study was approved by the Institutional Review Board of the University of Arizona with a waiver of patient consent given the retrospective nature of the study. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Overview

This study is an observational retrospective electronic health record (Cerner EHR) analysis in the Banner Health Care System (a nonprofit, large healthcare organization) which has 30 hospitals and several associated clinics across the western United States. The Banner Health Care System Monoclonal Antibody Treatment program was established in December 2020 (see Supplementary Document A). A multidisciplinary team reviews patients for eligibility for monoclonal antibody treatment, guided by the FDA EUA.

Among 29 635 patients who tested positive for COVID-19 (positive polymerase chain reaction (PCR) or direct antigen test) between 1 August 2021, and 30 October 2021, the study cohort was split into the treatment cohort who received Cas-Imd mAb (1200 mg) and the untreated control cohort (Figure 1). During the study period, there were 22 infusion sites (for the treatment cohort) and 128 testing sites (untreated control cohort) in the Banner Health Care System. The study index date for cohorts was determined as the date of Cas-Imd mAb administration or the date of the first positive COVID-19 test. Index dates were used as an enrollment date for the study. Patients who were <18 years old, were already hospitalized, had a pulse oximetry (SpO_2) reading <92% [26], were on hospice care. or had "do not resuscitate" status were excluded from the cohorts. Asymptomatic high-risk patients who received Cas-Imd mAb for postexposure prophylaxis were also excluded. Clinical and demographic covariates were extracted from the Cerner EHR for the remaining patients. The clinical covariates were derived from the Charlson Comorbidity Index [27] and extracted for each patient based on *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes documented in the 5 years preceding the patient index date. Then, one-to-one propensity score (PS) matching with no replacement was used to match both cohorts (Figure 2). Postmatch cohort size was determined as 4213 pairs. For additional analysis, the matched cohort was rematched based on the COVID-19 mRNA vaccination subgroups.

The PS-matched cohort spanned the Banner Health Care System sites in multiple states, with 82.1% from Arizona, 9.4% from Colorado, 4.1% from Wyoming, 2.5% from Nevada, 1.5% from California, and 0.5% from Nebraska. During the study period, the prevalence of the Delta variant among SARS-CoV-2–infected patients was between 95% and 100% in states where the Banner Health Care System sites exist (Supplementary Figure 1*A–F*). In addition, if vaccination status of a patient residing in Arizona was missing, the vaccination status was imported from the Arizona State Immunization Information System, an online verification resource.

Outcomes

The primary outcomes were the proportion of all-cause hospitalization, ICU admission, and all-cause mortality that was observed within our electronic medical record system, within 30 days of the index date. The secondary outcomes included hospitalization length of stay (LOS) and cumulative ICU LOS, oxygen therapy, and acute kidney injury (AKI) stages during the first hospitalization. AKI is defined according to the Kidney Disease Improving Global Outcomes (KDIGO) classification

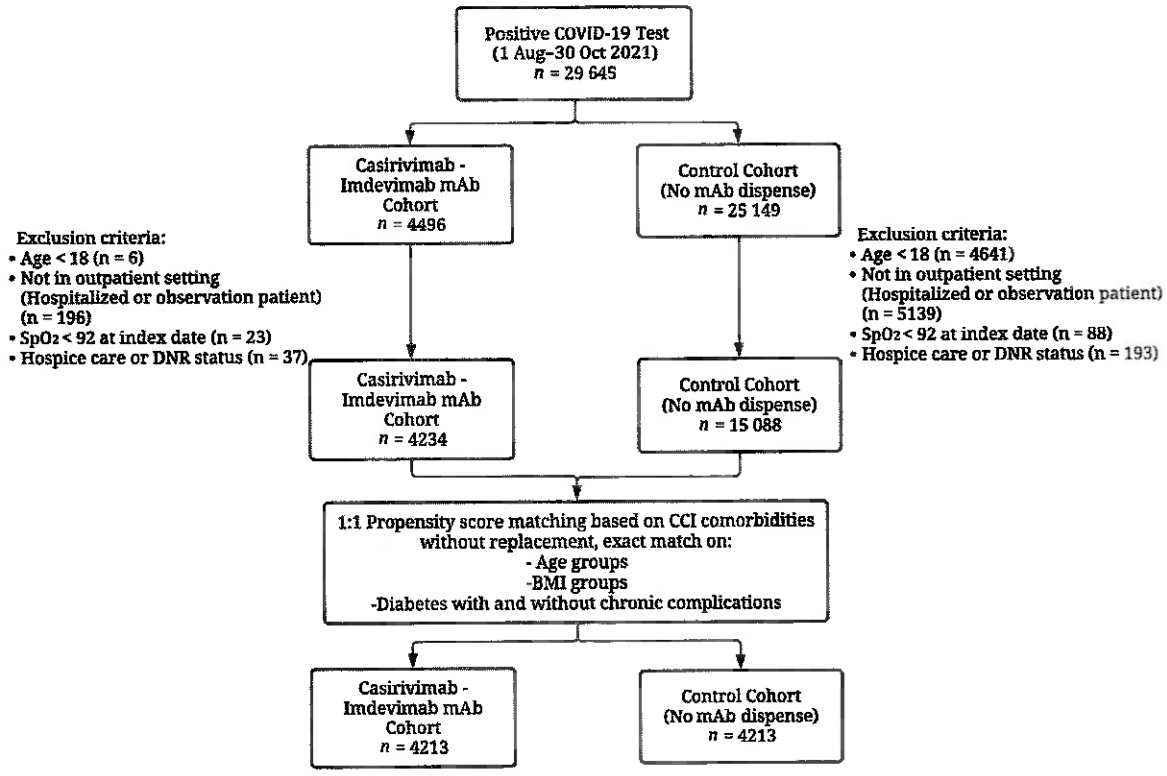

Figure 1. Flowchart for study cohort selection. Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; COVID-19, coronavirus disease 2019; DNR, do not resuscitate; mAb, monoclonal antibody; SpO_2, oxygen saturation.

[28]. The data were right censored on 30 November 2021. In this analysis, death was not used as competing risk to all-cause hospitalization or ICU admission due to small numbers.

Multivariable Propensity Score Matching

One-to-one PS matching with no replacement was performed using an optimal matching algorithm [29] that minimizes the sum of the absolute pairwise distance across the matched sample. The optimal matching algorithm was compared with nearest neighbors and complete matching algorithms and was determined the best per the covariate balance and the number of unmatched individuals. Pairs were matched exactly on age group, body mass index (BMI) group, and diabetes status (with or without complications). These variables along with the remaining demographics, clinical covariates, and time periods (composed of 2-week periods between the study start and end date) were included as predictors in a logistic regression model to estimate the PS. Distance function was determined considering its performance in minimizing the unmatched sample while keeping covariate standardized mean differences (SMDs) to a minimum. Covariate balance was assessed by looking at the SMD and empirical cumulative distribution function statistics for each covariate and by a covariate balance plot (Figure 2) that displays the SMDs before and after matching. The MatchIt package [30] from the statistical computing software R was utilized for building and assessing the PS-matching model.

Statistical Analysis

All statistical analyses were conducted on the paired (matched) dataset. For each primary outcome, the event count and percentage of the event was reported. Ninety-five percent Clopper-Pearson confidence intervals (CIs) for percentages were computed in the R package Exactci. Exact McNemar test was used to compare the difference in percentages between the treatment and control cohorts. Differences in percentages between cohorts and related 95% CIs were reported along with the McNemar test *P* value. Calculations were performed using the R package exact2x2. In addition, Kaplan-Meier survival analysis was performed to evaluate the difference in time to all-cause hospitalization and mortality rates (using Stata version 17 software, StataCorp, College Station, Texas).

For secondary continuous outcomes, hospital LOS and ICU LOS, mean and standard deviation (SD) of the outcome were reported. Individuals who were not hospitalized were considered as they had zero LOS in both outcomes. A 2-part generalized linear mixed model with random effect for matched pairs was fitted to compare LOS across cohorts among patients who

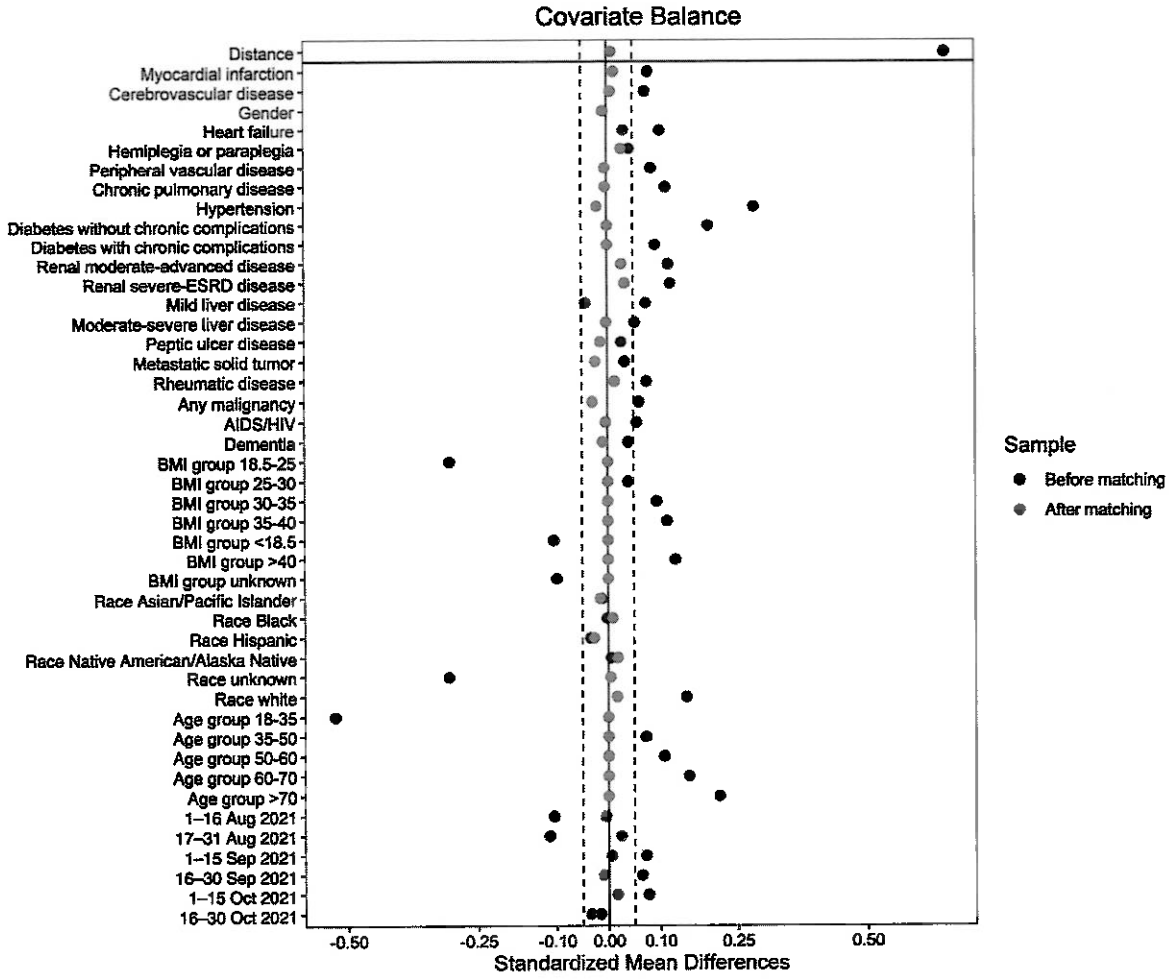

Figure 2. Covariate balance plot for before and after propensity score matching. Abbreviations: BMI, body mass index; ESRD, end-stage renal disease; HIV, human immunodeficiency virus.

have LOS >0, by evaluating the model's fixed effects for Cas-Imd mAb use. The estimated coefficient, 95% CI of the coefficient, and the statistical significance of the fixed antibody effect were reported. The R package GLMMadaptive was used to fit the mixed model.

For our categorical secondary outcomes, intensity of oxygen therapy and AKI stages during hospitalization, counts, and percentages were reported. The subcategories for both variables were grouped into 2 clinically meaningful categories due to the small sample size. Wald test of no differences was conducted to compare the distributions for treatment and control cohort cases, given a hospitalized patient.

An additional analysis was conducted to assess how the primary outcomes differ based on COVID-19 messenger RNA (mRNA) vaccination status. An individual was considered fully vaccinated if 14 days had passed after their final dose of the vaccine before the index date. First, the Stuart-Maxwell test for marginal homogeneity was used to compare vaccination status between the treatment and control cohorts. Then, the postmatch treatment and control cohorts were combined and then split into vaccinated and unvaccinated cohorts, excluding the individuals with missing vaccination status. The optimal matching method was used to rematch both vaccinated and unvaccinated cohorts separately for the PS calculation, using the same model in the previous analysis [31]. Following the optimal rematching, 949 pairs (n = 1898) were matched in the vaccinated cohort, and 2732 (n = 5464) were matched in the unvaccinated cohort. Primary outcome counts and percentages with Clopper-Pearson CIs were reported. Finally, the hazard ratio (HR) for the effect of Cas-Imd mAb treatment on time to primary outcomes was calculated using a Cox proportional hazards model adjusted for COVID-19 mRNA vaccination status.

Missing Data

Data were missing in 22 (2.4% of hospitalized) patients for intensity of oxygen therapy, 26 (2.8% hospitalized) patients for

serum creatinine and AKI categories, and 461 (5.5% of the study cohort) patients for vaccination status. Observations with missing data on secondary outcomes were considered free of the outcome for their respective statistical tests.

RESULTS

Patient Characteristics

Table 1 shows the characteristics of the Cas-Imd mAb and untreated control cohorts before and after PS matching. All post-PS-matching covariate SMDs were below a 0.05 threshold, indicating an optimal matching (Figure 2). In the post-PS-matched cohort, the median age of patients in the Cas-Imd mAb treatment arm was 50 (interquartile range [IQR], 34–64) years; 55.9% were female, and 67.8% were White race. Some of the high-risk characteristics were age ≥65 years (30.6%), BMI ≥35 kg/m^2 (35.3%), diabetes mellitus (17.6%), chronic lung disease (18.2%), kidney disease–any stage (8.5%), and human immunodeficiency virus (HIV)/AIDS (5.6%). The median time from COVID-19 PCR positivity to infusion was 1 day (IQR, 0–2 days) in the Cas-Imd mAb treatment cohort, shown in Supplementary Figure 2. In a subgroup analysis based on number of days from COVID-19 PCR positivity to Cas-Imd mAb infusion, we categorized time to mAb infusion variable as <2 vs ≥2 days and as <3 vs ≥3 days and calculated the proportion of patients who are hospitalized and died in the mAb-treated cohort (Supplementary Table 1). The results show no significant difference regarding the hospitalization and mortality in both categories.

Primary and Secondary Outcomes

Table 2 and Supplementary Table 2 show the results of the primary and/or secondary outcomes within 30 days in the post-PS-matched cohorts. Compared to the untreated control cohort, the percentage of patients with all-cause hospitalizations in the Cas-Imd mAb cohort was 4.2% (95% CI, 3.6%–4.8%) vs 17.6% (95% CI, 16.4%–18.7%) ($P < .001$); the percentage of patients with ICU admission in the Cas-Imd mAb cohort was 0.3% (95% CI, 0.25%–0.5%) vs 2.8% (95% CI, 2.3%–3.3%; $P < .001$); and the proportion of patients with all-cause mortality was 0.2% (95% CI, .1%–.4%) vs 2.0% (95% CI, 1.6%–2.4%; $P < .001$). Death rarely occurred (8 of 4213 patients in the Cas-Imd cohort and 83 of 4213 patients in the untreated control cohort) and mostly happened in the ICU (75 of 91). Sixteen patients died without hospitalization to the Banner Healthcare Centers (assumed to have died either at home or other healthcare facilities). Kaplan-Meier survival analysis showed significant differences in time to all-cause hospitalization and mortality between the Cas-Imd mAb treatment and PS-matched untreated cohort (Supplementary Figures 3 and 4). Supplementary Figures 5*A*, 5*B*, 6*A*, and 6*B* illustrate the substratification of Kaplan-Meier survival analysis according to baseline SpO_2 (substratifying the cohort SpO_2 92%–95% and ≥96%), demonstrating comparable results. In terms of the secondary outcomes, compared to the untreated control cohort, the mean for hospital LOS was 5.3 (SD, 5.3) days in the Cas-Imd mAb cohort vs 6.9 (SD, 7.9) days ($P = .06$), and the mean for ICU LOS was 3.6 (SD, 4.8) days in the Cas-Imd mAb cohort vs 3.8 (SD, 5.3) days ($P = .85$). The generalized linear mixed model that estimates the mean ratio of cohorts showed that upper 95% CIs of both hospital LOS and ICU LOS outcomes include 1. The percentage of the highest-intensity oxygen requirements (including mechanical ventilation/continuous positive airway pressure–bilevel positive airway pressure/high-flow oxygen) were lower in the Cas-Imd mAb cohort (25.8% vs 42.5%; $P < .001$) compared with the untreated control cohort. The percentage of the KDIGO AKI stage 2–3 in the Cas-Imd mAb cohort (1.4%) was lower than in the untreated cohort (6.1%; $P < .001$).

Subgroup Analysis Stratified Based on COVID-19 Vaccination Status

Table 3 shows the primary outcomes for the PS-rematched Cas-Imd mAb–treated and untreated cohorts, stratified by vaccination status. The study cohort received COVID-19 mRNA vaccines from Pfizer-BioNTech (67.9%) and Moderna (32.1%). The prevalence of COVID-19 mRNA vaccination was lower among study participants (28.3% in the Cas-Imd mAb cohort vs 23.8% in the control untreated cohort; $P < .001$) as compared to the state and national reported vaccination rates. In terms of the primary outcomes, the lowest all-cause hospitalization (1.7%)/ICU admission (0.0%)/mortality (0.0%) rates were observed in the vaccinated Cas-Imd mAb treatment cohort while the highest all-cause hospitalization (23.3%)/ICU admission (3.7%)/mortality (2.3%) rates were encountered in the unvaccinated untreated cohort. The primary outcomes were similar between the Cas-Imd mAb–treated unvaccinated cohort and the untreated vaccinated cohort. In multivariable Cox proportional hazards models, Cas-Imd mAb treatment and COVID-19 mRNA vaccination were independently associated with lower rate of all-cause hospitalization (HR, 0.22 [95% CI, .19–.26]; $P < .001$ vs HR, 0.23 [95% CI, .18–.30]; $P < .001$) and mortality (HR, 0.11 [95% CI, .06–.21]; $P < .001$ vs HR, 0.37 [95% CI, .20–.70]; $P = .02$), respectively.

DISCUSSION

This study is one of the largest real-world studies reporting the use of Cas-Imd mAb in reducing mortality and hospitalization among high-risk populations during the pandemic period when infections were caused predominantly by the SARS-CoV-2 Delta variant [32]. Our study includes a diverse population of adults (approximately 20% Hispanic, 5% Black, and 1.5% American Indian). The untreated cohort was also more predisposed to higher oxygen requirement and

Table 1. Clinical Covariate Balance Before and After Propensity Score Matching

Clinical Covariates	After PS Matching			Before PS Matching		
	Cas-Imd mAb Treatment Cohort	Untreated Control Cohort	SMD	Cas-Imd mAb Treatment Cohort	Untreated Control Cohort	SMD
No.	4213	4213		4234	15088	
Age, y, median (IQR)	50.0 (38.0–64.0)	50.0 (38.0–63.0)		50.0 (38.0–64.0)	40.0 (29.0–55.0)	
Age group, y						
18–35	822 (19.5)	822 (19.5)	0.00	827 (19.5)	6085 (40.3)	−0.52
36–50	1330 (31.6)	1330 (31.6)	0.00	1343 (31.7)	4278 (28.4)	0.07
51–60	769 (18.3)	769 (18.3)	0.00	771 (18.2)	2121 (14.1)	0.11
61–70	655 (15.5)	655 (15.5)	0.00	655 (15.5)	1489 (9.9)	0.15
>70	637 (15.1)	637 (15.1)	0.00	638 (15.1)	1115 (7.4)	0.21
Sex, male	1860 (44.1)	1877 (44.6)	−0.01	1872 (44.2)	6729 (44.6)	−0.01
Race/Ethnicity						
White	2855 (67.8)	2822 (67.0)	0.02	2869 (67.8)	9165 (60.7)	0.15
Black	233 (5.5)	225 (5.3)	0.01	234 (5.5)	842 (5.6)	0.00
Hispanic	885 (21.0)	932 (22.1)	−0.03	891 (21.0)	3392 (22.5)	−0.04
Asian/Pacific Islander	37 (0.9)	43 (1.0)	−0.02	37 (0.9)	148 (1.0)	−0.01
Native American/Alaska Native	62 (1.5)	53 (1.3)	0.02	62 (1.5)	211 (1.4)	0.01
Unknown	141 (3.3)	138 (3.3)	0.00	141 (3.3)	1330 (8.8)	−0.31
BMI, group, kg/m^2						
<18.5	31 (0.7)	31 (0.7)	0.00	33 (0.8)	257 (1.7)	−0.11
18.5–25	569 (13.5)	569 (13.5)	0.00	572 (13.5)	3605 (23.9)	−0.30
26–30	1210 (28.7)	1210 (28.7)	0.00	1214 (28.7)	4061 (26.9)	0.04
31–35	1036 (24.6)	1036 (24.6)	0.00	1045 (24.7)	3111 (20.6)	0.09
36–40	600 (14.2)	600 (14.2)	0.00	600 (14.2)	1538 (10.2)	0.11
>40	466 (11.1)	466 (11.1)	0.00	467 (11.0)	1050 (7.0)	0.13
Unknown	301 (7.1)	301 (7.1)	0.00	303 (7.2)	1466 (9.7)	−0.1
Myocardial infarction	118 (2.8)	109 (2.6)	0.00	118 (2.8)	224 (1.5)	0.08
Heart failure	154 (3.7)	129 (3.1)	0.03	155 (3.7)	263 (1.7)	0.10
Cerebrovascular disease	126 (3.0)	121 (2.9)	0.01	127 (3.0)	264 (1.7)	0.07
Hemiplegia or paraplegia	31 (0.7)	21 (0.5)	0.03	31 (0.7)	55 (0.4)	0.04
Peripheral vascular disease	134 (3.2)	137 (3.3)	0.00	136 (3.2)	258 (1.7)	0.09
Chronic pulmonary disease	767 (18.2)	773 (18.3)	0.00	774 (18.3)	2101 (13.9)	0.11
Hypertension	1234 (29.3)	1272 (30.2)	−0.02	1247 (29.5)	2487 (16.5)	0.28
Diabetes without chronic complications	590 (14.0)	590 (14.0)	0.00	604 (14.3)	1122 (7.4)	0.20
Diabetes with chronic complications	150 (3.6)	150 (3.6)	0.00	168 (4.0)	326 (2.2)	0.09
Renal disease, mild-moderate-advanced (CKD stage 1–4)	189 (4.5)	165 (3.9)	0.03	195 (4.6)	323 (2.1)	0.12
Renal disease, severe (CKD stage 5 and ESRD)	168 (4.0)	140 (3.3)	0.03	174 (4.1)	257 (1.7)	0.12
Mild liver disease	226 (5.4)	267 (6.3)	−0.04	229 (5.4)	562 (3.7)	0.07
Moderate to severe liver disease	44 (1.0)	45 (1.1)	0.00	45 (1.1)	79 (0.5)	0.05
Peptic ulcer disease	44 (1.0)	50 (1.2)	−0.01	44 (1.0)	117 (0.8)	0.03
Rheumatic disease	110 (2.6)	101 (2.4)	0.01	111 (2.6)	215 (1.4)	0.07
Malignancy including skin cancers and lymphoproliferative disorders	109 (2.6)	129 (3.1)	−0.03	109 (2.6)	245 (1.6)	0.06
Metastatic solid tumor	26 (0.6)	34 (0.8)	−0.02	26 (0.6)	54 (0.4)	0.03
HIV/AIDS	235 (5.6)	239 (5.7)	0.00	238 (5.6)	654 (4.3)	0.06
Dementia	39 (0.9)	43 (1.0)	−0.01	39 (0.9)	82 (0.5)	0.04
Time period						
1–16 Aug 2021	538 (12.8)	546 (13.0)	−0.01	540 (12.8)	2457 (16.3)	−0.11
17–31 Aug 2021	682 (16.2)	644 (15.3)	0.02	685 (16.2)	3071 (20.4)	−0.11
1–15 Sep 2021	848 (20.1)	838 (19.9)	0.01	850 (20.1)	2591 (17.2)	0.07
16–30 Sep 2021	757 (18.0)	771 (18.3)	−0.01	761 (18.0)	2341 (15.5)	−0.06
1–15 Oct 2021	730 (17.3)	703 (16.7)	0.02	735 (17.4)	2180 (14.4)	0.08
16–30 Oct 2021	658 (15.6)	711 (16.9)	−0.03	663 (15.7)	2448 (16.2)	−0.02

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; Cas-Imd mAb, casirivimab-imdevimab monoclonal antibody; CKD, chronic kidney disease; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; IQR, interquartile range; PS, propensity score; SMD, standardized mean difference.

Table 2. Primary and Secondary Outcomes in the Post–Propensity Score–Matched Cohorts

Outcome	Cas-Imd mAb Treatment Cohort (n = 4213)		Untreated Control Cohort (n = 4213)		Difference, % (95% CI)[b]	*P* Value
	No. (%)	(95% CI)[a]	No. (%)	(95% CI)[a]		
Primary outcomes in post-PS-matched cohorts						
All-cause hospitalization within 30 d	176 (4.2)	(3.6–4.8)	740 (17.6)	(16.4–18.7)	−13.4 (−14.7 to −12.0)	<.001
ICU admission within 30 d	13 (0.3)	(.2–.5)	116 (2.8)	(2.3–3.3)	−2.4 (−3.0 to −1.9)	<.001
Mortality in 30 d	8 (0.2)	(.1–.4)	83 (2.0)	(1.6–2.4)	−1.8 (−2.3 to −1.3)	<.001
Secondary outcomes in post-PS-matched cohorts	Cas-Imd mAb Treatment Cohort (n = 176)	Untreated Control Cohort (n = 740)	Ratio of Means for Cohorts[c]	95% CI for Mean Ratio of Cohorts[c]		*P* Value
Hospital LOS, d, mean (SD)	5.3 (5.3)	6.9 (7.9)	0.86	(.74–1.01)		.06
ICU LOS, d, mean (SD)	3.6 (4.8)	3.8 (5.3)	0.95	(.54–1.67)		.85
	CI mAb Treatment Cohort (n = 176)	Untreated Control Cohort (n = 740)	Difference Between Cohorts (Proportions)	95% CI for Difference (Proportions)		Wald Test of No Differences (*P* Value)
Highest intensity oxygen requirement						
MV, CPAP-BiPAP, high-flow oxygen	42 (25.8)	311 (42.5)	16.8 (3.9)	(9.1–24.4)		18.6 (<.001)
Nasal cannula–room air	121 (74.2)	420 (57.5)	−16.8 (3.9)	(−24.4 to −9.2)		
AKI in the hospitalization						
No AKI, KDIGO stage 1	138 (98.6)	601 (93.9)	−4.7 (1.4)	(−7.4 to −2.0)		11.5 (<.001)
KDIGO stage 2/3	2 (1.4)	39 (6.1)	4.7 (1.4)	(2.0–7.4)		

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: AKI, acute kidney injury; BiPAP, bilevel positive airway pressure; Cas-Imd mAb, casirivimab-imdevimab monoclonal antibody; CI, confidence interval; CPAP, continuous positive airway pressure; ICU, intensive care unit; KDIGO, Kidney Disease Improving Global Outcomes; LOS, length of stay; MV, mechanical ventilation; PS, propensity score; SD, standard deviation.

[a]The Clopper-Pearson method was used to calculate 95% CIs for the outcome percentages using the R package (Exactci).

[b]Exact McNemar test was used to compare the percentage difference between the treatment and control cohorts.

[c]Comparison between 2 continuous variables in paired data was calculated using R package GLMMadaptive for a fixed treatment effect from a 2-part mixed model.

Table 3. Distribution of Coronavirus Disease 2019 Vaccination Status Among Post–Propensity Score (PS)–Matched Cohort, the Primary Outcomes Stratified by Vaccination Status Among Post-PS-Matched Cohort, Multivariable Cox Proportional Hazard Models for All-Cause Hospitalization, and Mortality Adjusted for Vaccination Status Among Post-PS-Matched Cohort

	Distribution of COVID-19 mRNA Vaccination Status Among Post-PS-Matched Cohort					
	Cas-Imd mAb Treatment Cohort (n = 4213)	Untreated Control Cohort (n = 4213)	χ^2 Test[a]	*P* Value		
Fully vaccinated against COVID-19						
Yes	1192 (28.3)	1003 (23.8)	217.52	<.001		
No	2943 (69.9)	2827 (67.1)				
Missing	78 (1.9)	383 (9.1)				
Primary Outcomes Among COVID-19 mRNA Vaccinated Subgroup After PS Matching						
	Cas-Imd mAb (n = 949)		Control Cohort (n = 949)			
	No. (%)	(95% CI)	No. (%)	(95% CI)[b]	Difference, % (95% CI)[c]	*P* Value
All-cause hospitalization within 30 d	16 (1.7)	(1.0–2.7)	60 (6.3)	(4.9–8.1)	−4.6 (−6.5 to −2.8)	<.001
ICU admission within 30 d	0 (0.0)	(0–.4)	9 (0.9)	(.4–1.8)	−0.9 (−1.8 to −.2)	.004
Mortality in 30 d	0 (0.0)	(0–.4)	8 (0.8)	(.4–1.7)	−0.8 (−1.7 to −.2)	.01
Primary Outcomes Among COVID 19 Unvaccinated Subgroup of Patients After PS Matching						
	Cas-Imd mAb (n = 2732)		Control Cohort (n = 2732)			
	No. (%)	(95% CI)	No. (%)	(95% CI)[b]	Difference, % (95% CI)[c]	*P* Value
All-cause hospitalization within 30 d	150 (5.5)	(4.7–6.4)	637 (23.3)	(21.7–24.9)	−18.3 (−20.1 to −16.4)	<.001
ICU admission within 30 d	12 (0.4)	(.2–.8)	101 (3.7)	(3.0–4.5)	−3.3 (−4.1 to −2.6)	<.001
Mortality in 30 d	8 (0.3)	(.1–.6)	62 (2.3)	(1.7–2.9)	−2.6 (−3.2 to −1.9)	<.001
Multivariable Cox Proportional Hazards Model for All-Cause Hospitalization Within 30 d of Index Date in the Post-PS-Matched Cohort						
	HR	(95% CI)	*P* Value			
Cas-Imd mAb (Yes)	0.22	(.19–.26)	<.001			
Fully vaccinated against COVID-19						
Yes	0.23	(.18–.30)	<.001			
Missing	0.16	(.10–.26)	<.001			
Multivariable Cox Proportional Hazards Model for Mortality Within 30 d of Index Date in the Post-PS-Matched Cohort						
	HR	(95% CI)	*P* Value			
Cas-Imd mAb (Yes)	0.11	(.06–.21)	<.001			
Fully vaccinated against COVID-19						
Yes	0.37	(.20–.70)	.002			
Missing	0.50	(.20–1.23)	.13			

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: Cas-Imd mAb, casirivimab-imdevimab monoclonal antibody; CI, confidence interval; COVID-19, coronavirus disease 2019; HR, hazard ratio; ICU, intensive care unit; mRNA, messenger RNA; PS, propensity score.

[a]Stuart-Maxwell Test for marginal homogeneity χ^2 test.

[b]The Clopper-Pearson method was used to calculate 95% CIs for the outcome percentages using the R package (Exactci).

[c]The exact McNemar test was used to compare the percentage difference between the treatment and control cohorts.

mechanical ventilation and developed higher AKI stages than the Cas-Imd mAb group.

Cas-Imd efficacy against SARS-CoV-2 was shown previously in a clinical trial with COVID-19 patients who received Cas-Imd mAb having lower SARS-CoV-2 viral loads and hospitalization [14]. Another recent study from the Mayo Clinic showed that administration of Cas-Imd mAb was associated with a lower risk of hospitalization in high-risk populations [22]; however, that study included a smaller number of patients (N = 1392) during the period predating the Delta variant spread compared to our investigation. In addition, we demonstrate that the rates of 30-day ICU admission and all-cause mortality are significantly lower in the Cas-Imd mAb–treated group compared to previous studies.

In our subgroup analysis based on vaccination status, we found that Cas-Imd mAb retained its efficacy in lowering the rates of hospitalizations, ICU admissions, and all-cause mortality and endured its effect even when the individual was fully vaccinated, but the effect size was smaller compared to the unvaccinated cohort. Our study shows that approximately 25% of the PS-matched population, mainly from Arizona, were fully vaccinated, which is a number lower than that reported by the Arizona Department of Health Services (AZDHS) [33]. Such a difference in the number of vaccinated populations could be either secondary to the underlying characteristics of the population that visited our hospital system or secondary to lacking data of reported vaccinations. Moreover, our cohort had a higher percentage of hospitalizations and deaths than the

same period reported by AZDHS [33]. This could be related to the high-risk population included in the study as we matched our controls with the Cas-Imd mAb cohort on our institutional mAb eligibility criteria, or to a lesser extent because of the included population from the states of Montana and Colorado [19, 34]. Similar to previous reports [35], our study shows that fully vaccinated adults (not boosted) had significantly reduced hospitalization, ICU admission, and death compared to the unvaccinated cohort.

For the study's secondary outcomes, patients receiving Cas-Imd mAb had significantly reduced oxygen requirements and AKI, including the need for renal replacement therapy. The findings of our study corroborate with other randomized placebo-controlled trials which reported that the use of other mAb products reduced the risk of hospitalization and death in high-risk patients with mild to moderate COVID-19 infections [13].

This study has significant implications for treating COVID-19 and preventing its complications, as we show that delivering monoclonal antibodies directed toward a SARS-CoV-2 Delta variant can significantly lower hospitalization rates, ICU stay, and all-cause mortality. The Omicron variant has spread very quickly since December 2021; hence, there exists a pandemic with mainly the Omicron variant coinciding with declining incidence of Delta variant infections among newly infected patients [36]. It is crucial to know predominantly which variants are causing most infections in order to administer appropriate mAbs for patients infected with SARS-CoV-2 (ie, Cas-Imd mAb for the Delta variant and sotrovimab for the Omicron variant). This study highlights the role of mAbs in reducing COVID-19–associated complications; a similar approach can be used to assess the effectiveness of other mAbs or for other SARS-CoV-2 variants. Furthermore, our results show that irrespective of COVID-19 vaccination status, receiving mAbs led to significantly reduced hospitalization rates, ICU stays, and all-cause mortality, which is essential in treating breakthrough infections. Such findings have implications for unvaccinated individuals and immunocompromised individuals who will have attenuated immune responses to vaccines and may benefit from passive immunity for the treatment of COVID-19.

Our study has several strengths, including a large sample size from an extensive hospital network system that evaluated >8400 patients (the largest reported real-world experience) with analysis capturing the Delta variant period exclusively. This includes patients in both rural and urban settings with excellent representation of minority groups. Moreover, the study matched patients according to different risk factors that minimized bias by utilizing optimal PS matching. We also imported the vaccination data from the Arizona State Immunization Information System.

The limitations of our study include the retrospective design, which may be associated with reporting and selection biases, and the lack of information regarding possible hospitalizations and deaths that occurred outside of Banner Health. Lack of information about previous infections and possible missing immunization information limits further interpretation of the benefits of mAb based on previous immune status. In addition, a diverse subgroup of patients with hematopoietic stem-cell or solid organ transplants were not included as a separate category in the propensity analysis due to small sample size; such patients are known to have poorer outcomes and more likely to be referred to mAb treatment. Last, missing information regarding patients' earliest symptom date may have introduced a selection bias.

In conclusion, Cas-Imd mAb treatment was associated with a lower hospitalization rate, ICU admission, and all-cause mortality within 30 days among those with COVID-19 infections. Both Cas-Imd mAb treatment and COVID-19 mRNA vaccination were independently associated with a lower hospitalization and mortality rate.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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FDA STATEMENT

Coronavirus (COVID-19) Update: FDA Limits Use of Certain Monoclonal Antibodies to Treat COVID-19 Due to the Omicron Variant

The following is attributed to Patrizia Cavazzoni, M.D., director of the FDA's Center for Drug Evaluation and Research

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Statement From:

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Español (/news-events/press-announcements/actualizacion-sobre-el-coronavirus-covid-19-la-fda-limita-el-uso-de-ciertos-anticuerpos-monoclonales)

For recent updates on COVID-19 treatments that are approved or authorized by the FDA, please visit the CDER Statement website (https://www.fda.gov/drugs/drug-safety-and-availability/drug-alerts-and-statements#statements). Health care providers should also refer to the COVID variants and genomic surveillance information available on the COVID Data Tracker (https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fvariant-proportions.html%22%20\l%20%22nowcasting#variants-genomic-surveillance), which is updated regularly by the Centers for Disease Control and Prevention.

As we have throughout the COVID-19 pandemic, the U.S. Food and Drug Administration has used the best available science as the virus has evolved to make informed decisions with the health and safety of the American public in mind. Ensuring that healthcare providers on the frontlines have the best tools available to treat patients is a top priority for the agency.

In light of the most recent information and data available, today, the FDA revised the authorizations for two monoclonal antibody treatments – bamlanivimab and etesevimab (administered together) and REGEN-COV (casirivimab and imdevimab) – to limit their use to only when the patient is likely to have been infected with or exposed to a variant that is susceptible to these treatments.

Because data show these treatments are highly unlikely to be active against the omicron variant, which is circulating at a very high frequency throughout the United States, these treatments are not authorized for use in any U.S. states, territories, and jurisdictions at this time. In the future, if patients in certain geographic regions are likely to be infected or exposed to a variant that is susceptible to these treatments, then use of these treatments may be authorized in these regions.

Monoclonal antibodies are laboratory-made proteins that mimic the immune system's ability to fight off harmful pathogens such as viruses, like SARS-CoV-2. And like other infectious organisms, SARS-CoV-2 can mutate over time, resulting in certain treatments not working against certain variants such as omicron. This is the case with these two treatments for which we're making changes today.

Based on Centers for Disease Control and Prevention data, the omicron variant of SARS-CoV-2 is estimated to account for more than 99% of cases in the United States (https://covid.cdc.gov/covid-data-tracker/#monitoring-varaint-heading) as of Jan. 15. Therefore, it's highly unlikely that COVID-19 patients seeking care in the U.S. at this time are infected with a variant other than omicron, and these treatments are not authorized to be used at this time. This avoids exposing patients to side effects, such as injection site reactions or allergic reactions, which can be potentially serious, from specific treatment agents that are not expected to provide benefit to patients who have been infected with or exposed to the omicron variant.

The NIH COVID-19 Treatment Guidelines Panel (https://www.covid19treatmentguidelines.nih.gov/), an independent panel of national experts, recently recommended against the use of bamlanivimab and etesevimab (administered together) and REGEN-COV (casirivimab and imdevimab) because of markedly reduced activity against the omicron variant and because real-time testing to identify rare, non-omicron variants is not routinely available.

Importantly, there are several other therapies (https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs) – Paxlovid, sotrovimab, Veklury (remdesivir), and molnupiravir – that are expected to work against the omicron variant, and that are authorized or approved to treat patients with mild-to-moderate COVID-19 who are at high risk for progression to severe disease, including hospitalization or death. Healthcare providers should consult the NIH panel's COVID-19 treatment guidelines and assess whether these treatments are right for their patients.

While it's critical that we have ways to treat those who contract COVID-19, the authorized treatments are not a substitute for vaccination in individuals for whom COVID-19 vaccination and a booster dose are recommended. Data has clearly demonstrated that the available, safe and effective vaccines (https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines) can lower your risk of developing COVID-19 and experiencing the potential associated serious disease progression, including hospitalization and death.

The FDA is committed to continuing to review emerging data on all COVID-19 therapies related to the potential impact of variants and revise the authorizations further as appropriate to ensure healthcare providers have an effective arsenal of treatments for patients.

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Systemic Corticosteroids

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Multiple randomized trials indicate that systemic corticosteroid therapy improves clinical outcomes and reduces mortality in hospitalized patients with COVID-19 who require supplemental oxygen,[1,2] presumably by mitigating the COVID-19–induced systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. In contrast, in hospitalized patients with COVID-19 who do not require supplemental oxygen, the use of systemic corticosteroids provided no benefit and increased mortality.[3,4] The COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for the use of systemic corticosteroids in hospitalized patients with COVID-19 are based on results from these clinical trials (see Table 5a for more information). There are no data to support the use of systemic corticosteroids in nonhospitalized patients with COVID-19.

Recommendations

- The Panel **recommends against** the use of **dexamethasone** or other systemic corticosteroids in nonhospitalized patients in the absence of another indication **(AIIb)**.
- See Therapeutic Management of Hospitalized Adults With COVID-19 for the Panel's recommendations on the use of dexamethasone or other systemic corticosteroids in certain hospitalized patients.
- Patients with COVID-19 who are receiving **dexamethasone** or another corticosteroid for an underlying condition should continue this therapy as directed by their health care provider **(AIII)**.

Nonhospitalized Adults

There are no data to support the use of systemic corticosteroids in nonhospitalized patients with COVID-19. Therefore, the safety and efficacy of using systemic corticosteroids in this population have not been established. Generally, the use of systemic corticosteroids is associated with adverse events (e.g., hyperglycemia, neuropsychiatric symptoms, secondary infections), which may be difficult to detect and monitor in an outpatient setting. For more information, see General Management of Nonhospitalized Adults With Acute COVID-19.

Hospitalized Adults

The RECOVERY trial was a multicenter, open-label trial in the United Kingdom that randomly assigned 6,425 hospitalized patients to receive up to 10 days of dexamethasone 6 mg once daily plus standard care or standard care alone.[3] Mortality at 28 days was lower among the patients who received dexamethasone than among those who received standard care alone. This benefit of dexamethasone was observed in patients who were mechanically ventilated or who required supplemental oxygen at enrollment. In contrast, no benefit was seen in patients who did not require supplemental oxygen at enrollment.

Among critically ill patients receiving supplemental oxygen with or without mechanical ventilation, several clinical trials, some of which were terminated early, demonstrated lower all-cause mortality at 28 days when systemic corticosteroids were compared with standard of care or placebo.[1]

In addition to the randomized controlled trials, a large observational study evaluated the use of systemic corticosteroids in 15,404 hospitalized patients with positive SARS-CoV-2 polymerase chain reaction or antigen test results from a Department of Veteran Affairs database.[4] Corticosteroids were administered to

60% of the patients within 48 hours of admission, and 95% of the patients who received corticosteroids received dexamethasone. A total of 9,450 patients did not receive supplemental oxygen during the study. Of these patients, 3,514 (37%) received dexamethasone, administered for a median duration of 5 days (IQR 3–8 days). Using average treatment effect estimates, patients who received dexamethasone without supplemental oxygen had an increased risk of death within 90 days (HR 1.76; 95% CI, 1.47–2.12). Patients who received dexamethasone either without supplemental oxygen or with low-flow nasal cannula oxygen had a 60% higher risk of death. Although this study was observational, the investigators employed several statistical techniques to minimize potential bias, including propensity scoring and weighted analyses. Additionally, several subgroup and sensitivity analyses in this study confirmed the overall results.

Dexamethasone Dose

The RECOVERY platform trial studied the use of dexamethasone 6 mg once daily for up to 10 days,[3] which is the currently recommended dose for hospitalized adults with COVID-19. Several other randomized controlled trials evaluated the role of higher doses of dexamethasone or other corticosteroids in hospitalized patients with different levels of respiratory support. The results of some key studies are summarized below.

Patients Who Received Conventional Oxygen or No Supplemental Oxygen

The RECOVERY platform trial included an additional study in which patients with COVID-19 and evidence of hypoxemia (i.e., receiving conventional supplemental oxygen or had oxygen saturation <92% on room air) were randomized to usual care plus high-dose dexamethasone (20 mg once daily for 5 days, then 10 mg once daily for 5 days or until hospital discharge, whichever came first) or usual care alone, which included low-dose dexamethasone (usually 6 mg once daily for 10 days).[5] On May 11, 2022, the trial's independent data monitoring committee stopped enrolling participants receiving conventional oxygen therapy and those not receiving any supplemental oxygen. Among the 1,272 participants enrolled, 28-day mortality was higher in the high-dose dexamethasone arm than in the usual care arm (19% vs. 12%; rate ratio 1.59; 95% CI, 1.20–2.10; $P = 0.0012$).

Patients Who Received Noninvasive or Mechanical Ventilation

The COVID STEROID 2 trial investigated the use of different doses of corticosteroids in people with COVID-19 and severe hypoxemia.[6] In this multicenter trial, hospitalized patients who required at least 10 L/min of oxygen or mechanical ventilation were randomized to receive up to 10 days of dexamethasone 6 mg once daily (n = 485) or dexamethasone 12 mg once daily (n = 497). The median number of days alive without life support at 28 days after randomization was 20.5 days in the dexamethasone 6 mg arm and 22.0 days in the dexamethasone 12 mg arm, yielding an adjusted mean difference of 1.3 days (95% CI, 0–2.6; $P = 0.07$). No differences between the arms were found for 28- or 90-day mortality. Although these conventional analyses did not quite reach statistical significance, a preplanned Bayesian analysis found that dexamethasone 12 mg had a higher probability of benefit and a lower probability of harm than dexamethasone 6 mg.[7]

In the COVIDICUS trial, patients with COVID-19 and acute hypoxemic respiratory failure were randomized to receive dexamethasone 6 mg once daily for 10 days (n = 276, of which 37 received placebo prior to release of results from the RECOVERY trial)[3] or high-dose dexamethasone (i.e., 20 mg once daily for 5 days, then 10 mg once daily for 5 days; n = 270).[8] At baseline, 98 patients were receiving mechanical ventilation, 114 were receiving continuous positive airway pressure, 10 were receiving noninvasive ventilation, 199 were receiving high-flow nasal cannula oxygen, and 125 were receiving standard oxygen therapy through a nonrebreather mask. There was no difference in 60-day mortality between the arms (HR 0.96, 95% CI, 0.69–1.33, $P = 0.79$).

The mixed results from these studies have led the Panel to continue to recommend 6 mg once daily as the preferred dose of dexamethasone in hospitalized patients with COVID-19 who require supplemental oxygen, including patients receiving noninvasive or mechanical ventilation. However, the Panel notes that both the conventional and Bayesian analyses conducted during the COVID STEROID 2 trial suggest that a dose of 12 mg might confer a benefit in patients who require noninvasive or mechanical ventilation.[6,7]

Most patients in the COVID STEROID 2 trial did not receive additional immunomodulators beyond corticosteroids.[6] Currently, there are no data from clinical trials that evaluated the safety and efficacy of using more or less than dexamethasone 6 mg once daily in combination with other immunomodulators to treat hospitalized adults with COVID-19.

Combination Immunomodulator Therapy

Using systemic corticosteroids in combination with other agents, including tocilizumab (see Interleukin-6 Inhibitors)[9,10] or baricitinib (see Janus Kinase Inhibitors),[11] has been shown to have a clinical benefit in subsets of hospitalized patients with COVID-19, especially those with early critical illness and those with signs of systemic inflammation. For the Panel's recommendations on when to use dexamethasone with another immunomodulator, see Therapeutic Management of Hospitalized Adults With COVID-19.

See Table 5a for data from clinical trials that have evaluated the use of systemic corticosteroids in patients with COVID-19.

Systemic Corticosteroids Other Than Dexamethasone

Systemic corticosteroids other than dexamethasone, including hydrocortisone[12,13] and methylprednisolone,[14,15] have been studied for the treatment of COVID-19 in several randomized trials. Some of these trials were stopped early due to under-enrollment following the release of the RECOVERY trial results. Consequently, the sample size of many these trials was insufficient to assess efficacy (i.e., there were too few events to definitively confirm or exclude an effect, although many point estimates suggested a beneficial effect). Therefore, the evidence supporting the use of hydrocortisone or methylprednisolone for the treatment of COVID-19 is not as strong as the evidence supporting the use of dexamethasone. Based on the available evidence, the Panel has concluded the following:

- If dexamethasone is not available, alternative glucocorticoids (e.g., prednisone, methylprednisolone, hydrocortisone) can be used.
- For these drugs, the total daily dose equivalencies to dexamethasone 6 mg (orally or intravenously)[16] are:
  - Prednisone 40 mg
  - Methylprednisolone 32 mg
  - Hydrocortisone 160 mg
- Half-life, duration of action, and frequency of administration vary among corticosteroids.
  - *Long-acting corticosteroid:* Dexamethasone; half-life 36 to 72 hours, administer once daily.
  - *Intermediate-acting corticosteroids:* Prednisone and methylprednisolone; half-life 12 to 36 hours, administer once daily or in 2 divided doses daily.
  - *Short-acting corticosteroid:* Hydrocortisone; half-life 8 to 12 hours, administer in 2 to 4 divided doses daily.

- Hydrocortisone is commonly used to manage septic shock in patients with COVID-19; see Hemodynamics for Adults for more information. Unlike other corticosteroids that have previously been studied in patients with acute respiratory distress syndrome, dexamethasone lacks mineralocorticoid activity and, thus, its effects on sodium balance and fluid volume are minimal.[17]

Monitoring, Adverse Effects, and Drug-Drug Interactions

- Clinicians should closely monitor patients with COVID-19 who are receiving dexamethasone for certain adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects, avascular necrosis).
- The use of systemic corticosteroids may increase the risk of opportunistic fungal infections (e.g., mucormycosis, aspergillosis) and reactivation of latent infections (e.g., hepatitis B virus infection, herpesvirus infections, strongyloidiasis, tuberculosis).[18-22]
- Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.[23,24] Many clinicians would initiate empiric antiparasitic treatment (e.g., with the antiparasitic drug ivermectin) with or without serologic testing in patients who currently reside or who have previously resided in areas where *Strongyloides* is endemic (i.e., tropical, subtropical, or warm temperate areas).[25]
- Using systemic corticosteroids with other immunosuppressants, such as tocilizumab or baricitinib, could theoretically increase the risk of secondary infections. However, clinical trials have reported no difference in the rates of secondary infections between patients who received corticosteroids in combination with another immunomodulatory agent and those who received corticosteroids alone.
- Dexamethasone is a moderate cytochrome P450 (CYP) 3A4 inducer. Therefore, it could reduce the concentration and potential efficacy of concomitant medications that are CYP3A4 substrates. Clinicians should carefully review a patient's concomitant medications to assess the potential for drug-drug interactions.

Considerations in Pregnancy

See Pregnancy, Lactation, and COVID-19 Therapeutics for the Panel's guidance regarding the use of dexamethasone during pregnancy and lactation.

Considerations in Children

Dexamethasone is recommended for hospitalized children with COVID-19 who require supplemental oxygen. See Therapeutic Management of Hospitalized Children With COVID-19 for the Panel's recommendations. Methylprednisolone or another corticosteroid is recommended for the treatment of multisystem inflammatory syndrome in children (MIS-C). See Therapeutic Management of Hospitalized Children With MIS-C, Plus a Discussion on MIS-A for the Panel's recommendations.

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Effectiveness of Face Mask or Respirator Use in Indoor Public Settings for Prevention of SARS-CoV-2 Infection — California, February–December 2021

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The use of face masks or respirators (N95/KN95) is recommended to reduce transmission of SARS-CoV-2, the virus that causes COVID-19 (*1*). Well-fitting face masks and respirators effectively filter virus-sized particles in laboratory conditions (*2,3*), though few studies have assessed their real-world effectiveness in preventing acquisition of SARS-CoV-2 infection (*4*). A test-negative design case-control study enrolled randomly selected California residents who had received a test result for SARS-CoV-2 during February 18–December 1, 2021. Face mask or respirator use was assessed among 652 case-participants (residents who had received positive test results for SARS-CoV-2) and 1,176 matched control-participants (residents who had received negative test results for SARS-CoV-2) who self-reported being in indoor public settings during the 2 weeks preceding testing and who reported no known contact with anyone with confirmed or suspected SARS-CoV-2 infection during this time. Always using a face mask or respirator in indoor public settings was associated with lower adjusted odds of a positive test result compared with never wearing a face mask or respirator in these settings (adjusted odds ratio [aOR] = 0.44; 95% CI = 0.24–0.82). Among 534 participants who specified the type of face covering they typically used, wearing N95/KN95 respirators (aOR = 0.17; 95% CI = 0.05–0.64) or surgical masks (aOR = 0.34; 95% CI = 0.13–0.90) was associated with significantly lower adjusted odds of a positive test result compared with not wearing any face mask or respirator. These findings reinforce that in addition to being up to date with recommended COVID-19 vaccinations, consistently wearing a face mask or respirator in indoor public settings reduces the risk of acquiring SARS-CoV-2 infection. Using a respirator offers the highest level of personal protection against acquiring infection, although it is most important to wear a mask or respirator that is comfortable and can be used consistently.

This study used a test-negative case-control design, enrolling persons who received a positive (case-participants) or negative (control-participants) SARS-CoV-2 test result, from among all California residents, without age restriction, who received a molecular test result for SARS-CoV-2 during February 18–December 1, 2021 (*5*). Potential case-participants were randomly selected from among all persons who received a positive test result during the previous 48 hours and were invited to participate by telephone. For each enrolled case-participant, interviewers enrolled one control-participant matched by age group, sex, and state region; thus, interviewers were not blinded to participants' SARS-CoV-2 infection status. Participants who self-reported having received a previous positive test result (molecular, antigen, or serologic) or clinical diagnosis of COVID-19 were not eligible to participate. During February 18–December 1, 2021, a total of 1,528 case-participants and 1,511 control-participants were enrolled in the study among attempted calls placed to 11,387 case- and 17,051 control-participants (response rates were 13.4% and 8.9%, respectively).

After obtaining informed consent from participants, interviewers administered a telephone questionnaire in English or Spanish. All participants were asked to indicate whether they had been in indoor public settings (e.g., retail stores, restaurants or bars, recreational facilities, public transit, salons, movie theaters, worship services, schools, or museums) in the 14 days preceding testing and whether they wore a face mask or respirator all, most, some, or none of the time in those settings. Interviewers recorded participants' responses regarding COVID-19 vaccination status, sociodemographic characteristics, and history of exposure to anyone known or suspected to have been infected with SARS-CoV-2 in the 14 days before participants were tested. Participants enrolled during September 9–December 1, 2021, (534) were also asked to indicate the type of face covering typically worn (N95/KN95 respirator, surgical mask, or cloth mask) in indoor public settings.

The primary analysis compared self-reported face mask or respirator use in indoor public settings 14 days before SARS-CoV-2 testing between case- (652) and control- (1,176) participants. Secondary analyses accounted for consistency of face mask or respirator use all, most, some, or none of the time. To understand the effects of masking on community transmission, the analysis included the subset of participants who, during the 14 days before they were tested, reported visiting indoor public settings and who reported no known exposure to persons known or suspected to have been infected with SARS-CoV-2. An additional analysis assessed differences in protection against SARS-CoV-2 infection by the type of face covering worn, and was limited to a subset of participants

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enrolled after September 9, 2021, who were asked to indicate the type of face covering they typically wore; participants who indicated typically wearing multiple different mask types were categorized as wearing either a cloth mask (if they reported cloth mask use) or a surgical mask (if they did not report cloth mask use). Adjusted odds ratios comparing history of mask-wearing among case- and control-participants were calculated using conditional logistic regression. Match strata were defined by participants' week of SARS-CoV-2 testing and by county-level SARS-CoV-2 risk tiers as defined under California's Blueprint for a Safer Economy reopening scheme.† Adjusted models accounted for self-reported COVID-19 vaccination status (fully vaccinated with ≥2 doses of BNT162b2 [Pfizer-BioNTech] or mRNA-1273 [Moderna] or 1 dose of Ad.26.COV2.S [Janssen (Johnson & Johnson)] vaccine >14 days before testing versus zero doses), household income, race/ethnicity, age, sex, state region, and county population density. Statistical significance was defined by two-sided Wald tests with p-values <0.05. All analyses were conducted using R software (version 3.6.1; R Foundation). This activity was approved as public health surveillance by the State of California Health and Human Services Agency Committee for the Protection of Human Subjects.

A total of 652 case- and 1,176 control-participants were enrolled in the study equally across nine multi-county regions in California (Table 1). The majority of participants (43.2%) identified as non-Hispanic White; 28.2% of participants identified as Hispanic (any race). A higher proportion of case-participants (78.4%) was unvaccinated compared with control-participants (57.5%). Overall, 44 (6.7%) case-participants and 42 (3.6%) control-participants reported never wearing a face mask or respirator in indoor public settings (Table 2), and 393 (60.3%) case-participants and 819 (69.6%) control-participants reported always wearing a face mask or respirator in indoor public settings. Any face mask or respirator use in indoor public settings was associated with significantly lower odds of a positive test result compared with never using a face mask or respirator (aOR = 0.51; 95% CI = 0.29–0.93). Always using a face mask or respirator in indoor public settings was associated with lower adjusted odds of a positive test result compared with never wearing a face mask or respirator (aOR = 0.44; 95% CI = 0.24–0.82); however, adjusted odds of a positive test result suggested stepwise reductions in protection among participants who reported wearing a face mask or respirator most of the time (aOR = 0.55; 95% CI = 0.29–1.05) or some of the time (aOR = 0.71; 95% CI = 0.35–1.46) compared with participants who reported never wearing a face mask or respirator.

Wearing an N95/KN95 respirator (aOR = 0.17; 95% CI = 0.05–0.64) or wearing a surgical mask (aOR = 0.34; 95% CI = 0.13–0.90) was associated with lower adjusted odds of a positive test result compared with not wearing a mask (Table 3). Wearing a cloth mask (aOR = 0.44; 95% CI = 0.17–1.17) was associated with lower adjusted odds of a positive test compared with never wearing a face covering but was not statistically significant.

Discussion

During February–December 2021, using a face mask or respirator in indoor public settings was associated with lower odds of acquiring SARS-CoV-2 infection, with protection being highest among those who reported wearing a face mask or respirator all of the time. Although consistent use of any face mask or respirator indoors was protective, the adjusted odds of infection were lowest among persons who reported typically wearing an N95/KN95 respirator, followed by wearing a surgical mask. These data from real-world settings reinforce the importance of consistently wearing face masks or respirators to reduce the risk of acquisition of SARS-CoV-2 infection among the general public in indoor community settings.

These findings are consistent with existing research demonstrating that face masks or respirators effectively filter viruses in laboratory settings and with ecological studies showing reductions in SARS-CoV-2 incidence associated with community-level masking requirements (*6*,*7*). While this study evaluated the protective effects of mask or respirator use in reducing the risk the wearer acquires SARS-CoV-2 infection, a previous evaluation estimated the additional benefits of masking for source control, and found that wearing face masks or respirators in the context of exposure to a person with confirmed SARS-CoV-2 infection was associated with similar reductions in risk for infection (*8*). Strengths of the current study include use of a clinical endpoint of SARS-CoV-2 test result, and applicability to a general population sample.

The findings in this report are subject to at least eight limitations. First, this study did not account for other preventive behaviors that could influence risk for acquiring infection, including adherence to physical distancing recommendations. In addition, generalizability of this study is limited to persons seeking SARS-CoV-2 testing and who were willing to participate in a telephone interview, who might otherwise exercise other protective behaviors. Second, this analysis relied on an aggregate estimate of self-reported face mask or respirator use across, for some participants, multiple indoor public locations. However, the study was designed to minimize recall bias by enrolling both case- and control-participants within a 48-hour window of receiving a SARS-CoV-2 test result. Third, small strata limited the ability to differentiate between types of cloth masks or participants who wore different types of face

†https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/COVID-19/COVID19CountyMonitoringOverview.aspx

TABLE 1. Characteristics of case- and control-participants included in analysis of the effectiveness of mask use in indoor public settings, by SARS-CoV-2 test result — California,* February–December 2021

Characteristic	No. (%) Case-participants (SARS-CoV-2–positive) N = 652	No. (%) Control-participants (SARS-CoV-2–negative) N = 1,176
Age group, yrs		
0–6	8 (1.2)	43 (3.7)
7–12	15 (2.3)	49 (4.2)
13–17	25 (3.8)	57 (4.8)
18–29	210 (32.2)	359 (30.5)
30–49	237 (36.3)	409 (34.8)
50–64	109 (16.7)	180 (15.3)
≥65	48 (7.4)	79 (6.7)
Sex		
Male	321 (49.2)	581 (49.4)
Female	331 (50.8)	595 (50.6)
Annual household income		
<$50,000	191 (29.3)	258 (21.9)
$50,000–$99,999	147 (22.5)	254 (21.6)
$100,000–$150,000	60 (9.2)	171 (14.5)
>$150,000	77 (11.8)	197 (16.8)
Refused	106 (16.3)	184 (15.6)
Not sure	71 (10.9)	112 (9.5)
State region†		
San Francisco Bay Area	79 (12.1)	147 (12.5)
Greater Los Angeles Area	77 (11.8)	130 (11.1)
Greater Sacramento Area	53 (8.1)	131 (11.1)
San Diego and southern border	73 (11.2)	142 (12.1)
Central Coast	87 (13.3)	132 (11.2)
Northern Sacramento Valley	69 (10.6)	134 (11.4)
San Joaquin Valley	79 (12.1)	130 (11.1)
Northwestern California	78 (12.0)	113 (9.6)
Sierras	57 (8.7)	117 (9.9)
Race/Ethnicity		
White, non-Hispanic	292 (44.8)	506 (43.0)
Black, non-Hispanic	39 (6.0)	42 (3.6)
Hispanic (any race)	201 (30.8)	315 (26.8)
Asian, non-Hispanic	56 (8.6)	134 (11.4)
American Indian or Alaska Native, non-Hispanic	9 (1.4)	10 (0.9)
Native Hawaiian or Other Pacific Islander, non-Hispanic	2 (0.3)	12 (1.0)
More than one race	40 (6.1)	131 (11.1)
Refused	13 (2.0)	26 (2.2)
COVID-19 vaccination status§		
Unvaccinated or incompletely vaccinated	511 (78.4)	676 (57.5)
Fully vaccinated	115 (17.6)	377 (32.1)
Unknown	26 (4.0)	123 (10.5)
Reopening tier in California¶		
Tier 1 (most restrictive)	125 (19.2)	237 (20.2)
Tier 2	152 (23.3)	255 (21.7)
Tier 3	119 (18.3)	272 (23.1)
Tier 4 (least restrictive)	18 (2.8)	32 (2.7)
After June 15, 2021	238 (36.5)	380 (32.3)
Reasons for SARS-CoV-2 testing**		
Experiencing symptoms	508 (77.9)	196 (16.7)
Testing required for medical procedure	40 (6.1)	199 (16.9)
Routine screening through work or school	71 (10.9)	507 (43.1)
Pre-travel test	33 (5.1)	120 (10.2)
Just wanted to see if I was infected	65 (10.0)	172 (14.6)
Test required for admission to an event or gathering	3 (0.5)	21 (1.8)

* A random sample of California residents with a molecular SARS-CoV-2 test result was invited to participate in a telephone-based survey to document frequency of face mask or respirator use and type of face mask or respirator typically worn in indoor public settings 2 weeks before testing. For each enrolled case-participant (person with a positive SARS-CoV-2 test result), interviewers attempted to enroll one control-participant (person with a negative SARS-CoV-2 test result) whose test result was posted to the reportable disease registry during the 48 hours preceding the call and matched the case-participant by age group, sex, and state region. Among 1,947 case- and control-participants who visited indoor public settings and did not report a known or suspected exposure to SARS-CoV-2 in the 14 days before getting a SARS-CoV-2 test, 119 (6.1%) participants were unable to report face mask use and were excluded from analysis. Parents or guardians served as proxy respondents and answered questions throughout the telephone survey on behalf of children aged <13 years.

† California counties were divided into nine geographic regions. Counties included in each geographic region are listed online in Table S1. https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab640/6324500#supplementary-data

§ Vaccination status was defined using self-reported dates and manufacturers of doses received. Participants were asked to reference their COVID-19 vaccination card while providing vaccination history. Participants who could not provide a complete vaccination history (dates of doses received and manufacturers) were coded as unknown. Full vaccination was defined as receipt of 2 doses of BNT162b2 [Pfizer-BioNTech] or mRNA-1273 [Moderna], or receipt of 1 dose of Ad.26.COV2.S (Janssen [Johnson & Johnson]) >14 days before SARS-CoV-2 testing. Of the 492 fully vaccinated participants, 22 (4.5%) had received a booster dose at the time of enrollment. All other participants were considered unvaccinated or incompletely vaccinated.

¶ Reopening tiers in California were determined by the Blueprint for a Safer Economy the State of California implemented during February 24 to June 15, 2021. This was a tiered system of public health restrictions tied to county-level positive test results and incidence. On June 15, 2021, California retired the tiered reopening system and removed most restrictions on public gatherings, while some counties maintained guidelines for guests and workers to show proof of vaccination or a negative test result to gather in certain types of venues and workplaces. The tier of a given participant was determined by using the date that occurred 14 days before the SARS-CoV-2 specimen collection date recorded for each participant in the California Reportable Disease Registry.

** Case- and control-participants were asked to indicate their reasons for seeking a SARS-CoV-2 test as a free-text response. Trained interviewers (N = 29) recategorized the free-text response into the categories listed in the table. Interviewers were trained to ask probing questions if the free-text response could not be categorized into the reasons listed above. Probing questions and coding decisions may slightly vary by interviewer. Reasons for testing might sum to numbers larger than the total number of case-participants or control-participants because participants could indicate more than one reason for seeking a SARS-CoV-2 test.

TABLE 2. Face mask or respirator use in indoor public settings among persons with positive and negative SARS-CoV-2 test results — California, February–December 2021

Mask type and use*	SARS-CoV-2 infection status, no. (%)		Odds ratio (95% CI)	
	Positive (case-participant) N = 652	Negative (control-participant) N = 1,176	Unadjusted† [p-value]	Adjusted§ [p-value]
None (Ref)	44 (6.7)	42 (3.6)	—	—
Any use†	608 (93.3)	1,134 (96.4)	0.57 (0.37–0.90) [0.02]	0.51 (0.29–0.93) [0.03]
Some of the time	62 (9.5)	76 (6.5)	0.81 (0.47–1.41) [0.49]	0.71 (0.35–1.46) [0.36]
Most of the time	153 (23.5)	239 (20.3)	0.64 (0.40–1.05) [0.08]	0.55 (0.29–1.05) [0.07]
All of the time	393 (60.3)	819 (69.6)	0.49 (0.31–0.78) [<0.01]	0.44 (0.24–0.82) [<0.01]

Abbreviation: Ref = referent group.

* Trained interviewers administered a structured telephone-based questionnaire and asked participants to indicate whether they attended indoor public spaces during the 2 weeks before seeking a SARS-CoV-2 test. Participants who indicated attending these settings were further asked to specify whether they typically wore a face mask or respirator all, most, some, or none of the time while in these settings.

† Conditional logistic regression models were used to estimate the unadjusted odds of mask use by type of face mask or respirator worn in indoor public settings during the 2 weeks before testing. Models included matching strata defined by (for the period before June 15, 2021) the reopening tier of California in the county of residence and the week of SARS-CoV-2 testing.

§ Conditional logistic regression models were used to estimate the odds of face mask or respirator use in indoor public settings during the 2 weeks before testing, adjusting for COVID-19 vaccination status, household income, race/ethnicity, age group, sex, state region, and county population density. All models included matching strata defined by (for the period before June 15, 2021) the reopening tier of California in the county of residence, and the week of SARS-CoV-2 testing. To understand the effects of masking in community settings, this analysis was restricted to a subset of persons who did not indicate a known or suspected exposure to a SARS-CoV-2 case within 14 days of seeking a SARS-CoV-2 test. Adjusted models used a complete case analysis (454 case-participants and 789 control-participants). A sensitivity analysis using multiple imputation of missing covariate values obtained results similar to those reported in the table: adjusted odds ratios were 0.54 (95% CI = 0.33–0.89) for any mask use, 0.44 (95% CI = 0.27–0.73) for mask use all of the time, 0.62 (95% CI = 0.37–1.04) for mask use most of the time, and 0.77 (95% CI = 0.43–1.40) for mask use some of the time. An additional sensitivity analysis was conducted with additional adjustment for the reasons for SARS-CoV-2 testing as listed in Table 1 (experiencing symptoms, testing required for medical procedure, routine screening through work or school, pre-travel test, just wanted to see if I was infected, test required for admission to an event or gathering). The adjusted odds ratio was 0.42 (95% CI = 0.20–0.89) for any mask use as compared to no mask use upon additional adjustment for testing indications.

TABLE 3. Types of face mask or respirator worn in indoor public settings among persons with positive or negative SARS-CoV-2 test results — California, September–December 2021

Mask type*	SARS-CoV-2 infection status, no. (%)		Odds ratio (95% CI)	
	Positive (case-participant) N = 259	Negative (control-participant) N = 275	Unadjusted† [p-value]	Adjusted§ [p-value]
None (Ref)	24 (9.3)	11 (4.0)	—	—
Cloth mask	112 (43.2)	104 (37.8)	0.50 (0.23–1.06) [0.07]	0.44 (0.17–1.17) [0.10]
Surgical mask	113 (43.6)	139 (50.5)	0.38 (0.18–0.81) [0.01]	0.34 (0.13–0.90) [0.03]
N95/KN95 respirator	10 (3.9)	21 (7.6)	0.22 (0.08–0.62) [<0.01]	0.17 (0.05–0.64) [<0.01]

Abbreviation: Ref = referent group.

* Trained interviewers administered a structured telephone-based questionnaire and asked participants enrolled after September 9, 2021, to identify the type of face covering typically worn in indoor public settings during the 2 weeks before seeking a SARS-CoV-2 test. Participants who indicated typically wearing multiple different mask types were categorized as wearing either a cloth mask (if they reported cloth mask use) or a surgical mask (if they didn't report cloth mask use).

† Conditional logistic regression models were used to estimate the unadjusted odds of mask use by type of face mask or respirator worn in indoor public settings during the 2 weeks before testing. Models included matching strata defined by the week of SARS-CoV-2 testing.

§ This analysis was not restricted to persons with no self-reported known or suspected SARS-CoV-2 contact given that this secondary analysis was underpowered upon exclusion of these participants (N = 316) because adjusted models did not converge. Instead, models adjusted for history of known or suspected contact as a covariate. In a sensitivity analysis restricting to participants who did not report known or suspected contact (N = 316), conditional logistic regression models were used to estimate that the unadjusted odds ratios of face mask use by type of face mask with matching strata defined by the week of SARS-CoV-2 testing: 0.13 (95% CI = 0.03–0.61), 0.32 (95% CI = 0.12–0.89), and 0.36 (95% CI = 0.13–1.00) for N95/KN95 respirators, surgical masks, or cloth masks, respectively, relative to no face mask or respirator use.

masks in differing settings, and also resulted in wider CIs and statistical nonsignificance for some estimates that were suggestive of a protective effect. Fourth, estimates do not account for face mask or respirator fit or the correctness of face mask or respirator wearing; assessing the effectiveness of face mask or respirator use under real-world conditions is nonetheless important for developing policy. Fifth, data collection occurred before the expansion of the SARS-CoV-2 B.1.1.529 (Omicron) variant, which is more transmissible than earlier variants. Sixth, face mask or respirator use was self-reported, which could introduce social desirability bias. Seventh, small strata limited the ability to account for reasons for testing in the adjusted analysis, which may be correlated with face mask or respirator use. Finally, this analysis does not account for potential differences in the intensity of exposures, which could vary by duration, ventilation system, and activity in each of the various indoor public settings visited.

The findings of this report reinforce that in addition to being up to date with recommended COVID-19 vaccinations, consistently wearing face masks or respirators while in indoor public settings protects against the acquisition of SARS-CoV-2 infection (*9*,*10*).

Summary

What is already known about this topic?

Face masks or respirators (N95/KN95s) effectively filter virus-sized particles in laboratory settings. The real-world effectiveness of face coverings to prevent acquisition of SARS-CoV-2 infection has not been widely studied.

What is added by this report?

Consistent use of a face mask or respirator in indoor public settings was associated with lower odds of a positive SARS-CoV-2 test result (adjusted odds ratio = 0.44). Use of respirators with higher filtration capacity was associated with the most protection, compared with no mask use.

What are the implications for public health practice?

In addition to being up to date with recommended COVID-19 vaccinations, consistently wearing a comfortable, well-fitting face mask or respirator in indoor public settings protects against acquisition of SARS-CoV-2 infection; a respirator offers the best protection.

This highlights the importance of improving access to high-quality masks to ensure access is not a barrier to use. Using a respirator offers the highest level of protection from acquisition of SARS-CoV-2 infection, although it is most important to wear a well-fitting mask or respirator that is comfortable and can be used consistently.

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SARS-CoV-2 B.1.1.529 (Omicron) Variant Transmission Within Households — Four U.S. Jurisdictions, November 2021–February 2022

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The B.1.1.529 (Omicron) variant, first detected in November 2021, was responsible for a surge in U.S. infections with SARS-CoV-2, the virus that causes COVID-19, during December 2021–January 2022 (*1*). To investigate the effectiveness of prevention strategies in household settings, CDC partnered with four U.S. jurisdictions to describe Omicron household transmission during November 2021–February 2022. Persons with sequence-confirmed Omicron infection and their household contacts were interviewed. Omicron transmission occurred in 124 (67.8%) of 183 households. Among 431 household contacts, 227 were classified as having a case of COVID-19 (attack rate [AR] = 52.7%).† The ARs among household contacts of index patients who had received a COVID-19 booster dose, of fully vaccinated index patients who completed their COVID-19 primary series within the previous 5 months, and of unvaccinated index patients were 42.7% (47 of 110), 43.6% (17 of 39), and 63.9% (69 of 108), respectively. The AR was lower among household contacts of index patients who isolated (41.2%, 99 of 240) compared with those of index patients who did not isolate (67.5%, 112 of 166) (p-value <0.01). Similarly, the AR was lower among household contacts of index patients who ever wore a mask at home during their potentially infectious period (39.5%, 88 of 223) compared with those of index patients who never wore a mask at home (68.9%, 124 of 180) (p-value <0.01). Multicomponent COVID-19 prevention strategies, including up-to-date vaccination, isolation of infected persons, and mask use at home, are critical to reducing Omicron transmission in household settings.

Persons with sequence-confirmed Omicron variant infections during November 2021–February 2022 were identified from four U.S. jurisdictions (Chicago, Illinois; Connecticut; Milwaukee, Wisconsin; and Utah) and contacted by telephone to assess eligibility of the household to participate in the investigation.§ A household was eligible if the index patient did not live in a congregate setting and did live with at least one other person for most of their potentially infectious period, defined as 2 days before through 10 days after the index date (the date of the index patient's positive SARS-CoV-2 nucleic acid amplification test result or antigen test result or symptom onset, whichever occurred first). Index patients were defined as the first person within each household to recently experience COVID-19–compatible symptoms¶ or have a positive SARS-CoV-2 test result. Household contacts were defined as any persons who spent one or more overnights in the residence with the index patient during their potentially infectious period. If it was unclear who within the household was the index patient (e.g., if multiple persons developed COVID-19–compatible symptoms in the household on the same day or had the same SARS-CoV-2 exposure) or if household contacts had confirmed or probable cases and were known to have a SARS-CoV-2 exposure to someone other than the index patient, the household was excluded from analyses.

Index patients and household contacts participated in voluntary telephone interviews to retrospectively collect information on demographic characteristics, SARS-CoV-2 testing, symptoms, COVID-19 vaccination history, previous SARS-CoV-2 infection, index patient isolation practices (defined as always or sometimes isolating in a room by oneself at any point during

* These authors contributed equally to this report.

† In this investigation, a confirmed case in a household contact was defined as having received a positive SARS-CoV-2 nucleic acid amplification test result or antigen test result ≤14 days after the index date (date of the index patient's symptom onset or positive SARS-CoV-2 nucleic acid amplification test result or antigen test result), and a probable case in a household contact was defined as the presence of COVID-19–compatible symptoms during the same 14-day period but without a positive SARS-CoV-2 test confirmation. Persons without symptoms and who did not have a positive SARS-CoV-2 test result were not considered to have a case of COVID-19. Analysis of AR among household contacts excluded eight persons with unknown case status (persons for whom it was not known whether COVID-19–compatible symptoms were present and whether SARS-CoV-2 testing had occurred [or if testing occurred, the results were unknown]).

§ Jurisdictions identified persons who were considered potentially eligible for participation through obtaining laboratory line lists of persons who had sequence-confirmed Omicron (B.1.1.529 lineage and its sublineages) or whose sequencing results were pending. Two jurisdictions attempted to contact all households on their line lists, and two jurisdictions attempted to contact households on their line lists based on specimen collection date.

¶ Persons were provided with the following list of signs and symptoms compatible with COVID-19: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, and diarrhea or abdominal pain during the course of their recent illness. Persons who reported any signs or symptoms during the course of their recent illness were considered to have COVID-19–compatible symptoms. Persons who only had signs or symptoms (and no positive SARS-CoV-2 test result) were considered to have a probable case.

their potentially infectious period), and index patient mask use practices (defined as ever wearing a mask at home during their potentially infectious period). For this investigation, a confirmed case in a household contact was defined as a positive SARS-CoV-2 nucleic acid amplification test result or antigen test result (through local or home testing)** ≤14 days after the index date. A probable case in a household contact was defined as the presence of COVID-19–compatible symptoms in a household contact during the same 14-day period, but without confirmation by a SARS-CoV-2 test.†† Vaccination status was based primarily on self-report§§; participants were categorized as having received a booster dose, fully vaccinated (<5 or ≥5 months before the index date), partially vaccinated, or unvaccinated.¶¶

The interval between the index date and onset of symptoms or positive test result in a household contact was calculated. ARs among household contacts were estimated overall, by household contact characteristics, and by index patient characteristics, by dividing the number of household contacts with confirmed and probable cases by the total number of household contacts within a given stratum. P-values comparing differences in stratum-specific ARs were calculated using a generalized estimating equation approach to account for clustering by household (*2*). Statistical significance was defined as $p<0.05$. Subanalyses were conducted to examine potential secondary transmission (as opposed to all household transmission); the interval was calculated for households of two persons (index patient and another household contact), and ARs were calculated after restricting the case definition to cases identified ≤7 days*** after the index date. Data were collected and managed using REDCap (version 11.1.8; Vanderbilt University) and analyzed using R (version 4.0.3; R Foundation). This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.†††

A total of 3,558 persons were considered potentially eligible for participation in the investigation, among whom jurisdictions attempted to contact 1,461 (41.1%). Of the 562 households successfully contacted, 175 (31.1%) declined to participate, and 204 (36.3%) were excluded; 183 (32.6%) were enrolled. §§§ Enrolled households included 183 index patients and 439 household contacts (Table). The median index patient age was 37 years (IQR = 23–54 years). A majority of index patients were White (59.0%, 108 of 183), and 21.3% (39 of 183) were Hispanic/Latino.

Index dates occurred during November 21, 2021–February 3, 2022.¶¶¶ Among index patients, 172 (94.0%) had a positive SARS-CoV-2 test result (confirmed COVID-19) and 11 (6.0%) had COVID-19–compatible symptoms but without SARS-CoV-2 test confirmation (probable COVID-19). Among 439 household contacts, cases were identified in 227 (51.7%), including 178 (40.5%) confirmed and 49 (11.2%) probable cases; among the remaining household contacts, 204 (46.5%) were classified as non–COVID-19 patients and eight (1.8%) as having unknown status.**** A negative SARS-CoV-2 test result was reported on the day of or after symptom onset by 38.8% (19 of 49) of household contacts classified as having probable COVID-19 and 68.6% (140 of 204) of those classified as not having COVID-19. The median interval between index patient onset date and household contact onset date was 4 days (IQR = 2–7 days) (Figure 1).

Most index patients (88.4%, 152 of 172) and household contacts (78.7%, 140 of 178) with confirmed cases reported COVID-19–compatible symptoms. Of those with known SARS-CoV-2 infection history, eleven (6.1%) of 181 index patients and nine (4.7%) of 192 household contacts with confirmed or probable COVID-19 reported a previous SARS-CoV-2 infection.

** Persons provided retrospective information about any SARS-CoV-2 testing that they chose and were able to perform. Thus, whether someone was tested and how many times they were tested depended on individual and social factors. Interviewers encouraged household contacts who had not received testing to receive testing if the telephone interview occurred ≤14 days after the index date and instructed them to call back with test results. When possible, SARS-CoV-2 testing data were supplemented with or verified using state or jurisdiction registry data.

†† Persons with probable cases included symptomatic persons who did not have SARS-CoV-2 testing and symptomatic persons who received negative SARS-CoV-2 test results.

§§ When possible, vaccination data were supplemented with or verified using state or jurisdiction registry data.

¶¶ Received a booster dose was defined as having received an additional dose after completion of the primary COVID-19 vaccination series before the index date. Fully vaccinated was defined as completion of the primary vaccination series ≥2 weeks before the index date and stratified into completion <5 months or ≥5 months before the index date. Some persons who were fully vaccinated had unknown dates for completion of their primary vaccination series. Partially vaccinated was defined as having only 1 dose of a 2-dose series or completing the primary vaccination series <2 weeks before the index date.

*** Seven days was chosen for this analysis, because 75% of cases occurred ≤7 days after the index date.

††† 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

§§§ Among the 204 excluded households, 143 did not meet eligibility criteria, 47 were excluded because the index patient could not be identified, 11 were excluded because household contacts had confirmed or probable cases and were known to have a SARS-CoV-2 exposure other than exposure to the index patient, and three were excluded when sequencing results (pending at the time of interview) indicated a variant that was not Omicron. All but one of the 183 included households had sequence-confirmed Omicron; this one household had probable Omicron through variant specific qPCR in which the specimen had mutations consistent with the Omicron variant (K417N+ and L452R–).

¶¶¶ The median interval between index date and date of interview was 24 days (IQR = 17–29 days).

**** Case status of household contacts was unknown if the occurrence of COVID-19–compatible symptoms was not known and if the contact's testing results were unknown.

Transmission occurred within 67.8% (124 of 183) of households, and the overall AR among household contacts with known status was 52.7% (227 of 431) (Figure 2). Similar ARs were observed across age groups for household contacts, including those aged 0–4 years (51.2%, 21 of 41). ARs were high across all household contact vaccination categories but lowest among those who received a booster dose (47.8%, 54 of 113) or were fully vaccinated <5 months before the index date (50.0%, 14 of 28). The AR among household contacts with previous SARS-CoV-2 infection was 40.9% (9 of 22) compared with 59.8% (183 of 306) among those without previous infection (p-value = 0.08).

Household contact ARs ranged from a low of 47.5% (19 of 40) when the index patient was aged 5–11 years to a high of 72.0% (18 of 25) when the index patient was aged 0–4 years. The ARs among household contacts by index patient vaccination status were lowest among those who received a booster dose (42.7%, 47 of 110) and those who were fully vaccinated <5 months before the index date (43.6%, 17 of 39). The AR was lower among household contacts of index patients who isolated (41.2%, 99 of 240) compared with those of index patients who did not isolate (67.5%, 112 of 166, p-value<0.01). The AR was lower among household contacts of index patients who reported ever wearing a mask at home during their potentially infectious period (39.5%, 88 of 223) compared with household contacts of index patients who reported never wearing a mask at home during this period (68.9%, 124 of 180, p-value<0.01). Subanalyses focusing on secondary household

TABLE. Characteristics* and vaccination status of index COVID-19 patients (n = 183) and their household contacts (n = 439) — four U.S. jurisdictions, November 2021–February 2022

Characteristic	No. (column %) Index patients, n = 183	Household contacts, n = 439	Total, N = 622
Jurisdiction			
Chicago, Illinois	26 (14.2)	51 (11.6)	**77 (12.4)**
Connecticut	93 (50.8)	218 (49.7)	**311 (50.0)**
Milwaukee, Wisconsin	36 (19.7)	101 (23.0)	**137 (22.0)**
Utah	28 (15.3)	69 (15.7)	**97 (15.6)**
Age group, yrs†			
0–4	8 (4.4)	41 (9.3)	**49 (7.9)**
5–11	11 (6.0)	51 (11.6)	**62 (10.0)**
12–17	14 (7.7)	42 (9.6)	**56 (9.0)**
18–64	134 (73.2)	262 (59.7)	**396 (63.7)**
≥65	14 (7.7)	27 (6.2)	**41 (6.6)**
Unknown	2 (1.1)	16 (3.6)	**18 (2.9)**
Gender			
Female	95 (51.9)	229 (52.2)	**324 (52.1)**
Male	88 (48.1)	199 (45.3)	**287 (46.1)**
Unknown	0 (—)	11 (2.5)	**11 (1.8)**
Race			
White	108 (59.0)	209 (47.6)	**317 (51.0)**
Black	27 (14.8)	35 (8.0)	**62 (10.0)**
Asian	15 (8.2)	25 (5.7)	**40 (6.4)**
Other/Multiple§	16 (8.7)	33 (7.5)	**49 (7.9)**
Unknown	17 (9.3)	137 (31.2)	**154 (24.8)**
Ethnicity			
Non-Hispanic/Latino	130 (71.0)	219 (49.9)	**349 (56.1)**
Hispanic/Latino	39 (21.3)	98 (22.3)	**137 (22.0)**
Other/Unknown	14 (7.7)	122 (27.8)	**136 (21.9)**
COVID-19 vaccination status¶			
Received a booster	57 (31.1)	114 (26.0)	**171 (27.5)**
Fully vaccinated	85 (46.4)	154 (35.1)	**239 (38.4)**
<5 months before index date	12 (6.6)	28 (6.4)	**40 (6.4)**
≥5 months before index date	70 (38.3)	88 (20.0)	**158 (25.4)**
Timing of vaccination unknown	3 (1.6)	38 (8.7)	**41 (6.6)**
Partially vaccinated	2 (1.1)	15 (3.4)	**17 (2.7)**
Not vaccinated	36 (19.7)	129 (29.4)	**165 (26.5)**
Unknown	3 (1.6)	27 (6.2)	**30 (4.8)**
Previous COVID-19 infection status			
Previous infection	11 (6.0)	22 (5.0)	**33 (5.3)**
No previous infection	170 (92.9)	306 (69.7)	**476 (76.5)**
Unknown	2 (1.1)	111 (25.3)	**113 (18.2)**
COVID-19 case status**			
Confirmed	172 (94.0)	178 (40.5)	**350 (56.3)**
Probable	11 (6.0)	49 (11.2)	**60 (9.6)**
Not a case	0 (—)	204 (46.5)	**204 (32.8)**
Unknown	0 (—)	8 (1.8)	**8 (1.3)**

* Persons self-reported their race (White, Black, Asian, American Indian or Alaska Native, or Native Hawaiian or other Pacific Islander), ethnicity (Hispanic/Latino or non-Hispanic/Latino), and gender (male or female) from lists of options and had the opportunity to state another option if their race, ethnicity, or gender was not listed.

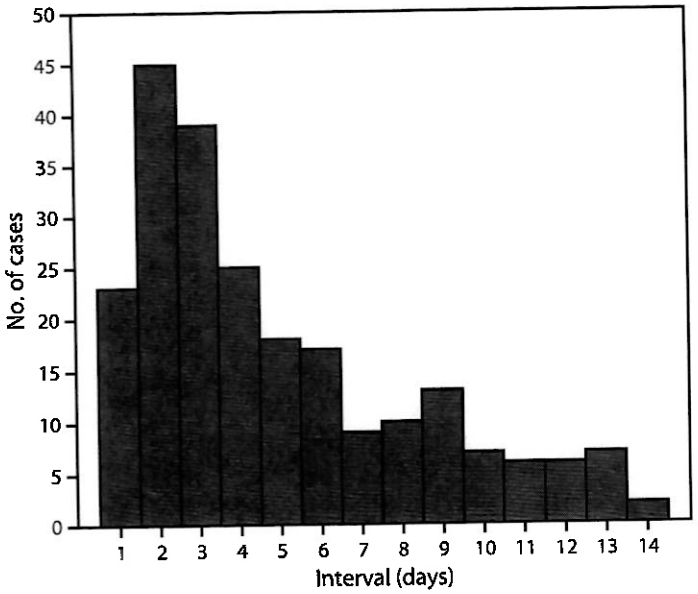
† Age at index date was determined from date of birth or self-reported age.

§ The "other/multiple" race category included American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, another race specified by the person not in the provided list, or multiple races.

¶ Received a booster dose was defined as having received an additional dose after completion of the primary COVID-19 vaccination series before the index date. Fully vaccinated was defined as completion of the primary vaccination series ≥2 weeks before the index date and stratified into completion <5 months or ≥5 months before the index date. Some persons who were fully vaccinated had unknown dates for completion of their primary vaccination series. Partially vaccinated was defined as having only 1 dose of a 2-dose series or completing the primary vaccination series <2 weeks before the index date.

** An index patient with a confirmed COVID-19 case was the first person with a positive SARS-CoV-2 nucleic acid amplification test result or antigen test result (through local or home testing) reported in a household. An index patient with a probable COVID-19 case was the first person with onset of any symptom consistent with COVID-19, but without a positive SARS-CoV-2 test confirmation, reported in a household. A confirmed case in a household contact was receipt of a positive SARS-CoV-2 nucleic acid amplification test result or antigen test result (through local or home testing) reported ≤14 days after the index date. A probable case in a household contact was the presence of any symptom consistent with COVID-19 during the same 14-day period but without a positive SARS-CoV-2 test confirmation.

FIGURE 1. Interval*,† between index patient onset date and household contact onset date — four U.S. jurisdictions, November 2021–February 2022



* The interval was estimated by calculating the number of days between the symptom onset or positive test result date for the index patient and that of the household contact. For both index patients and household contacts, the onset date was either the date of SARS-CoV-2 positive test result or date of symptom onset, whichever occurred first.

† Transmission can occur within a household setting on the first day an index patient is infected or on any subsequent day during which they are still shedding viable virus.

transmission demonstrated a similar interval (median = 3 days, IQR = 2–5) (Supplementary Figure 1, https://stacks.cdc.gov/view/cdc/114723) and similar patterns in ARs (Supplementary Figure 2, https://stacks.cdc.gov/view/cdc/114722).

Discussion

Omicron infection resulted in high ARs among household contacts in this investigation, particularly among those who lived with index patients who were not vaccinated or who did not practice prevention measures (isolating or ever wearing a mask at home). The estimated overall AR in this investigation is consistent with the range of ARs observed in other Omicron transmission studies†††† (*3*), and higher than those associated with some other SARS-CoV-2 variants.§§§§ These findings underscore the importance of implementation of multicomponent prevention measures for reducing SARS-CoV-2 transmission in household settings, including from the Omicron variant (*4*).

ARs were consistently high across household contact and index patient age groups, including those aged 0–4 years. This age group is currently not eligible for vaccination and

Summary

What is already known about this topic?

The SARS-CoV-2 B.1.1.529 (Omicron) variant contributed to a surge of SARS-CoV-2 infections in the United States during December 2021–January 2022.

What is added by this report?

In a study of household transmission in four U.S. jurisdictions, Omicron infection resulted in high transmission among household contacts, particularly among those who lived with index patients who were not vaccinated or who did not take measures to reduce the risk of transmission to household contacts.

What are the implications for public health practice?

Multicomponent COVID-19 prevention strategies, including up-to-date vaccination, isolation of infected persons, and mask use at home, are important to reduce Omicron transmission in household settings.

is a population in which some prevention strategies, such as isolation and mask use, might be difficult or impractical to implement. These findings further highlight young children's potential contribution to household transmission of SARS-CoV-2, as well as their ongoing susceptibility to infection when SARS-CoV-2 is introduced in the home¶¶¶¶ (*5*).

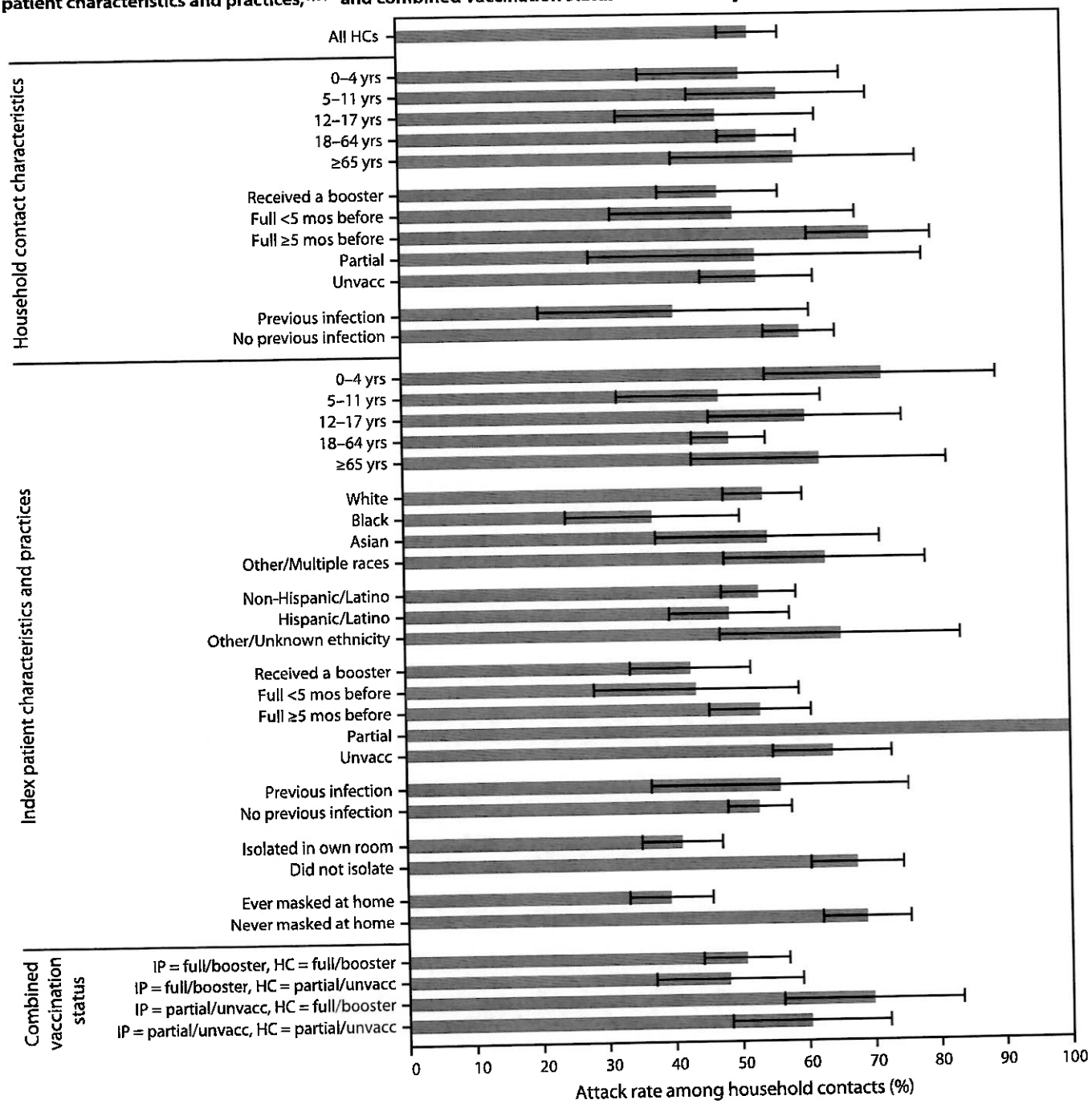
These findings are subject to at least six limitations. First, this investigation used a convenience sample of persons with sequence-confirmed Omicron infections, and participation in this investigation was voluntary. The small sample size, especially for certain stratum-specific ARs, may limit overall generalizability of the results. Households with high transmission or with more attention to public health measures may have been more likely to participate. Second, the investigation relied primarily on self-reported data. Vaccination status was not always verified, and the analysis did not account for potential variations in prevention practices (e.g., frequency of mask use). Third, COVID-19 prevention measures (vaccination, isolation, and mask use) are likely highly correlated within households, and the identified risk factors might not be independent predictors of transmission. Fourth, the interval analysis reflected time between dates of a positive test result or symptom onset, not date of infection, and did not account for duration of symptoms and prevention strategies, such as frequency of mask use. Fifth, this investigation did not definitively distinguish between secondary and potential tertiary cases within a household. Finally, this investigation occurred during a period when testing and sequencing capacity was strained and when many persons traveled and attended gatherings, increasing the possibility that household contacts had unknown SARS-CoV-2 exposures outside the home (*6*).

†††† https://www.medrxiv.org/content/10.1101/2021.12.27.21268278v1

§§§§ https://www.medrxiv.org/content/10.1101/2022.01.09.22268984v1

¶¶¶¶ https://www.medrxiv.org/content/10.1101/2021.08.16.21262121v2

FIGURE 2. SARS-CoV-2 infection attack rates* among household contacts (N = 431) with known case status, by household contact characteristics,†,§ index patient characteristics and practices,†,§,¶ and combined vaccination status — four U.S. jurisdictions, November 2021–February 2022**



Abbreviations: Full = fully vaccinated; HC = household contact; IP = index patient; Partial = partially vaccinated; Unvacc = unvaccinated.

* Analysis of attack rates among HCs excluded persons with unknown case status or "unknown" categorization within a given stratum. 95% CIs for attack rates are represented by error bars.

† Age at index date was determined from date of birth or self-reported age.

§ Received a booster dose was defined as having received an additional dose after completion of the primary COVID-19 vaccination series before the index date. Fully vaccinated was defined as completion of the primary vaccination series ≥2 weeks before the index date and stratified into completion <5 months or ≥5 months before the index date. Some persons who were fully vaccinated had unknown dates for completion of their primary vaccination series. Partially vaccinated was defined as having only 1 dose of a 2-dose series or completing the primary vaccination series <2 weeks before the index date.

¶ Persons reported their race (White, Black, Asian, American Indian or Alaska Native, or Native Hawaiian or other Pacific Islander) and ethnicity (Hispanic/Latino or non-Hispanic/Latino) from lists of options and had the opportunity to state another option if their race or ethnicity was not listed. The "other/multiple races" category included American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, another race specified by the person not in the provided list, or multiple races.

** Analysis for attack rates by combined vaccination status combined persons who were fully vaccinated or had received a booster dose into one category (full/booster) and persons who were partially vaccinated or unvaccinated into another category (partial/unvacc).

Because SARS-CoV-2 testing was not available for all household contacts, ability to detect asymptomatic infections was limited. Without sequencing results for all household contact cases, it was not possible to confirm that transmission occurred from index patients to household contacts or that household contacts were infected with the same variant.

The findings from this investigation reinforce the importance of multi-component prevention strategies, including up-to-date vaccination, isolation of infected persons, and mask use at home, to reduce Omicron transmission in household settings.

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School Masking Policies and Secondary SARS-CoV-2 Transmission

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abstract

OBJECTIVES: Throughout the COVID-19 pandemic, masking has been a widely used mitigation practice in kindergarten through 12th grade (K–12) school districts to limit within-school transmission. Prior studies attempting to quantify the impact of masking have assessed total cases within schools; however, the metric that more optimally defines effectiveness of mitigation practices is within-school transmission, or secondary cases. We estimated the impact of various masking practices on secondary transmission in a cohort of K–12 schools.

METHODS: We performed a multistate, prospective, observational, open cohort study from July 26, 2021 to December 13, 2021. Districts reported mitigation practices and weekly infection data. Districts that were able to perform contact tracing and adjudicate primary and secondary infections were eligible for inclusion. To estimate the impact of masking on secondary transmission, we used a quasi-Poisson regression model.

RESULTS: A total of 1 112 899 students and 157 069 staff attended 61 K–12 districts across 9 states that met inclusion criteria. The districts reported 40 601 primary and 3085 secondary infections. Six districts had optional masking policies, 9 had partial masking policies, and 46 had universal masking. In unadjusted analysis, districts that optionally masked throughout the study period had 3.6 times the rate of secondary transmission as universally masked districts; and for every 100 community-acquired cases, universally masked districts had 7.3 predicted secondary infections, whereas optionally masked districts had 26.4.

CONCLUSIONS: Secondary transmission across the cohort was modest (<10% of total infections) and universal masking was associated with reduced secondary transmission compared with optional masking.

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Drs Boutzoukas and Inkelas conceptualized and designed the study, designed the data collection instruments, collected data, conducted the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript; Drs Butteris, DeMuri, and Mr Koval designed the data collection instruments, collected data, and reviewed and revised the manuscript; Drs Benjamin and Brookhart carried out the analyses and reviewed and revised the manuscript; Drs. Manuel, Smith, McGann, Weber, Falk, Kalu, Shane, Schuster, Goldman, Mr Koval, Mr Hickerson, Ms Edwards, Ms Erickson, and Ms Benjamin collected data and reviewed and revised the manuscript; Drs Zimmerman and Benjamin, Jr. designed the data collection instruments, collected data, reviewed and revised the manuscript, conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for

WHAT IS KNOWN ON THE SUBJECT: During the coronavirus disease 2019 pandemic, masking has been a widely used mitigation strategy Prior studies have been limited in their ability to evaluate whether masking is associated with decreased secondary transmission in schools.

WHAT THIS PAPER ADDS: Within-school (secondary) transmission was modest (<10%) in this multistate cohort of 61 K–12 districts, representing over 1 million students and staff. On unadjusted analysis, universal masking was associated with a 72% reduction in secondary transmission compared with optional masking.

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Throughout the coronavirus disease 2019 (COVID-19) pandemic, kindergarten through 12th grade (K–12) school safety has been a major focus of the Centers for Disease Control and Prevention, as well as state and local authorities. Earlier work suggested that mitigation through masking and distancing prevented school environments from being major drivers of transmission;[1–10] however, the arrival of the delta variant in the summer of 2021 intensified concerns about possible K–12 transmission, since the delta variant induced a substantial increase in community-derived cases compared with prior variants.[9] Given the evolving pandemic, coupled with changing national guidance and local policies, K–12 schools used a variety of methods to prevent transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the fall of 2021. These methods often differed substantially from the homogenous environments of universal masking, some physical distancing, and prolonged quarantines following exposure described in early studies of K–12 SARS-CoV-2 transmission. Moreover, prior studies assessing the impact of specific mitigation strategies also used total cases as a measure of K–12 school safety,[11,12] without attempting to distinguish between cases acquired in the community (primary infections) and those acquired at school (secondary infections). Importantly, the definitive metric of interest in determining the safety of in-person instruction is the proportion of total infections in a school community that are attributed to within-school (secondary) transmission. This metric is also critical to help districts determine the direct impact of individual mitigation strategies and policies.

Variability in K–12 school mitigation practices have made it possible to evaluate the relative contribution of each practice to reducing within-school transmission, especially when community rates are high.[13] The aim of the current study was to demonstrate the impact of various masking practices on secondary transmission in K–12 districts across the United States, using primary and secondary infection case metrics.

METHODS

We performed a national, prospective, observational, open cohort study from July 26, 2021 to December 13, 2021. Notably, these data were primarily collected during a period of the COVID-19 pandemic when the delta variant was the predominant variant. Data collection concluded at the start of the omicron variant surge in the United States. To assess whether surrounding county vaccination rates across categories of masking influenced the ratio of secondary to primary infections, we re-estimated our model, allowing for vaccination rates to have different effects across masking regimes.

School District Recruitment and Data Collection

We sought to conduct an inclusive and broad assessment of national policies and transmission within schools, so participating districts were recruited from states in which study team members were located, supplemented by districts that responded to an offer sent to every public school district in the United States (more than 13 800 districts) using an e-mail list derived from state education agency websites. Subsequent criteria for inclusion in the study can be seen in Fig 1. School districts that expressed interest in the study ($n = 143$) received initial surveys that included questions specific to a district's demographics, district-level policies on masking, requirements for quarantine, lunch procedures, definitions of close contacts, and vaccination requirements; of these, 85 districts (59%) completed the initial survey.

We invited participating school districts to provide weekly counts of SARS-CoV-2 primary cases, secondary cases, and quarantines for staff and students. These data were provided as aggregate counts at the school level and were analyzed at an aggregate district level; therefore, details on cases including student versus staff were not available. On a monthly basis, we administered brief surveys on district-level policies to assess changes in policies during the study period. Districts submitted data via AirTable (San Francisco, CA). Web-based data display enabled districts to visualize case counts and rates, as well as quarantine counts for their own data and (anonymously) for other participating districts over time.

Of the 85 participating districts, 73 (86%) districts submitted at least 1 week of infection and quarantine data; most districts that submitted at least 1 week of infection and quarantine data ultimately completed >5 weeks of data entry (64 of 73; 87.7%), while a minority of districts completed <3 weeks (8 of 73; 11%) or 3 to 5 weeks of data entry (1 of 73; 1.4%). Of the 73 districts that reported infection data, 67 districts reported case data with adjudication of primary and secondary infections. Finally, 6 districts did not consistently (100% of the reporting period) adjudicate case source as primary versus secondary infections and were excluded from analyses; ultimately 61 districts were included in quasi-Poisson regressions.

Definitions and Outcome Measures

Primary infections were those deemed to have been acquired in the community. Secondary infections were those deemed to have been acquired in the school environment

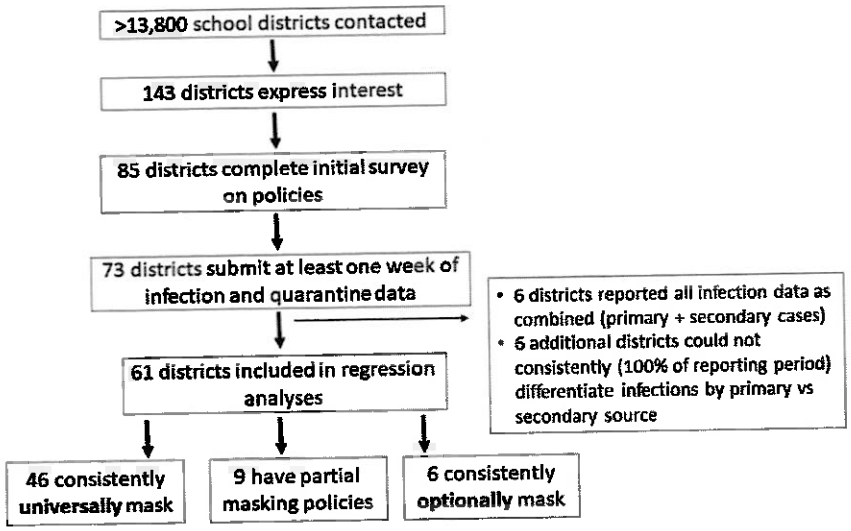

FIGURE 1
Enrollment and subsequent study inclusion. This figure displays the study population, from enrollment through exclusions, to the final study population comprised of 61 school districts: of these, 46 districts consistently universally masked, 9 partially masked, and 6 consistently optionally masked.

(ie, school-associated infections). In general, classification of primary versus secondary infection was adjudicated by school health staff in collaboration with the local public health department, according to the above definitions. There was not a category for "uncertain" source of transmission, and all local health departments followed their individual practices to determine whether the case was primarily or secondarily acquired. For analysis of secondary transmission by various masking categories, we characterized each district into 1 of the following categories: universal, optional, or partial masking. We defined a district as having either a universal or optional masking policy if they maintained this practice for the entire study period. Districts that had varying masking policies throughout the course of the study were categorized as having partial masking policies. The most common versions of partial masking policies were either: (1) starting the semester with optional masking but moving toward universal masking across the entire district; or (2) requiring masking in some grade levels, but not others; or (3) requiring masking when the community reached a specific transmission rate.

The primary outcome of interest was the number of secondary cases expected to result from additional primary cases, which we called the secondary-to-primary infection ratio, a practical measure that allows districts to measure the effectiveness of mitigation measures within schools. A higher secondary-to-primary infection ratio signifies more within-school transmission events occurring for each person who enters school with a community-acquired SARS-CoV-2 infection. Additional outcomes of interest included rates of secondary infections adjusted for district size and number of weeks reporting.

Data Monitoring and Cleaning

The research team convened monthly calls with districts to discuss data results and quality, contacting districts when potential data quality issues were identified. Each study team member was responsible for a given region of the country; when possible, team members were assigned to districts where relationships with district leadership already existed. Research team members were responsible for monitoring data from their districts and maintaining close collaboration, including multiple phone calls with district leadership to ensure that primary and secondary infections were consistently reported and that policy changes were captured. Where in-person student or staff enrollment numbers (not infection data) were missing from districts, several attempts were made to obtain these data from the districts; if these attempts were unsuccessful, then publicly available data on staff and student enrollment numbers were imputed.

Statistical Analysis

We performed descriptive analyses on aggregate data from contributing districts and characterized the demographics of participating districts, initial policies, and changes to policies. To predict secondary transmission among students and staff by masking policy, we used a quasi-Poisson regression model using the log of student and staff primary cases as an offset (denominator) and estimated predicted secondary transmission per 100 primary infections with 95% confidence intervals that accounted for overdispersion of the observed counts. We calculated the relative rate of secondary transmission from the quasi-Poisson regression model using universal masking as the reference category. To evaluate the influence of large districts' data on the results, we conducted 2 sensitivity analyses removing all districts with more than 20 000 students enrolled and more than 10 000 students enrolled and repeated the above analyses. As a secondary analysis, we evaluated secondary transmission per 1000 district population (calculated by

summing students and staff in-person) per total weeks each district reported data, via repeated quasi-Poisson regression, with primary infections per 1000 district population as the denominator. To assess whether surrounding county vaccination rates across categories of masking influenced the ratio of secondary to primary infections, we re-estimated our model, allowing for vaccination rates to have different effects across masking regimes. We conducted analyses using Stata (StataCorp, Stata Statistical Software: Release 16.1. College Station, TX: StataCorp LLC) and R version 4.0.2.[14]

Institutional Review Board

No personal health information data were obtained or transmitted. This study was approved by the Duke University Hospital System Institutional Review Board (Pro00108129).

RESULTS

The 61 districts that met inclusion criteria were composed of 1 112 899 students and 157 069 staff attending in-person school across 9 states: 29 from North Carolina, 23 from Wisconsin, 3 from Missouri, 1 from California, 1 from Washington, 1 from Georgia, 1 from Tennessee, 1 from Kansas, and 1 from Texas (Table 1).[15,16] These districts reported an average of 13.5 weeks (standard deviation of 4.8) of infection data. In total, these 61 districts had 40 601 primary infections (36 032 among students, and 4569 among staff) and 3085 secondary infections (2844 among students, and 241 among staff), with an aggregate secondary-to-primary ratio of .08.

Six districts (10%) had optional masking policies, 9 had partial masking (15%), and the remaining 46 districts (75%) had required masking for the entirety of the study. Of those with partial masking policies, 4 districts switched from optional to universal masking during the study period, 2 districts transitioned between optional and required masking more than once during the reporting period, and 3 districts had optional masking with requirements for masking at either various grade levels or based on community transmission thresholds. We did not see a difference between transmission at elementary, middle, or high school levels using a univariate analysis. Districts that were fully masked had lower predicted secondary infections per primary infection than districts that

TABLE 1 Demographics, Policies Used by Districts, Vaccination Rates, and Community Transmission

	All Districts $n = 61$ (%)	Universal Masking Policy[a] $n = 46$ (%)	Partial Masking Policies $n = 9$ (%)	Optional Masking Policy $n = 6$ (%)
Students in-person	1 112 899	1 075 982	32 967	3950
Staff in-person	157 069	151 149	5294	626
District size[b]				
0–4999	34 (56)	23 (50)	5 (56)	6 (100)
5000–20 000	16 (26)	12 (26)	4 (44)	0 (0)
>20 000	11 (18)	11 (24)	0 (0)	0 (0)
Initial quarantine policy[c]				
CDC guidance	21 (34)	17 (38)	1 (11)	3 (50)
Unmasked and unvaccinated close contacts quarantine	32 (52)	24 (53)	6 (67)	2 (33)
None	1 (2)	0 (0)	0 (0)	1 (17)
Other	3 (5)	1 (2)	2 (2)	0 (0)
Not reported	4 (7)	4 (9)	0 (0)	0 (0)
Lunch policy[d]				
Distancing and/or outdoor eating	40 (66)	31 (67)	7 (78)	2 (33)
No lunch policy	21 (34)	15 (33)	2 (22)	4 (67)
Vaccine required for eligible students	1 (2)	1 (2)	0 (0)	0 (0)
Vaccine required for eligible staff	6 (10)	6 (13)	0 (0)	0 (0)
Vaccination rates in surrounding county[e]				
Initiation of study (12–18 y), %	36	41	23	20
Termination of study (5–18 y), %	38	42	25	23
County community transmission, cases per 100 000 population per 7 d[f]				
Initiation of study	97	100	107	63
Termination of study	295	266	369	417

CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; K–5, kindergarten through fifth grade.

[a] "Partial" masking districts included: 4 districts that initially had optional masking and transitioned to masks required, 2 districts that transitioned between mask optional and required more than once during the study period, and 3 districts that had required and optional masking varying by either school grade level, or by community transmission threshold.

[b] District size determined by number of students enrolled.

[c] Initial quarantine policy was reported by the schools on the initial policy survey. "Unmasked and unvaccinated close contacts quarantine" category includes districts that required quarantine only if the exposed person was unmasked and unvaccinated. In the case that the exposed person was either masked during exposure or vaccinated, quarantine was in general not required. "Other" districts include 1 district that quarantinec all K–5 classrooms if there was a positive case, but in grades 6 to 12, quarantine was only required for unmasked exposures; 1 district that required quarantine for any unvaccinated person within 3 feet or within 90 d of COVID-19 infection; and 1 district where quarantine depended on level of school.

[d] "Distancing and/or outdoor eating" category included those districts who either ate indoors and implemented distancing or staggering of lunches or ate outdoors (with or without a distancing requirement).

[e] Vaccination rates as reported by CDC vaccinations in the United States,[15] by County dataset include percent of ages 12 to 18 y in the county containing the district with at least 1 vaccine at start of study (as of July 26, 2021); as authorization of COVID-19 vaccine for ages 5 to 11 y occurred during the study period, termination of study vaccination rates include percent of ages 5 to18 y with at least 1 vaccine in the county containing the districts (as of December 13, 2021).

[f] Community transmission for each county corresponding to a district as reported by the CDC County Level of Community Transmission, including Historical Changes database,[16] as cases per 100 000 population per 7 days. "Initiation of study" date was July 26, 2021 and "termination of study" date was December 13, 2021.

TABLE 2 Quasi-Poisson Regression of Predicted Secondary Cases and Relative Rate of Secondary Transmission by Masking Policy

Masking Policy	Districts, *n* (%)	Students and Staff, *n*	Total Primary Infections, *n*	Total Secondary Infections, *n*	Predicted Secondary Cases per 100 Primary Cases	95% CI	Relative Rate of Secondary Transmission	95% CI
Universal	46	1 227 131	38 200	2776	7.3	6.3–8.4	—	—
Partial[a]	9	38 261	2106	231	11.0	6.5–18.4	1.5	0.88–2.59
Optional	6	4576	295	78	26.4	10.9–64.4	3.6	1.47–8.98

CI, confidence interval; —, reference group for regression analysis.

[a] Partial masking districts included: 4 districts that initially had optional masking and transitioned to masks required, 2 districts that transitioned between mask optional and required more than once during the study period, and 3 districts that had required and optional masking varying by either school grade level, or by community transmission threshold.

had an optional masking policy using a quasi-Poisson regression analysis (Table 2). Among the various policies, 100 additional primary cases were predicted to yield 26.4 secondary cases in districts with optional masking, 11.0 secondary cases in districts with partial masking, and 7.3 secondary cases in districts with universal masking. The relative rate of secondary transmission in optionally masked districts was 3.6 times the rate of secondary transmission in universally masked districts; equivalently, universal masking was associated with an estimated 72% reduction in secondary transmission compared with districts with optional masking (Fig 2). When we accounted for the possibility that differences in vaccination rates might have different effects across masking regimes, we found that the estimates of the effects of masking policies were substantively identical to our original estimates. A sensitivity analysis removing the 11 districts in the largest size class (more than 20 000 students) and the results were substantively unchanged (Supplemental Table 4); a sensitivity analysis removing the 15 districts with >10 000 students had similar results (Supplemental Table 5).

Upon an additional analysis that adjusted for district size and weeks reporting data, we found consistent results: districts with optional masking had 7.5 times the predicted rate of secondary transmission compared with universally masked districts (Table 3). Universal masking was associated with an 87% reduction in predicted secondary transmission rates compared with optionally masked districts.

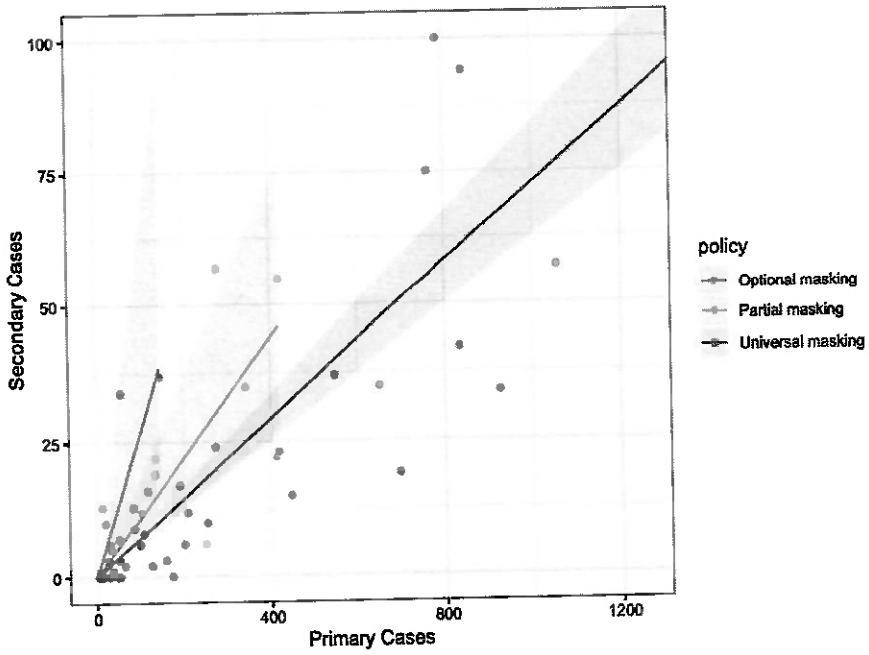

FIGURE 2
Predicted impact of masking policy on secondary transmission. Predicted impact of masking policy on secondary transmission according to optional masking, partial masking, or universal masking. Actual observations are shown by dots, predicted secondary cases are shown by solid lines, and 95% confidence intervals for the mean predictions are shown by shaded areas.

DISCUSSION

This study provides estimates of secondary transmission from a multistate, diverse network of K–12 school districts in the fall of 2021. Consistent with earlier data,[1–4,7,8] secondary transmission across the entire study cohort was low, with more than 90% of cases identified in school members originating from the community. As more students have returned to in-person instruction, schools have been more constrained in their ability to implement physical distancing. The predominant mitigation strategies have been masking and vaccinations for children 5 years of age and older. Among districts with universal masking policies, secondary transmission was reduced by 72% on unadjusted analysis, comparedwith districts having optional masking policies.

TABLE 3 Quasi-Poisson Regression of Predicted Secondary Cases and Relative Rate of Secondary Transmission by Masking Policy, Adjusted Per Capita and by Weeks Reporting to Study

Masking Policy	Districts, *n* (%)	Students and Staff, *n*	Mean Primary Infections per 1000 Students and Staff per Week, *n*	Mean Secondary Infections per 1000 Students and Staff per Week, *n*	Predicted Secondary Cases per 100 Primary Cases	95% CI	Relative Rate of Secondary Transmission	95% CI
Universal	46	1 227 131	2.7	0.16	5.8	3.62–9.27	—	—
Partial[a]	9	38 261	4.3	0.52	12.0	6.64–21.53	2.1	0.97–4.38
Optional	6	4576	5.4	2.33	43.5	30.99–61.10	7.5	4.21–13.42

CI, confidence interval; —, reference group for regression analysis.
[a] Partial masking districts included: 4 districts that initially had optional masking and transitioned to masks required, 2 districts that transitioned between mask optional and required more than once during the study period, and 3 districts that had required and optional masking varying by either school grade level, or by community transmission threshold.

At least 2 prior studies have examined the relationship between masking policies and SARS-CoV-2 infections in schools; both studies concluded that universal masking reduced infections compared with no masking,[11,12] but these studies were limited in their ability to specifically evaluate school-associated transmission. Documentation of within-school transmission is important because during periods of increased community rates, the total number of infections in a school's students and staff are expected to increase but evaluating the proportion of infections acquired within school can shed light on safety specific to the school environment. Therefore, the findings from our current study are important, particularly in times of higher community infection rates with more transmissible variants, like omicron. In such times, masking remains a critical mitigation effort to support continued in-person education. Assessment of primary and secondary infection metrics requires contact tracing to adjudicate the infection source.

Our study also highlights a framework for the current and future pandemics, allowing districts to self-monitor the success of their highly variable mitigation measures, make decisions based on their unique risk tolerances, respond to local politics, and inform on- and off-ramp decisions, particularly as vaccinations of school-aged children have become available. Though we did not notice systematic differences between transmission rates by school level, we did note some heterogeneity in transmission in a subset of schools within a district that could often be linked to mitigation practice adherence. For example, district leaders from 1 large district that had a universal masking policy noticed that the proportion of secondary infections early in the fall 2021 was higher than in previous time periods throughout the pandemic, specifically within a small subset of schools; at one point, 5% of the schools in the district were responsible for more than 30% of the secondary transmission. District leadership systematically monitored masking compliance at each school as previously described,[17] and observed a subsequent decrease to near 0 in secondary infections in high-risk schools. Through close monitoring, a second district observed a substantial increase in secondary transmission after instituting optional masking and returned to universal masking to preserve in-person learning. Notably, the measures in this study are limited by practical considerations and by the ability of school districts and their local public health authorities to test and adjudicate potential secondary cases. When testing is accessible and contact tracing is supported and performed, districts that can monitor trends in their schools will be able to make decisions to best support their local communities as the pandemic evolves.

LIMITATIONS

Our study had some limitations. First, our study was observational; policies were not randomized and, therefore, potential confounders may not be balanced among masking policy groups. Second, some districts changed policies during the study period, possibly in response to within-school transmission rates (eg, districts that started with universal masking may have switched to optional masking if transmission rates were low, and similarly, optional masking districts may have switched to universal masking if confronted with high levels of within-school transmission). Nonetheless, this dynamic should attenuate the contrast between the universal masking and optional masking districts. Third, our study relied on contact tracing, which is dependent upon local resources and testing accessibility, and may become strained at times of high community transmission. There may have been mis-adjudicated cases and missed diagnoses because testing was not required across the entire cohort following exposure; however, we do not suspect that these challenges

with contact tracing are systematically different in masked versus unmasked districts. In 1 prior study, contact tracing in the K–12 environment was consistent with infection source determined by genomic sequencing;[6] however, contact tracing and testing are admittedly limited by available public health resources. In turn, this may limit the generalizability of our findings. Fourth, volunteer bias may have influenced the initial decision to participate in the study and individual districts' ongoing participation. Fifth, the participating optional masking districts originated from only smaller-sized districts, but after performing a sensitivity analysis that removed the larger districts, we found substantively identical results. Additionally, study results were robust to control for district size and weeks reported. Sixth, our study was largely completed around the time the more highly infectious omicron variant emerged, so the results may not be directly generalizable to the current context of SARS-CoV-2 mitigation. Finally, though our study is large and diverse, it is not nationally representative since it originated from 9 states.

CONCLUSIONS

Our study assessed secondary transmission, the metric of interest in evaluating the success of SARS-CoV-2 mitigation, across a multistate sample of K–12 school districts in the United States. We found that overall rates of secondary transmission were modest, and that universal masking policies were associated with markedly reduced secondary transmission compared with optional masking districts. Maintaining in-person instruction is critical for children. Providing districts with the tools to monitor transmission data in real time enables schools to respond to changing national and local policies, as well as adjust their mitigation efforts to keep in-person education as safe as possible for the remainder of the COVID-19 pandemic.

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ABBREVIATIONS

COVID-19: coronavirus disease 2019
K–12: kindergarten through 12th grade
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

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Effectiveness of Mask Wearing to Control Community Spread of SARS-CoV-2

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Prior to the coronavirus disease 2019 (COVID-19) pandemic, the efficacy of community mask wearing to reduce the spread of respiratory infections was controversial because there were no solid relevant data to support their use. During the pandemic, the scientific evidence has increased. Compelling data now demonstrate that community mask wearing is an effective nonpharmacologic intervention to reduce the spread of this infection, especially as source control to prevent spread from infected persons, but also as protection to reduce wearers' exposure to infection.

COVID-19 spreads primarily through respiratory droplets exhaled when infected people breathe, talk, cough, sneeze, or sing. Most of these droplets are smaller than 10 μm in diameter, often referred to as *aerosols*. The amount of small droplets and particles increases with the rate and force of airflow during exhalation (eg, shouting, vigorous exercise). Exposure is greater the closer a person is to the source of exhalations. Larger droplets fall out of the air rapidly, but small droplets and the dried particles formed from them (ie, droplet nuclei) can remain suspended in the air. In circumstances with poor ventilation, typically indoor enclosed spaces where an infected person is present for an extended period, the concentrations of these small droplets and particles can build sufficiently to transmit infection.

Community mask wearing substantially reduces transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 2 ways. First, masks prevent infected persons from exposing others to SARS-CoV-2 by blocking exhalation of virus-containing droplets into the air (termed *source control*). This aspect of mask wearing is especially important because it is estimated that at least 50% or more of transmissions are from persons who never develop symptoms or those who are in the presymptomatic phase of COVID-19 illness.[1] In recent laboratory experiments, multilayer cloth masks were more effective than single-layer masks, blocking as much as 50% to 70% of exhaled small droplets and particles.[2,3] In some cases, cloth masks have performed similar to surgical or procedure masks for source control. Second, masks protect uninfected wearers. Masks form a barrier

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Additional Information: The science summarized in this article is reviewed in greater detail with a full set of references on the Centers for Disease Control and Prevention's COVID-19 website Scientific Brief: Community Use of Cloth Masks to Control the Spread of SARS-CoV-2 (https://www.cdc.gov/coronavirus/2019-ncov/more/masking-sciencesars-cov2.html). This website and a public slide deck will be updated periodically.

to large respiratory droplets that could land on exposed mucous membranes of the eye, nose, and mouth. Masks can also partially filter out small droplets and particles from inhaled air. Multiple layers of fabric and fabrics with higher thread counts improve filtration. However, the observed effectiveness of cloth masks to protect the wearer is lower than their effectiveness for source control,[3] and the filtration capacity of cloth masks can be highly dependent on design, fit, and materials used. Standards for cloth masks are needed to help consumers select marketed products.

Epidemiological investigations have helped quantify the benefit of mask wearing to prevent the spread of SARS-CoV-2 (Table; Supplement). At a hair salon in which all staff and clients were required to wear a mask under local ordinance and company policy, 2 symptomatic, infected stylists attended to 139 clients and no infections were observed in the 67 clients who were reached for interviewing and testing. During a COVID-19 outbreak on the USS Theodore Roosevelt, persons who wore masks experienced a 70% lower risk of testing positive for SARS-CoV-2 infection.[4] Similar reductions have been reported in case contact investigations when contacts were masked[5] and in household clusters in which household members were masked.[6]

An increasing number of ecological studies have also provided persuasive evidence that universal mandatory mask wearing policies have been associated with reductions in the number or rate of infections and deaths (Table). These studies did not distinguish the types of masks (cloth, surgical, or N95) used in the community. This association is strengthened because, in many cases, other mitigation strategies (eg, school and workplace closures, recommendations for social distancing, hand hygiene) had already been deployed before enactment of mask wearing policies, after which the reductions were observed. A study that examined changes in growth rates for infections in 15 states and the District of Columbia before and after mask mandates showed that rates were growing before the mandates were enacted and slowed significantly after, with greater benefit the longer the mandates had been in place.[7]

Wearing a mask can become uncomfortable, particularly for long periods in warm environments, and covering the nose and mouth may inhibit verbal and nonverbal communication, particularly for children and deaf individuals. However, children aged 7 to 13 years have been shown to be able to make accurate inferences about the emotions of others with partially covered faces,[8] and the US Food and Drug Administration recently approved a transparent surgical mask that may be useful in such circumstances. Concerns about reduced oxygen saturation and carbon dioxide retention when wearing a mask have not been supported by available data.[9]

The overall community benefit of wearing masks derives from their combined ability to limit both exhalation and inhalation of infectious virus. Similar to the principle of herd immunity for vaccination, the greater the extent to which the intervention–mask wearing in this case–is adopted by the community, the larger the benefit to each individual member. The prevalence of mask use in the community may be of greater importance than the type of mask worn. It merits noting that a recent study has been improperly characterized by some sources as showing that cloth or surgical masks offer no benefit. This randomized trial

in Denmark was designed to detect at least a 50% reduction in risk for persons wearing surgical masks. Findings were inconclusive,[10] most likely because the actual reduction in exposure these masks provided for the wearer was lower. More importantly, the study was far too small (ie, enrolled about 0.1% of the population) to assess the community benefit achieved when wearer protection is combined with reduced source transmission from mask wearers to others.

During past national crises, persons in the US have willingly united and endured temporary sacrifices for the common good. Recovery of the nation from the COVID-19 pandemic requires the combined efforts of families, friends, and neighbors working together in unified public health action. When masks are worn and combined with other recommended mitigation measures, they protect not only the wearer but also the greater community. Recommendations for masks will likely change as more is learned about various mask types and as the pandemic evolves. With the emergence of more transmissible SARS-CoV-2 variants, it is even more important to adopt widespread mask wearing as well as to redouble efforts with use of all other nonpharmaceutical prevention measures until effective levels of vaccination are achieved nationally.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table.

Studies of the Effect of Mask Wearing on SARS-CoV-12 Infection Risk[a]

Source	Location	Population studied	Intervention	Outcome
Hendrix et al	Hair salon in Springfield, Missouri	139 Patrons at a salon with 2 infected and symptomatic stylists	Universal mask wearing in salon (by local ordinance and company policy)	No COVID-19 infections among 67 patrons who were available for follow-up
Payne et al	USS Theodore Roosevelt, Guam	382 US Navy service members	Self-reported mask wearing	Mask wearing reduced risk of infection by 70% (unadjusted odds ratio, 0.30 [95% CI, 0.17-0.52])
Wang Y et al	Households in Beijing, China	124 Households of diagnosed cases comprising 335 people	Self-reported mask wearing by index cases or ≥1 household member prior to index case's diagnosis	Mask wearing reduced risk of secondary infection by 79% (adjusted odds ratio, 0.21 [95% CI, 0.06-0.79])
Doung-ngern et al	Bangkok, Thailand	839 Close contacts of 211 index cases	Self-reported mask wearing by contact at time of high-risk exposure to case	Always having used a mask reduced infection risk by 77% (adjusted odds ratio, 0.23 [95% CI, 0.09-0.60])
Gallaway et al	Arizona	State population	Mandatory mask wearing in public	Temporal association between institution of mask wearing policy and subsequent decline in new diagnoses
Rader et al	US	374 021 Persons who completed web-based surveys	Self-reported mask wearing in grocery stores and in the homes of family or friends	A 10% increase in mask wearing tripled the likelihood of stopping community transmission (adjusted odds ratio, 3.53 [95% CI, 2.03-6.43])
Wang X et al	Boston, Massachusetts	9850 Health care workers (HCWs)	Universal masking of HCWs and patients in the Mass General Brigham health care system	Estimated weekly decline in new diagnoses among HCWs of 3.4% after full implementation of the mask wearing policy
Mitze et al	Jena (Thuringia), Germany	City population aged ≥15 y	Mandatory mask wearing in public spaces (eg, public transport, shops)	Estimated daily decline in new diagnoses of 1.32% after implementation of the mask mandate
Van Dyke et al	Kansas	State population	Mandatory mask wearing in public spaces	Estimated case rate per 100 000 persons decreased by 0.08 in counties with mask mandates but increased by 0.11 in those without
Lyu and Wehby	15 US states and Washington, DC	State populations	Mandatory mask wearing in public	Estimated overall initial daily decline in new diagnoses of 0.9% grew to 2.0% at 21 days following mandates
Karaivanov et al	Canada	Country population	Mandatory mask wearing indoors	Estimated weekly 25%-40% decline in new diagnoses following mask mandates

[a]See the Supplement for the complete table.

CellPress

Uniting Infectious Disease and Physical Science Principles on the Importance of Face Masks for COVID-19

Monica Gandhi[1,*] and Linsey C. Marr[2]

This commentary will summarize the evidence on face masks for COVID-19 from both the infectious diseases and physical science viewpoints; standardize recommendations on types of masks that afford the best protection to the public; and provide guidelines on messaging for this important non-pharmaceutical intervention as we await widespread vaccine distribution.

Epidemiologic Evidence for the Importance of Masking during COVID-19

The Centers for Disease Control and Prevention (CDC) advised the U.S. population to wear cloth face coverings in public on April 3, 2020, initially citing the reasoning that masks would protect others during the COVID-19 pandemic. However, mask wearing prevalence in the U.S. has been variable across regions of the country, compared to 95% adherence in countries where cultural norms or mandates facilitated the practice.[1] In the U.S., there has not yet been a federal mask mandate, although individual counties and states have successively (but not uniformly) instituted individual mandates.

Epidemiologic and observational evidence for the importance of mask wearing in reducing COVID-19 transmission has been accumulating, much of which was recently summarized in a scientific brief by the CDC, including a case control study from Thailand and data from Beijing households and commercial airplanes.[2] Table 1 outlines the seminal studies. For instance, impressive reductions in COVID-19 transmission were seen during the summer 2020 surge with institution of a state-wide mask mandate, among other interventions, in Arizona.[3] Similarly, when Kansas counties imposed mask mandates unevenly during the summer surge, COVID-19 incidence decreased in the counties with mask mandates, but continued to increase in those without.[4] A recent paper showed a 47% reduction in new COVID-19 transmissions (estimate between 15% and 75%) over a period of 20 days after the institution of regional mask mandates in Germany.[5]

In contrast, a recent study in Denmark randomized individuals to an arm where surgical masks were recommended and provided versus a standard-of-care arm and demonstrated only a modest benefit in limiting COVID-19 transmission.[7] However, several design limitations of the trial—including low incidence at the time of the trial, inadequate sample size, randomization at the level of the individual instead of a community, and issues with adherence to mask-wearing and outcome ascertainment—likely hindered its ability to more substantially show the benefits of mask-wearing for COVID-19,[8] making the epidemiologic and implementation evidence more compelling.

Beyond the impact on COVID-19 transmission rates, our group[9] and others have hypothesized that facial masking could reduce the size of the viral inoculum to which people are exposed and, if they become infected, decrease the severity of the resultant COVID-19 disease. The association between inoculum size and disease severity has been seen in a Syrian hamster model with SARS-CoV-2, and surgical mask partitions were shown to reduce infections and disease severity in another hamster model. By reducing inhalation of viral particles by the mask wearer, masks can protect the individual from COVID-19 acquisition[2] or, if acquired, possibly lead to a milder or asymptomatic infection.

Laboratory Evidence on How Surgical and Cloth Masks Protect the Wearer and Others from COVID-19

Initial guidance from the CDC on the use of cloth face coverings was focused on the protection this would afford to others (an approach termed source control). In a scientific brief published November 9, 2020, the CDC reiterated the benefit of face coverings to protect others, while emphasizing that masks also protect the wearer (filtration for personal protection).[2]

Masks work by blocking or filtering out viruses that are carried in aerosols. Filtering is not sieving out things that are too large to pass through holes in the material. Rather, air must curve as it flows around individual, tightly packed fibers of the material, like a race car swerving around cones of an obstacle course. As the air curves, the aerosols it carries cannot make the sharp bends and therefore slam into the fibers, or they come too close to the fibers and stick to them. Very small aerosols acquire random motion from

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Table 1. Epidemiologic and Observational Studies Showing the Effectiveness of Masks in Reducing COVID-19 Transmission

Setting	Exposure of interest	Effect
USS Theodore Roosevelt aircraft carrier	face coverings during an outbreak	service members who wore face coverings had lower infection rate than those who did not (55.8% versus 80.8%)
Hair salons in Missouri	two masked hair stylists infected with COVID-19 exposed 139 clients, all masked	none of the 139 clients developed symptoms with 67 testing negative for SARS-CoV-2
Boston health care settings	institution of universal surgical masking with provision in hospitals	significantly lower rate of SARS-CoV-2 positivity among health care workers after masking
Arizona during summer surge	mask mandates, limiting large crowds, social distancing	transmission rates were up by 151% prior to these measures and then stabilized and decreased by 75% with continued application
Kansas counties during summer surge	state mask mandate with option for counties to opt-out in Kansas	COVID-19 incidence decreased in 24 counties with mask mandates after July 3, but continued to increase in 81 counties without mask mandates[4]
Tennessee counties	mask requirements	areas with mask requirements had a slower growth rate in hospitalizations for COVID-19 (without controlling for cases) than those without mask requirements[6]
States in the U.S.	mask mandates in 15 states and Washington, DC over summer	reduction in COVID-19 transmission rates in states mandating face mask use in public compared to those without mandates
Germany	regional mandates for mandatory mask wearing in public transport and shops	face masks reduced the number of new COVID-19 infections 45% (between 15% and 75%) over a period of 20 days after the mandates[5]

*Unless indicated, all references are found in the CDC Scientific Brief[2]

air molecules bouncing off them and end up crashing into the fibers. This process works in both directions as air flows through a mask. With those principles in mind, we will now discuss evidence from the physical sciences about how masks block both transmission and acquisition of SARS-CoV-2 in order to reinforce this message that masks protect you and others. We also provide recommendations on specific face coverings that maximize protection.

Laboratory studies have demonstrated the ability of surgical masks to block SARS-COV-2 and other viruses. Viruses are carried in respiratory droplets and aerosols that, even when fully dried, contain far more salts and proteins than virus, so the size of concern is much larger than that of a naked virus. Surgical masks are made of melt-blown, nonwoven polypropylene, similar to N95 masks. Researchers tested surgical masks on two manikins that were facing each other. SARS-CoV-2 virions were nebulized out the mouth of one manikin and were sampled through the mouth of the opposite manikin. The masks were 60%–70% effective at protecting others and 50% effective at protecting the wearer.[10] The mechanism by which masks block viruses depends purely on the physical characteristics of the carrier droplet or aerosol and not the virus itself, so evidence for other viruses can be extended to SARS-COV-2 with careful consideration of the size of the droplets and aerosols involved. For instance, in a study of patients with documented infections with either seasonal coronaviruses or influenza virus, surgical masks blocked coronaviruses released into the air to undetectable levels and partially blocked influenza virus.[11] Testing of eight different surgical masks on a manikin exposed to influenza virus in droplets and aerosols found that they protected the wearer by an average of 80%.[12] The protective ability of cloth masks is more variable. Studies of dozens of materials have found material filtration efficiencies of <10% for polyurethane foam to nearly 100% for a vacuum cleaner bag.[13,14] According to fit tests on humans, homemade masks are 50%–60% efficient at protecting the wearer against air pollution particles.[15]

Our group recently tested ten different types of face coverings for their effectiveness at protecting others as well as the wearer.[14] Masks in our study protected the wearer more than others but this difference was not statistically significant. Based on our and others' results, we recommend a high-quality surgical mask or a fabric mask of at least two layers with high thread count for basic protection (Figure 1, top panel) for the public. For maximal protection (Figure 1, bottom panel), members of the public can either (1) wear a cloth mask tightly on top of a surgical mask where the surgical mask acts as a filter and the cloth mask provides an additional layer of filtration while improving the fit; or (2) wear a three-layer mask with outer layers consisting of a flexible, tightly woven fabric that can conform well to the face and a middle layer consisting of a nonwoven high-efficiency filter material (e.g., vacuum bag material). If the masks fit well, these combinations should produce an overall efficiency of >90% for particles 1 μm and larger, which corresponds to the size of respiratory aerosols that we think are most important in mediating transmission of COVID-19.[14]

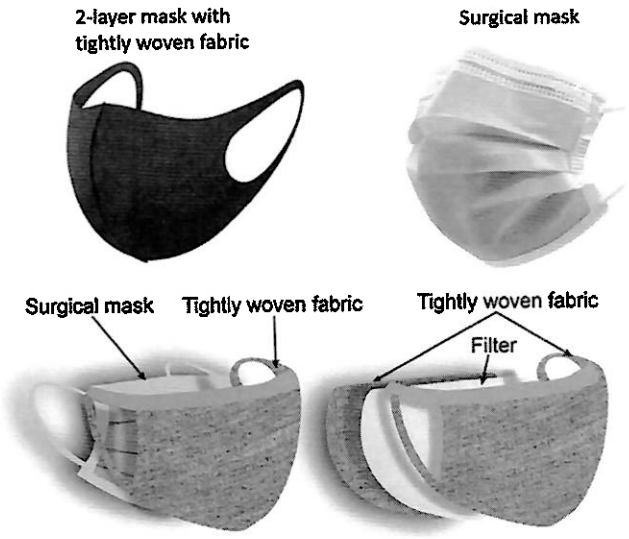

Figure 1. Recommended Masks for Public
Top: basic; bottom: maximal protection.

Ways to Effectively Provide Public Health Messaging on the Importance of Facial Masks during COVID-19

Finally, we recommend a variety of techniques to more effectively communicate the importance of facial masking in the U.S. to control COVID-19. Modeling of public health guidelines—such as facial masking—by leaders can encourage the populace to adopt this recommendation. Under new Presidential leadership as of January 2021, we suspect that mask modeling will gain in prominence as we enter the second year of the pandemic. For instance, President-Elect Biden has urged Americans to wear masks for the first 100 days of his administration as we await widespread vaccine distribution. Mask provision in essential workplaces can encourage mask adherence. Mask mandates, with enforcement strategies as needed, can be highly effective in expanding mask wearing prevalence.[1]

Finally, we recommend a harm reduction-based, non-stigmatizing approach to our public health messaging on face masking. Harm reduction—when applied to disease prevention for infectious diseases—is the principle of advising individuals how to mitigate risk while acknowledging the real-world conditions that may lead individuals to take some risks. Mask-shaming or calling individuals selfish for not wearing a mask is the most ineffective way to achieve trust in public health officials and should not be part of our messaging. We are recommending a new non-pharmacological intervention (NPI) for the American public that was not previously a part of our cultural norms. This NPI will be necessary to adhere to for some time as we achieve equitable and widespread distribution of a safe and effective vaccine.

Although the recent news that the Moderna and Pfizer/BioNTech mRNA vaccines are more than 94% efficacious in protecting against symptomatic COVID-19 is very encouraging, asymptomatic infection could not be ruled out in either trial among vaccine recipients. Moreover, the duration of vaccine protection is not yet known and widespread vaccination to reach an appropriate level of population-level immunity (60%–70%) will take some time. Therefore, mask wearing will need to continue until the cessation of this pandemic and may be required if there is another. We recommend messaging on the importance of facial masks with kindness, evidence, and empathy and a nationwide mask mandate[1] to encourage adherence and get through this pandemic together.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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Respiratory Virus Shedding in Exhaled Breath and Efficacy of Face Masks

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Abstract

We identified seasonal human coronaviruses, influenza viruses and rhinoviruses in the exhaled breath and coughs of children and adults with acute respiratory illness. Surgical face masks significantly reduced detection of influenza virus RNA in respiratory droplets and coronavirus RNA in aerosols, with a marginally significant reduction in coronavirus RNA in respiratory droplets. Our results indicate that surgical facemasks could prevent transmission of human coronaviruses and influenza viruses from symptomatic individuals.

Keywords

influenza virus; coronavirus; aerosol; face mask; public health

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AUTHOR CONTRIBUTIONS

All authors meet the ICMJE criteria for authorship. The study protocol was drafted by NHLL and BJC. Data were collected by NHLL, EYCS and BJPH. Laboratory testing was done by DKWC and KHC. Statistical analyses were done by NHLL. NHLL and BJC wrote the first draft of the manuscript, and all authors provided critical review and revision of the text and approved the final version.

COMPETING INTERESTS STATEMENT

BJC consults for Roche and Sanofi Pasteur. The authors report no other potential conflicts of interest.

INTRODUCTION

Respiratory virus infections cause a broad and overlapping spectrum of symptoms collectively referred to as acute respiratory virus illnesses (ARIs), or more commonly the "common cold". Although mostly mild, these ARIs can sometimes cause severe disease and death[1]. These viruses spread between humans through direct or indirect contact, respiratory droplets (including larger droplets that fall rapidly near the source as well as coarse aerosols with aerodynamic diameter >5μm) and fine particle aerosols (droplets and droplet nuclei with aerodynamic diameter ≤5μm)[2,3]. Although hand hygiene and use of face masks, primarily targeting contact and respiratory droplet transmission, have been suggested as important mitigation strategies against influenza virus transmission[4], little is known about the relative importance of these modes in the transmission of other common respiratory viruses[2,3,5]. Uncertainties similarly apply to the modes of transmission of COVID-19[6,7].

Some health authorities recommend that masks are worn by ill individuals to prevent onwards transmission (i.e. source control)[4,8]. Surgical face masks were originally introduced to protect participants from wound infection and contamination from surgeons (the wearer) during surgical procedures, and were later adopted to protect healthcare workers against acquiring infection from their patients. However, most of the existing evidence on the filtering efficacy of face masks and respirators comes from in vitro experiments with non-biological particles[9,10] which may not be generalizable to infectious respiratory virus droplets. There is little information on the efficacy of face masks in filtering respiratory viruses and reducing viral release from an individual with respiratory infections[8], with most research focusing on influenza[11,12].

Here we aimed to explore the importance of respiratory droplet and aerosol routes of transmission with a particular focus on coronaviruses, influenza viruses and rhinoviruses, by quantifying the amount of respiratory viruses in exhaled breath of participants with medically-attended ARI and determining the potential efficacy of surgical face masks to prevent respiratory virus transmission.

RESULTS

We screened 3,363 individuals in two study phases, ultimately enrolling 246 individuals who provided exhaled breath samples (Supporting Figure 1). Among these 246 participants, 122 (50%) participants were randomized to not wearing a face mask during the first exhaled breath collection and 124 (50%) participants randomized to wearing a face mask. 49 (20%) voluntarily provided a second exhaled breath collection of the alternate type.

Infections by at least one respiratory virus were confirmed by RT-PCR in 123/246 (50%) participants. Of these 123 participants, 111 (90%) were infected by human (seasonal) coronavirus (n=17), influenza virus (n=43), or rhinovirus (n=54) (Supporting Figure 1, Supporting Figure 2), including one participant co-infected by both coronavirus and influenza virus, and another two participants co-infected by both rhinovirus and influenza virus. These 111 participants were the focus of our analyses.

There were some minor differences in characteristics of the 111 participants with the different viruses (Table 1a). 24% of participants had a measured fever ≥37.8°C, with influenza patients more than twice as likely than coronavirus and rhinovirus-infected patients to have a measured fever. Coronavirus-infected participants coughed the most with an average of 17 (SD 30) coughs during the 30-minute exhaled breath collection. The profiles of the participants randomized to with-mask vs without-mask groups were similar (Supplementary Table 1).

We tested viral shedding (in terms of viral copies per sample) in nasal swabs, throat swabs, respiratory droplet samples, and aerosol samples, and compared the latter two between the samples collected with or without a face mask (Figure 1a–c). On average the viral shedding was higher in nasal swabs than in throat swabs for each of coronavirus (median 8.1 $\log_{10}$ virus copies per sample vs. 3.9), influenza virus (6.7 vs. 4.0) and rhinovirus (6.8 vs. 3.3) respectively. Viral RNA was identified from both respiratory droplets and aerosols for all three viruses, including 30%, 26% and 28% of the respiratory droplets, and 40%, 35% and 56% of the aerosols collected while not wearing a face mask, from coronavirus, influenza virus and rhinovirus-infected participants respectively (Table 1b). In particular for coronavirus, we identified OC43 and HKU1 from both respiratory droplets and aerosols, but only identified NL63 from aerosols and not from respiratory droplets (Supplementary Table 2, Supporting Figure 3).

We detected coronavirus in respiratory droplets and aerosols in 3/10 (30%) and 4/10 (40%) of the samples collected without face masks, respectively, but did not detect any virus in respiratory droplets or aerosols either collected from participants wearing face masks, this difference was significant in aerosols and marginally significant in respiratory droplets (Table 1b). For influenza virus, we detected virus in 6/23 (26%) and 8/23 (35%) of the respiratory droplet and aerosol samples collected without face masks, respectively. There was a significant reduction by wearing face masks to 1/27 (4%) in detection of influenza virus in respiratory droplets, but no significant reduction in detection in aerosols (Table 1b). Moreover, among the 8 participants who had influenza virus detected by RT-PCR from without-mask aerosols, 5 were tested by viral culture and 4 were culture positive. Among the 6 participants who had influenza virus detected by RT-PCR from with-mask aerosols, 4 were tested by viral culture and 2 were culture positive. For rhinovirus, there were no significant differences between detection of virus with or without face masks, both in respiratory droplets and in aerosols (Table 1b). Conclusions were similar in comparisons of viral shedding (Table 1b). In addition, we found a significant reduction in viral shedding (Supplementary Table 2) in respiratory droplets for OC43 (Supporting Figure 4) and influenza B virus (Supporting Figure 5), and in aerosols for NL63 (Supporting Figure 4).

We identified correlations between viral loads in different samples (Supporting Figures 6–8) and some evidence of declines in viral shedding by time since onset for influenza virus but not for coronavirus or rhinovirus (Supporting Figure 9). In univariable analyses of factors associated with detection of respiratory viruses in various sample types, we did not identify significant association in viral shedding with days since symptom onset (Supplementary Table 3) for respiratory droplets or aerosols (Supplementary Tables 4–6).

A subset of participants (72/246, 29%) did not cough at all during at least one exhaled breath collection, including 37/147 (25%) during the without-mask and 42/148 (28%) during the with-mask breath collection. In this subset for coronavirus (n=4), we did not detect any virus in respiratory droplets or aerosols from any participants. In the subset for influenza virus (n=9), we detected virus in aerosols but not respiratory droplets from one participant. For rhinovirus (n=17), we detected virus in respiratory droplets from 3 participants, and we detected virus in aerosols in 5 participants.

DISCUSSION

Our results indicate that aerosol transmission is a potential mode of transmission for coronaviruses as well as influenza viruses and rhinoviruses. Published studies detected respiratory viruses[13,14] such as influenza[12,15] and rhinovirus[16] from exhaled breath, and the detection of SARS-CoV[17] and MERS-CoV[18] from air samples (without size fractionation) collected from hospitals treating SARS and MERS patients, but ours is the first to demonstrate detection of human seasonal coronaviruses in exhaled breath, including the detection of OC43 and HKU1 from respiratory droplets, and NL63, OC43 and HKU1 from aerosols.

Our findings indicate that surgical masks can efficaciously reduce the emission of influenza virus particles into the environment in respiratory droplets, but not in aerosols[12]. Both the previous and current study used a bioaerosol collecting device, the Gesundheit-II (G-II)[12,15,19], to capture exhaled breath particles and differentiated into two size fractions, where exhaled breath coarse particles >5μm (respiratory droplets) were collected by impaction with a 5.0μm slit inertial Teflon impactor and the remaining fine particles ≤5μm (aerosols) were collected by condensation in buffer. We also demonstrated the efficacy of surgical masks to reduce coronavirus detection and viral copies in large respiratory droplets and in aerosols (Table 1b). This has important implications for control of COVID-19, suggesting that surgical face masks could be used by ill persons to reduce onwards transmission.

Among the samples collected without a face mask, we found that the majority of participants with influenza virus and coronavirus infection did not shed detectable virus in respiratory droplets or aerosols, while for rhinovirus we detected virus in aerosols in 19/34 (56%) participants (compared to 4/10 (40%) for coronavirus and 8/23 (35%) for influenza). For those who did shed virus in respiratory droplets and aerosols, viral load in both tended to be low (Figure 1). Given the high collection efficiency of the G-II[19], and given that each exhaled breath collection was done for 30 minutes, this might imply that prolonged close contact would be required for transmission to occur, even if transmission was primarily via aerosols as has been described for rhinovirus colds[20]. Our results also indicate that there could be considerable heterogeneity in contagiousness of individuals with coronavirus and influenza virus infections.

The major limitation of our study was the large proportion of participants with undetectable viral shedding in exhaled breath for each of the viruses studied. We could have increased the sampling duration beyond 30 minutes to increase the viral shedding being captured, at the

cost of acceptability in some participants. An alternative approach would be to invite participants to perform forced coughs during exhaled breath collection[12]. However, it was the aim of our present study to focus on recovering respiratory virus in exhaled breath in a real-life situation, and we expected some individuals during an acute respiratory illness would not cough much or at all. Indeed, we identified virus RNA in a small number of participants who did not cough at all during the 30-minute exhaled breath collection, which would suggest droplet and aerosol routes of transmission are possible from individuals with no obvious signs or symptoms. Another limitation is that we did not confirm infectivity of coronavirus or rhinovirus detected in exhaled breath. While the G-II was designed to preserve viability of viruses in aerosols, and in the present study we were able to identify infectious influenza virus in aerosols, we did not attempt to culture coronavirus or rhinovirus from the corresponding aerosol samples.

METHODS

Study design

Participants were recruited year-round from March 2013 through May 2016 in a general outpatient clinic of a private hospital in Hong Kong. As routine practice, clinic staff screened all individuals attending the clinics for respiratory and any other symptoms regardless of the purpose of the visit at the triage. Study staff then approached immediately those who reported at least one of the following symptoms of acute respiratory illness (ARI) for further screening: fever≥37.8°C, cough, sore throat, runny nose, headache, myalgia and phlegm. Individuals who reported ≥2 ARI symptoms, within 3 days of illness onset and ≥11 years of age were eligible to participate. After explaining the study to and obtaining informed consent from the participant, a rapid influenza diagnostic test, the Sofia Influenza A+B Fluorescent Immunoassay Analyzer (Cat #20218, Quidel, San Diego, CA), was used to identify influenza A or B virus infection as an incentive to participate. All participants provided a nasal swab for the rapid test, and an additional nasal swab and a separate throat swab for subsequent virologic confirmation at the laboratory. All participants also completed a questionnaire to record basic information including age, sex, symptom severity, medication, medical conditions and smoking history. In the first phase of the study from March 2013 to February 2014 ('Influenza Study'), the result of the rapid test was used to determine eligibility for further participation in the study and exhaled breath collection; while in the second phase of the study from March 2014 to May 2016 ('Respiratory Virus Study'), the rapid test did not affect eligibility. Eligible participants were then invited to provide an exhaled breath sample for 30 minutes in the same clinic visit.

Prior to the exhaled breath collection, each participant was randomly allocated in a 1:1 ratio to either wearing a surgical face mask (Cat #62356, Kimberly-Clark, Roswell, Georgia) or not during the collection. To mimic the real-life situation, under the observation by the study staff participants were asked to attach the surgical mask themselves, but instruction on how to wear the mask properly was given when the participant wore the mask incorrectly. Participants were instructed to breathe as normal during the collection, but (natural) coughing was allowed and the number of coughs was recorded by study staff. Participants were then invited to provide a second exhaled breath sample of the alternate type (e.g. if the

participant was first assigned to wearing a mask he/she would then provide a second sample without a mask), but most participants did not agree to stay for a second measurement because of time constraints. Participants were compensated for each 30-minute exhaled breath collection with a supermarket coupon worth approximately US$30 and all participants were gifted a tympanic thermometer worth approximately US$20.

Ethical approval

Written informed consent was obtained from all participants ≥18 years of age, and written informed consent was obtained from parents or legal guardians of participants 11–17 years of age in addition to their own written informed consent. The study protocol was approved by the Institutional Review Board of The University of Hong Kong and the Clinical and Research Ethics Committee of Hong Kong Baptist Hospital.

Collection of swabs and exhaled breath particles

Nasal swabs and throat swabs were collected separately, placed in virus transport medium (VTM), stored and transported to the laboratory at 2–8°C, and the VTM were aliquoted and stored at −70°C until further analysis. Exhaled breath particles were captured and differentiated into two size fractions, the coarse fraction containing particles with aerodynamic diameter >5μm (referred to here as 'respiratory droplets') included droplets up to approximately 100 μm in diameter) and the fine fraction with particles ≤5μm (referred to here as 'aerosols') by the "G-II" bioaerosol collecting device[12,15,19]. In the G-II device, exhaled breath coarse particles >5μm were collected by a 5.0μm slit inertial Teflon impactor, and the remaining fine particles ≤5μm were condensed and collected into about 170ml of 0.1%BSA/PBS. Both the impactor and the condensate were stored and transported to the laboratory at 2–8°C. The virus on the impactor was recovered into 1ml, and the condensate was concentrated into 2ml of 0.1% BSA/PBS, aliquoted and stored at −70°C until further analysis. In a validation study, the G-II was able to recover over 85% of fine particles >0.05μm in size, and had comparable collection efficiency of influenza virus as the SKC BioSampler[19].

Laboratory testing

Samples collected from the two Studies were tested at the same time. Nasal swab samples were first tested by a diagnostic-use viral panel, xTAG Respiratory Viral Panel (Abbott Molecular, Illinois, USA), to detect qualitatively twelve common respiratory viruses and subtypes including coronaviruses (NL63, OC43, 229E and HKU1), influenza A (non-specific, H1 and H3) and B viruses, respiratory syncytial virus (RSV), parainfluenza virus (types 1–4), adenovirus, human metapneumovirus, and enterovirus/rhinovirus. After one or more of the candidate respiratory viruses was detected by the Viral Panel from the nasal swab, all the samples from the same participant, i.e. the nasal swab, throat swab, the respiratory droplets and aerosols, were then tested with reverse transcriptase real-time polymerase chain reaction (RT-PCR) specific to the candidate virus(s) for determination of virus concentration in the samples. Infectious influenza virus was identified by viral culture using MDCK cells as described previously[21], while viral culture was not done for coronavirus and rhinovirus.

Statistical analyses

The primary outcome of the study was the virus generation rate in the tidal breathing of participants infected by different respiratory viruses, and the efficacy of face mask in preventing virus dissemination in exhaled breath, separately considering the respiratory droplets and aerosols. The secondary outcomes were the correlation between viral shedding in nose swabs, throat swabs, respiratory droplets and aerosols, and factors affecting viral shedding in respiratory droplets and aerosols.

We identified three groups of respiratory viruses with highest frequency of infection as identified by RT-PCR, namely coronavirus (including NL63, OC43, HKU1 and 229E), influenza virus, and rhinovirus, for further statistical analyses. We defined viral shedding as $\log_{10}$ virus copies per sample, and plotted viral shedding in each sample, i.e. the nasal swab, throat swab, respiratory droplets and aerosols, the latter two stratified by the mask intervention. As a proxy for the efficacy of face masks in preventing transmission of respiratory viruses via the respiratory droplet and aerosol routes, we compared the respiratory virus viral shedding in respiratory droplet and aerosol samples between participants wearing face mask or not, by comparing the frequency of detection with two-sided Fisher's exact test, and by comparing viral load (defined as $\log_{10}$ virus copies per sample) by an unadjusted univariate Tobit regression model which allowed for censoring at the lower limit of detection of the RT-PCR assay. We also used the unadjusted univariate Tobit regression to investigate factors affecting viral shedding in respiratory droplets and aerosols without mask use, for example age, days since symptom onset, prior influenza vaccination, current medication and number of coughs during exhaled breath collection. We investigated the correlations between viral shedding in nasal swab, throat swab, respiratory droplets and aerosols with scatterplots and calculated the Spearman's rank correlation coefficient between any two types of samples. We imputed 0.3 $\log_{10}$ virus copies/ml for the undetectable values before transformation to $\log_{10}$ virus copies per sample. All analyses were conducted with R version 3.6.0[22] and the *VGAM* package version 1.1.1[23].

DATA AVAILABILITY

Anonymized raw data and R syntax to reproduce all the analyses, figures, tables and supplementary tables in the published article are available at: https://doi.org/10.5061/dryad.w9ghx3fkt.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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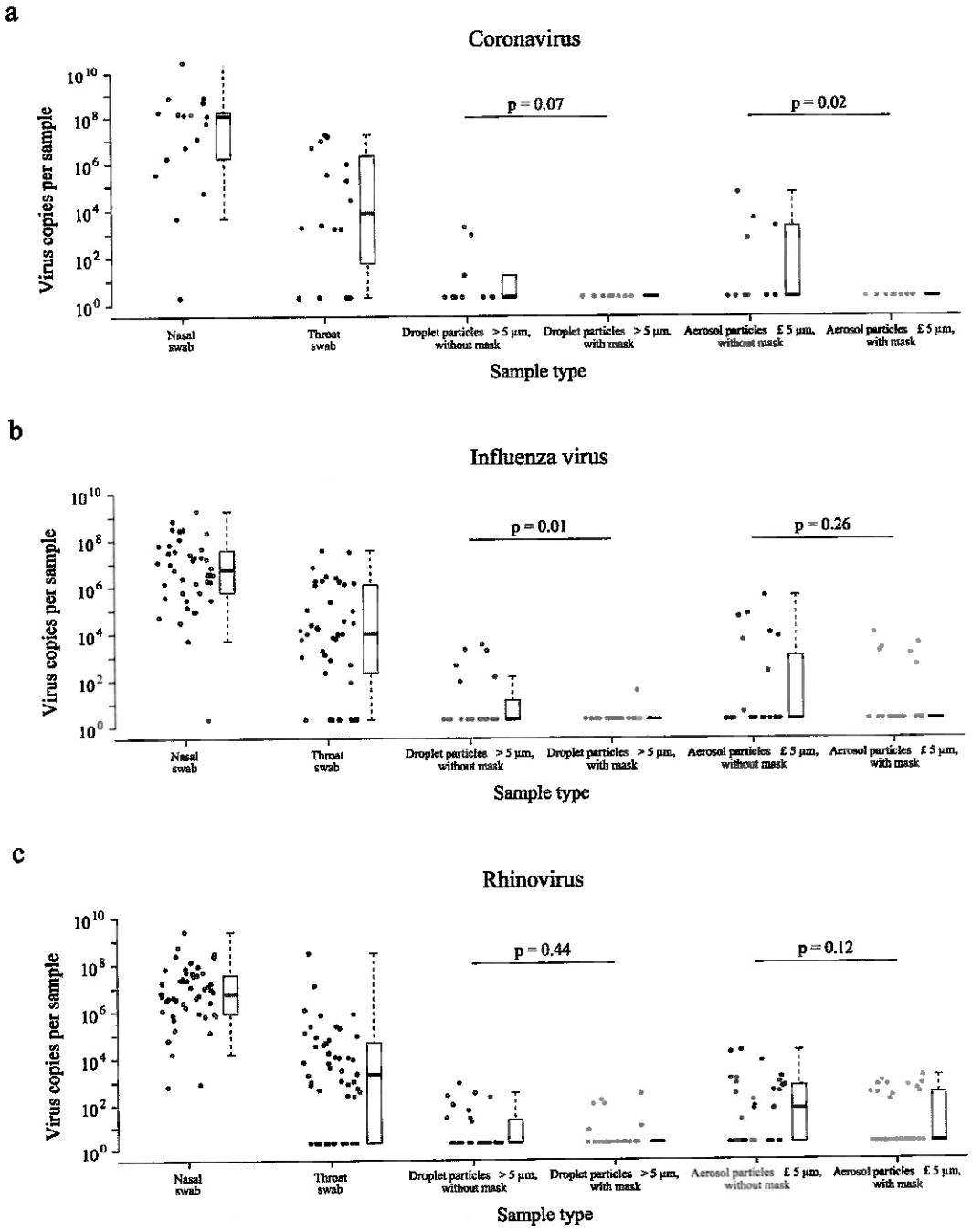

Figure 1. Efficacy of surgical face masks in reducing respiratory virus shedding in respiratory droplets and aerosols of symptomatic individuals with (a) coronavirus, (b) influenza virus or (c) rhinovirus infection.

The figure showed the virus copies per sample collected in nasal swab (red), throat swab (blue), respiratory droplets collected for 30 minutes while not wearing (dark green) or wearing (light green) a surgical face mask, and aerosols collected for 30 minutes while not wearing (brown) or wearing (orange) a face mask, collected from individuals with acute respiratory symptoms who were RT-PCR positive for coronavirus, influenza virus and rhinovirus in any samples. P-values for mask intervention as predictor of $\log_{10}$virus copies

per sample in an unadjusted univariate Tobit regression model which allowed for censoring at the lower limit of detection of the RT-PCR assay were shown, with significant difference in bold. For nasal swabs and throat swabs, all infected individuals were included (coronavirus, n = 17; influenza virus, n = 43; rhinovirus, n = 54). For respiratory droplets and aerosols, numbers of infected individuals who provided exhaled breath samples while not wearing, or wearing, a surgical face mask respectively were: coronavirus (n = 10, 11), influenza virus (n = 23, 28), rhinovirus (n = 36, 32). A subset of participants provided exhaled breath samples for both mask intervention (coronavirus, n = 4; influenza virus, n = 8; rhinovirus, n = 14). The box plots indicated the median with the interquartile range (lower/ upper hinge) and ± 1.5*interquartile range from the first/ third quartile (lower/ upper whisker).

Table 1a.

Characteristics of individuals with symptomatic coronavirus, influenza virus or rhinovirus infection.

	All who provided exhaled breath	Coronavirus	Influenza virus	Rhinovirus
	(n = 246)	(n = 17)	(n = 43)	(n = 54)
	n (%)	n (%)	n (%)	n (%)
Female	144 (59)	13 (76)	22 (51)	30 (56)
Age group (in years)				
11–17	12 (5)	0 (0)	8 (19)	4 (7)
18–34	114 (46)	10 (59)	11 (26)	24 (44)
35–50	79 (32)	2 (12)	16 (37)	18 (33)
51–64	35 (14)	4 (24)	8 (19)	5 (9)
≥ 65	6 (2)	1 (6)	0 (0)	3 (6)
Chronic medical conditions				
Any	49 (20)	5 (29)	5 (12)	10 (19)
Respiratory	18 (7)	0 (0)	4 (9)	3 (6)
Influenza vaccination				
Ever	94 (38)	6 (35)	15 (35)	20 (37)
Current season	23 (9)	2 (12)	1 (2)	4 (7)
Prior season only	71 (29)	4 (24)	14 (33)	16 (30)
Ever smoker	31 (13)	1 (6)	6 (14)	6 (11)
Time since illness onset, hours				
<24	22 (9)	0 (0)	5 (12)	2 (4)
24–48	100 (41)	9 (53)	13 (30)	25 (46)
48–72	85 (35)	8 (47)	18 (42)	20 (37)
72–96	39 (16)	0 (0)	7 (16)	7 (13)
History of measured fever ≥37.8°C	58 (24)	3 (18)	17 (40)	8 (15)
Measured fever ≥37.8°C at presentation	36 (15)	2 (12)	18 (42)	2 (4)
Measured body temperature (°C) at enrolment (Mean, SD)	36.8 (0.8)	36.9 (0.8)	37.4 (0.9)	36.6 (0.7)
Symptoms at presentation				
Feverishness	111 (45)	10 (59)	27 (63)	16 (30)
Cough	198 (80)	15 (88)	40 (93)	44 (81)
Sore throat	211 (86)	15 (88)	31 (72)	49 (91)
Runny nose	200 (81)	17 (100)	36 (84)	48 (89)
Headache	186 (76)	13 (76)	30 (70)	38 (70)
Myalgia	176 (72)	12 (71)	31 (72)	34 (63)
Phlegm	176 (72)	9 (53)	34 (79)	41 (76)
Chest tightness	64 (26)	3 (18)	12 (28)	9 (17)
Shortness of breath	103 (42)	6 (35)	14 (33)	25 (46)
Chills	100 (41)	8 (47)	29 (67)	16 (30)

	All who provided exhaled breath	Coronavirus	Influenza virus	Rhinovirus
	(n = 246)	(n = 17)	(n = 43)	(n = 54)
	n (%)	n (%)	n (%)	n (%)
Sweats	95 (39)	5 (29)	18 (42)	20 (37)
Fatigue	218 (89)	16 (94)	38 (88)	48 (89)
Vomiting	19 (8)	2 (12)	5 (12)	2 (4)
Diarrhea	17 (7)	2 (12)	1 (2)	6 (11)
Number of cough during exhaled breath collection (Mean, SD)	8 (14)	17 (30)	8 (11)	5 (9)

Seasonal coronavirus (n = 17), seasonal influenza virus (n = 43) and rhinovirus (n = 54) infection were confirmed in individuals with acute respiratory symptoms by RT-PCR in any samples (nasal swab, throat swab, respiratory droplets and aerosols) collected.

Table 1b.

Efficacy of surgical face masks in reducing respiratory virus frequency of detection and viral shedding in respiratory droplets and aerosols of symptomatic individuals with coronavirus, influenza virus or rhinovirus infection.

	Droplet particles >5μm			Aerosol particles ≤5μm		
Virus type	**Without surgical face mask**	**With surgical face mask**	***p***	**Without surgical face mask**	**With surgical face mask**	***p***
DETECTION OF VIRUS						
	No. Positive / No. Total (%)	**No. Positive / No. Total (%)**		**No. Positive / No. Total (%)**	**No. Positive / No. Total (%)**	
Coronavirus	3/10 (30)	0/11 (0)	0.09	**4/10 (40)**	**0/11 (0)**	**0.04**
Influenza virus	**6/23 (26)**	**1/27 (4)**	**0.04**	8/23 (35)	6/27 (22)	0.36
Rhinovirus	9/32 (28)	6/27 (22)	0.77	19/34 (56)	12/32 (38)	0.15
VIRAL LOAD (log_{10} virus copies per sample)						
	Median (IQR)	**Median (IQR)**		**Median (IQR)**	**Median (IQR)**	
Coronavirus	0.3 (0.3, 1.2)	0.3 (0.3, 0.3)	0.07	**0.3 (0.3, 3.3)**	**0.3 (0.3, 0.3)**	**0.02**
Influenza virus	**0.3 (0.3, 1.1)**	**0.3 (0.3, 0.3)**	**0.01**	0.3 (0.3, 3.0)	0.3 (0.3, 0.3)	0.26
Rhinovirus	0.3 (0.3, 1.3)	0.3 (0.3, 0.3)	0.44	1.8 (0.3, 2.8)	0.3 (0.3, 2.4)	0.12

P-values for comparing the frequency of respiratory virus detection between the mask intervention were obtained by two-sided Fisher's exact test, and (two-sided) p-values for mask intervention as predictor of log_{10} virus copies per sample were obtained by an unadjusted univariate Tobit regression model which allowed for censoring at the lower limit of detection of the RT-PCR assay, with significant difference in bold. Undetectable values were imputed as 0.3 log_{10} virus copies per sample.

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Efficacy of face masks, neck gaiters and face shields for reducing the expulsion of simulated cough-generated aerosols

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Abstract

Face masks are recommended to reduce community transmission of SARS-CoV-2. One of the primary benefits of face masks and other coverings is as source control devices to reduce the expulsion of respiratory aerosols during coughing, breathing, and speaking. Face shields and neck gaiters have been proposed as an alternative to face masks, but information about face shields and neck gaiters as source control devices is limited. We used a cough aerosol simulator with a pliable skin headform to propel small aerosol particles (0 to 7 μm) into different face coverings. An N95 respirator blocked 99% (standard deviation (SD) 0.3%) of the cough aerosol, a medical grade procedure mask blocked 59% (SD 6.9%), a 3-ply cotton cloth face mask blocked 51% (SD 7.7%), and a polyester neck gaiter blocked 47% (SD 7.5%) as a single layer and 60% (SD 7.2%) when folded into a double layer. In contrast, the face shield blocked 2% (SD 15.3%) of the cough aerosol. Our results suggest that face masks and neck gaiters are preferable to face shields as source control devices for cough aerosols.

Keywords

Infection control; Airborne transmission; Infectious disease transmission; Face masks; Face shields

Introduction

SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19), can be transmitted from person-to-person by large respiratory aerosols (airborne liquid droplets and dried particles greater than about 10 μm in diameter) produced by people who are infectious while they are talking, singing, coughing, breathing or sneezing (CDC 2020a; Hamner et al. 2020). Smaller aerosols also are emitted by people during these activities, suggesting that short-range airborne transmission of SARS-CoV-2 might be possible under some circumstances (Anderson et al. 2020; CDC 2020a; Fennelly 2020; Ma et al. 2020; Morawska and Milton 2020).

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Declaration of Interests Statement

The authors declare no competing interests.

To interrupt this potential transmission route, the Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO), and other public health organizations recommend the wearing of face masks or other face coverings by the general public during the ongoing COVID-19 pandemic (CDC 2020b; c; Edelstein and Ramakrishnan 2020; WHO 2020). One of the primary benefits of face coverings is to act as source control devices to reduce the expulsion of aerosols containing the virus from people who are infectious during coughing, breathing, and speaking. Source control devices are intended to protect other people from infectious aerosols emitted by the wearer, as compared with personal protective equipment such as N95 respirators which are primarily intended to protect the wearer. A face covering can provide source control in two ways (Diaz and Smaldone 2010). First, and most importantly, the covering may collect aerosol particles by filtration, impaction, or other mechanisms, and thus prevent infectious aerosols from entering the environment. Second, the face covering may change the direction of travel and the velocity of the aerosol stream and thus possibly divert the aerosol away from a potential recipient. However, deflection is more uncertain as a source control mechanism. For example, if large aerosols are deflected downward, they may settle to the floor or otherwise be unable to reach the breathing zones of other people. However, since exhaled breath is often warmer than the surrounding air, this downward deflection may be counteracted by the buoyancy of the breath for smaller aerosols. In addition, if the respiratory aerosols are deflected sideways, they may be diverted away from a person directly in front of the wearer but toward someone to the side or behind the wearer.

Studies using manikins (Lai et al. 2012; Patel et al. 2016) and patients with respiratory infections (Leung et al. 2020; Milton et al. 2013) have shown that wearing medical face masks can reduce the dispersion of potentially infectious aerosols from patients. Two studies in which face masks were required for visitors and healthcare workers interacting with patients in bone marrow transplant centers found a reduction in respiratory viral infections among patients (Sokol et al. 2016; Sung et al. 2016). Studies of cloth face masks have suggested that they also can be effective at reducing the release of respiratory aerosols into the environment (Asadi et al. 2020; Davies et al. 2013; Konda et al. 2020). Several computational fluid dynamics studies have examined the generation and expulsion of respiratory aerosols and have provided important insights into the ability of face coverings to reduce the dispersion of large and small aerosols from the wearer (Dbouk and Drikakis 2020; Mittal et al. 2020).

Unfortunately, the use of face masks and other face coverings by the general public can present challenges. People often dislike wearing masks, and compliance can be low and inconsistent (Longtin et al. 2009). Mask wearers may repeatedly don, doff and adjust face masks, which can contaminate the hands and potentially lead to disease transmission, especially when the masks are reused (Brady et al. 2017; Casanova et al. 2008). For cloth masks, the filtration efficiency and air flow resistance of different textiles varies widely (Konda et al. 2020; Teesing et al. 2020; Wilson et al. 2020). Alternative face coverings such as neck gaiters (an elastic fabric tube that fits snugly around the head and neck) are commonly used, but information about their performance as source control devices is limited. Factors such as how well the mask fits the face and the coverage provided by a mask can have a substantial impact on the effectiveness of face masks (Davies et al. 2013;

Lawrence et al. 2006). Comparisons of face coverings have found substantial differences in the ability of different types of these devices to reduce the release of respiratory aerosols (Asadi et al. 2020; Davies et al. 2013).

An opinion article in JAMA proposed that face shields would be more effective than face masks at reducing community disease transmission, in large part because the authors felt that face shields were more comfortable and thus that they were more likely to be widely adopted by the public (Perencevich et al. 2020). A previous study by our group of face shields used as personal protective devices showed that face shields protect the wearer from large cough aerosols directed at the face but are much less effective against smaller aerosols which were able to flow around the edges of the shield and be inhaled (Lindsley et al. 2014). However, very little work has been done examining face shields as source control devices. Two qualitative flow visualization studies of face shields and masks found that, although face shields deflected the air flow from the mouth, they did not stop aerosol particles from traveling around the face shield and entering the environment (Verma et al. 2020; Viola et al. 2020). Beyond these studies, quantitative data on the efficacy of face shields for source control are lacking.

The objective of our study was to conduct a quantitative comparison of the efficacy of an N95 respirator, a medical procedure mask, a commercial 3-ply cloth face mask, a single and double layer fabric neck gaiter, and a commercial disposable face shield as source control devices to reduce the expulsion of small cough-generated aerosol particles into the environment. Our results provide more information about the effectiveness of different types of source control devices and will help the public health community make recommendations about the best ways to use these devices to help reduce the spread of COVID-19.

Materials and Methods

Experimental Design

In our experiments, a cough aerosol simulator propelled a test aerosol through a headform into a collection chamber (Figure 1), and the amount of aerosol in the collection chamber was measured in each of six size fractions. The collection efficiency of each face mask, neck gaiter, or face shield was determined by comparing the amount of aerosol that was collected from the chamber with and without the device. Our test method was similar to the modified Greene and Vesley method used to test medical masks (Quesnel 1975), with the human test subject replaced by the cough aerosol simulator.

Cough aerosol simulator

The cough aerosol simulator is a modified version of the NIOSH cough aerosol simulator described previously (Lindsley et al. 2019; Lindsley et al. 2014; Lindsley et al. 2013). The experimental cough aerosol was generated by nebulizing a solution of 14% KCl and 0.4% sodium fluorescein using a single-jet Collison nebulizer (BGI, Butler, NJ) at 103 kPa (15 lbs./in^2), passing the aerosol through a diffusion drier (Model 3062, TSI, Shoreview, MN), and mixing it with 10 L/min of dry filtered air. The test aerosol was loaded into an elastomeric bellows, and the cough airflow was produced by a computer-controlled linear

motor that compresses the bellows. The cough aerosol was expelled through the mouth of a headform into a collection chamber. The headform used in the study has pliable skin that mimics the elastic properties of human skin in order to create a realistic simulation of how each face covering or shield would fit a human face (Bergman et al. 2014).

Source control devices

The source control devices tested were an N95 medical respirator (3M model 1860), a medical grade (ASTM Level 3) procedure mask with ear loops (Kimberly-Clark model 47107), a cloth face mask with 3 layers of cotton fabric and ear loops (Hanes Defender), a fabric neck gaiter (FKGIONG Sun UV Protection Neck Gaiter, 95% polyester, 5% Spandex) and a disposable face shield (Fisher Scientific # 19-181-600A). The neck gaiter was tested both as a single layer of fabric and doubled over to provide two layers of fabric. The masks and respirator were not equipped with exhalation valves. The face shield was 25 cm tall and extended from the forehead of the headform to 3 cm below the chin and around the side to 3 cm before the front of the ear. Photographs of the source control devices on the headform are shown in the supplemental online materials.

Mask fit test

For the experiments, either no device, a face mask, a neck gaiter, or a face shield were placed on the head form. Each device was used for two consecutive tests. For face masks and gaiters, a respirator fit test was performed using a PortaCount (TSI). The fit factor is a measure of the protection against airborne particles that is provided by a respiratory protective device. It is defined as the ratio of the aerosol concentration outside the respiratory protective device to the aerosol concentration inside the device (i.e., the aerosol concentration that is inhaled by the wearer). For example, a fit factor of 10 means that the ambient aerosol concentration is 10 times higher than the concentration inside the mask, and that the mask is therefore filtering out 90% of the ambient aerosol.

Aerosol collection and analysis

After placing the device on the headform and performing the fit test, the system was sealed. The test aerosol was then generated and propelled with a simulated cough through the headform and into the collection chamber. The Andersen impactor at the bottom of the collection chamber collected the aerosol particles that traveled through or around the device for 20 minutes after each cough. The Andersen impactor operates at a flow rate of 28.3 liters/minute and has six collection stages and a filter that separate the aerosol particles into seven size fractions based on the aerodynamic diameter of the particles: <0.6 μm; 0.6–1.1 μm; 1.1–2.1 μm; 2.1–3.3 μm; 3.3–4.7 μm; 4.7–7.0 μm; and >7 μm. Because the amount of aerosol in the largest size fraction was small and because of possible losses due to settling of the large aerosol particles, data for the largest size fraction was not included in the analysis. The impactor collection plates were coated with a solution of glycerol and Brij 35 to prevent particles from bouncing off the plates during collection (Mitchell 2003). After aerosol collection was completed, the impactor plates were rinsed with 0.1 M Tris solution and the fluorescence of the solution was measured using a fluorometer (SpectraMax M4, Molecular Devices). The complete experimental protocol is given in the supplemental online materials.

Statistical Analysis

The performance of each device was evaluated by comparing the total mass of the aerosol particles from a single cough that passed through or around the device and was collected by the Andersen impactor. The results were evaluated using a one-way ANOVA and multiple comparisons among the different devices and the control experiments without a device were conducted using a Tukey-Kramer test. To control for variations in the amount of aerosol in each cough, a sample of each cough aerosol was collected from the bellows prior to coughing and used to normalize the aerosol mass collection results for each experiment.

Results

The cough aerosol simulator provides a cough with a controlled cough airflow rate containing a test aerosol with a consistent aerosol size distribution. The simulator allows for a direct quantitative comparison of the ability of different types of source control devices to block the expulsion of simulated cough aerosol particles of different sizes into the environment. The flow rate of the simulated cough used in our experiments was based on cough flow profiles recorded from influenza patients and had a volume of 4.2 L with a peak flow rate of 11 L/s (Lindsley et al. 2013). The cough aerosol collected from the control experiments without a face covering had a mass median aerodynamic diameter of 1.3 μm, a geometric standard deviation of 2.3 and a total aerosol mass of 505 μg (standard deviation 69).

For our study, we tested the collection efficiencies (that is, the fraction of the cough aerosol that was blocked) of a medical grade procedure mask, a cotton cloth face mask, a polyester neck gaiter, an N95 medical respirator and a disposable face shield. These source control devices were chosen to provide representative samples of the different types of face coverings and face shields that are in common use during the pandemic. Neck gaiters are typically worn either as a single layer of fabric over the mouth and nose or doubled over to provide two layers of fabric; for our experiments, we tested both configurations. The quantity of aerosol particles in six size fractions that were able to travel through or around each source control device are shown in Figure 2. The collection efficiencies of the devices are shown as a function of aerosol size in Figure 3. All the devices showed increased collection efficiencies as the aerosol size increased.

On average, the N95 respirator blocked 99% of the total mass of test aerosol from being released into the environment, while the medical procedure mask blocked 59%, the cloth face mask blocked 51%, the single-layer gaiter blocked 47%, the double-layer gaiter blocked 60%, and the face shield blocked 2% of the total aerosol (Table 1). The N95 respirator, procedure mask, cloth mask, and the single-layer and double-layer gaiters all significantly reduced the aerosol emitted into the environment compared with no device ($P < 0.0001$ for each), but the face shield did not ($P = 0.9993$). The collection efficiencies of the procedure mask, cloth mask, and the single and double-layer gaiters did not differ significantly from each other, but all blocked cough aerosols significantly better than did the face shield ($P < 0.0001$). The N95 respirator outperformed all the other devices ($P < 0.0001$) (Table 2).

Discussion

Humans continuously emit aerosols of respiratory fluids as they breathe, talk, cough, sneeze, sing, or carry out other respiratory activities. These respiratory aerosols can have a very broad size range, from tens of nanometers in diameter to visible droplets of a millimeter or more (Bourouiba et al. 2014; Fennelly 2020; Gralton et al. 2011; Morawska et al. 2009). Airborne particles larger than 100 μm are ballistic; that is, they are affected primarily by gravity and fall quickly to the ground. Respiratory aerosol particles in this size range tend to deposit within a few meters of the source (Prather et al. 2020). As the aerosol particle diameter decreases from 100 μm, a gradual transition occurs where the settling velocity rapidly decreases and the particles remain airborne for longer times. For example, a 100 μm aerosol particle takes 4 seconds to fall 1 meter in still air, while a 10 μm aerosol particle takes 5.4 minutes and a 1 μm aerosol particle takes 8 hours to settle the same distance (Hinds 1999). Air currents such as plumes of warm air rising from the body can lift these particles and extend the time for which they stay in the air. Thus, small aerosol particles can remain airborne for minutes to hours and can accumulate over time in environments with poor ventilation (Bahl et al. 2020). Small aerosol particles also are easier to inhale and can travel more deeply into the lungs (Vincent 2005).

The amount and sizes of aerosol particles containing SARS-CoV-2 that are expelled by people who are infected are not yet known. Two studies of aerosol samples collected in patient rooms found infectious (replication-competent) SARS-CoV-2 in aerosol particles <4 μm in diameter (Santarpia et al. 2020a) and <10 μm in diameter (Lednicky et al. 2020). Other studies have reported SARS-CoV-2 RNA in exhaled breath from infected patients (Ma et al. 2020), aerosol samples from biocontainment and quarantine units housing SARS-CoV-2 infected persons (Santarpia et al. 2020b), and in aerosol samples at multiple locations throughout two hospitals in Wuhan, China during a COVID-19 outbreak (Liu et al. 2020). The presence of small aerosol particles containing infectious SARS-CoV-2 detected in these studies suggests that in addition to large aerosols, these small aerosols might play a role in SARS-CoV-2 transmission (Anderson et al. 2020; Bahl et al. 2020; Ma et al. 2020; Morawska and Milton 2020).

Source control devices like face coverings and face shields collect respiratory particles larger than 0.3 μm primarily by impaction and interception of the aerosol particles against the fibers or solid surfaces of the device. As noted earlier, source control devices may also deflect aerosols, but this mechanism can be problematic as a means of source control because the infectious aerosol is not prevented from entering the surrounding environment; it is merely sent in a different direction which may or may not be protective depending upon local airflows and the locations of other people. Our experimental system measures particle collection only; any particles that are deflected but not collected by the face covering are still collected by the Andersen impactor. Thus, we are able to measure the particle collection efficiency of the face coverings without the potentially confounding variable of particle deflection. On the other hand, this does means that any potential benefits from, for example, deflecting large aerosol particles toward the ground were not measured by our system.

Small aerosols require much higher air velocities to deposit by impaction than do larger aerosols, and thus are more difficult to block with source control devices (Hinds 1999; Lindsley 2016). Consequently, small aerosols present the most challenging scenario for testing source control devices since devices that block small aerosol particles would be expected to block larger ones as well. Our results show that face masks and neck gaiters can significantly reduce the expulsion of small respiratory aerosol particles during coughing. This suggests that various types of face coverings can make an important contribution to reducing the quantity of aerosol particles containing SARS-CoV-2 released into the environment by people who are infected. N95 respirators, which are worn for personal protection by healthcare workers and others at highest risk of exposure, are also very effective source control devices. In contrast, the face shield blocked very little of the cough aerosol, indicating that face shields are not effective as source control devices for small respiratory aerosols.

The collection efficiencies of all the devices tested increased as the aerosol particle size increased, and this trend would be expected to continue for larger aerosol particles than were tested here. For example, the collection efficiency of the cloth face mask was 28% for the < 0.6 μm particles and increased to 76% for the 4.7 to 7 μm particles. Similarly, the double-layer gaiter blocked 24% of the < 0.6 μm particles and 76% of the 4.7 to 7 μm particles. These results suggest that cloth face coverings would be effective as source control devices against the large respiratory aerosols that are thought to play an important role in SARS-CoV-2 transmission.

Our study has several limitations. We used a single cough volume, air flow profile, and aerosol size distribution for our studies; these parameters can vary greatly from person to person. We examined the performance of these devices during simulated coughing but not breathing or speaking, which have different air flow rates and aerosol size distributions. Some internal losses of the test aerosol particles likely occurred due to settling or impaction on the surfaces of the collection chamber, which may affect the estimates of the collection efficiencies. We only used a single representative example of each type of device. The shape and composition of face coverings vary widely, and this would be expected to affect the performance of individual devices. Some face masks have exhalation valves or vents which could reduce their efficacy as source control devices. The fit of a particular mask to an individual wearer and compliance in wearing the mask correctly (i.e., over the nose and mouth) also are important factors in how well the mask performs as a source control device. Because we used a <0.6 to 7 μm test aerosol, our results do not indicate if face shields would be more effective as source control devices for large droplets. The face shield that we tested has a widely used design, but alternative designs are being marketed that provide greater facial coverage and, in some cases, include fabric skirts between the shield and the face. These alternative face shield designs might perform better as source control devices.

Previous studies have shown that face shields provide eye and facial protection to the wearer from droplets and splashes (Lindsley et al. 2014; Roberge 2016). When a face shield is worn in addition to a face mask, the face shield can also help reduce surface contamination of the mask by large aerosols and reduce the likelihood of hand contamination when the mask is removed or inadvertently touched (Lindsley et al. 2014). Our previous study showed

that face shields provide some benefits as personal protective equipment when face masks cannot be worn (Lindsley et al. 2014), but as with all personal protection and source control devices, their limitations must be respected. Our results suggest that face masks and neck gaiters are more effective than face shields as source control devices to reduce the expulsion of respiratory aerosols into the environment as a public health measure to reduce the community transmission of SARS-CoV-2.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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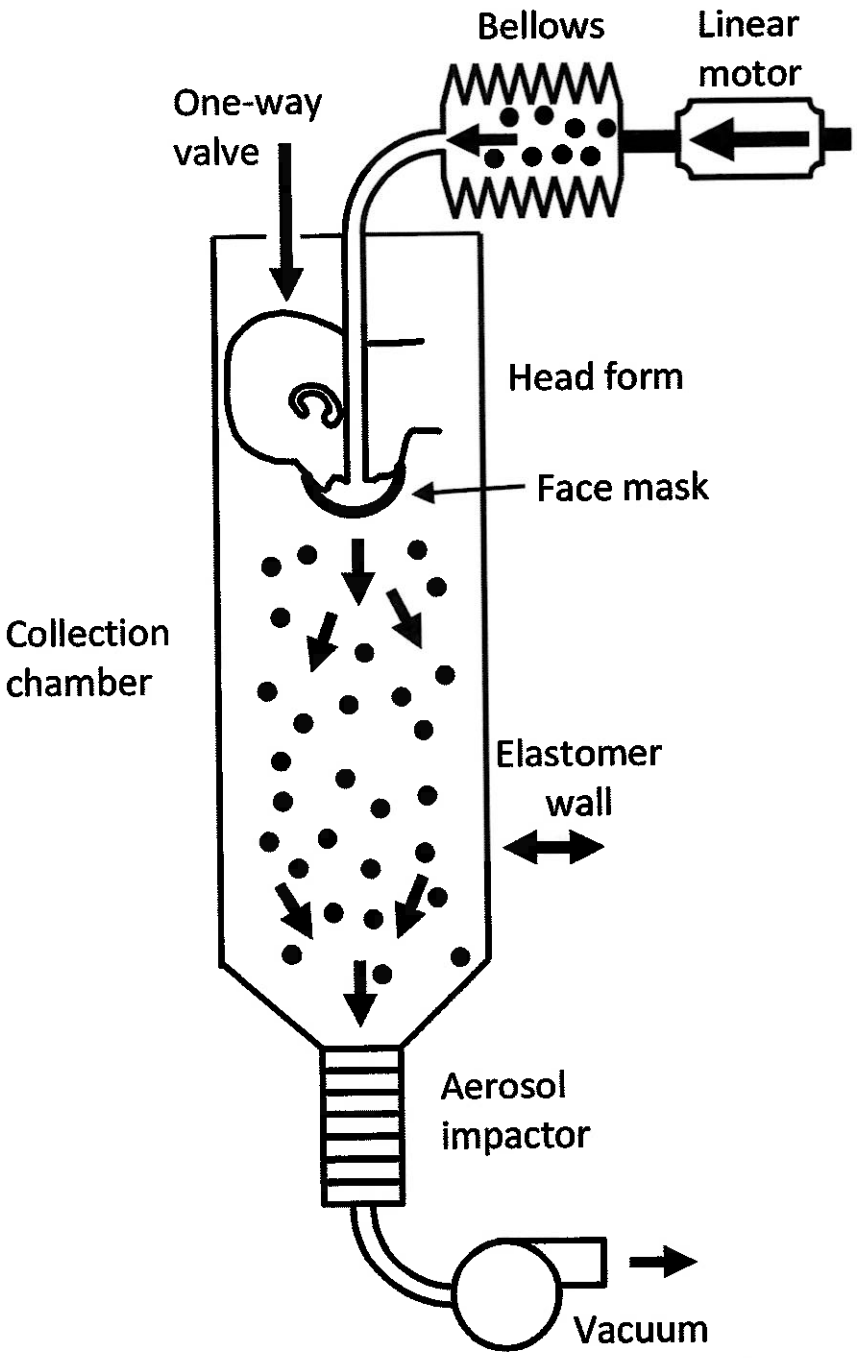

Figure 1:
Cough aerosol simulator system for source control measurements. The system consists of an aerosol generation system, a bellows and linear motor to produce the simulated cough, a pliable skin head form on which the face mask, neck gaiter or face shield is placed, a 105 liter collection chamber into which the aerosol is coughed, and an Andersen impactor to separate the aerosol particles by size and collect them. More information about the cough aerosol simulator is provided in the supplemental online materials.

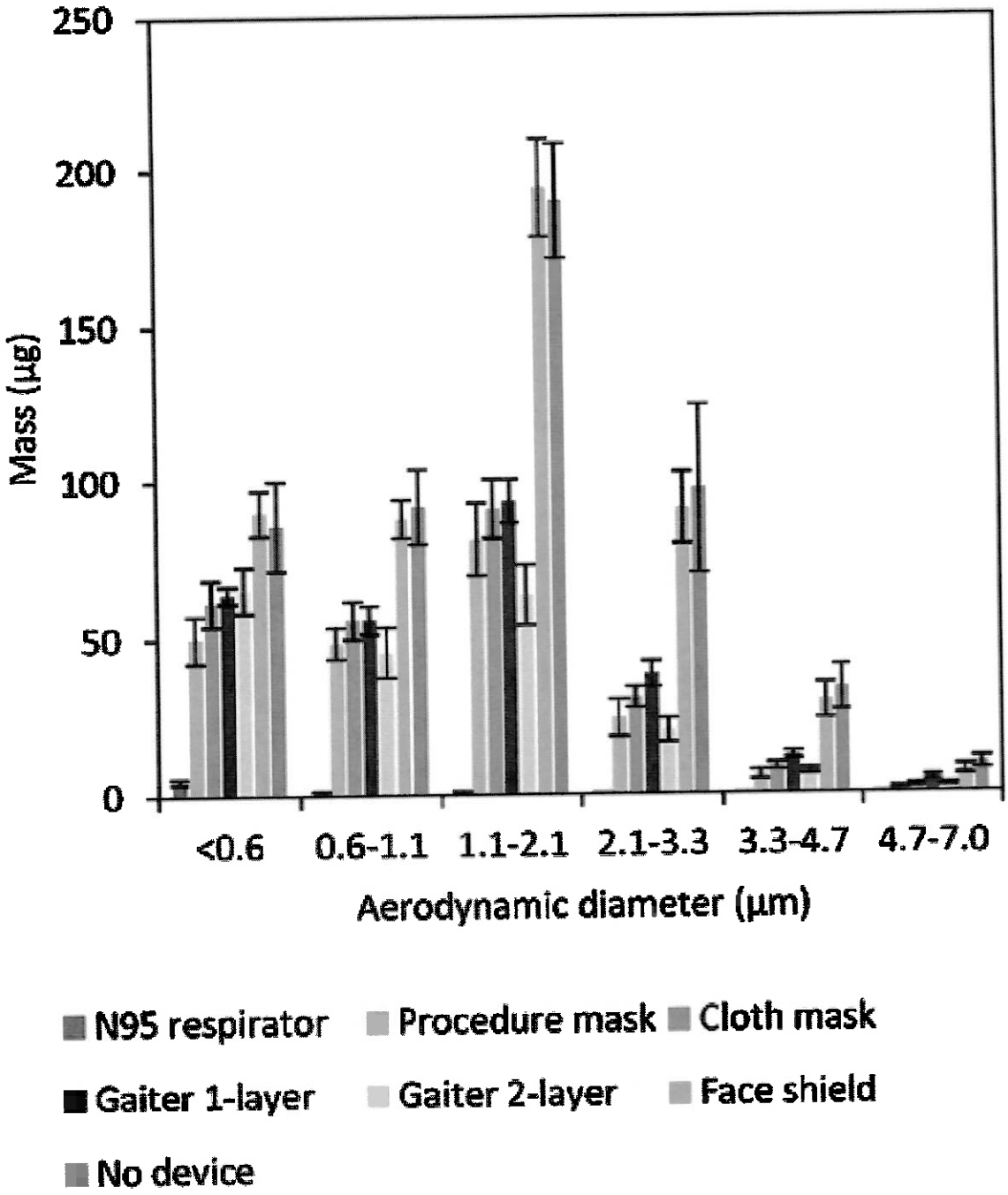

Figure 2:
Mass of aerosol collected in each size fraction. The graph shows the amount of simulated respiratory aerosol that was collected from the collection chamber in each aerosol particle size fraction after a single simulated cough. The bars show the mean and standard deviation. A larger color version of this figure is shown in the supplemental online materials.

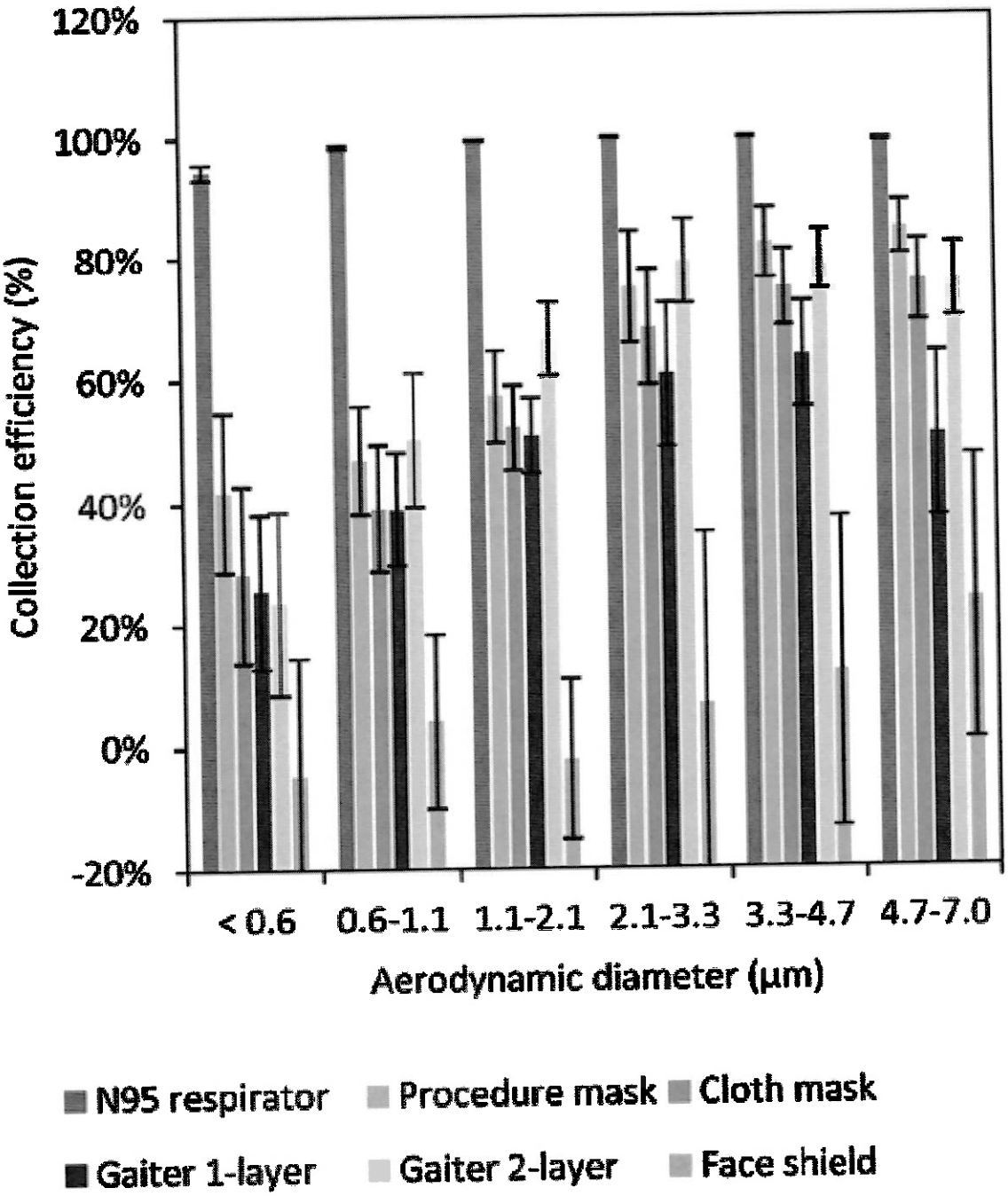

Figure 3:
Collection efficiency of face masks, neck gaiter and face shield. The collection efficiency is the percentage of aerosol particles that were blocked by the face mask, neck gaiter or face shield compared with experiments without a device. The plot shows the means and standard deviations of the collection efficiency in each size fraction. A larger version of this figure is shown in color in the supplemental online materials.

Table 1:

Total mass of aerosol expelled into collection chamber and device collection efficiencies. The fit factor, aerosol mass, and collection efficiency are given as mean (standard deviation).

Device tested	Number of experiments	Fit factor	Aerosol mass (μg)	Collection efficiency
No device	12	n/a	512 (64)	n/a
Procedure mask	6	2.9 (0.5)	212 (23)	58.5% (6.9%)
Cloth mask	6	1.3 (0.1)	251 (23)	50.9% (7.7%)
Neck gaiter (single layer)	6	1.7 (0.5)	270 (18)	47.2% (7.5%)
Neck gaiter (double layer)	6	1.9 (0.4)	206 (26)	59.8% (7.2%)
Face shield	6	n/a	502 (46)	1.8% (15.3%)
N95 respirator	6	198 (3.5)	7.2 (1.2)	98.6% (0.3%)

Table 2:

Comparison of aerosol mass expelled into the collection chamber while wearing face masks, neck gaiters and face shields.

PPE types compared		95% confidence intervals for mean differences (μg)			P-value
		Lower limit	Mean difference	Upper limit	
N95 respirator	No device	−567	−504	−442	<0.0001
Procedure mask	No device	−361	−299	−237	<0.0001
Cloth mask	No device	−322	−260	−198	<0.0001
Gaiter (single layer)	No device	−304	−241	−179	<0.0001
Gaiter (double layer)	No device	−368	−306	−243	<0.0001
Face shield	No device	−71	−9	53	0.9993
N95 respirator	Face shield	−567	−495	−423	<0.0001
Procedure mask	Face shield	−362	−290	−218	<0.0001
Cloth mask	Face shield	−323	−251	−179	<0.0001
Gaiter (single layer)	Face shield	−304	−232	−160	<0.0001
Gaiter (double layer)	Face shield	−369	−297	−225	<0.0001
N95 respirator	Gaiter (double layer)	−271	−199	−127	<0.0001
Procedure mask	Gaiter (double layer)	−65	7	79	0.9999
Cloth mask	Gaiter (double layer)	−26	46	118	0.4505
Gaiter (single layer)	Gaiter (double layer)	−7	64	136	0.1051
N95 respirator	Gaiter (single layer)	−335	−263	−191	<0.0001
Procedure mask	Gaiter (single layer)	−130	−58	14	0.1900
Cloth mask	Gaiter (single layer)	−91	−19	53	0.9825
N95 respirator	Cloth mask	−316	−244	−172	<0.0001
Procedure mask	Cloth mask	−111	−39	33	0.6336
N95 respirator	Procedure mask	−277	−205	−133	<0.0001

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RESEARCH ARTICLE

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Potential utilities of mask-wearing and instant hand hygiene for fighting SARS-CoV-2

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Abstract

The surge of patients in the pandemic of COVID-19 caused by the novel coronavirus SARS-CoV-2 may overwhelm the medical systems of many countries. Mask-wearing and handwashing can slow the spread of the virus, but currently, masks are in shortage in many countries, and timely handwashing is often impossible. In this study, the efficacy of three types of masks and instant hand wiping was evaluated using the avian influenza virus to mock the coronavirus. Virus quantification was performed using real-time reverse transcription-polymerase chain reaction. Previous studies on mask-wearing were reviewed. The results showed that instant hand wiping using a wet towel soaked in water containing 1.00% soap powder, 0.05% active chlorine, or 0.25% active chlorine from sodium hypochlorite removed 98.36%, 96.62%, and 99.98% of the virus from hands, respectively. N95 masks, medical masks, and homemade masks made of four-layer kitchen paper and one-layer cloth could block 99.98%, 97.14%, and 95.15% of the virus in aerosols. Medical mask-wearing which was supported by many studies was opposed by other studies possibly due to erroneous judgment. With these data, we propose the approach of mask-wearing plus instant hand hygiene (MIH) to slow the exponential spread of the virus. This MIH approach has been supported by the experiences of seven countries in fighting against COVID-19. Collectively, a simple approach to slow the exponential spread of SARS-CoV-2 was proposed with the support of experiments, literature review, and control experiences.

KEYWORDS
coronavirus, COVID-19, hand hygiene, mask, pandemic, soap

1 | INTRODUCTION

The emerging disease COVID-19 caused by the new coronavirus SARS-CoV-2 was first identified in Wuhan, China in December 2019.[1,2] The virus has led to thousands of deaths in China, and the outbreak of COVID-19 has been well controlled in China through tremendous efforts.[2] However, the virus has sparked a pandemic and is spreading rapidly in many countries.[3] To avoid the tragedy of Wuhan in this February that the surge of too many patients overwhelmed the medical systems,[2-7] a simple and effective approach to slow the spread of the virus is emergently desired worldwide.

Handwashing and mask-wearing are important to slow the spread of SARS-CoV-2.[6-15] However, it is often difficult to wash hands in time, and current medical masks which are usually called

This work was conducted in the College of Veterinary Medicine, Qingdao Agricultural University.

surgical masks are in shortage in many countries. People in some countries have been encouraged to make masks by themselves at home to guard against SARS-CoV-2, but it remains unclear whether these homemade masks are effective to block the virus. Moreover, many people have been confused about the claims of some politicians and scientists that medical masks are not useful to protect humans from the infection of SARS-CoV-2.

In this study, we evaluated the efficacy of three types of masks in blocking avian influenza virus (AIV) in aerosols and the efficacy of instant hand wiping in removing AIV from hands. AIV was used to mock SARS-CoV-2 because they are both enveloped and pleomorphic spherical viruses with a diameter of around 80 to 120 nm. We also reviewed previous reports regarding the efficacy of masks.[8-15] With these data, we propose a simple approach to slow the spread of the pandemic coronavirus.

2 | MATERIALS AND METHODS

Low pathogenic AIV A/chicken/Qingdao/211/2019 was isolated from Qingdao live bird market in 2019. The virus was propagated using embryonated eggs. Virus quantification was performed using a real-time TaqMan reverse transcription-polymerase chain reaction (RT-PCR) assay reported previously.[16]

The efficacy of instant hand wiping in removing AIV from hands was evaluated using a towel soaked in water containing soap powder or sodium hypochlorite.

Type 403 nebulizer (Yuyue Medical Equipment & Supply Company, Jiangsu, China) was used to produce aerosols. The aerosols have the median diameters 3.9 μm, and 65% of the aerosols have the diameters less than 5.0 μm, as given in the specification of the nebulizer. The top parts of 60-mL syringes were removed and then wrapped with the tested masks, namely one-layer polyester cloth, a homemade mask made of one-layer polyester cloth plus four-layer kitchen paper (Hengan Company, Fujian, China; each layer contains three thin layers), a medical mask (AMMEX Company, Shanghai, China), and an N95 mask (Type: New 2001, Jiande Chaomei Daily Chemical Company, Zhejiang, China), respectively (Figure 1). QVS facial cleaning sponge (8-mm thick; Watsons Company, Guangdong, China) made of hydrophilic polyvinyl alcohol was set inside the syringe behind the mask (Figure 1) for collecting the virus passing through the masks. The four syringes were then aligned and bound seamlessly together.

3 | RESULTS

3.1 | Virus quantification using real-time RT-PCR

In principle, if the virus amount declines by 50%, the C_t value of the real-time TaqMan RT-PCR shall increase by 1. Our experiment with three repeats showed that the virus amount declined by 50%, the C_t value increased by 0.96 (95% confidence interval: 0.86-1.04), using 1:8 serially diluted allantoic fluid of inoculated embryonated eggs containing the AIV. Taken together, we presumed that the virus amount declines by 50% if the C_t value increases by 1, and the virus amount declines by (100 × (1 − 1/(2^Y)))% if the C_t value increases by Y, in this study.

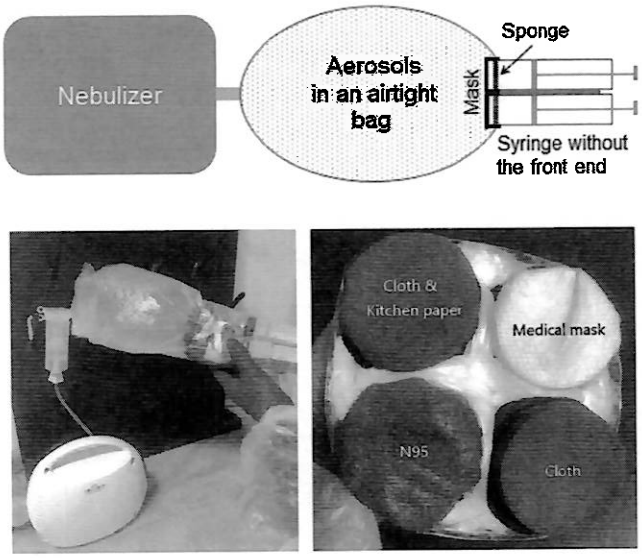

FIGURE 1 The system mocking human breath for evaluation of the efficacy of masks

3.2 | Efficacy of hand wiping

We put 5 μL of the undiluted allantoic fluid containing the AIV on the hand of one author of this study, and spread the fluid around the palm, and kept for 3 minutes. We then wiped the palm three times from the root of the palm to the tips of the fingers, using a towel soaked in water containing soap or sodium hypochlorite and then wrung to remove most of the water inside. We eluted the hand using 5 mL phosphate-buffered saline (PBS), and RNA from 200 μL of the eluted PBS was extracted for the detection of the amount of the virus using the TaqMan RT-PCR. Each treatment and the control without wiping were conducted independently for three times. Table 1 showed, as compared with the control without the towel wiping, the virus on the palm declined by 98.36%, 96.62%, and 99.98% through wiping using the wet towel soaked in water containing 1.00% (g/g) soap powder, 0.05% (g/g) active chlorine from sodium hypochlorite, or 0.25% (g/g) active chlorine from sodium hypochlorite, respectively. All the relevant C_t values in Table 1 were of significant difference ($P < .01$) by the t test, except those two pertaining to 1.00% soap powder and 0.05% active chlorine.

3.3 | Efficacy of masks

The allantoic fluid containing the AIV was 1:10 diluted using PBS. The fluid was added into the nebulizer for producing the aerosols containing the virus. The aerosols were collected using a seamless

TABLE 1 Percentage of AIV removed through instant wiping as compared without wiping

Material for towel soaking	C_t increase ($\bar{X} \pm SD$)	Percentage removed (95% CI)
1.00% Soap powder	5.93 ± 1.24	98.36% (96.11%-99.31%)
0.05% Active chlorine	4.89 ± 0.74	96.62% (94.37%-97.97%)
0.25% Active chlorine	12.01 ± 1.25	99.98% (99.94%-99.99%)

Abbreviations: AIV, avian influenza virus; CI, confidence interval; SD, standard deviation.

plastic bag (Figure 1). The nebulizer was paused when the bag was bulging. The air containing the aerosols was inhaled into and out of the syringes for 100 times through the synchronous piston movement of the four syringes, to mock human breath. Then the mask was unwrapped, and the sponge inside the syringe was taken out and added with 2 mL PBS. The sponge was pressed for five times using a 200-μL pipette tip. RNA from 1 mL of the PBS was extracted for the detection of the amount of the virus using the TaqMan RT-PCR. Each treatment was conducted independently for four times. Table 2 showed that, as compared with the polyester cloth, the N95 mask blocked 99.98% of the virus, and the medical mask blocked 97.14% of the virus, and the homemade mask blocked 95.15% of the virus. All the relevant C_t values were of significant difference ($P < .01$) by the t test, except those two pertaining to the medical masks and the homemade masks.

4 | DISCUSSION

Because clean water is often unavailable at hand, people can be infected through hand-mouth, hand-nose, or hand-eye contact before handwashing. In this sense, it is important to have one item at hand, such as 75% alcohol, hand sanitizer gel, disinfecting wipes, for instant hand hygiene after we have touched something possibly contaminated by the virus. This is more important for those traveling long-distance using public vehicles or having touched some items frequently touched by other people. This study suggested that instant hand wiping using a wet towel containing soap or sodium hypochlorite removed most viruses from hands. Water containing 1.00% soap powder is not only helpful for wiping away the virus using its surfactant activity but also efficiently inactivates enveloped viruses including coronavirus, as proved by multiple previous studies.[17-19] Moreover, water containing 1.00% soap powder is safe for skin and other items including clothes. It is worth noting that the concentration of soap powder and sodium hypochlorite is vital for their wiping and virucidal effects.

TABLE 2 Percentage of AIV blocked by masks as compared with one layer of cloth

	C_t increase ($\bar{X} \pm SD$)	Percentage blocked (95% CI)
N95 mask	12.49 ± 0.33	99.98% (99.98%-99.99%)
Medical mask	5.13 ± 0.98	97.14% (94.36%-98.55%)
Homemade mask	4.37 ± 0.90	95.15% (90.97%-97.39%)

Abbreviations: AIV, avian influenza virus; CI, confidence interval; SD, standard deviation.

Various studies have suggested that SARS-CoV-2 can be transmitted through droplets and aerosols,[1-7] and so hand hygiene is inadequate to prevent infection of SARS-CoV-2, and blocking masks are needed. This study showed that N95 masks blocked nearly all the mock virus, and medical masks blocked approximately 97% of the virus, and the homemade mask blocked approximately 95% of the virus. Therefore, the medical masks are not fully protective in hospitals but are useful for common social occasions. When medical masks are in shortage, the homemade masks made of four-layer kitchen paper (each layer contains three thin layers) and one layer of polyester cloth should be helpful, as indicated by this study. The kitchen paper is effective in blocking the virus possibly because of its multiple layers, nonwoven structure, and virus-absorbing property. As we have tested by ourselves, the tested homemade masks are more breathable than the N95 masks. One advantage of the homemade mask is that the kitchen paper can be changed frequently. It is worth noting that the homemade masks shall be of less blocking efficacy if made of fewer layers of kitchen paper. Other types of homemade masks, especially those made of cloth alone, may be unable to block the virus and thus confer no protection against the virus.[20,21] Additionally, although a person inhales much more than 100 times a day, the mocking data are reliable because aerosols containing the virus to be inhaled by a person on most common social occasions are fewer than in this experiment.

Some randomized controlled trials (RCTs) did not support the efficacy of medical masks because medical masks could not reduce infection rates of some viral respiratory diseases.[14,15] Consequently, people in some countries opposed to using medical masks on common social occasions. In effect, the conclusions of these RCTs could be erroneous, as reflected by the following assumed scenario. Supposed the virus could have ten opportunities to infect a human during a period of 30 days, wearing medical masks could block three of the 10 opportunities and thus reduce the infection risk by 30%, although it itself could not block the other seven opportunities during the 30 days. Therefore, the fact that medical mask-wearing did not reduce the infection rate could suggest that medical mask-wearing is inadequate to prevent the infection, rather than useless for reducing the infection risk. Some other RCTs and many nonrandomized studies regarding the use of medical masks supported the notion that wearing medical masks could reduce infection risks of some viral respiratory diseases.[8-14] Moreover, medical mask-wearing can enhance one's vigilance, prevent direct hand-mouth or hand-nose

contact, and reduce air contamination of pathogens from infected people.

With the above data and discussion, we propose herein the approach of mask-wearing and instant hand hygiene (MIH), namely that common people should wear effective masks and bring an appropriate item for instant hand hygiene when needed, to slow the rapid spread of the virus worldwide. This is crucial for the world to reduce severe and fatal cases of the virus before successful marketing of the effective vaccines against the coronavirus, and avoid the tragedy of medical systems being overwhelmed by a surge of too many patients. As indicated in this study, when medical masks and disinfectants are in shortage, the homemade masks made of kitchen paper can be used to temporally surrogate medical masks, and so soap powder is used for instant hand hygiene.

From the news we know that the MIH approach has been implemented in China, Republic of Korea, and Japan, where mask-wearing is widely accepted and items for instant hand hygiene are usually accessible in public areas. The spread of the coronavirus in all these three countries has been well controlled.[3,6] In contrast, Iran, Italy, Spain, and the USA did not implement the MIH approach in the beginning weeks, and many people in those countries are reluctant to wear medical masks. None of these four countries have decelerated the spread of the coronavirus so far.[3,5]

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTION

Design: JMC, QXM, HS; experiment: QXM, HLZ, GML, RMY; data analysis: JMC, QXM, HS; funding: HS; manuscript writing: JMC, HS.

DATA AVAILABILITY STATEMENT

The derived data supporting the findings of this study are available within the article, and the raw data supporting the findings of this study are available from the corresponding author JC on request.

ETHICS STATEMENT

The article does not contain the participation of animals and humans other than the authors.

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Please note: This report has been corrected.

Morbidity and Mortality Weekly Report

Maximizing Fit for Cloth and Medical Procedure Masks to Improve Performance and Reduce SARS-CoV-2 Transmission and Exposure, 2021

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Universal masking is one of the prevention strategies recommended by CDC to slow the spread of SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19) (*1*). As of February 1, 2021, 38 states and the District of Columbia had universal masking mandates. Mask wearing has also been mandated by executive order for federal property* as well as on domestic and international transportation conveyances.† Masks substantially reduce exhaled respiratory droplets and aerosols from infected wearers and reduce exposure of uninfected wearers to these particles. Cloth masks§ and medical procedure masks¶ fit more loosely than do respirators (e.g., N95 facepieces). The effectiveness of cloth and medical procedure masks can be improved by ensuring that they are well fitted to the contours of the face to prevent leakage of air around the masks' edges. During January 2021, CDC conducted experimental simulations using pliable elastomeric source and receiver headforms to assess the extent to which two modifications to medical procedure masks, 1) wearing a cloth mask over a medical procedure mask (double masking) and 2) knotting the ear loops of a medical procedure mask where they attach to the mask's edges and then tucking in and flattening the extra material close to the face (knotted and tucked masks), could improve the fit of these masks and reduce the receiver's exposure to an aerosol of simulated respiratory droplet particles of the size considered most important for transmitting SARS-CoV-2. The receiver's exposure was maximally reduced (>95%) when the source and receiver were fitted with modified medical procedure masks. These laboratory-based experiments highlight the importance of good fit to optimize mask performance. Until vaccine-induced population immunity is achieved, universal masking is a highly effective means to slow the spread of SARS-CoV-2** when combined with other protective measures, such as physical distancing, avoiding crowds and poorly ventilated indoor spaces, and good hand hygiene. Innovative efforts to improve the fit of cloth and medical procedure masks to enhance their performance merit attention.

At least two recent studies examined use of mask fitters to improve the fit of cloth and medical procedure masks. Fitters can be solid (*2*) or elastic (*3*) and are worn over the mask, secured with head ties or ear loops. The results indicated that when fitters are secured over a medical procedure mask, they can potentially increase the wearer's protection by ≥90% for aerosols in the size range considered to be the most important for transmitting SARS-CoV-2 (generally <10 μm). Other studies found that knotting and tucking a medical procedure mask or placing a sleeve made of sheer nylon hosiery material around the neck and pulling it up over either a cloth or medical procedure mask (*3,4*) also significantly improved the wearer's protection by fitting the mask more tightly to the wearer's face and reducing edge gaps. A recent expert commentary (*5*) proposed double masking as another means to improve the fit of medical procedure masks and maximize the filtration properties of the materials from which they are typically constructed, such as spun-bond and melt-blown polypropylene. Based on experiments that measured the filtration efficiencies of various cloth masks and a medical procedure mask (*6*), it was estimated that the better fit achieved by combining these two mask types, specifically a cloth mask over a medical procedure mask, could reduce a wearer's exposure by >90%.

During January 2021, CDC conducted various experiments to assess two methods to improve medical procedure mask performance by improving fit and, in turn, filtration: 1) double masking and 2) knotting and tucking the medical procedure mask (Figure 1). The first experiment assessed how effectively various mask combinations reduced the amount of particles emitted during a cough (i.e., source control) in terms of collection efficiency. A pliable elastomeric headform was used

* https://www.whitehouse.gov/briefing-room/presidential-actions/2021/01/20/executive-order-protecting-the-federal-workforce-and-requiring-mask-wearing

† https://www.whitehouse.gov/briefing-room/presidential-actions/2021/01/21/executive-order-promoting-covid-19-safety-in-domestic-and-international-travel

§ A cloth mask refers to any mask constructed from textiles or fabrics (both natural and synthetic) that is not a surgical mask or N95 respirator and is not intended for use as personal protective equipment. At present, there are no national standards established for cloth masks although such standards are under consideration by ASTM (formerly known as American Society for Testing and Materials).

¶ A medical procedure mask refers to any commercially produced mask regulated by the Food and Drug Administration under 21 CFR 878.4040 for performing medical procedures. These are variably labeled as surgical, laser, isolation, dental, or medical procedure masks. They may be variably shaped, including flat pleated, cone shaped, or duck bill. Medical procedure masks are loose fitting and are not expected to provide a reliable level of protection against airborne or aerosolized particles as N95 respirators regulated by the National Institute for Occupational Safety and Health. A more detailed comparison of medical procedure masks and respirators is available. https://www.cdc.gov/niosh/npptl/pdfs/UnderstandDifferenceInfographic-508.pdf

** https://www.cdc.gov/coronavirus/2019-ncov/more/masking-science-sars-cov2.html

to simulate a person coughing by producing aerosols from a mouthpiece (0.1–7 μm potassium chloride particles) (*7*). The effectiveness of the following mask configurations to block these aerosols was assessed: a three-ply medical procedure mask alone, a three-ply cloth cotton mask alone, and the three-ply cloth mask covering the three-ply medical procedure mask (double masking). The second experiment assessed how effectively the two modifications to medical procedure masks reduced exposure to aerosols emitted during a period of breathing. Ten mask combinations, using various configurations of no mask, double masks, and unknotted or knotted and tucked medical procedure masks, were assessed (e.g., source with no mask and receiver with double mask or source with double mask and receiver with no mask). A knotted and tucked medical procedure mask is created by bringing together the corners and ear loops on each side, knotting the ears loops together where they attach to the mask, and then tucking in and flattening the resulting extra mask material to minimize the side gaps[††] (Figure 1). A modified simulator with two pliable elastomeric headforms (a source and a receiver) was used to simulate the receiver's exposure to aerosols produced by the source (*8*). In a chamber approximately 10 ft (3.1 m) long by 10 ft wide by 7 ft (2.1 m) high, which simulated quiet breathing during moderate work, the source headform was programmed to generate the aerosol from its mouthpiece at 15 L/min (International Organization for Standardization [ISO] standard for a female performing light work), and the receiver headform's minute ventilation was set at 27 L/min (ISO average of a male or female engaged in moderate work).[§§] For each of the 10 masking configurations, three 15-minute runs were completed.

[††] https://youtu.be/UANi8Cc71A0
[§§] https://www.iso.org/standard/67530.html

Results from the first experiment demonstrated that the unknotted medical procedure mask alone blocked 56.1% of the particles from a simulated cough (standard deviation [SD] = 5.8), and the cloth mask alone blocked 51.4% (SD = 7.1). The combination of the cloth mask covering the medical procedure mask (double mask) blocked 85.4% of the cough particles (SD = 2.4), and the knotted and tucked medical procedure mask blocked 77.0% (SD = 3.1).

In the second experiment, adding a cloth mask over the source headform's medical procedure mask or knotting and tucking the medical procedure mask reduced the cumulative exposure of the unmasked receiver by 82.2% (SD = 0.16) and 62.9% (SD = 0.08), respectively (Figure 2). When the source was unmasked and the receiver was fitted with the double mask or the knotted and tucked medical procedure mask, the receiver's cumulative exposure was reduced by 83.0% (SD = 0.15) and 64.5% (SD = 0.03), respectively. When the source and receiver were both fitted with double masks or knotted and tucked masks, the cumulative exposure of the receiver was reduced 96.4% (SD = 0.02) and 95.9% (SD = 0.02), respectively.

Discussion

These laboratory-based experiments highlight the importance of good fit to maximize overall mask performance. Medical procedure masks are intended to provide source control (e.g., maintain the sterility of a surgical field) and to block splashes. The extent to which they reduce exhalation and inhalation of particles in the aerosol size range varies substantially, in part because air can leak around their edges, especially through the side gaps (*9*). The reduction in simulated inhalational exposure observed for the medical procedure mask in this report was lower than reductions reported in studies of other medical procedure masks that were assessed under similar experimental conditions, likely because of substantial air leakage around the edges of the mask used here (*10*). In

FIGURE 1. Masks tested, including *A*, unknotted medical procedure mask; *B*, double mask (cloth mask covering medical procedure mask); and *C*, knotted/tucked medical procedure mask

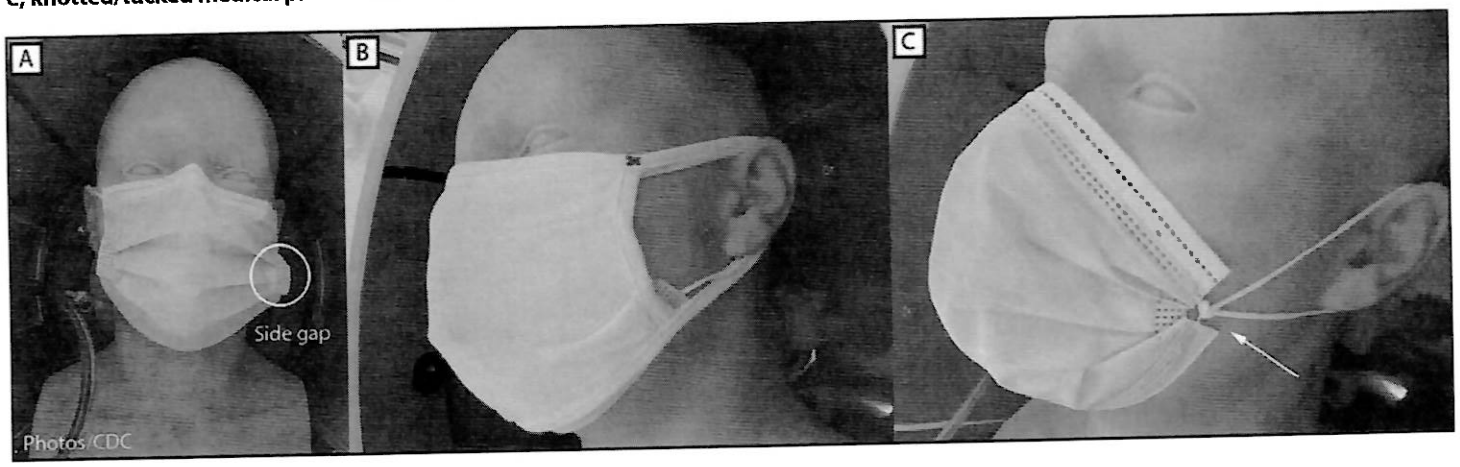
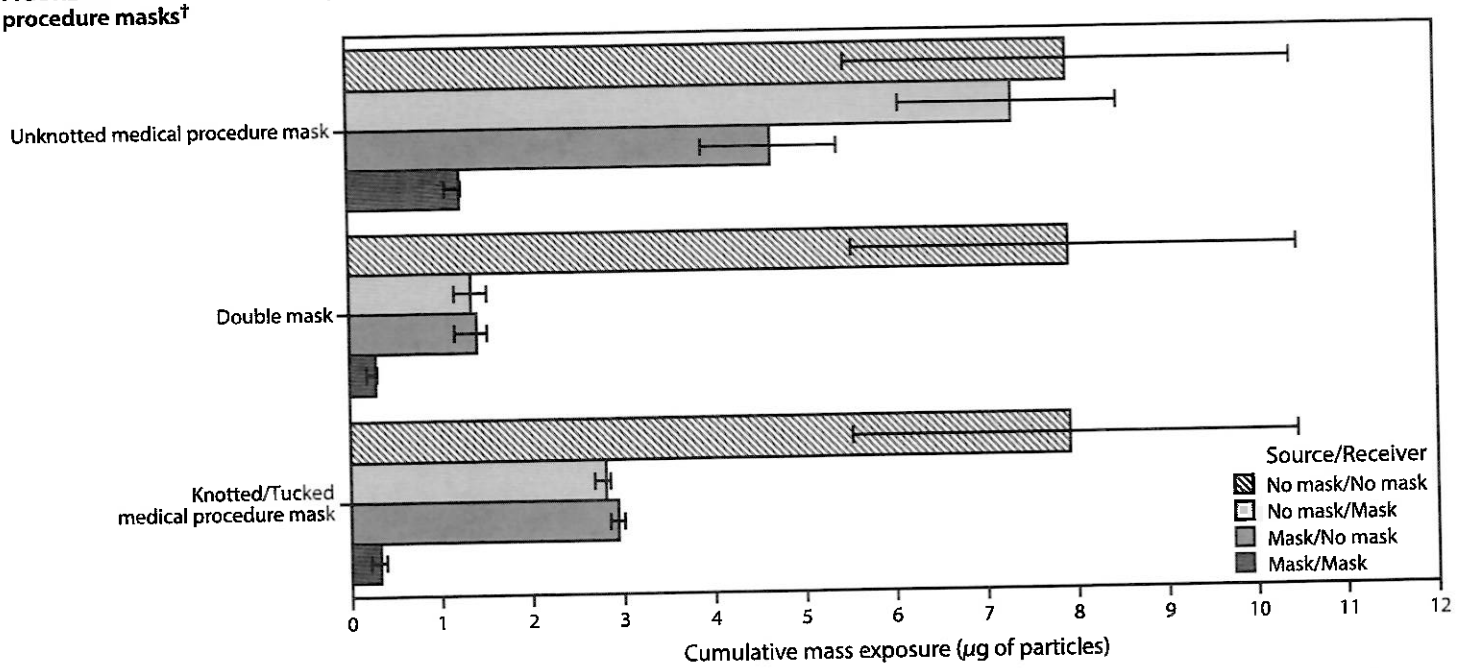


FIGURE 2. Mean cumulative exposure* for various combinations of no mask, double masks, and unknotted and knotted/tucked medical procedure masks†



* To an aerosol of 0.1–7 μm potassium chloride particles (with 95% confidence intervals indicated by error bars) measured at mouthpiece of receiver headform configured face to face 6 ft from a source headform, with no ventilation and replicated 3 times. Mean improvements in cumulative exposures compared with no mask/no mask (i.e., no mask wearing, or 100% exposure) were as follows: *unknotted medical procedure mask*: no mask/mask = 7.5%, mask/no mask = 41.3%, mask/mask = 84.3%; *double mask*: no mask/mask = 83.0%, mask/no mask = 82.2%, mask/mask = 96.4%; *knotted/tucked medical procedure mask*: no mask/mask = 64.5%, mask/no mask = 62.9%, mask/mask = 95.9%.

† Double mask refers to a three-ply medical procedure mask covered by a three-ply cloth cotton mask. A knotted and tucked medical procedure mask is created by bringing together the corners and ear loops on each side, knotting the ears loops together where they attach to the mask, and then tucking in and flattening the resulting extra mask material to minimize the side gaps.

Summary

What is already known about this topic?

Universal masking is recommended to slow the spread of COVID-19. Cloth masks and medical procedure masks substantially reduce exposure from infected wearers (source control) and reduce exposure of uninfected wearers (wearer exposure).

What is added by this report?

CDC conducted experiments to assess two ways of improving the fit of medical procedure masks: fitting a cloth mask over a medical procedure mask, and knotting the ear loops of a medical procedure mask and then tucking in and flattening the extra material close to the face. Each modification substantially improved source control and reduced wearer exposure.

What are the implications for public health?

These experiments highlight the importance of good fit to maximize mask performance. There are multiple simple ways to achieve better fit of masks to more effectively slow the spread of COVID-19.

another study, adding mask fitters to two medical procedure masks, which produced different reductions in exposure when unmodified, enhanced their efficiencies to the same equally high levels (*2*). This observation suggests that modifications to improve fit might result in equivalent improvements, regardless of the masks' baseline filtration efficiencies.

The findings in this report are subject to at least four limitations. First, these experiments were conducted with one type of medical procedure mask and one type of cloth mask among the many choices that are commercially available and were intended to provide data about their relative performance in a controlled setting. The findings of these simulations should neither be generalized to the effectiveness of all medical procedure masks or cloths masks nor interpreted as being representative of the effectiveness of these masks when worn in real-world settings. Second, these experiments did not include any other combinations of masks, such as cloth over cloth, medical procedure mask over medical procedure mask, or medical procedure mask over cloth. Third, these findings might not be generalizable to children because of their smaller

size or to men with beards and other facial hair, which interfere with fit. Finally, although use of double masking or knotting and tucking are two of many options that can optimize fit and enhance mask performance for source control and for wearer protection, double masking might impede breathing or obstruct peripheral vision for some wearers, and knotting and tucking can change the shape of the mask such that it no longer covers fully both the nose and the mouth of persons with larger faces.

Controlling SARS-CoV-2 transmission is critical not only to reduce the widespread effects of the COVID-19 pandemic on human health and the economy but also to slow viral evolution and the emergence of variants that could alter transmission dynamics or affect the usefulness of diagnostics, therapeutics, and vaccines. Until vaccine-induced population immunity is achieved, universal masking is a highly effective means to slow the spread of SARS-CoV-2 when combined with other protective measures, such as physical distancing, avoiding crowds and poorly ventilated indoor spaces, and good hand hygiene. The data in this report underscore the finding that good fit can increase overall mask efficiency. Multiple simple ways to improve fit have been demonstrated to be effective. Continued innovative efforts to improve the fit of cloth and medical procedure masks to enhance their performance merit attention.

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ORIGINAL RESEARCH

Testing the Efficacy of Homemade Masks: Would They Protect in an Influenza Pandemic?

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ABSTRACT

Objective: This study examined homemade masks as an alternative to commercial face masks.

Methods: Several household materials were evaluated for the capacity to block bacterial and viral aerosols. Twenty-one healthy volunteers made their own face masks from cotton t-shirts; the masks were then tested for fit. The number of microorganisms isolated from coughs of healthy volunteers wearing their homemade mask, a surgical mask, or no mask was compared using several air-sampling techniques.

Results: The median-fit factor of the homemade masks was one-half that of the surgical masks. Both masks significantly reduced the number of microorganisms expelled by volunteers, although the surgical mask was 3 times more effective in blocking transmission than the homemade mask.

Conclusion: Our findings suggest that a homemade mask should only be considered as a last resort to prevent droplet transmission from infected individuals, but it would be better than no protection. (*Disaster Med Public Health Preparedness.* 2013;7:413-418)

Key Words: homemade facemasks, respirators, airborne transmission, microbial dispersion, pandemic prevention

Wearing a face mask in public areas may impede the spread of an infectious disease by preventing both the inhalation of infectious droplets and their subsequent exhalation and dissemination. In the event of a pandemic involving an airborne-transmissible agent, the general public will have limited access to the type of high-level respiratory protection worn by health care workers, such as N95 respirators. Images of members of the public wearing surgical masks were often used to illustrate the 2009 H1N1 flu pandemic. However, the evidence of proportionate benefit from widespread use of face masks is unclear.

A recent prospective cluster-randomized trial comparing surgical masks and non-fit-tested P2 masks (filters at least 94% of airborne particles) with no mask use in the prevention of influenza-like illness. The findings of the study found that adherence to mask use significantly reduced (95% CI, 0.09-0.77; $P = .015$) the risk for infection associated with influenza-like illness, but that less than 50% of participants wore masks most of the time.[1] Facemasks may prevent contamination of the work space during the outbreak of influenza or other droplet-spread communicable disease by reducing aerosol transmission. They may also be used to reduce the risk of body fluids, including blood, secretions, and excretions, from reaching the wearer's mouth and nose.

To date, studies on the efficacy and reliability of face masks have concentrated on their use by health care workers. Although health care workers are likely to be one of the highest risk groups in terms of exposure, they are also more likely to be trained in the use of masks and fit tested than the general public. Should the supply of standard commercial face masks not meet demand, it would be useful to know whether improvised masks could provide any protection to others from those who are infected.

METHODS AND MATERIALS

In this study, common household materials (see Table 1) were challenged with high concentrations of bacterial and viral aerosols to assess their filtration efficiencies. Surgical masks have been considered the type of mask most likely to be used by the general public, and these were used as a control. The pressure drop across each of the materials was measured to determine the comfort and fit between face and mask that would be needed to make the material useable in mask form. We devised a protocol for constructing a "homemade" mask, based on the design of a surgical mask, and volunteers were invited to make their own masks. These were then quantitatively fit tested. To determine the effect of homemade and surgical masks in preventing the dispersal of droplets and aerosol particles produced by the wearer, the total bacterial

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TABLE 1

Filtration Efficiency and Pressure Drop Across Materials Tested with Aerosols of *Bacillus atrophaeus* and Bacteriophage MS2 (30 L/min)[a]

Material	*B atrophaeus*		Bacteriophage MS2		Pressure Drop Across Fabric	
	Mean % Filtration Efficiency	SD	Mean % Filtration Efficiency	SD	Mean	SD
100% cotton T-shirt	69.42 (70.66)	10.53 (6.83)	50.85	16.81	4.29 (5.13)	0.07 (0.57)
Scarf	62.30	4.44	48.87	19.77	4.36	0.19
Tea towel	83.24 (96.71)	7.81 (8.73)	72.46	22.60	7.23 (12.10)	0.96 (0.17)
Pillowcase	61.28 (62.38)	4.91 (8.73)	57.13	10.55	3.88 (5.50)	0.03 (0.26)
Antimicrobial Pillowcase	65.62	7.64	68.90	7.44	6.11	0.35
Surgical mask	96.35	0.68	89.52	2.65	5.23	0.15
Vacuum cleaner bag	94.35	0.74	85.95	1.55	10.18	0.32
Cotton mix	74.60	11.17	70.24	0.08	6.18	0.48
Linen	60.00	11.18	61.67	2.41	4.50	0.19
Silk	58.00	2.75	54.32	29.49	4.57	0.31

[a] Numbers in parentheses refer to the results from 2 layers of fabric.

count was measured when the volunteers coughed wearing their homemade mask, a surgical mask, and no mask.

Testing the Filtration Efficiency

A range of common household materials were tested, together with the material from a surgical mask (Mölnlycke Health Care Barrier face mask 4239, EN14683 class I), for comparison. Circular cutouts of the tested materials were placed without tension in airtight casings, creating a "filter" in which the material provided the only barrier to the transport of the aerosol.

A Henderson apparatus allows closed-circuit generation of microbial aerosols from a Collison nebulizer at a controlled relative humidity. This instrument was used to deliver the challenge aerosol across each material at 30 L/min using the method of Wilkes et al,[2] which is about 3 to 6 times per minute the ventilation of a human at rest or doing light work, but is less than 0.1 the flow of an average cough.

Downstream air was sampled simultaneously for 1 minute into 10 ml of phosphate buffer manucol antifoam using 2 all-glass impingers. One impinger sampled the microorganisms that had penetrated through the material filter, while the other sampled the control (no filter). The collecting fluid was removed from the impingers and assayed for microorganisms. This test was performed 9 times for each material. The filtration efficiency (FE) of the fabric was calculated using the following formula (cfu indicate colony-forming units):

$$FE = \frac{\text{Upstream cfu} - \text{Downstream cfu} \times 100}{\text{Upstream cfu}}$$

The pressure drop across the fabric was measured using a manometer (P200UL, Digitron), with sensors placed on either side of the filter casing, while it was challenged with a clean aerosol at the same flow rate.

Microorganisms

Two microorganisms were used to simulate particle challenge: *Bacillus atrophaeus* is a rod-shaped spore-forming bacterium (0.95-1.25 μm) known to survive the stresses caused by aerosolization.[3] The suspension was prepared from batches previously prepared by the Health Protection Agency, Centre for Emergency Preparedness and Response Production Division.[4] Each material was challenged with approximately 10^7 cfu *B atrophaeus*.

Bacteriophage MS2 (MCIMB10108) is a nonenveloped single-stranded RNA coliphage, 23 nm in diameter, known to survive the stresses of aerosolization.[5] Each material was challenged with approximately 10^9 plaque-forming units (pfu) of bacteriophage MS2.

The two test organisms can be compared in size to influenza virus, which is pleomorphic and ranges from 60 to 100 nm; *Yersinia pestis*, which is 0.75 μm; *B anthracis*, which is 1 to 1.3 μm; *Francisella tularensis*, which is 0.2 μm; and *Mycobacterium tuberculosis*, which is 0.2 to 0.5 μm.[6] Bacteriophage MS2 and *B atrophaeus* were chosen as the test organisms to represent influenza virus. This decision was made not only because of the lower risks of associated infection but also because the work would be technically easier to carry out using an Advisory Committee on Dangerous Pathogens (ACDP) class 1 organism versus an ACDP class 2 organism influenza.

Making the Face Mask

For this study, 21 healthy volunteers were recruited, 12 men and 9 women. The participants were aged between 20 and 44 years; the majority was in the 20- to 30-year age range. Each volunteer made a homemade face mask following a protocol devised by the authors. All face masks were made with 100% cotton t-shirt fabric using sewing machines to speed construction. A surgical mask (Mölnlycke Health Care

Barrier face mask 4239, EN14683 class I) was used as a control. Also, all volunteers completed a questionnaire indicating their opinions of mask wearing.

Determining the Fit Factor of the Mask

A commercial fit test system (TSI PortaCount Plus Respirator Fit Tester and N95- Companion Module model 8095) was used to measure respirator fit by comparing the concentration of microscopic particles outside the respirator with the concentration of particles that have leaked into the respirator. The ratio of these 2 concentrations is known as the fit factor. To conduct the fit test, the apparatus was set up and operated according to the manufacturer's instructions.

Volunteers were instructed to fit their surgical and homemade face masks with no help or guidance from the operator; to ensure that the mask was comfortable for 2 minutes; the participants were given time to purge any particles trapped inside the mask. The fit test was then conducted with volunteers performing the following consecutive exercises, each lasting 96 seconds: (1) normal breathing, (2) deep breathing,[7] (3) head moving side to side, (4) head moving up and down, (5) talking aloud (reading a prepared paragraph), (6) bending at the waist as if touching their toes, and (7) normal breathing.

Determining the Effect of Masks in Preventing the Dispersal of Droplets and Aerosol

An enclosed 0.5-m^3 mobile sampling chamber, or cough box, which was constructed for the purpose of sampling aerosols and droplets from healthy volunteers (PFI Systems Ltd, Milton Keynes), was placed in a 22.5-m^3 high-frequency particulate air-filtered environmental room. Four settle plates were placed in the cough box to sample for droplets, together with a 6-stage Andersen sampler to sample and separate small particles.[8] A Casella slit-air sampler[9] was also attached to the cough box. Tryptose soya agar was used as the culture medium. Volunteers wearing protective clothing (Tyvek suits) coughed twice into the box, and the air inside was sampled for 5 minutes. Each volunteer was sampled 3 times: wearing the homemade mask, the surgical mask, and no mask. The air within the cough box was high-frequency particulate air filtered for 5 minutes between each sample to prevent cross-contamination between samples. The plates were incubated for a minimum of 48 hours at 37°C before counting.

Statistical Analysis

To evaluate the face mask fit, the median and interquartile range were calculated for each exercise and face mask for the 21 individuals. Wilcoxon sign rank tests were used to compare the masks. The same approach was used to determine differences between the different mask types and their efficacy in preventing dissemination of droplets and particles

RESULTS

Filtration Efficacy

All the materials tested showed some capability to block the microbial aerosol challenges. In general, the filtration efficiency for bacteriophage MS2 was 10% lower than for *B atrophaeus* (Table 1). The surgical mask had the highest filtration efficiency when challenged with bacteriophage MS2, followed by the vacuum cleaner bag, but the bag's stiffness and thickness created a high pressure drop across the material, rendering it unsuitable for a face mask. Similarly, the tea towel, which is a strong fabric with a thick weave, showed relatively high filtration efficiency with both *B atrophaeus* and bacteriophage MS2, but a high pressure drop was also measured.

The surgical mask (control) showed the highest filtration efficiency with *B atrophaeus*. Also, as expected, its measured low pressure drop showed it to be the most suitable material among those tested for use as a face mask. The pillowcase and the 100% cotton t-shirt were found to be the most suitable household materials for an improvised face mask. The slightly stretchy quality of the t-shirt made it the more preferable choice for a face mask as it was considered likely to provide a better fit.

Although doubling the layers of fabric did significantly increase the pressure drop measured across all 3 materials ($P < .01$ using Wilcoxon sign rank test), only the 2 layers of tea towel material demonstrated a significant increase in filtration efficiency that was marginally greater than that of the face mask.

In the questionnaire on mask use during a pandemic, 6 participants said they would wear a mask some of the time, 6 said they would never wear a mask, and 9 either did not know or were undecided. None of the participants said that they would wear a mask all of the time. With 1 exception, all participants reported that their face mask was comfortable. However, the length of time each participant kept their mask on during testing was minimal (15 min), and with long-term wear, comfort might decrease.

Facemask Fit Testing

A Wilcoxon sign rank test showed a significant difference between the homemade and surgical mask for each exercise and in total (all tests showed $P < .001$). The median and interquartile range for each mask and exercise are given in Table 2.

Prevention of Droplet and Particle Dissemination When Coughing

Results from the cough box experiments showed that both the surgical mask and the homemade mask reduced the total number of microorganisms expelled when coughing ($P < .001$ and $P = .004$, respectively; see Table 3).

TABLE 2

Median and Interquartile Range Results from Respirator Fit Testing of Homemade and Surgical Masks

	Median Interquartile Range			
Condition	**Homemade Mask**		**Surgical Mask**	
Normal breathing	2.0	(2.0, 2.5)	6.0	(2.5, 9.0)
Heavy breathing	2.0	(2.0, 3.0)	7.0	(2.5, 13.5)
Head moving side to side	2.0	(1.0, 2.0)	5.0	(3.0, 7.0)
Head moving up and down	2.0	(1.5, 2.0)	5.0	(3.0, 7.0)
Bending over	1.0	(1.0, 2.0)	3.0	(2.0, 9.0)
Talking	2.0	(1.0, 2.0)	6.0	(3.0, 12.0)
Normal	2.0	(1.0, 2.0)	5.0	(2.0, 8.5)
All data	2.0	(1.0, 2.0)	5.0	(3.0, 9.0)

TABLE 3

Median Colony-Forming Units by Sampling Method Isolated From Volunteers Coughing When Wearing a Surgical Mask, a Homemade Mask, and No Mask

	Median Interquartile Range				
Sampling Method	**No Mask**		**Homemade Mask**		***P***
Air	6.0	(1.0, 26.5)	1.0	(0.5, 6.5)	.007
Settle plates	1.0	(0.0, 3.0)	1.0	(0.0, 2.0)	.224
Total	2.0	(0.0, 12.3)	1.0	(0.0, 3.0)	.004
	Median Interquartile Range				
Sampling Method	**No Mask**		**Surgical Mask**		***P***
Air	6.0	(1.0, 26.5)	1.0	(0.5, 3.0)	.002
Settle plates	1.0	(0.0, 3.0)	0.0	(0.0, 0.0)	.002
Total	2.0	(0.0, 12.3)	0.0	(0.0, 1.0)	<.001

On analyzing the effect of mask wearing in reducing the number of microorganisms isolated from the Anderson air sampler (Table 4), the surgical mask was found to be generally more effective in reducing the number of microorganisms expelled than the homemade mask, particularly at the lowest particle sizes. The number of microorganisms isolated from the coughs of healthy volunteers was generally low, although this varied according to the individual sampled (Table 3). It is possible, therefore, that the sampling limitations negatively affected the statistical analysis.

Pearson χ^2 tests comparing the proportion of particles greater than 4.7 μm in diameter and particles less than 4.7 μm in diameter found that the homemade mask did not significantly reduce the number of particles emitted ($P = .106$). In contrast, the surgical mask did have a significant effect ($P < .001$).

TABLE 4

Total Colony-Forming Units Isolated by Particle Size From 21 Volunteers Coughing When Wearing a Surgical Mask, Homemade Mask, and No Mask

Particle Diameter, μm	No Mask	Homemade Mask	Surgical Mask
>7	9	3	5
4.7-7	18	7	7
3.3-4.7	5	4	4
2.1-3.3	47	7	5
1.1-2.1	100	16	6
0.65-1.1	21	6	3
Total	200	43	30

DISCUSSION

Facemasks reduce aerosol exposure by a combination of the filtering action of the fabric and the seal between the mask and the face. The filtration efficiency of the fabric depends on a variety of factors: the structure and composition of the fabric, and the size, velocity, shape, and physical properties of the particles to which it is exposed.[10] Although any material may provide a physical barrier to an infection, if as a mask it does not fit well around the nose and mouth, or the material freely allows infectious aerosols to pass through it, then it will be of no benefit.

The test organisms in this study can be used to estimate the efficacy of these masks against influenza virus because essentially any aerosolized particle will behave predominately in the air as a result of its physical characteristics rather than its biological properties (ie, influenza virus particles will travel in the air in the same manner as particles of an equivalent size). Therefore, as we have tested a viral pathogen smaller than influenza and a bacterial pathogen larger than influenza, we have tested the face masks with a suitable challenge across the size range of influenza virus particles. Furthermore, the data from this study could also be applied to other organisms within this size range that are potentially transmitted via the aerosol route.

Quantitative fit testing can only estimate the combined effects of filtration efficiency and goodness of fit. Although sensitive to particles with diameters as small as 0.02 μm, it is not sensitive to variations in particle size, shape, composition, or refractive index. As a result, this method of fit testing does not allow the distinction between true bioaerosols and droplet contamination.

A study conducted in the Netherlands using a commercial fit-test system (Portacount Plus Respirator Fit Tester) on volunteers wearing both improvised masks made from tea cloths and surgical masks over a 3-hour period found results similar to those found in this study.[11] The authors demonstrated a median protection factor of between 2.2 and 2.5 for various activities when wearing a mask with a tea

towel filter and protection factors of between 4.1 and 5.3 for the surgical mask. It was interesting that the study also found that median protection factors increased over the 3-hour period for those wearing the homemade masks, decreased for those wearing filtering face piece (FFP2) masks that lower the wearer's exposure to airborne particles by a factor of 10, and showed no consistent pattern for those wearing a surgical mask.[11]

The materials used in this published study were fresh and previously unworn. It is likely that materials conditioned with water vapor, to create a fabric similar to that which has been worn for a couple of hours, would show very different filtration efficiencies and pressure drops. In contrast, a study of breathing system filters found a greater breakthrough of bacteriophage MS2 on filters that had been preconditioned. Although the droplet sizes for both virus and bacteria were the same and affected the filter media in a similar manner, it was suggested that the viruses, after contact with the moisture on the filter, were released from their droplet containment, and driven onward by the flow of gas.[12]

The average concentration of *Streptococcus* organisms in saliva has been estimated to be 6.7×10^7 cfu/mL,[13] which is higher than that of influenza viruses in inoculated volunteers.[14] Therefore, the number of oral microorganisms isolated may well provide an indication of the concentration of influenza being shed. Results from the cough box demonstrated that surgical masks have a significant effect in preventing the dispersal of large droplets and some smaller particles when healthy volunteers coughed. The homemade mask also prevented the release of some particles, although not at the same level as the surgical mask. The numbers of microorganisms isolated from the coughs of healthy volunteers was in general very low, and it is likely that had we used volunteers with respiratory infections, the homemade mask may have shown a more significant effect in preventing the release of droplets.

It was observed during this study that there was greater variation among volunteers in their method of fitting the surgical mask. The need to tie the straps at the back of the head meant that the surgical mask was fit in a variety of ways. In contrast, the face mask had looped elastic straps that were easier for the volunteer to fit.

Comfort should be an important factor in the material used to make a homemade mask. The pressure drop across a mask is a useful measure both of resistance to breathing and the potential for bypass of air around the filter seal. If respiratory protection is not capable of accommodating the breathing demands of the wearer, then the device will impose an extra breathing load on the wearer, which is especially impracticable for people with breathing difficulties. Furthermore, the extra breathing load may induce leakage owing to the increased negative pressure in the face mask.[15]

In practice, people will not wear an uncomfortable mask for a long period; even if they do, it is unlikely that they will wear the mask properly. During the outbreak of severe acute respiratory syndrome, an account of a flight from Bangkok, Thailand, to Manchester, England. described mask wearers removing their mask to cough, sneeze, and wipe their nose (not necessarily into a handkerchief) and to sort through the communal bread basket.[16] For those who wear a mask for necessity, such as health care workers, regular training and fit testing must be emphasized. Whereas, for those who choose to wear a homemade mask, the requirements of cleaning and changing the mask should be highlighted. Most importantly, the lower protective capabilities of a homemade mask should be emphasized so that unnecessary risks are not taken.

CONCLUSION

A protective mask may reduce the likelihood of infection, but it will not eliminate the risk, particularly when a disease has more than 1 route of transmission. Thus any mask, no matter how efficient at filtration or how good the seal, will have minimal effect if it is not used in conjunction with other preventative measures, such as isolation of infected cases, immunization, good respiratory etiquette, and regular hand hygiene. An improvised face mask should be viewed as the last possible alternative if a supply of commercial face masks is not available, irrespective of the disease against which it may be required for protection. Improvised homemade face masks may be used to help protect those who could potentially, for example, be at occupational risk from close or frequent contact with symptomatic patients. However, these masks would provide the wearers little protection from microorganisms from others persons who are infected with respiratory diseases. As a result, we would not recommend the use of homemade face masks as a method of reducing transmission of infection from aerosols.

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Efficacy of face masks, neck gaiters and face shields for reducing the expulsion of simulated cough-generated aerosols

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Abstract

Face masks are recommended to reduce community transmission of SARS-CoV-2. One of the primary benefits of face masks and other coverings is as source control devices to reduce the expulsion of respiratory aerosols during coughing, breathing, and speaking. Face shields and neck gaiters have been proposed as an alternative to face masks, but information about face shields and neck gaiters as source control devices is limited. We used a cough aerosol simulator with a pliable skin headform to propel small aerosol particles (0 to 7 μm) into different face coverings. An N95 respirator blocked 99% (standard deviation (SD) 0.3%) of the cough aerosol, a medical grade procedure mask blocked 59% (SD 6.9%), a 3-ply cotton cloth face mask blocked 51% (SD 7.7%), and a polyester neck gaiter blocked 47% (SD 7.5%) as a single layer and 60% (SD 7.2%) when folded into a double layer. In contrast, the face shield blocked 2% (SD 15.3%) of the cough aerosol. Our results suggest that face masks and neck gaiters are preferable to face shields as source control devices for cough aerosols.

Keywords

Infection control; Airborne transmission; Infectious disease transmission; Face masks; Face shields

Introduction

SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19), can be transmitted from person-to-person by large respiratory aerosols (airborne liquid droplets and dried particles greater than about 10 μm in diameter) produced by people who are infectious while they are talking, singing, coughing, breathing or sneezing (CDC 2020a; Hamner et al. 2020). Smaller aerosols also are emitted by people during these activities, suggesting that short-range airborne transmission of SARS-CoV-2 might be possible under some circumstances (Anderson et al. 2020; CDC 2020a; Fennelly 2020; Ma et al. 2020; Morawska and Milton 2020).

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Declaration of Interests Statement

The authors declare no competing interests.

To interrupt this potential transmission route, the Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO), and other public health organizations recommend the wearing of face masks or other face coverings by the general public during the ongoing COVID-19 pandemic (CDC 2020b; c; Edelstein and Ramakrishnan 2020; WHO 2020). One of the primary benefits of face coverings is to act as source control devices to reduce the expulsion of aerosols containing the virus from people who are infectious during coughing, breathing, and speaking. Source control devices are intended to protect other people from infectious aerosols emitted by the wearer, as compared with personal protective equipment such as N95 respirators which are primarily intended to protect the wearer. A face covering can provide source control in two ways (Diaz and Smaldone 2010). First, and most importantly, the covering may collect aerosol particles by filtration, impaction, or other mechanisms, and thus prevent infectious aerosols from entering the environment. Second, the face covering may change the direction of travel and the velocity of the aerosol stream and thus possibly divert the aerosol away from a potential recipient. However, deflection is more uncertain as a source control mechanism. For example, if large aerosols are deflected downward, they may settle to the floor or otherwise be unable to reach the breathing zones of other people. However, since exhaled breath is often warmer than the surrounding air, this downward deflection may be counteracted by the buoyancy of the breath for smaller aerosols. In addition, if the respiratory aerosols are deflected sideways, they may be diverted away from a person directly in front of the wearer but toward someone to the side or behind the wearer.

Studies using manikins (Lai et al. 2012; Patel et al. 2016) and patients with respiratory infections (Leung et al. 2020; Milton et al. 2013) have shown that wearing medical face masks can reduce the dispersion of potentially infectious aerosols from patients. Two studies in which face masks were required for visitors and healthcare workers interacting with patients in bone marrow transplant centers found a reduction in respiratory viral infections among patients (Sokol et al. 2016; Sung et al. 2016). Studies of cloth face masks have suggested that they also can be effective at reducing the release of respiratory aerosols into the environment (Asadi et al. 2020; Davies et al. 2013; Konda et al. 2020). Several computational fluid dynamics studies have examined the generation and expulsion of respiratory aerosols and have provided important insights into the ability of face coverings to reduce the dispersion of large and small aerosols from the wearer (Dbouk and Drikakis 2020; Mittal et al. 2020).

Unfortunately, the use of face masks and other face coverings by the general public can present challenges. People often dislike wearing masks, and compliance can be low and inconsistent (Longtin et al. 2009). Mask wearers may repeatedly don, doff and adjust face masks, which can contaminate the hands and potentially lead to disease transmission, especially when the masks are reused (Brady et al. 2017; Casanova et al. 2008). For cloth masks, the filtration efficiency and air flow resistance of different textiles varies widely (Konda et al. 2020; Teesing et al. 2020; Wilson et al. 2020). Alternative face coverings such as neck gaiters (an elastic fabric tube that fits snugly around the head and neck) are commonly used, but information about their performance as source control devices is limited. Factors such as how well the mask fits the face and the coverage provided by a mask can have a substantial impact on the effectiveness of face masks (Davies et al. 2013;

Lawrence et al. 2006). Comparisons of face coverings have found substantial differences in the ability of different types of these devices to reduce the release of respiratory aerosols (Asadi et al. 2020; Davies et al. 2013).

An opinion article in JAMA proposed that face shields would be more effective than face masks at reducing community disease transmission, in large part because the authors felt that face shields were more comfortable and thus that they were more likely to be widely adopted by the public (Perencevich et al. 2020). A previous study by our group of face shields used as personal protective devices showed that face shields protect the wearer from large cough aerosols directed at the face but are much less effective against smaller aerosols which were able to flow around the edges of the shield and be inhaled (Lindsley et al. 2014). However, very little work has been done examining face shields as source control devices. Two qualitative flow visualization studies of face shields and masks found that, although face shields deflected the air flow from the mouth, they did not stop aerosol particles from traveling around the face shield and entering the environment (Verma et al. 2020; Viola et al. 2020). Beyond these studies, quantitative data on the efficacy of face shields for source control are lacking.

The objective of our study was to conduct a quantitative comparison of the efficacy of an N95 respirator, a medical procedure mask, a commercial 3-ply cloth face mask, a single and double layer fabric neck gaiter, and a commercial disposable face shield as source control devices to reduce the expulsion of small cough-generated aerosol particles into the environment. Our results provide more information about the effectiveness of different types of source control devices and will help the public health community make recommendations about the best ways to use these devices to help reduce the spread of COVID-19.

Materials and Methods

Experimental Design

In our experiments, a cough aerosol simulator propelled a test aerosol through a headform into a collection chamber (Figure 1), and the amount of aerosol in the collection chamber was measured in each of six size fractions. The collection efficiency of each face mask, neck gaiter, or face shield was determined by comparing the amount of aerosol that was collected from the chamber with and without the device. Our test method was similar to the modified Greene and Vesley method used to test medical masks (Quesnel 1975), with the human test subject replaced by the cough aerosol simulator.

Cough aerosol simulator

The cough aerosol simulator is a modified version of the NIOSH cough aerosol simulator described previously (Lindsley et al. 2019; Lindsley et al. 2014; Lindsley et al. 2013). The experimental cough aerosol was generated by nebulizing a solution of 14% KCl and 0.4% sodium fluorescein using a single-jet Collison nebulizer (BGI, Butler, NJ) at 103 kPa (15 lbs./in^2), passing the aerosol through a diffusion drier (Model 3062, TSI, Shoreview, MN), and mixing it with 10 L/min of dry filtered air. The test aerosol was loaded into an elastomeric bellows, and the cough airflow was produced by a computer-controlled linear

motor that compresses the bellows. The cough aerosol was expelled through the mouth of a headform into a collection chamber. The headform used in the study has pliable skin that mimics the elastic properties of human skin in order to create a realistic simulation of how each face covering or shield would fit a human face (Bergman et al. 2014).

Source control devices

The source control devices tested were an N95 medical respirator (3M model 1860), a medical grade (ASTM Level 3) procedure mask with ear loops (Kimberly-Clark model 47107), a cloth face mask with 3 layers of cotton fabric and ear loops (Hanes Defender), a fabric neck gaiter (FKGIONG Sun UV Protection Neck Gaiter, 95% polyester, 5% Spandex) and a disposable face shield (Fisher Scientific # 19-181-600A). The neck gaiter was tested both as a single layer of fabric and doubled over to provide two layers of fabric. The masks and respirator were not equipped with exhalation valves. The face shield was 25 cm tall and extended from the forehead of the headform to 3 cm below the chin and around the side to 3 cm before the front of the ear. Photographs of the source control devices on the headform are shown in the supplemental online materials.

Mask fit test

For the experiments, either no device, a face mask, a neck gaiter, or a face shield were placed on the head form. Each device was used for two consecutive tests. For face masks and gaiters, a respirator fit test was performed using a PortaCount (TSI). The fit factor is a measure of the protection against airborne particles that is provided by a respiratory protective device. It is defined as the ratio of the aerosol concentration outside the respiratory protective device to the aerosol concentration inside the device (i.e., the aerosol concentration that is inhaled by the wearer). For example, a fit factor of 10 means that the ambient aerosol concentration is 10 times higher than the concentration inside the mask, and that the mask is therefore filtering out 90% of the ambient aerosol.

Aerosol collection and analysis

After placing the device on the headform and performing the fit test, the system was sealed. The test aerosol was then generated and propelled with a simulated cough through the headform and into the collection chamber. The Andersen impactor at the bottom of the collection chamber collected the aerosol particles that traveled through or around the device for 20 minutes after each cough. The Andersen impactor operates at a flow rate of 28.3 liters/minute and has six collection stages and a filter that separate the aerosol particles into seven size fractions based on the aerodynamic diameter of the particles: <0.6 μm; 0.6–1.1 μm; 1.1–2.1 μm; 2.1–3.3 μm; 3.3–4.7 μm; 4.7–7.0 μm; and >7 μm. Because the amount of aerosol in the largest size fraction was small and because of possible losses due to settling of the large aerosol particles, data for the largest size fraction was not included in the analysis. The impactor collection plates were coated with a solution of glycerol and Brij 35 to prevent particles from bouncing off the plates during collection (Mitchell 2003). After aerosol collection was completed, the impactor plates were rinsed with 0.1 M Tris solution and the fluorescence of the solution was measured using a fluorometer (SpectraMax M4, Molecular Devices). The complete experimental protocol is given in the supplemental online materials.

Statistical Analysis

The performance of each device was evaluated by comparing the total mass of the aerosol particles from a single cough that passed through or around the device and was collected by the Andersen impactor. The results were evaluated using a one-way ANOVA and multiple comparisons among the different devices and the control experiments without a device were conducted using a Tukey-Kramer test. To control for variations in the amount of aerosol in each cough, a sample of each cough aerosol was collected from the bellows prior to coughing and used to normalize the aerosol mass collection results for each experiment.

Results

The cough aerosol simulator provides a cough with a controlled cough airflow rate containing a test aerosol with a consistent aerosol size distribution. The simulator allows for a direct quantitative comparison of the ability of different types of source control devices to block the expulsion of simulated cough aerosol particles of different sizes into the environment. The flow rate of the simulated cough used in our experiments was based on cough flow profiles recorded from influenza patients and had a volume of 4.2 L with a peak flow rate of 11 L/s (Lindsley et al. 2013). The cough aerosol collected from the control experiments without a face covering had a mass median aerodynamic diameter of 1.3 μm, a geometric standard deviation of 2.3 and a total aerosol mass of 505 μg (standard deviation 69).

For our study, we tested the collection efficiencies (that is, the fraction of the cough aerosol that was blocked) of a medical grade procedure mask, a cotton cloth face mask, a polyester neck gaiter, an N95 medical respirator and a disposable face shield. These source control devices were chosen to provide representative samples of the different types of face coverings and face shields that are in common use during the pandemic. Neck gaiters are typically worn either as a single layer of fabric over the mouth and nose or doubled over to provide two layers of fabric; for our experiments, we tested both configurations. The quantity of aerosol particles in six size fractions that were able to travel through or around each source control device are shown in Figure 2. The collection efficiencies of the devices are shown as a function of aerosol size in Figure 3. All the devices showed increased collection efficiencies as the aerosol size increased.

On average, the N95 respirator blocked 99% of the total mass of test aerosol from being released into the environment, while the medical procedure mask blocked 59%, the cloth face mask blocked 51%, the single-layer gaiter blocked 47%, the double-layer gaiter blocked 60%, and the face shield blocked 2% of the total aerosol (Table 1). The N95 respirator, procedure mask, cloth mask, and the single-layer and double-layer gaiters all significantly reduced the aerosol emitted into the environment compared with no device ($P < 0.0001$ for each), but the face shield did not ($P = 0.9993$). The collection efficiencies of the procedure mask, cloth mask, and the single and double-layer gaiters did not differ significantly from each other, but all blocked cough aerosols significantly better than did the face shield ($P < 0.0001$). The N95 respirator outperformed all the other devices ($P < 0.0001$) (Table 2).

Discussion

Humans continuously emit aerosols of respiratory fluids as they breathe, talk, cough, sneeze, sing, or carry out other respiratory activities. These respiratory aerosols can have a very broad size range, from tens of nanometers in diameter to visible droplets of a millimeter or more (Bourouiba et al. 2014; Fennelly 2020; Gralton et al. 2011; Morawska et al. 2009). Airborne particles larger than 100 μm are ballistic; that is, they are affected primarily by gravity and fall quickly to the ground. Respiratory aerosol particles in this size range tend to deposit within a few meters of the source (Prather et al. 2020). As the aerosol particle diameter decreases from 100 μm, a gradual transition occurs where the settling velocity rapidly decreases and the particles remain airborne for longer times. For example, a 100 μm aerosol particle takes 4 seconds to fall 1 meter in still air, while a 10 μm aerosol particle takes 5.4 minutes and a 1 μm aerosol particle takes 8 hours to settle the same distance (Hinds 1999). Air currents such as plumes of warm air rising from the body can lift these particles and extend the time for which they stay in the air. Thus, small aerosol particles can remain airborne for minutes to hours and can accumulate over time in environments with poor ventilation (Bahl et al. 2020). Small aerosol particles also are easier to inhale and can travel more deeply into the lungs (Vincent 2005).

The amount and sizes of aerosol particles containing SARS-CoV-2 that are expelled by people who are infected are not yet known. Two studies of aerosol samples collected in patient rooms found infectious (replication-competent) SARS-CoV-2 in aerosol particles <4 μm in diameter (Santarpia et al. 2020a) and <10 μm in diameter (Lednicky et al. 2020). Other studies have reported SARS-CoV-2 RNA in exhaled breath from infected patients (Ma et al. 2020), aerosol samples from biocontainment and quarantine units housing SARS-CoV-2 infected persons (Santarpia et al. 2020b), and in aerosol samples at multiple locations throughout two hospitals in Wuhan, China during a COVID-19 outbreak (Liu et al. 2020). The presence of small aerosol particles containing infectious SARS-CoV-2 detected in these studies suggests that in addition to large aerosols, these small aerosols might play a role in SARS-CoV-2 transmission (Anderson et al. 2020; Bahl et al. 2020; Ma et al. 2020; Morawska and Milton 2020).

Source control devices like face coverings and face shields collect respiratory particles larger than 0.3 μm primarily by impaction and interception of the aerosol particles against the fibers or solid surfaces of the device. As noted earlier, source control devices may also deflect aerosols, but this mechanism can be problematic as a means of source control because the infectious aerosol is not prevented from entering the surrounding environment; it is merely sent in a different direction which may or may not be protective depending upon local airflows and the locations of other people. Our experimental system measures particle collection only; any particles that are deflected but not collected by the face covering are still collected by the Andersen impactor. Thus, we are able to measure the particle collection efficiency of the face coverings without the potentially confounding variable of particle deflection. On the other hand, this does means that any potential benefits from, for example, deflecting large aerosol particles toward the ground were not measured by our system.

Small aerosols require much higher air velocities to deposit by impaction than do larger aerosols, and thus are more difficult to block with source control devices (Hinds 1999; Lindsley 2016). Consequently, small aerosols present the most challenging scenario for testing source control devices since devices that block small aerosol particles would be expected to block larger ones as well. Our results show that face masks and neck gaiters can significantly reduce the expulsion of small respiratory aerosol particles during coughing. This suggests that various types of face coverings can make an important contribution to reducing the quantity of aerosol particles containing SARS-CoV-2 released into the environment by people who are infected. N95 respirators, which are worn for personal protection by healthcare workers and others at highest risk of exposure, are also very effective source control devices. In contrast, the face shield blocked very little of the cough aerosol, indicating that face shields are not effective as source control devices for small respiratory aerosols.

The collection efficiencies of all the devices tested increased as the aerosol particle size increased, and this trend would be expected to continue for larger aerosol particles than were tested here. For example, the collection efficiency of the cloth face mask was 28% for the < 0.6 μm particles and increased to 76% for the 4.7 to 7 μm particles. Similarly, the double-layer gaiter blocked 24% of the < 0.6 μm particles and 76% of the 4.7 to 7 μm particles. These results suggest that cloth face coverings would be effective as source control devices against the large respiratory aerosols that are thought to play an important role in SARS-CoV-2 transmission.

Our study has several limitations. We used a single cough volume, air flow profile, and aerosol size distribution for our studies; these parameters can vary greatly from person to person. We examined the performance of these devices during simulated coughing but not breathing or speaking, which have different air flow rates and aerosol size distributions. Some internal losses of the test aerosol particles likely occurred due to settling or impaction on the surfaces of the collection chamber, which may affect the estimates of the collection efficiencies. We only used a single representative example of each type of device. The shape and composition of face coverings vary widely, and this would be expected to affect the performance of individual devices. Some face masks have exhalation valves or vents which could reduce their efficacy as source control devices. The fit of a particular mask to an individual wearer and compliance in wearing the mask correctly (i.e., over the nose and mouth) also are important factors in how well the mask performs as a source control device. Because we used a <0.6 to 7 μm test aerosol, our results do not indicate if face shields would be more effective as source control devices for large droplets. The face shield that we tested has a widely used design, but alternative designs are being marketed that provide greater facial coverage and, in some cases, include fabric skirts between the shield and the face. These alternative face shield designs might perform better as source control devices.

Previous studies have shown that face shields provide eye and facial protection to the wearer from droplets and splashes (Lindsley et al. 2014; Roberge 2016). When a face shield is worn in addition to a face mask, the face shield can also help reduce surface contamination of the mask by large aerosols and reduce the likelihood of hand contamination when the mask is removed or inadvertently touched (Lindsley et al. 2014). Our previous study showed

that face shields provide some benefits as personal protective equipment when face masks cannot be worn (Lindsley et al. 2014), but as with all personal protection and source control devices, their limitations must be respected. Our results suggest that face masks and neck gaiters are more effective than face shields as source control devices to reduce the expulsion of respiratory aerosols into the environment as a public health measure to reduce the community transmission of SARS-CoV-2.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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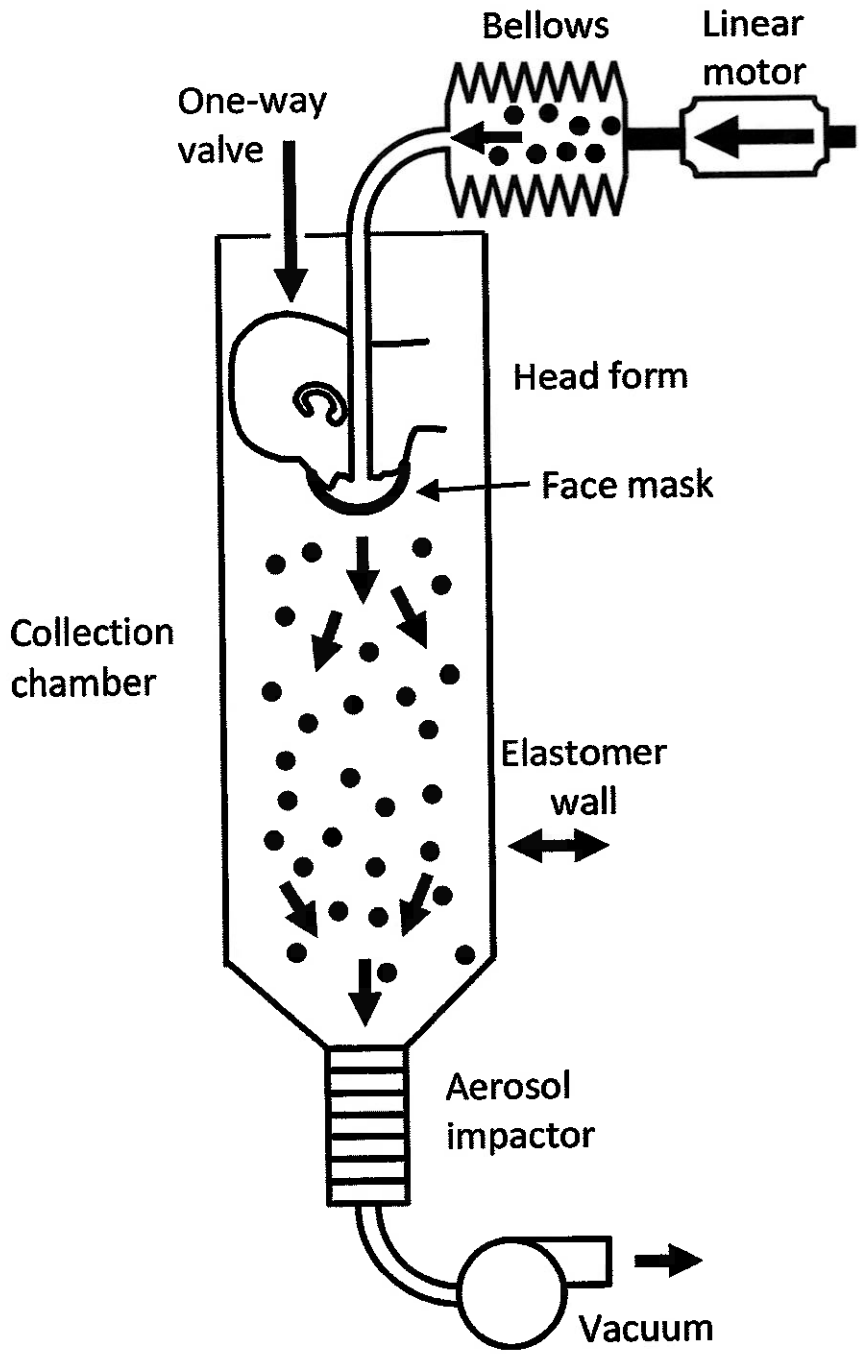

Figure 1:
Cough aerosol simulator system for source control measurements. The system consists of an aerosol generation system, a bellows and linear motor to produce the simulated cough, a pliable skin head form on which the face mask, neck gaiter or face shield is placed, a 105 liter collection chamber into which the aerosol is coughed, and an Andersen impactor to separate the aerosol particles by size and collect them. More information about the cough aerosol simulator is provided in the supplemental online materials.

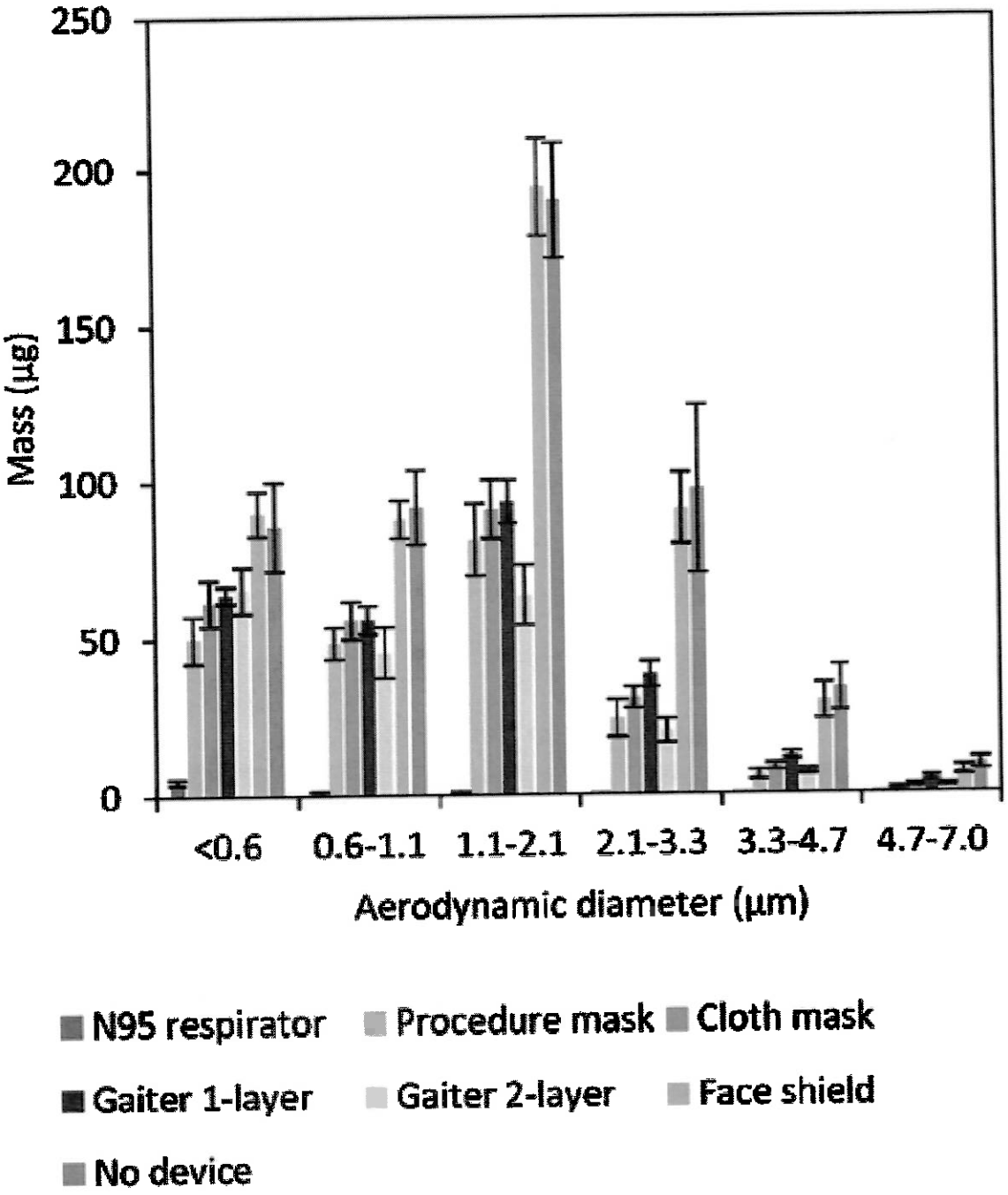

Figure 2:
Mass of aerosol collected in each size fraction. The graph shows the amount of simulated respiratory aerosol that was collected from the collection chamber in each aerosol particle size fraction after a single simulated cough. The bars show the mean and standard deviation. A larger color version of this figure is shown in the supplemental online materials.

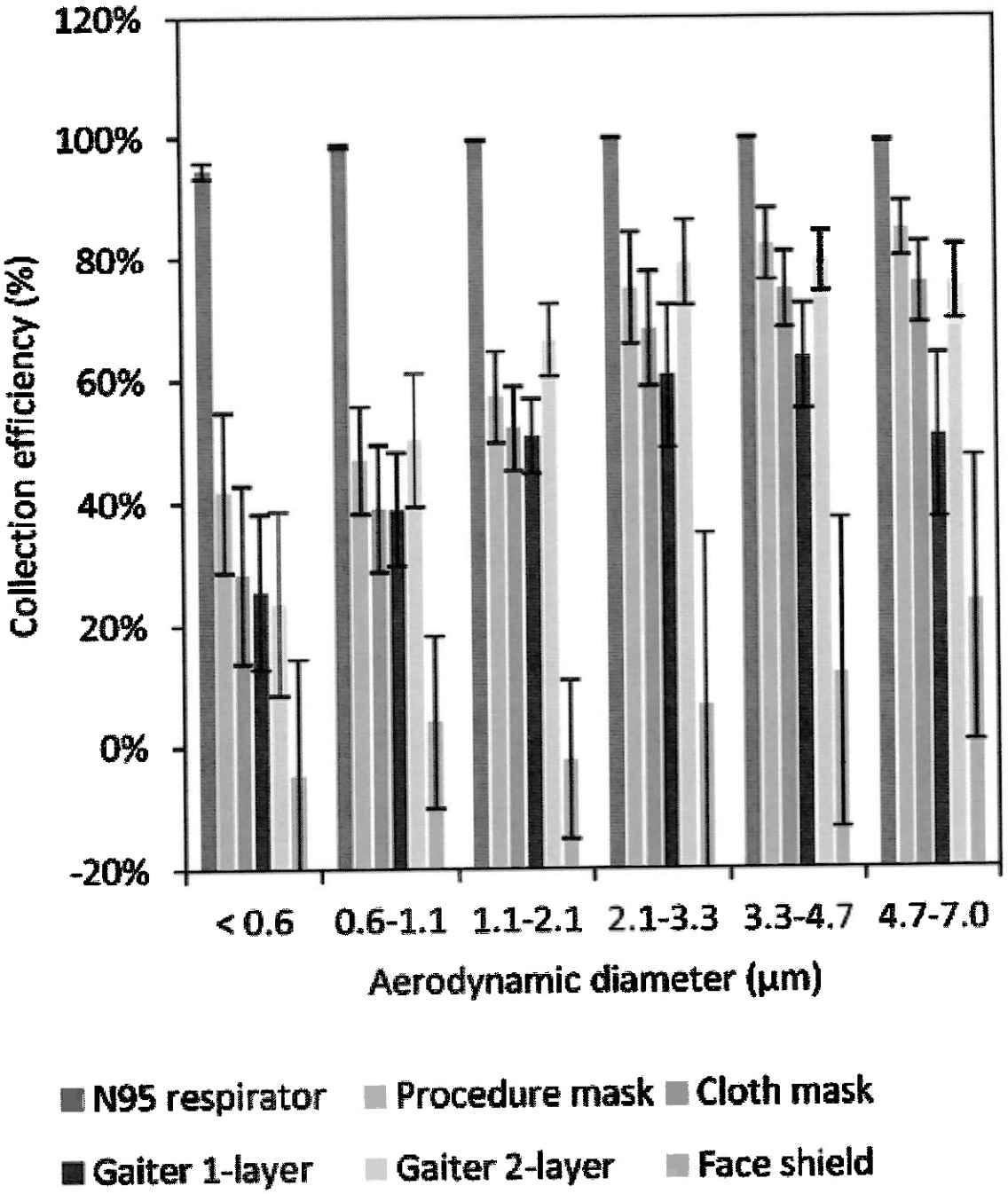

Figure 3:
Collection efficiency of face masks, neck gaiter and face shield. The collection efficiency is the percentage of aerosol particles that were blocked by the face mask, neck gaiter or face shield compared with experiments without a device. The plot shows the means and standard deviations of the collection efficiency in each size fraction. A larger version of this figure is shown in color in the supplemental online materials.

Table 1:

Total mass of aerosol expelled into collection chamber and device collection efficiencies. The fit factor, aerosol mass, and collection efficiency are given as mean (standard deviation).

Device tested	Number of experiments	Fit factor	Aerosol mass (μg)	Collection efficiency
No device	12	n/a	512 (64)	n/a
Procedure mask	6	2.9 (0.5)	212 (23)	58.5% (6.9%)
Cloth mask	6	1.3 (0.1)	251 (23)	50.9% (7.7%)
Neck gaiter (single layer)	6	1.7 (0.5)	270 (18)	47.2% (7.5%)
Neck gaiter (double layer)	6	1.9 (0.4)	206 (26)	59.8% (7.2%)
Face shield	6	n/a	502 (46)	1.8% (15.3%)
N95 respirator	6	198 (3.5)	7.2 (1.2)	98.6% (0.3%)

Table 2:

Comparison of aerosol mass expelled into the collection chamber while wearing face masks, neck gaiters and face shields.

PPE types compared		95% confidence intervals for mean differences (μg)			P-value
		Lower limit	Mean difference	Upper limit	
N95 respirator	No device	−567	−504	−442	<0.0001
Procedure mask	No device	−361	−299	−237	<0.0001
Cloth mask	No device	−322	−260	−198	<0.0001
Gaiter (single layer)	No device	−304	−241	−179	<0.0001
Gaiter (double layer)	No device	−368	−306	−243	<0.0001
Face shield	No device	−71	−9	53	0.9993
N95 respirator	Face shield	−567	−495	−423	<0.0001
Procedure mask	Face shield	−362	−290	−218	<0.0001
Cloth mask	Face shield	−323	−251	−179	<0.0001
Gaiter (single layer)	Face shield	−304	−232	−160	<0.0001
Gaiter (double layer)	Face shield	−369	−297	−225	<0.0001
N95 respirator	Gaiter (double layer)	−271	−199	−127	<0.0001
Procedure mask	Gaiter (double layer)	−65	7	79	0.9999
Cloth mask	Gaiter (double layer)	−26	46	118	0.4505
Gaiter (single layer)	Gaiter (double layer)	−7	64	136	0.1051
N95 respirator	Gaiter (single layer)	−335	−263	−191	<0.0001
Procedure mask	Gaiter (single layer)	−130	−58	14	0.1900
Cloth mask	Gaiter (single layer)	−91	−19	53	0.9825
N95 respirator	Cloth mask	−316	−244	−172	<0.0001
Procedure mask	Cloth mask	−111	−39	33	0.6336
N95 respirator	Procedure mask	−277	−205	−133	<0.0001

FDA U.S. FOOD & DRUG ADMINISTRATION

September 11, 2023

Pfizer, Inc.
Attention: Leslie Sands
500 Arcola Road
Collegeville, PA 19426

Dear Ms. Sands:

On February 4, 2020, as amended on March 15, 2023, pursuant to Section 564(b)(1)(C) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act or the Act), the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency, or a significant potential for a public health emergency, that affects, or has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes Coronavirus Disease 2019 (COVID-19).[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act (21 U.S.C. 360bbb-3), subject to the terms of any authorization issued under that section.[2]

On December 11, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent)[3] for the prevention of COVID-19 for individuals 16 years of age and older pursuant to Section 564 of the Act. FDA reissued the letter of authorization on: December 23, 2020,[4]

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[1] U.S. Department of Health and Human Services, Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the FD&C Act, 21 U.S.C. § 360bbb-3, February 4, 2020. U.S. Department of Health and Human Services, *Amended Determination of a Public Health Emergency or Significant Potential for a Public Health Emergency Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3(b)*. March 15, 2023. 88 FR 16644 (March 20, 2023) ("Amended Determination").

[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020). See Amended Determination ("The declarations issued pursuant to section 564(b)(1) of the FD&C Act that circumstances exist justifying the authorization of emergency use of certain in vitro diagnostics, personal respiratory protective devices, other medical devices and drugs and biological products, as set forth in those declarations, and that are based on the February 4, 2020 determination, remain in effect until those declarations are terminated in accordance with section 564 of the FD&C Act.").

[3] For purposes of this letter, Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) refers to the vaccine that encodes the spike protein of only the Original SARS-CoV-2.

[4] In the December 23, 2020 revision, FDA removed reference to the number of doses per vial after dilution from the letter of authorization, clarified the instructions for vaccination providers reporting to VAERS, and made other technical corrections. FDA also revised the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) to clarify the number of doses of vaccine per vial after dilution and the instructions for reporting to VAERS. In addition, the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination

February 25, 2021,[5] May 10, 2021,[6] June 25, 2021,[7] and August 12, 2021.[8] On August 23, 2021, FDA approved COMIRNATY (COVID-19 Vaccine, mRNA)[9] and reissued the letter in its entirety for both Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and certain uses of COMIRNATY (COVID-19 Vaccine, mRNA).[10]

Providers) and the Fact Sheet for Recipients and Caregivers were revised to include additional information on safety monitoring and to clarify information about the availability of other COVID-19 vaccines.

[5] In the February 25, 2021 revision, FDA allowed flexibility on the date of submission of monthly periodic safety reports and revised the requirements for reporting of vaccine administration errors by Pfizer Inc. The Fact Sheet for Health Care Providers Administering Vaccine (Vaccination Providers) was revised to provide an update to the storage and transportation temperature for frozen vials, direct the provider to the correct CDC website for information on monitoring vaccine recipients for the occurrence of immediate adverse reactions, to include data from a developmental toxicity study, and add adverse reactions that have been identified during post authorization use. The Fact Sheet for Recipients and Caregivers was revised to add adverse reactions that have been identified during post authorization use.

[6] In the May 10, 2021 revision, FDA authorized Pfizer-BioNTech Vaccine (Original monovalent) for the prevention of COVID-19 in individuals 12 through 15 years of age, as well as for individuals 16 years of age and older. In addition, FDA revised the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) to include the following Warning: "Syncope (fainting) may occur in association with administration of injectable vaccines, in particular in adolescents. Procedures should be in place to avoid injury from fainting." In addition, the Fact Sheet for Recipients and Caregivers was revised to instruct vaccine recipients or their caregivers to tell the vaccination provider about fainting in association with a previous injection.

[7] In the June 25, 2021 revision, FDA clarified terms and conditions that relate to export of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) from the United States. In addition, the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) was revised to include a Warning about myocarditis and pericarditis following administration of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) The Fact Sheet for Recipients and Caregivers was updated to include information about myocarditis and pericarditis following administration of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent).

[8] In the August 12, 2021 revision, FDA authorized a third dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) administered at least 28 days following the two dose series of this vaccine in individuals 12 years of age or older who have undergone solid organ transplantation, or individuals 12 years of age or older who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

[9] COMIRNATY (COVID-19 Vaccine, mRNA) was approved for active immunization to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older.

[10] In the August 23, 2021 revision, FDA clarified that, subsequent to the FDA approval of COMIRNATY (COVID-19 Vaccine, mRNA) for the prevention of COVID-19 for individuals 16 years of age and older, this EUA would remain in place for the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) for the previously-authorized indication and uses. It also authorized COMIRNATY (COVID-19 Vaccine, mRNA) under this EUA for certain uses that are not included in the approved biologics license application (BLA). In addition, the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) was revised to provide updates on expiration dating of the authorized Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and updated language regarding warnings and precautions related to myocarditis and pericarditis. The Fact Sheet for Recipients and Caregivers was updated as the Vaccine Information Fact Sheet for Recipients and Caregivers, which comprises the Fact Sheet for the authorized Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and information about the FDA-licensed vaccine, COMIRNATY (COVID-19 Vaccine, mRNA).

Subsequently, FDA reissued the letter of authorization on September 22, 2021,[11] October 20, 2021,[12] October 29, 2021,[13] November 19, 2021,[14] December 9, 2021,[15] December 16, 2021,[16]

[11] In the September 22, 2021 revision, FDA authorized the administration of a single booster dose of COMIRNATY (COVID-19 Vaccine, mRNA) or Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) at least 6 months after completing the primary series of this vaccine in individuals: 65 years of age and older; 18 through 64 years of age at high risk of severe COVID-19; and 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 put them at high risk of serious complications of COVID-19 including severe COVID-19.

[12] In the October 20, 2021 revision, FDA clarified eligibility for the booster dose of COMIRNATY (COVID-19 Vaccine, mRNA) or Pfizer-BioNTech COVID-19 Vaccine and authorized the administration of a single booster dose of Pfizer-BioNTech COVID-19 Vaccine or COMIRNATY (COVID-19 Vaccine, mRNA) was a heterologous booster dose following completion of primary vaccination with another authorized COVID-19 vaccine. The eligible population(s) and dosing interval for the heterologous booster dose were the same as those authorized for a booster dose of the vaccine used for primary vaccination.

[13] In the October 29, 2021 revision, FDA authorized: 1) the use of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) for children 5 through 11 years of age; and 2) a manufacturing change to include an additional formulation of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) that uses tromethamine (Tris) buffer instead of phosphate buffered saline (PBS) used in the originally authorized Pfizer-BioNTech COVID-19 Vaccine (Original monovalent). The formulation of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) that uses Tris buffer was authorized in two presentations: 1) multiple dose vials, with gray caps and labels with a gray border, formulated to provide, without need for dilution, doses (each 0.3 mL dose containing 30 microgram (mcg) nucleoside-modified messenger RNA (modRNA)) for individuals 12 years of age and older; and 2) multiple dose vials, with orange caps and labels with an orange border, formulated to provide, after dilution, doses (each 0.2 mL dose containing 10 mcg modRNA) for individuals 5 through 11 years of age. The formulation that uses Tris buffer is the only formulation that is authorized for use in individuals 5 through 11 years of age.

[14] In the November 19, 2021 revision, FDA authorized the use of COMIRNATY (COVID-19 Vaccine, mRNA) and the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) as a single booster dose in individuals 18 years of age or older at least 6 months after completing the primary series of this vaccine (i.e., as a homologous booster dose), and as a single booster dose following completion of primary vaccination with another authorized COVID-19 vaccine (i.e., as a heterologous booster dose) in individuals 18 years of age or older. The dosing interval for the heterologous booster dose was authorized to be the same as that authorized for a booster dose of the vaccine used for primary vaccination.

[15] In the December 9, 2021 revision, FDA authorized the use of the vaccine as a single booster dose in individuals 16 and 17 years of age, at least 6 months after completing the primary series of this vaccine (i.e., as a homologous booster dose).

[16] On December 16, 2021, FDA approved a supplement to the COMIRNATY (COVID-19 Vaccine, mRNA) BLA to include a new 30 mcg dose formulation of COMIRNATY (COVID-19 Vaccine, mRNA) that uses Tris buffer instead of the PBS buffer used in the originally approved vaccine. At that time the EUA was revised to clarify that the Pfizer-BioNTech COVID-19 Vaccine that uses Tris buffer and COMIRNATY (COVID-19 Vaccine, mRNA) that uses the Tris buffer have the same formulation and could be used interchangeably. In addition, FDA extended the expiration date of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) that uses the Tris buffer from 6 months to 9 months when held at -90 °C to -60 °C. FDA also updated the fact sheets to reflect these revisions.

January 3, 2022,[17] March 29, 2022,[18] May 17, 2022,[19] and on June 17, 2022.[20]

On July 8, 2022, FDA approved a supplement submitted by BioNTech Manufacturing GmbH to the biologics license application (BLA) for COMIRNATY (COVID-19 Vaccine, mRNA),[21] and reissued the letter of authorization in its entirety for both Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and certain uses of COMIRNATY (COVID-19 Vaccine, mRNA).[22] Subsequently, FDA reissued the letter of authorization on August 31, 2022.[23] The August 31, 2022 reissuance provided for certain emergency uses of the Pfizer-BioNTech COVID-19

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[17] In the January 3, 2022 revision, FDA: (i) authorized the use of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) as a single booster dose in individuals 12 through 15 years of age; (ii) lowered the authorized dosing interval of the homologous booster dose to at least five (5) months after completion of the primary series; and (iii) authorized a third primary series dose of the vaccine administered at least 28 days following the two dose series of this vaccine in individuals 5 through 11 years of age who have undergone solid organ transplantation, or 5 through 11 years of age who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise. In addition, FDA revised the Fact Sheets for Healthcare Providers Administering Vaccine (Vaccination Providers) and the Fact Sheet for Recipients and Caregivers to reflect these revisions.

[18] In the March 29, 2022 revision, FDA authorized a second booster dose of COMIRNATY (COVID-19 Vaccine, mRNA) or the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) at least 4 months after receipt of a first booster dose of any FDA-authorized or approved COVID-19 vaccine to: 1) individuals 50 years of age and older; and 2) individuals 12 years of age or older who have undergone solid organ transplantation, or individuals 12 years of age or older who have been diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

[19] In the May 17, 2022 revision, FDA authorized the administration of a single booster dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) in individuals 5 through 11 years of age, at least 5 months after completing a primary series with this vaccine.

[20] In the June 17, 2022 revision, FDA authorized the administration of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) as a 3-dose primary series for the prevention of COVID-19 in individuals 6 months through 4 years of age; and an additional presentation of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) in multiple dose vials with maroon caps and labels with maroon borders (each 0.2 mL dose containing 3 mcg mRNA) for use in individuals 6 months through 4 years of age.

[21] FDA approved COMIRNATY (COVID-19 Vaccine, mRNA) for active immunization to prevent COVID-19 caused by SARS-CoV-2 in adolescents 12 through 15 years of age.

[22] In the July 8, 2022 authorization, FDA clarified that the EUA would remain in place for the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) for the previously authorized uses, and authorized use of COMIRNATY (COVID-19 Vaccine, mRNA) under this EUA for certain uses that are not included in the approved BLA. In addition, the Vaccine Information Fact Sheet for Recipients and Caregivers: For 12 Years of Age and Older and the Fact Sheets for Healthcare Providers Administering Vaccine (Vaccination Providers): For 12 Years of Age and Older were updated to reflect this.

[23] In the August 31, 2022 revision, FDA authorized the Pfizer-BioNTech Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in single dose vials and multiple dose vials with gray caps and labels with gray borders (each 0.3 mL dose containing a total of 30 mcg modRNA) for the prevention of COVID-19 in individuals 12 years of age and older as a single booster dose administered at least 2 months after either: 1) completion of primary vaccination with any FDA authorized or approved monovalent COVID-19 vaccine, or 2) receipt of the most recent booster dose with any FDA authorized or approved monovalent COVID-19 vaccine. FDA also revised the scope of authorization for COMIRNATY (COVID-19 Vaccine, mRNA) and Pfizer BioNTech COVID-19 Vaccine (Original monovalent) to remove their use as a booster dose for individuals 12 years of age and older. Finally, FDA revised the Fact Sheets for Pfizer-BioNTech COVID-19 Vaccine (Original monovalent), as applicable, to reflect these changes and to reflect updates to the Conditions of Authorization regarding VAERS reporting.

Vaccine, Bivalent (Original and Omicron BA.4/BA.5)[24] after either completion of primary vaccination with any FDA approved or authorized monovalent COVID-19 vaccine[25] or receipt of the most recent booster dose with any FDA authorized or approved monovalent COVID-19 vaccine. Subsequently, FDA reissued the letter of authorization on October 12, 2022,[26] December 8, 2022,[27]

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[24] Hereinafter, this letter refers to this vaccine as the "Pfizer-BioNTech COVID-19 Vaccine, Bivalent."

[25] For purposes of this letter, monovalent COVID-19 vaccine refers to any COVID-19 vaccine that contains or encodes the spike protein of only the Original SARS-CoV-2. We note that the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) is also monovalent, and encodes the spike protein of SARS-CoV-2 Omicron variant lineage XBB 1.5.

[26] In the October 12, 2022 revision, FDA authorized the Pfizer-BioNTech COVID-19 Vaccine, Bivalent in multiple dose vials with orange caps and labels with orange borders (each 0.2 mL dose containing a total of 10 mcg modRNA) for the prevention of COVID-19 in individuals 5 through 11 years of age as a single booster dose administered at least 2 months after either: 1) completion of primary vaccination with any FDA authorized or approved monovalent COVID-19 vaccine, or 2) receipt of the most recent booster dose with any FDA authorized or approved monovalent COVID-19 vaccine. FDA also revised the scope of authorization for Pfizer BioNTech COVID-19 Vaccine (Original monovalent) to remove its use as a booster dose for individuals 5 through 11 years of age. Finally, FDA revised the following Fact Sheets to reflect these changes: 1) Fact Sheet for Recipients and Caregivers About the Pfizer-BioNTech COVID-19 Vaccine and the Pfizer-BioNTech COVID-19 Vaccine Bivalent (Original and Omicron BA.4/BA.5) to Prevent Coronavirus Disease (COVID-19) for Use in Individuals 5 Through 11 Years of Age; 2) Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers): Emergency Use Authorization (EUA) of Pfizer-BioNTech COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19) Primary Series For 5 Through 11 Years of Age Dilute Before Use; and 3) Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers): Emergency Use Authorization (EUA) Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) Booster Dose for 12 Years of Age and Older.

[27] On December 8, 2022, FDA revised the third dose in the 3-dose primary series authorized for individuals 6 months through 4 years of age. Specifically, the Pfizer-BioNTech COVID-19 Vaccine, Bivalent supplied in multiple dose vials with maroon caps and labels with maroon borders (each 0.2 mL dose containing a total of 3 mcg of modRNA) was authorized for the prevention of COVID-19 in individuals 6 months through 4 years of age as the third dose in the 3-dose primary series dose administered at least 8 weeks after a second primary series dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent). FDA also revised the scope of the authorization for Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) supplied in multiple dose vials with maroon caps and labels with maroon borders, to remove its use as the third primary series dose in the 3-dose primary series authorized for individuals 6 months through 4 years of age. Thus, Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (each in multiple dose vials with maroon caps and labels with maroon borders) were authorized for use in individuals 6 months through 4 years of age to provide a 3-dose primary series as follows: Dose 1: Pfizer-BioNTech COVID-19 Vaccine (Original monovalent); Dose 2: Pfizer-BioNTech COVID-19 Vaccine (Original monovalent); Dose 3: Pfizer-BioNTech COVID-19 Vaccine, Bivalent. In addition, because the authorized primary series for individuals 6 months through 4 years of age no longer consists of only Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) doses, FDA revised the scope of authorization for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent for use in individuals 5 through 11 years of age and individuals 12 years of age and older so that the Pfizer-BioNTech COVID-19 Vaccine, Bivalent can be administered as a booster dose regardless of whether primary vaccination was completed with a monovalent COVID-19 vaccine. Specifically, FDA authorized the Pfizer-BioNTech COVID-19 Vaccine, Bivalent supplied in multiple dose vials with orange caps and labels with orange borders for use in individuals 5 through 11 years of age (each 0.2 mL dose containing 10 mcg modRNA) and the Pfizer-BioNTech COVID-19 Vaccine, Bivalent supplied in multiple dose and single dose vials with gray caps and labels with gray borders for use in individuals 12 years of age and older (each 0.3 mL dose containing 30 mcg modRNA) as a single booster dose administered at least 2 months after either: 1) completion of primary vaccination with any FDA authorized or approved COVID-19 vaccine, or 2) receipt of the most recent booster dose with any FDA authorized or approved monovalent COVID-19 vaccine. FDA also revised the applicable Fact Sheets to reflect these changes. FDA also authorized an extension of expiration dating for the Pfizer-

March 14, 2023,[28] April 18 2023,[29] and April 28, 2023.[30]

On September 11, 2023, FDA approved COMIRNATY (COVID-19 Vaccine, mRNA), (2023-2024 Formula)[31] for active immunization to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

On September 11, 2023, having concluded that revising this EUA is appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA is reissuing the April 28, 2023 letter of authorization in its entirety with revisions to:

1. Authorize Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula)[32] in multiple dose vials with yellow caps and labels with yellow borders (each 0.3 mL dose containing 3 mcg of modRNA) for use in individuals 6 months through 4 years of age as described in Section II;

BioNTech COVID-19 Vaccine (Original monovalent) formulated in Tris/Sucrose buffer that provide 30-, 10-, and 3-mcg mRNA per dose from 12 months to 18 months from the date of manufacture when stored at -90 to -60 °C. This extension is also applicable to the Pfizer-BioNTech COVID-19 Vaccine, Bivalent presentations that provide 30- and 10-mcg mRNA per dose. The Fact Sheets for Healthcare Providers Administering Vaccine (Vaccination Providers) were updated to reflect these changes.

[28] In the March 14, 2023 revision, FDA authorized Pfizer-BioNTech COVID-19 Vaccine, Bivalent supplied in multiple dose vials with maroon caps and labels with maroon borders (each 0.2 mL dose containing a total of 3 mcg of modRNA) for use in individuals 6 months through 4 years of age to provide a single booster dose at least 2 months after completion of primary vaccination with 3 doses of the Pfizer-BioNTech COVID-19 Vaccine. FDA also revised the applicable Fact Sheets for Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and Pfizer-BioNTech COVID-19 Vaccine, Bivalent, to reflect these changes.

[29] In the April 18, 2023 revision, FDA: 1) revised the dosing regimen and schedule of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent, as described in Section II of the April 18, 2023 reissuance of this letter; 2) no longer authorized the use of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and certain uses of COMIRNATY (COVID-19 Vaccine; mRNA) in the United States; 3) clarified the terms and conditions that relate to export of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) from the United States; and 4) revised Condition G to require the inclusion of distribution data for Pfizer-BioNTech COVID-19 Vaccine, Bivalent in the monthly periodic safety reports. FDA also revised the applicable Fact Sheets for Pfizer-BioNTech COVID-19 Vaccine, Bivalent, to reflect these changes. In addition, the Fact Sheets for Healthcare Providers Administering Vaccine (Vaccination Providers) were consolidated into a single Fact Sheet for Healthcare Providers Administering Vaccine for all authorized presentations of Pfizer-BioNTech COVID-19 Vaccine, Bivalent; and the Fact Sheets for Recipient and Caregivers were consolidated into a single Fact Sheet for Recipients and Caregivers for all authorized presentations of Pfizer-BioNTech COVID-19 Vaccine, Bivalent.

[30] In the April 28, 2023 revision, FDA authorized the following uses of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent with maroon caps and labels with maroon borders (each 0.2 mL dose containing 3 mcg of modRNA) for individuals 6 months through 4 years of age with certain kinds of immunocompromise who previously received three 0.2 mL doses (Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) or Pfizer-BioNTech COVID-19 Vaccine, Bivalent): (1) a fourth dose administered at least 1 month following the most recent dose; and (2) additional doses that may be administered at the discretion of the healthcare provider, taking into consideration the individual's clinical circumstances. FDA also revised the Fact Sheets for Pfizer-BioNTech COVID-19 Vaccine, Bivalent, to reflect these changes.

[31] COMIRNATY (COVID-19 Vaccine, mRNA) (2023-2024 Formula) encodes the spike protein of SARS-CoV-2 Omicron variant lineage XBB.1.5 (Omicron XBB.1.5).

[32] Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) encodes the spike protein of SARS-CoV-2 Omicron variant lineage XBB.1.5 (Omicron XBB.1.5).

2. Authorize Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) in single dose vials with blue caps and labels with blue borders (each 0.3 mL dose containing 10 mcg of modRNA) for use in individuals 5 through 11 years as described in Section II;
3. Revise the conditions related to printed matter, advertising, and promotion to add additional requirements;
4. Remove the requirement that distribution of vaccines authorized under this EUA must be distributed to emergency response stakeholders as directed by the U.S. Government and make corresponding changes to the Conditions of Authorization;
5. Remove the requirement that vaccines authorized under this EUA be administered only by vaccination providers enrolled in the CDC COVID-19 Vaccination Program and make corresponding changes to the Conditions of Authorization;
6. Revise Condition G to provide flexibility to determine a different reporting interval for periodic safety reports, if appropriate;
7. No longer authorize the use of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent in the United States; and
8. Clarify the terms and conditions that relate to export of Pfizer-BioNTech COVID-19 Vaccine, Bivalent from the United States.

Additionally, FDA is authorizing the Fact Sheets for Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) that reflect the relevant changes.

For the December 11, 2020 authorization for individuals 16 years of age and older, FDA reviewed safety and effectiveness data from an ongoing Phase 1/2/3 trial in approximately 44,000 participants randomized 1:1 to receive Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) or saline control. The trial enrolled participants 12 years of age and older. FDA's review at that time considered the safety and effectiveness data as they related to the request for emergency use authorization in individuals 16 years of age and older. FDA's review of the available safety data from 37,586 of the participants 16 years of age and older, who were followed for a median of two months after receiving the second dose, did not identify specific safety concerns that would preclude issuance of an EUA. FDA's analysis of the available efficacy data from 36,523 participants 12 years of age and older without evidence of SARS-CoV-2 infection prior to 7 days after dose 2 confirmed that the vaccine was 95% effective (95% credible interval 90.3, 97.6) in preventing COVID-19 occurring at least 7 days after the second dose (with 8 COVID-19 cases in the vaccine group compared to 162 COVID-19 cases in the placebo group). Based on these data, and review of manufacturing information regarding product quality and consistency, FDA concluded that it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) may be effective. Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) outweigh the known and potential risks of the vaccine, for the prevention of COVID-19 in individuals 16 years of age and older. Finally, on December 10, 2020, the Vaccines and Related Biological Products Advisory Committee voted in agreement with this conclusion.

For the May 10, 2021 authorization for individuals 12 through 15 years of age, FDA reviewed safety and effectiveness data from the above-referenced, ongoing Phase 1/2/3 trial that enrolled approximately 46,000 participants, including 2,260 participants 12 through 15 years of age.

Trial participants were randomized 1:1 to receive Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) or saline control. FDA's review of the available safety data from 2,260 participants 12 through 15 years of age, who were followed for a median of 2 months after receiving the second dose, did not identify specific safety concerns that would preclude issuance of an EUA. FDA's analysis of SARS-CoV-2 50% neutralizing antibody titers 1 month after the second dose of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) in a subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection confirm that the geometric mean antibody titer in participants 12 through 15 years of age was non-inferior to the geometric mean antibody titer in participants 16 through 25 years of age. FDA's analysis of available descriptive efficacy data from 1,983 participants 12 through 15 years of age without evidence of SARS-CoV-2 infection prior to 7 days after dose 2 confirm that the vaccine was 100% effective (95% confidence interval 75.3, 100.0) in preventing COVID-19 occurring at least 7 days after the second dose (with no COVID-19 cases in the vaccine group compared to 16 COVID-19 cases in the placebo group). Based on these data, FDA concluded that it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) may be effective in individuals 12 through 15 years of age. Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) outweigh the known and potential risks of the vaccine, for the prevention of COVID-19 in individuals 12 through 15 years of age.

For the August 12, 2021 authorization of a third primary series dose in individuals 12 years of age or older who have undergone solid organ transplantation, or individuals 12 years of age or older who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise[33], FDA reviewed safety and effectiveness data reported in two manuscripts on solid organ transplant recipients. The first study was a single arm study conducted in 101 individuals who had undergone various solid organ transplant procedures (heart, kidney, liver, lung, pancreas) a median of 97±8 months earlier. A third dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) was administered to 99 of these individuals approximately 2 months after they had received a second dose. Levels of total SARS-CoV-2 binding antibodies meeting the pre-specified criteria for success occurred four weeks after the third dose in 26/59 (44.0%) of those who were initially considered to be seronegative and received a third dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent); 67/99 (68%) of the entire group receiving a third vaccination were subsequently considered to have levels of antibodies indicative of a significant response. In those who received a third vaccine dose, the adverse event profile was similar to that after the second dose and no grade 3 or grade 4 events were reported. A supportive secondary study was a double-blind, randomized-controlled study conducted in 120 individuals who had undergone various solid organ transplant procedures (heart, kidney, kidney-pancreas, liver, lung, pancreas) a median of 3.57 years earlier (range 1.99-6.75 years). A third dose of a similar messenger RNA vaccine (the Moderna COVID-19 vaccine) was administered to 60 individuals approximately 2 months after they had received a second dose (i.e., doses at 0, 1 and 3 months); saline placebo was given to 60 individuals for comparison. The primary outcome was anti-RBD antibody at 4 months greater than 100 U/mL. This titer was selected based on NHP challenge studies as well as a large clinical cohort study to

[33] Certain kinds of immunocompromise refers to individuals who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

indicate this antibody titer was protective. Secondary outcomes were based on a virus neutralization assay and polyfunctional T cell responses. Baseline characteristics were comparable between the two study arms as were pre-intervention anti-RBD titer and neutralizing antibodies. Levels of total SARS-CoV-2 binding antibodies indicative of a significant response occurred four weeks after the third dose in 33/60 (55.0%) of the Moderna COVID-19 vaccinated group and 10/57 (17.5%) of the placebo individuals. In the 60 individuals who received a third vaccine dose, the adverse event profile was similar to that after the second dose and no grade 3 or grade 4 adverse events were reported. Despite the moderate enhancement in antibody titers, the totality of data (i.e., supportive paper by Hall et al. demonstrated efficacy of the product in the elderly and persons with co-morbidities) supports the conclusion that a third dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) may be effective in this population, and that the known and potential benefits of a third dose of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) outweigh the known and potential risks of the vaccine for immunocompromised individuals at least 12 years of age who have received two doses of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

For the September 22, 2021 authorization of a single booster dose administered at least 6 months after completing the primary series in individuals: 65 years of age and older; 18 through 64 years of age at high risk of severe COVID-19; and 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19, FDA reviewed safety and effectiveness data from the above-referenced, ongoing Phase 1/2/3 trial in which 329 participants 18 through 75 years of age received a booster dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) approximately 6 months (range 4.8 to 8.8 months) after completion of the primary series. FDA's review of the available safety data from 329 participants 18 through 75 years of age, who had been followed for a median of 2.6 months after receiving the booster dose, did not identify specific safety concerns that would preclude issuance of an EUA. The effectiveness of the booster dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) is based on an assessment of 50% neutralizing antibody titers (NT50) against SARS-CoV-2 (USA_WA1/2020). FDA's analysis of SARS-CoV-2 NT50 one month after the booster dose compared to 1 month after the primary series in study participants 18 through 55 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster dose confirmed noninferiority for both geometric mean ratio and difference in seroresponse rates. Based on the totality of the scientific evidence available, including data from the above-referenced clinical trial, FDA concluded that a booster dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) may be effective, and that the known and potential benefits of a single booster dose at least 6 months after completing the primary series outweigh the known and potential risks for individuals 65 years of age and older; individuals 18 through 64 years of age at high risk of severe COVID-19; and individuals 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19.

For the October 20, 2021 authorization of a single booster dose as a heterologous booster dose following completion of primary vaccination with another authorized COVID-19 vaccine, FDA

reviewed data from an ongoing Phase1/2 clinical trial in participants 19-85 years of age. In this trial, adults who had completed primary vaccination with a Moderna COVID-19 Vaccine 2-dose series (N=151), a Janssen COVID-19 Vaccine single dose (N=156), or a Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) 2-dose series (N=151) at least 12 weeks prior to enrollment and who reported no history of SARS-CoV-2 infection were randomized 1:1:1 to receive a booster dose of one of three vaccines: Moderna COVID-19 Vaccine (Original monovalent), Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine (Original monovalent). Adverse events were assessed through 28 days after the booster dose. An overall review of adverse reactions reported following the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) heterologous booster dose did not identify any new safety concerns, as compared with adverse reactions reported following Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) primary series doses or homologous booster dose. Neutralizing antibody titers, as measured by a pseudovirus neutralization assay using a lentivirus expressing the SARS-CoV-2 Spike protein with D614G mutation, were assessed on Day 1 prior to administration of the booster dose and on Day 15 after the booster dose. A booster response to the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) was demonstrated regardless of primary vaccination. Based on the on the totality of the scientific evidence available, including data from the above-referenced clinical trial, FDA concluded that a heterologous booster dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) may be effective, and that the known and potential benefits of a heterologous booster dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) following completion of primary vaccination with another authorized COVID-19 vaccine outweigh the known and potential risks.

For the October 29, 2021 authorization for the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) that uses Tris buffer for individuals 5 through 11 years of age, FDA reviewed safety and effectiveness data from an ongoing Phase 1/2/3 trial that has enrolled 4,695 participants 5 through 11 years of age, of whom 3,109 participants received Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) (containing 10 mcg modRNA) formulated using PBS buffer and approximately 1,538 participants received saline control in Phase 2/3. FDA's review of the available safety data from 3,109 participants 5 through 11 years of age who received Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) (containing 10 mcg modRNA), including 1,444 who were followed for at least 2 months after receiving the second dose, did not identify specific safety concerns that would preclude issuance of an EUA. SARS-CoV-2 50% neutralizing antibody titers 1 month after the second dose were compared between a subset of participants 5 through 11 years of age who received Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) (containing 10 mcg modRNA) and a subset of participants 16 through 25 years of age who received Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) (containing 30 mcg modRNA) in the above-referenced ongoing Phase 1/2/3 trial that enrolled approximately 46,000 participants. Immunobridging analyses included a subset of participants from each study who had no serological or virological evidence of past SARS-CoV-2 infection. FDA's analyses confirm that immunobridging criteria were met for both geometric mean antibody titers and seroresponse rates. FDA's analysis of available descriptive efficacy data from 1,968 participants 5 through 11 years of age without evidence of SARS-CoV-2 infection prior to 7 days after dose 2 confirm that the vaccine was 90.7% effective (95% confidence interval 67.7, 98.3) in preventing COVID-19 occurring at least 7 days after the second dose (with 3 COVID-19 cases in the vaccine group compared to 16 COVID-19 cases in the placebo group).

Based on these data, FDA concluded that it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) may be effective in individuals 5 through 11 years of age. Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) outweigh the known and potential risks of the vaccine, for the prevention of COVID-19 in individuals 5 through 11 years of age. Finally, on October 26, 2021, the Vaccines and Related Biological Products Advisory Committee voted in agreement with this conclusion.

For the October 29, 2021 authorization of the manufacturing change to include an additional formulation of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) that uses Tris buffer instead of PBS buffer used in the originally authorized Pfizer-BioNTech COVID-19 Vaccine (Original monovalent), FDA reviewed data on analytical comparability, which uses laboratory testing to demonstrate that a change in product formulation is not expected to impact safety or effectiveness[34] In the case of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent), multiple different release parameters were evaluated, ranging from product appearance to size of the lipid-nanoparticle to the integrity of the modRNA in the product. Release and characterization tests include tests for purity, composition, and critical attributes of mRNA associated with the activity of the vaccine. In this case, analytical comparability to the current PBS formulation of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) was demonstrated for the Tris formulation of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) through a combination of release and characterization testing.

For the November 19, 2021 authorization expanding the eligible population for the homologous and heterologous booster doses to individuals 18 years of age and older, FDA reviewed data provided by the sponsor and other data available to FDA, including real world evidence. Data previously reviewed to support the September 22, 2021 authorization of a homologous booster dose, together with new real-world data indicating increasing COVID-19 cases in the United States, including among vaccinated individuals, and suggesting a decreased risk of myocarditis following mRNA COVID-19 vaccine booster doses compared with second primary series doses, support expansion of the population eligible for a Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) homologous booster dose to include all individuals 18 years of age and older who completed the primary series at least 6 months previously. Data previously reviewed to support the October 20, 2021 authorization of a heterologous booster dose, together with data and information to support authorization of the EUA amendment to expand the eligible population for a homologous booster dose of the Moderna COVID-19 Vaccine, support a revision to the Pfizer-BioNTech COVID-19 Vaccine EUA such that the eligible population for a heterologous booster dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) is

[34] Analytical comparability assessments use laboratory testing to demonstrate that a change in product formulation does not impact a product's safety or effectiveness. For the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent), multiple different release parameters were evaluated to assess the comparability of the modified formulation (the formulation with the Tris buffer) to the originally-authorized formulation (the formulation with the PBS buffer). These release parameters ranged from product appearance to size of the lipid-nanoparticle to the integrity of the modRNA in the product. Release and characterization tests include tests for purity, composition, and critical attributes of mRNA associated with the activity of the vaccine. The combination of release testing and characterization testing demonstrated that the modified formulation was analytically comparable to the original formulation.

all adults 18 years of age and older who completed primary vaccination with another authorized COVID-19 vaccine. Based on the totality of the scientific evidence available, FDA concluded that a homologous or heterologous booster dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) may be effective, and that the known and potential benefits of the booster dose of the Pfizer-BioNTech Vaccine (Original monovalent) following completion of primary vaccination with Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) or another authorized COVID-19 vaccine, outweigh the known and potential risks in individuals 18 years of age and older.

For the December 9, 2021 authorization expanding the eligible population for the homologous booster doses to individuals 16 years of age and older, FDA reviewed: data submitted previously by the sponsor to support the September 22, 2021 and November 19, 2021 authorization of a homologous booster dose under EUA; real-world data, which includes data that indicates increasing COVID-19 cases in the United States amongst vaccinated and unvaccinated individuals, and data suggesting a decreased risk of myocarditis following administration of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) booster doses compared with second primary series doses among vaccinated individuals; and a benefit-risk assessment from the sponsor, to support the expansion of the population eligible for a Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) homologous booster dose to include all individuals 16 years of age and older who completed the primary series at least 6 months previously. Based on the totality of the scientific evidence available, FDA concluded that a homologous booster dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) may be effective, and that the known and potential benefits of the booster dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) following completion of primary vaccination with Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) outweigh the known and potential risks in individuals 16 years of age and older.

For the December 16, 2021 authorization, the FDA reviewed manufacturing information indicating that the expiration date of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) that uses the Tris buffer could be extended from 6 months to 9 months when held at -90 °C to -60 °C.

For the January 3, 2022 authorization expanding the use of the vaccine as a single booster dose in individuals 12 through 15 years of age and lowering the authorized dosing interval of the homologous booster dose to at least 5 months after completion of the primary series, the FDA reviewed: prepublications; accepted publications; published publications; real world evidence on the safety of booster doses provided by the Israeli Ministry of Health, which includes data from over 6,300 individuals 12 to 15 years of age who received a Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) booster dose at least 5 months following completion of the primary series, noting no cases of myocarditis or pericarditis reported to date; and real world evidence data from approximately 4.7 million third (booster) doses of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) given to individuals 16 years of age and older at least 5 months after the primary series. Based on the totality of the scientific evidence available, FDA concluded that a homologous booster dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) may be effective and that the known and potential benefits of the booster dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) following completion of

primary vaccination with the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) outweigh the known and potential risks in individuals 12 years of age and older when given at least 5 months following the primary series.

For the January 3, 2022 authorization of a third primary series dose in individuals 5 through 11 years of age who have undergone solid organ transplantation, or individuals 5 through 11 years of age who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise, data on safety in this population is inferred from the experience in healthy children 5 through 11 years of age who were vaccinated with the primary series, and data from vaccine efficacy in individuals 12 years of age and older is extrapolated to determine efficacy. Based on the totality of the scientific evidence available, FDA concluded that a third dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) may be effective and that the known and potential benefits of a third dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) outweigh the known and potential risks of the vaccine for immunocompromised individuals 5 through 11 years of age who have received two doses of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

For the March 29, 2022 authorization of a second booster dose of the Pfizer-BioNTechCOVID-19 Vaccine (Original monovalent) for administration to individuals 50 years of age and older and to individuals 12 years of age or older with certain kinds of immunocompromise[6] at least 4 months after receipt of a first booster dose of any of the FDA authorized or approved COVID-19 vaccines, the sponsor submitted a publication which included immunogenicity data from an ongoing study in Israel. (*Gili Regev-Yochay, Tal Gonen, Mayan Gilboa, et al. 2022 DOI: 10.1056/NEJMc2202542*)). In this open-label, non-randomized clinical study in healthcare workers at a single center in Israel, 154 individuals 18 years of age and older who had received primary vaccination and a first booster dose with Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) were administered a second booster dose of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) at least four months after the first booster dose. Among these individuals, approximately 11-fold increases in geometric mean neutralizing antibody titers against wild-type virus and Delta and Omicron variants, respectively, were reported at two weeks after the second booster dose as compared to 5 months after the first booster dose. Safety surveillance data from the Ministry of Health of Israel on the administration of approximately 700,000 fourth doses of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) given at least 4 months after the third dose in adults 18 years of age and older (approximately 600,000 of whom were 60 years of age and older) revealed no new safety concerns. Based on the totality of the scientific evidence available, FDA concluded that a second booster dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) may be effective and that the known and potential benefits of a second booster dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) following receipt of a first booster dose of any FDA authorized or approved COVID-19 vaccine outweigh the known and potential risks in the authorized populations when given at least 4 months following the first booster dose.

For the May 17, 2022 authorization of a single booster dose administered at least 5 months after completing a primary series of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent)

in individuals 5 through 11 years of age, FDA reviewed safety and effectiveness data from a subset of participants 5 through 11 years of age enrolled in an ongoing study described above (see October 29, 2021 authorization). A total of 401 participants 5 through 11 years of age received a booster dose of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) (10 mcg modRNA) at least 5 months after completing the primary series (range 5 to 9 months, 86.8% of participants received the booster dose at least 8 months after Dose 2). FDA's review of the available safety data collected up to the cutoff date of March 22, 2022 (median follow-up time of 1.3 months), did not identify specific safety concerns that would preclude issuance of an EUA. The geometric mean SARS-CoV-2 50% neutralizing antibody titer (NT50) 1 month after the booster dose was compared to the pre- booster dose geometric mean titers (GMT) in 67 participants 5 through 11 years of age who had no serological or virological evidence of SARS-CoV-2 infection up to one month after the booster dose. The NT50 GMT at 1 month after the booster dose was increased compared to before the booster dose. Based on the totality of the scientific evidence available, FDA concluded that a booster dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) following completion of primary vaccination with the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) may be effective and that the known and potential benefits of a booster dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) following completion of primary vaccination with the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) outweigh the known and potential risks in individuals 5 through 11 years of age when given at least 5 months following the primary series.

For the June 17, 2022 authorization for the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) that uses Tris buffer for individuals 6 months through 4 years of age, FDA reviewed safety and effectiveness data from an ongoing Phase 1/2/3 trial. This study enrolled 1,776 participants 6 through 23 months of age, of whom 1,178 participants received at least one dose of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) (containing 3 mcg modRNA) and 598 participants received at least one dose of saline placebo; and also enrolled 2,750 participants 2 through 4 years of age, of whom 1,835 participants received at least one dose of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) (containing 3 mcg modRNA) and 915 participants received at least one dose of saline placebo in Phase 2/3. In an analysis of Study 3 (Phase 2/3), based on data in the blinded placebo-controlled follow-up period up to the cutoff date of April 29, 2022, 570 participants 6 through 23 months of age who received a 3-dose primary series [386 Pfizer BioNTech COVID 19 Vaccine (Original monovalent); 184 placebo] have been followed for a median of 1.3 months after the third dose. In an analysis of Study 3 (Phase 2/3), based on data in the blinded placebo-controlled follow-up period up to the cutoff date of April 29, 2022, 886 participants 2 through 4 years of age who received a 3 dose primary series [606 Pfizer BioNTech COVID 19 Vaccine (Original monovalent); 280 placebo] have been followed a median of 1.4 months after the third dose. The median duration of combined blinded and unblinded follow-up after the third dose was 2.1 months for each age group. FDA's review of the available safety data from participants 6 through 23 months of age and participants 2 through 4 years of age did not identify specific safety concerns that would preclude issuance of an EUA. SARS-CoV-2 50% neutralizing antibody titers were compared between a subset of participants 6 through 23 months of age, or a subset of participants 2 through 4 years of age, at 1 month after the three-dose primary series of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) (containing 3 mcg modRNA per dose) and a subset of participants 16 through 25 years of age at 1 month after the two-dose primary series of Pfizer-BioNTech COVID-19

Vaccine (Original monovalent) (containing 30 mcg modRNA per dose) in the above-referenced ongoing Phase 1/2/3 trial that enrolled approximately 46,000 participants. Immunobridging analyses included a subset of participants from each study who had no evidence of prior SARS-CoV-2 infection up to 1 month after completion of the primary series. FDA's analyses confirm that for both age groups, 6 through 23 months of age and 2 through 4 years of age, immunobridging criteria were met for both geometric mean antibody titers and seroresponse rates. Based on these data, FDA concluded that it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) may be effective in individuals 6 months through 4 years of age. Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) outweigh the known and potential risks of the vaccine for the prevention of COVID-19 in individuals 6 months through 4 years of age. Finally, on June 15, 2022, the Vaccines and Related Biological Products Advisory Committee voted in agreement with this conclusion.

The August 31, 2022 authorization of a booster dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent in individuals 12 years and older is based on: 1) safety and effectiveness data from clinical trials which evaluated primary and booster vaccination with Pfizer-BioNTech COVID-19 Vaccine (Original monovalent); 2) postmarketing safety data with Pfizer-BioNTech COVID-19 Vaccine (Original monovalent); and 3) safety and immunogenicity data from a clinical trial (Study 4) which evaluated a booster dose of Pfizer's and BioNTech's bivalent COVID-19 vaccine (Original and Omicron BA.1), not authorized or approved in the U.S., hereafter referred to as bivalent vaccine (Original and Omicron BA.1). FDA considered safety and effectiveness data previously reviewed by FDA in support of the December 11, 2020, May 10, 2021, and October 29, 2021 authorizations of primary vaccinations and the September 22, 2021, October 20, 2021, November 19, 2021, December 9, 2021, January 3, 2022, and March 29, 2022 authorizations of booster vaccinations in individuals 12 years and older with Pfizer-BioNTech COVID-19 Vaccine (Original monovalent), as well as postmarketing safety data. In Study 4, a total of 610 participants greater than 55 years of age previously vaccinated with a 2-dose primary series and 1 booster dose of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) received a second booster dose with either Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) (305 participants) or the bivalent vaccine (Original and Omicron BA.1) (305 participants). The bivalent vaccine (Original and Omicron BA.1) booster dose was administered 4.7 to 11.5 months (median 6.3 months) after the first booster dose. The Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) booster dose was administered 5.3 to 13.1 months (median 6.3 months) after the first booster dose. The median duration of follow-up was 1.7 months for those that received the bivalent vaccine (Original and Omicron BA.1) and 1.8 months for those that received Pfizer-BioNTech COVID-19 Vaccine (Original monovalent). FDA's review of the safety data accrued with the bivalent vaccine (Original and Omicron BA.1) together with the previously submitted safety data and post-marketing data with Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) did not identify specific safety concerns that would preclude issuance of an EUA. In study 4, primary immunogenicity analyses assessed superiority with respect to level of 50% neutralizing titer (NT50) and noninferiority with respect to seroresponse rate of the anti-Omicron BA.1 immune response induced by a second booster dose with the bivalent vaccine (Original and Omicron BA.1) relative to the response elicited by a second booster dose with Pfizer BioNTech COVID-19 Vaccine (Original monovalent) 1 month

after vaccination. Superiority of the anti-Omicron BA.1 NT50 and non-inferiority of the seroresponse rate to the Omicron BA.1 variant for the bivalent vaccine (Original and Omicron BA.1) relative to Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) were met. In a secondary analysis of NT50 to the Original SARS-CoV-2 strain, a second booster dose with the bivalent vaccine (Original and Omicron BA.1) was non-inferior to a second booster dose with Pfizer-BioNTech COVID-19 Vaccine (Original monovalent). In a descriptive analysis, 50.0% (95% CI 42.6, 57.4) of participants who received a second booster dose with the bivalent vaccine (Original and Omicron BA.1) and 49.2% (95% CI 41.6, 56.7) of participants who received a second booster dose with the Pfizer-BioNTech COVID-19 Vaccine achieved seroresponse (≥ 4-fold rise from baseline before the second booster dose) to the Original strain. Based on the totality of the scientific evidence available, including these data and previously submitted data on the effectiveness of primary and booster vaccination with Pfizer-BioNTech COVID-19 Vaccine (Original monovalent), FDA concluded that it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine, Bivalent may be effective as a booster dose in individuals 12 years of age and older when administered at least 2 months after completion of primary vaccination or receipt of the most recent booster dose with any FDA authorized or approved monovalent COVID-19 vaccine. Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine, Bivalent outweigh the known and potential risks of the vaccine for the prevention of COVID-19 in individuals 12 years of age and older when administered at least 2 months after completion of primary vaccination or receipt of the most recent booster dose with any FDA authorized or approved monovalent COVID-19 vaccine. In addition, authorization of Pfizer-BioNTech COVID-19 Vaccine, Bivalent was considered for the express purpose of improving protection conferred by COVID-19 vaccine booster doses against the currently circulating Omicron variant of SARS-CoV-2, resulting in a more favorable anticipated benefit/risk balance compared to Pfizer-BioNTech COVID-19 Vaccine (Original monovalent). Consequently, revising the EUA to no longer provide for the use of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) as a booster dose for individuals 12 years of age and older was appropriate for the protection of the public health.

The October 12, 2022 authorization of a booster dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent in individuals 5 through 11 years of age is based on the data that FDA relied on for the August 31, 2022 authorization of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent in individuals 12 years of age and older, including data previously reviewed by FDA for the October 29, 2021 authorization for the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) as a primary series for individuals 5 through 11 years of age and for the May 17, 2022 authorization of a single booster dose of Pfizer-BioNTech COVID-19 Vaccine in individuals 5 through 11 years of age, administered at least 5 months after completing a primary series with this vaccine. FDA also considered additional data reviewed for the May 17, 2022 authorization of a single booster dose of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) in this age group. Based on the totality of the scientific evidence available, FDA concluded that it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine, Bivalent may be effective as a booster dose in individuals 5 through 11 years of age when administered at least 2 months after completion of primary vaccination or receipt of the most recent booster dose with any FDA authorized or approved monovalent COVID-19 vaccine. Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available,

that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine, Bivalent outweigh the known and potential risks of the vaccine for the prevention of COVID-19 in individuals 5 through 11 years of age when administered at least 2 months after completion of primary vaccination or receipt of the most recent booster dose with any FDA authorized or approved monovalent COVID-19 vaccine. In addition, authorization of Pfizer-BioNTech COVID-19 Vaccine, Bivalent was considered for the express purpose of improving protection conferred by COVID-19 vaccine booster doses against the currently circulating Omicron variant of SARS-CoV-2, resulting in a more favorable anticipated benefit/risk balance compared to Pfizer-BioNTech COVID-19 Vaccine (Original monovalent). Consequently, it was appropriate for the protection of the public health to revise this EUA to no longer provide for the use of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent). as a booster dose for individuals 5 through 11 years of age.

The December 8, 2022 authorization of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent, as the third dose in the 3-dose primary series administered at least 8 weeks after the second primary series dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) in individuals 6 months through 4 years of age is based on safety and effectiveness data previously reviewed. Specifically, the safety of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent for the third dose of the primary series in individuals 6 months through 4 years of age is based on: 1) safety data from a clinical study which evaluated a booster dose with bivalent vaccine (Original and Omicron BA.1), in individuals greater than 55 years of age;[35] 2) safety data from clinical studies which evaluated primary vaccination with Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) in individuals 6 months of age and older; 3) safety data from clinical studies which evaluated booster vaccination with Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) (previously, but no longer, authorized) in individuals 5 years of age and older; and 4) postmarketing safety data with the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and the Pfizer-BioNTech COVID-19 Vaccine, Bivalent. Effectiveness is based on: 1) efficacy of primary vaccination with Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) in individuals 16 years of age and older; 2) effectiveness of primary vaccination with Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) in individuals 6 months through 4 years of age; and 3) immunogenicity of a second booster dose with bivalent vaccine (Original and Omicron BA.1) in individuals greater than 55 years of age in Study 4. Based on the totality of scientific evidence available, FDA concluded that it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine, Bivalent may be effective in individuals 6 months through 4 years of age when given as the third dose in the 3-dose primary series administered at least 8 weeks after a second primary series dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent). Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine, Bivalent outweigh the known and potential risks of the vaccine for the prevention of COVID-19 in individuals 6 months through 4 years of age when given as the third dose in the 3-dose primary series administered at least 8 weeks after a second primary series dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent). In addition, authorization of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent has been considered for the express purpose

[35] The safety data accrued with the bivalent vaccine (Original and Omicron BA.1) and with the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) are relevant to the Pfizer-BioNTech COVID-19 Vaccine, Bivalent because these vaccines are manufactured using the same process.

of improving protection conferred by the third dose of the primary series in individuals 6 months through 4 years of age against the currently circulating Omicron variant of SARS-CoV-2, resulting in a more favorable anticipated benefit/risk balance compared to Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) for the third dose. Consequently, at this time, revising this EUA to no longer provide for the use of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) as a third dose in the primary series in this age group is appropriate for the protection of the public health.

The March 14, 2023 authorization of Pfizer-BioNTech COVID-19 Vaccine, Bivalent as a single booster dose in individuals 6 months through 4 years at least 2 months after completion of primary vaccination with 3 doses of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) is based on data previously reviewed to support the December 8, 2022 authorization of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent as the third dose in the 3-dose primary series administered at least 8 weeks after the second primary series dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) in individuals 6 months through 4 years of age, as well as safety and immunogenicity of a booster dose with Pfizer-BioNTech COVID-19 Vaccine, Bivalent in individuals 6 months through 4 years of age and safety of a booster dose with Pfizer-BioNTech COVID-19 Vaccine, Bivalent in individuals ≥5 years of age. FDA's review of the available safety data in individuals 6 months through 4 years of age and individuals ≥5 years of age did not identify specific safety concerns that would preclude issuance of an EUA. Study 6 enrolled participants 6 months through 11 years of age to receive a booster (fourth dose) of Pfizer-BioNTech COVID-19 Vaccine, Bivalent. In this study, 113 participants 5 through 11 years of age previously vaccinated with a 2-dose primary series and 1 booster dose of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) (10 mcg modRNA) received a booster (fourth dose) with Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) (10 mcg modRNA). Participants received a booster (fourth dose) with Pfizer-BioNTech COVID-19, Bivalent 2.6 to 8.5 months after receiving their third dose with Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and had a median follow-up time of 1.6 months (range 1.1 to 2.3 months) up to a data cutoff date of November 25, 2022. In Study 6, a subset of 60 participants 6 months through 4 years of age received a booster dose (fourth dose) of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (3 mcg modRNA) after receiving 3 prior doses of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) (3 mcg modRNA). Neutralizing antibody levels following the fourth dose were summarized. Data from a subset of participants 6 months through 4 years of age in Study 3 who received 3 doses of Pfizer BioNTech COVID-19 Vaccine (Original monovalent) (3 mcg modRNA) were reviewed as a reference. There were no formal statistical comparisons of the immune response between subsets from the two studies. Based on the totality of scientific evidence available, FDA concluded that it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine, Bivalent may be effective in individuals 6 months through 4 years of age when given as a booster dose at least 2 months after completion of primary vaccination with 3 doses of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent). Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent outweigh the known and potential risks of the vaccine for the prevention of COVID-19 in individuals 6 months through 4 years of age when given as a single booster dose at least 2 months after completion of primary vaccination with 3 doses of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent).

For the April 18, 2023 authorization, the effectiveness of Pfizer-BioNTech COVID-19 Vaccine, Bivalent for individuals 6 months of age and older is based on previously reviewed data on 1) effectiveness of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) in individuals 6 months of age and older, 2) immunogenicity of the bivalent vaccine (Original and Omicron BA.1) in individuals greater than 55 years of age, and 3) immunogenicity of Pfizer-BioNTech COVID-19 Vaccine, Bivalent in individuals 6 months through 4 years of age. Effectiveness of a single dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent for most individuals 5 years of age and older is based on seroprevalence surveys that estimate that almost all of the U.S. population 5 years of age and older now have antibodies (from vaccination and/or infection) against SARS-CoV-2 (*Centers for Disease Control and Prevention. COVID Data Tracker. Atlanta, GA: US Department of Health and Human Services, CDC; 2023, March 31.* https://covid.cdc.gov/covid-data-tracker) and an observational, test-negative, case-control study (*Powell AA, et al. Lancet Infect Dis. 2023. PMID: 36436536).* This study included symptomatic individuals aged 12 to 17 years of age with SARS-CoV-2 polymerase-chain-reaction (PCR) testing results in England from August 9, 2021 to March 31, 2022. Among 1,161,704 SARS-CoV-2 PCR tests linked to COVID-19 vaccination status, there were 390,467 SARS-CoV-2 PCR confirmed positive tests during Delta variant predominance and 212,433 SARS-CoV-2 positive tests during Omicron variants BA.1 and BA.2 predominance. Among adolescents who had received only one dose of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent), those who had evidence of previous infection with Alpha, Delta, or Omicron variants had increased protection against symptomatic Omicron infection compared with those with no evidence of previous infection. At 2 to 14 weeks following one dose of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent), the estimated vaccine effectiveness was 18.8% (95% CI: 17.2%, 20.3%), 81.5% (95% CI: 80.0%, 82.9%), 78.8% (95% CI: 77.9, 79.5%), and 79.6% (95% CI: 44.9%, 92.4%) for individuals with no evidence of prior infection, and evidence of prior Alpha, Delta, and Omicron infection, respectively. The safety of Pfizer-BioNTech COVID-19 Vaccine, Bivalent in individuals 6 months of age and older is based on previously reviewed safety data from clinical studies which evaluated primary and booster vaccination with Pfizer BioNTech COVID-19 Vaccine (Original monovalent), booster vaccination with Pfizer-BioNTech COVID-19 Vaccine, Bivalent, and a booster dose of bivalent vaccine (Original and Omicron BA.1); and postmarketing safety data with Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and Pfizer-BioNTech COVID-19 Vaccine, Bivalent. FDA's review of the available safety data in individuals 6 months of age and older did not identify specific safety concerns that would preclude issuance of an EUA. Based on the totality of the scientific evidence available, FDA concluded that it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine, Bivalent may be effective in individuals 6 months of age and older for the prevention of COVID-19 when administered in accordance with the revised dosing regimen and schedule. Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent outweigh the known and potential risks of the vaccine for the prevention of COVID-19 in individuals 6 months of age and older when administered according to the revised dosing regimen and schedule. The revised dosing regimen and schedule are set forth in the Scope of Authorization (Section II). In addition, simplification of the vaccine composition (i.e., single vaccine composition for all doses) and schedule was considered for the express purpose of reducing complexity, decreasing vaccine administration errors due to the complexity of the

number of different vial presentations, and potentially increasing vaccine uptake. Revising the EUA to provide for a simplified vaccine composition and schedule in the United States, by no longer providing for the use of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) in the United States, is appropriate for the protection of the public health.

The April 28, 2023 authorization of additional doses of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent in individuals 6 months through 4 years of age with certain kinds of immunocompromise is based on previously reviewed data. Specifically, the safety and effectiveness are based on 1) the safety and effectiveness of a fourth dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent in individuals 6 months through 4 years of age after three previous doses, and 2) immunogenicity of a third primary series dose of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) in individuals with compromised immunity. FDA also reviewed literature on immunogenicity of a fourth dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent in adults. Based on the totality of scientific evidence available, FDA concluded that it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine, Bivalent may be effective in individuals 6 months through 4 years of age with certain kinds of immunocompromise who have received three 0.2 mL doses (Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) or Pfizer-BioNTech COVID-19 Vaccine, Bivalent), as 1) a fourth dose administered at least 1 month following the most recent dose; and 2) additional doses that may be administered at the discretion of the healthcare provider, taking into consideration the individual's clinical circumstances. Additionally, FDA determined that it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent outweigh the known and potential risks of the vaccine for the prevention of COVID-19 in individuals 6 months through 4 years of age with certain kinds of immunocompromise who have received three 0.2 mL doses (Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) or Pfizer-BioNTech COVID-19 Vaccine, Bivalent), when given as 1) a fourth dose administered at least 1 month following the most recent dose; and 2) additional doses that may be administered at the discretion of the healthcare provider, taking into consideration the individual's clinical circumstances

The September 11, 2023 authorization of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) for individuals 6 months through 11 years of age is based on: 1) effectiveness of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) in individuals 6 months of age and older, 2) immunogenicity of Pfizer-BioNTech COVID-19 Vaccine, Bivalent in individuals 6 months through 4 years of age, and 3) safety data previously reviewed. FDA's review of previously submitted safety data with Pfizer-BioNTech COVID-19 Vaccine (Original monovalent), Pfizer and BioNTech's bivalent vaccine (Original and Omicron BA.1) and Pfizer-BioNTech COVID-19 Vaccine, Bivalent, and postmarketing safety data from Pfizer-BioNTech COVID-19 Vaccine (Original monovalent), and Pfizer-BioNTech COVID-19 Vaccine, Bivalent did not identify specific safety concerns that would preclude issuance of an EUA. The safety data accrued with the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent), bivalent vaccine (Original and Omicron BA.1), and Pfizer-BioNTech COVID-19 Vaccine, Bivalent are relevant to Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) because these vaccines are manufactured using the same process. Based on the totality of the scientific evidence available, FDA concluded that it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) may be effective in individuals 6 months through 11 years of age for the

prevention of COVID-19 when administered in accordance with the dosing regimen and schedule as outlined in Section II. Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) outweigh the known and potential risks of the vaccine for the prevention of COVID-19 in individuals 6 months through 11 years of age when administered according to the authorized dosing regimen and schedule.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula), Pfizer-BioNTech COVID-19 Vaccine, Bivalent and Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) for the prevention of COVID-19, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula)[36] for the prevention of COVID-19 when administered as described in the Scope of Authorization (Section II) meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

A. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

B. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) may be effective in preventing COVID-19, and that, when used under the conditions described in this authorization, the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) when used to prevent COVID-19 outweigh its known and potential risks; and

C. There is no adequate, approved, and available alternative[37] to Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) to prevent COVID-19.[38]

[36] In this section (Section I), references to Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) also apply to Pfizer-BioNTech COVID-19 Vaccine, Bivalent and Pfizer-BioNTech COVID-19 Vaccine (Original monovalent).

[37] There are no COVID-19 vaccines that are approved to provide additional doses to certain immunocompromised populations as described in this EUA or COVID-19 vaccination in individuals younger than 12 years of age. Although SPIKEVAX (COVID-19 Vaccine, mRNA) and Comirnaty (COVID-19 Vaccine, mRNA) are approved to prevent COVID-19 in certain individuals, available information indicates that availability of COVID-19 vaccines is needed for individuals who might not receive the approved vaccines.

[38] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Pfizer Inc. will supply Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula), Pfizer-BioNTech COVID-19 Vaccine, Bivalent and Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) either directly or through authorized distributor(s)[39], for use consistent with the terms and conditions of this EUA;
- Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula), Pfizer-BioNTech COVID-19 Vaccine, Bivalent, and Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) may be administered by a vaccination provider[40] without an individual prescription for each vaccine recipient; and
- The Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula), Pfizer-BioNTech COVID-19 Vaccine, Bivalent, and the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) formulations that use either Tris or PBS buffer, as described in more detail under *Product Description* and covered by this authorization, will be administered by vaccination providers in accordance with the uses described in this Scope of Authorization (Section II).

Table 1. Authorized Uses of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) for Use in Individuals 6 Months Through 4 Years of Age

Number of Previous Doses of Pfizer-BioNTech COVID-19 vaccine(s)[a]	Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) Vial Cap and Label Border Color	Dosing Regimen, Dose and Schedule[b]
0[c]	Yellow	3 doses[d], 0.3 mL each Dose 1: Week 0 Dose 2: Week 3 Dose 3: ≥ 8 weeks after Dose 2

[39] "Authorized Distributor(s)" are identified by Pfizer Inc., as an entity or entities allowed to distribute authorized Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula), Pfizer-BioNTech COVID-19 Vaccine, Bivalent, or Pfizer-BioNTech COVID-19 Vaccine (Original monovalent).

[40] For purposes of this letter, "vaccination provider" refers to the facility, organization, or healthcare provider (e.g., non-physician healthcare professionals, such as nurses, pharmacists) licensed or otherwise authorized to administer or provide vaccination services pursuant to State law. If the vaccine is exported from the United States, a "vaccination provider" is a provider that is authorized to administer this vaccine in accordance with the laws of the country in which it is administered. For purposes of this letter, "vaccination provider" also includes a person authorized by the U.S. Department of Health and Human Services (e.g., under the PREP Act Declaration for Medical Countermeasures against COVID-19) to administer FDA-authorized COVID-19 vaccine (e.g., qualified pharmacy technicians and State-authorized pharmacy interns acting under the supervision of a qualified pharmacist). See, e.g., HHS, *Eleventh Amendment to the Declaration Under the Public Readiness and Emergency Preparedness Act for Medical Countermeasures Against COVID-19 and Republication of the Declaration*. (88 FR 30769, May 12, 2023). In addition, for purposes of this letter, the term "State" includes any State or Territory of the United States, the District of Columbia, and the Commonwealth of Puerto Rico. See Section 201(a)(1) of the Act.

1	Yellow	2 doses[d], 0.3 mL each Dose 1: 3 weeks after receipt of previous dose of Pfizer-BioNTech COVID-19 vaccine[a] Dose 2: ≥8 weeks after Dose 1
2 to 4	Yellow	Single dose, 0.3 mL ≥8 weeks after receipt of the last previous dose of Pfizer-BioNTech COVID-19 vaccine[a]

a. Previous doses of Pfizer-BioNTech COVID-19 vaccine(s) refers to doses with Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and Pfizer-BioNTech COVID-19 Vaccine, Bivalent. These vaccines are no longer authorized for use in the United States.
b. For individuals with certain kinds of immunocompromise previously vaccinated with Pfizer-BioNTech COVID-19 vaccines, see text below tables for dosing information.
c. Not previously vaccinated with any COVID-19 vaccine.
d. Notwithstanding the age limitations for use of the vaccine, individuals turning from 4 to 5 years of age during the vaccination series may receive all doses with Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) supplied in vials with yellow caps and labels with yellow borders.

Table 2. Authorized Uses of the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) for Use in Individuals 5 Through 11 Years of Age Irrespective of COVID-19 Vaccination Status

Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) Vial Cap and Label Border Color	**Dosing Regimen, Dose and Schedule[a]**
Blue	Single dose, 0.3 mL If previously vaccinated, ≥2 months after receipt of the last previous dose of COVID-19 vaccine[b]

[a] For individuals with certain kinds of immunocompromise, see text below tables for dosing information.
[b] COVID-19 vaccine refers to the monovalent COVID-19 vaccines that encode the spike protein of the Original SARS-CoV-2 and the bivalent COVID-19 vaccines encoding the spike protein of Original SARS-CoV-2 and of the Omicron-variant lineages BA.4 and BA.5 that are no longer authorized for use in the United States.

Individuals 6 Months Through 11 Years of Age with Certain Kinds of Immunocompromise

The Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) is authorized for use in individuals 6 months through 11 years of age with certain kinds of immunocompromise according to the following dosing regimen and schedule:

Complete at least a 3-dose series with an age-appropriate dose and dosing schedule[41,42] of a COVID-19 vaccine, in which at least 1 dose of the series is with a COVID-19 vaccine (2023-2024 Formula).

- If previously not vaccinated, complete the 3-dose series with age-appropriate doses of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula).
- If previously vaccinated with 1 or 2 dose(s) of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and/or the Pfizer-BioNTech COVID-19 Vaccine, Bivalent, complete the remaining dose(s) in the 3-dose series with age-appropriate doses of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula).
- If previously vaccinated with 3 or more doses, administer a single age-appropriate dose of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) at least 2 months following the last previous dose.[43,44]

An age-appropriate additional dose of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) may be administered at least 2 months following the last dose of a COVID-19 vaccine (2023-2024 Formula).[45,46] Age-appropriate additional doses of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) may be administered at the discretion of the healthcare provider, taking into consideration the individual's clinical circumstances. The timing of the additional doses may be based on the individual's clinical circumstances.

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[41] Dosing schedule for individuals 6 months through 4 years of age for Pfizer-BioNTech COVID-19 vaccines: Dose 1: Week 0; Dose 2: Week 3; Dose 3: ≥8 Weeks after Dose 2. Notwithstanding the age limitations for use of the vaccines, for individuals turning from 4 to 5 years of age during the vaccination series, complete the series with doses of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) supplied in vials with yellow caps and labels with yellow borders.

[42] Dosing schedule for individuals 5 through 11 years of age for Pfizer-BioNTech COVID-19 vaccines: Dose 1: Week 0; Dose 2: Week 3; Dose 3: ≥4 weeks after Dose 2. Notwithstanding the age limitations for use of the vaccines, individuals turning from 11 to 12 years of age during the vaccination series may complete the series with doses of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) supplied in vials with blue caps and labels with blue borders.

[43] For immunocompromised individuals 6 months through 4 years of age, the last previous dose refers to the last dose of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) or Pfizer-BioNTech COVID-19 Vaccine, Bivalent, which are no longer authorized for use in the U.S.

[44] For immunocompromised individuals 5 through 11 years of age, the last previous dose refers to the last dose of a COVID-19 vaccine (Original monovalent) or bivalent COVID-19 vaccine, which are no longer authorized for use in the U.S.

[45] For immunocompromised individuals 6 months through 4 years of age, the last dose of a COVID-19 vaccine (2023-2024 Formula) refers to a dose with Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula).

[46] For immunocompromised individuals 5 through 11 years of age, the last dose of a COVID-19 vaccine (2023-2024 Formula) refers to a dose with Moderna COVID-19 Vaccine (2023-2024 Formula) or Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula).

Pfizer-BioNTech COVID-19 Vaccine (Original Monovalent)

The Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) is no longer authorized for use in the United States. However, the authorized presentations of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) described in Section II of the March 14, 2023 reissuance of this Letter remain authorized when exported from the United States in accordance with Section III.W. Under Section III.W, the Fact Sheets for Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) that were authorized as of March 14, 2023 and that describe the scope of FDA's March 14, 2023 authorization must, upon request, be made available to the regulatory authorities of the country in which the vaccine will be used.

Pfizer-BioNTech COVID-19 Vaccine, Bivalent

The Pfizer-BioNTech COVID-19 Vaccine, Bivalent is no longer authorized for use in the United States. However, the authorized presentations of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent described in Section II of the April 28, 2023 reissuance of this Letter remain authorized when exported from the United States in accordance with Section III.W. Under Section III.W, the Fact Sheets for Pfizer-BioNTech COVID-19 Vaccine, Bivalent that were authorized as of April 28, 2023 (Fact Sheet for Recipients and Caregivers) and as of July 14, 2023 (Fact Sheet for Healthcare Providers Administering Vaccine), and that describe the scope of FDA's April 28, 2023 authorization must, upon request, be made available to the regulatory authorities of the country in which the vaccine will be used.

Product Description

The Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) is provided in two vial presentations:

Table 4: Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) Vial Presentations

Presentation	Authorized age	Dose Volume and Quantity of mRNA	Buffer used	Dilution
Multiple Dose Vials with Yellow Caps and Labels with Yellow Borders	6 months through 4 years of age	0.3 mL dose (each containing 3 mcg modRNA)	Tris	Dilute with 1.1 mL sterile 0.9% Sodium Chloride Injection, USP
Single Dose Vials with Blue Caps and Labels with Blue Borders	5 through 11 years of age	0.3 mL dose (each containing 10 mcg modRNA)	Tris	Not to be diluted

Multiple dose vials with yellow caps and labels with yellow borders

Each 0.3 mL dose of the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) is formulated to contain 3 mcg of modRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2 Omicron variant lineage XBB.1.5 (Omicron XBB.1.5). Each 0.3 mL dose also includes the following ingredients: lipids (0.04 mg ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.005 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 0.01 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.02 mg cholesterol), 9.4 mg sucrose, 0.02 mg tromethamine, and 0.12 mg tromethamine hydrochloride. The diluent (sterile 0.9% Sodium Chloride Injection, USP) contributes 1.88 mg sodium chloride per dose. The Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) does not contain a preservative.

Single dose vials with blue caps and labels with blue borders

Each 0.3 mL dose of the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) is formulated to contain 10 mcg of modRNA encoding the S-glycoprotein of SARS-CoV-2 Omicron variant lineages XBB.1.5 (Omicron XBB.1.5). Each 0.3 mL dose also includes the following ingredients: lipids (0.14 mg ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.02 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 0.03 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.06 mg cholesterol), 31 mg sucrose, 0.06 mg tromethamine, and 0.4 mg tromethamine hydrochloride. The Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) does not contain a preservative.

The manufacture of the authorized Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) is limited to those facilities identified and agreed upon in Pfizer's request for authorization.

For Pfizer-BioNTech COVID-19 Vaccine (Original monovalent), Section III.W refers to the Fact Sheets for the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) that were authorized under the March 14, 2023 reissuance of this Letter. Those Fact Sheets describe different presentations of the vaccine that were authorized for use in the United States as of that date and that remain authorized for export in accordance with Section III.W.

For Pfizer-BioNTech COVID-19 Vaccine, Bivalent Section III.W refers to the Fact Sheets for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent that were authorized on April 28, 2023 (Fact Sheet for Recipients and Caregivers) and July 14, 2023 (Fact Sheet for Healthcare Providers Administering Vaccine). Those Fact Sheets describe different presentations of the vaccine that were authorized for use in the United States as of April 28, 2023 and that remain authorized for export in accordance with Section III.W.

The Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula), Pfizer-BioNTech COVID-19 Vaccine, Bivalent, and Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) vial labels and carton labels are clearly marked for "Emergency Use Authorization." The Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula), Pfizer-BioNTech COVID-19 Vaccine, Bivalent and

Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) are authorized to be distributed, stored, further redistributed, and administered when packaged in the authorized manufacturer packaging (i.e., vials and cartons), despite the fact that the vial and carton labels may not contain information that otherwise would be required under the FD&C Act.

Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) is authorized for emergency use with the following product-specific information required to be made available to vaccination providers and recipients, respectively (referred to as "authorized labeling"):

> Fact Sheet for Healthcare Providers Administering Vaccine: Emergency Use Authorization of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula), For 6 Months Through 11 Years of Age
>
> Fact Sheet for Recipients and Caregivers About Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) Which Has Emergency Use Authorization (EUA) to Prevent Coronavirus Disease 2019 (COVID-19) in Individuals 6 Months Through 11 Years of Age

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula), Pfizer-BioNTech COVID-19 Vaccine, Bivalent, and Pfizer-BioNTech COVID-19 Vaccine (Original monovalent), when used to prevent COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh their known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula), Pfizer-BioNTech COVID-19 Vaccine, Bivalent, and Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) may be effective in preventing COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula), Pfizer-BioNTech COVID-19 Vaccine, Bivalent, and Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) (as described in this Scope of Authorization (Section II)) meet the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula), Pfizer-BioNTech COVID-19 Vaccine, Bivalent, and Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) under this EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula), Pfizer-BioNTech COVID-19 Vaccine, Bivalent, and Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) are authorized to prevent COVID-19 as described in the Scope of

Authorization (Section II) under this EUA, despite the fact that they do not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

Pfizer Inc. and Authorized Distributor(s)

A. Pfizer Inc. and authorized distributor(s) will ensure that the authorized labeling (i.e., Fact Sheets) for Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) will be made available to vaccination providers, recipients, and caregivers consistent with the terms of this letter.

B. Pfizer Inc. and authorized distributor(s) will ensure that appropriate storage and cold chain is maintained until delivered to healthcare facilities or other vaccine receipt sites.

C. Pfizer Inc. will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., authorized distributors and vaccination providers) involved in distributing or receiving authorized Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula). Pfizer Inc. will provide to all relevant stakeholders a copy of this letter of authorization and communicate any subsequent amendments that might be made to this letter of authorization and its authorized labeling.

D. Pfizer Inc. may develop and disseminate instructional and educational materials (e.g., video regarding vaccine handling, storage/cold-chain management, preparation, disposal) that are consistent with the authorized emergency use of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) as described in the letter of authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs during an emergency. Any instructional and educational materials that are inconsistent with the authorized labeling are prohibited.

E. Pfizer Inc. may request changes to this authorization, including to the authorized Fact Sheets. Any request for changes to this EUA must be submitted to Office of Vaccines Research and Review (OVRR)/Center for Biologics Evaluation and Research (CBER). Such changes require appropriate authorization prior to implementation.[47]

[47] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study. All changes to the authorization require review and concurrence from OVRR. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), or (7), review and

F. Pfizer Inc. will report to Vaccine Adverse Event Reporting System (VAERS):
- Serious adverse events (irrespective of attribution to vaccination);
- Cases of myocarditis;
- Cases of pericarditis;
- Cases of Multisystem Inflammatory Syndrome; and
- Cases of COVID-19 that result in hospitalization or death, that are reported to Pfizer Inc.

These reports should be submitted to VAERS as soon as possible but no later than 15 calendar days from initial receipt of the information by Pfizer Inc.

G. Pfizer Inc. must submit to Investigational New Drug application (IND) number 19736 periodic safety reports monthly, or at another appropriate interval determined by Office of Biostatistics and Pharmacovigilance (OBPV)/CBER, in accordance with a due date agreed upon with OBPV/CBER beginning after the first full calendar month after authorization. Each periodic safety report is required to contain descriptive information which includes:
- A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest;
- A narrative summary and analysis of vaccine administration errors, whether or not associated with an adverse event, that were identified since the last reporting interval;
- Newly identified safety concerns in the interval;
- Actions taken since the last report because of adverse experiences (for example, changes made to Healthcare Providers Administering Vaccine (Vaccination Providers) Fact Sheet, changes made to studies or studies initiated); and
- Cumulative doses distributed, and doses distributed during the reporting interval, for Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula).

H. No changes will be implemented to the description of the product, manufacturing process, facilities, or equipment without notification to and concurrence by FDA.

I. All manufacturing facilities will comply with Current Good Manufacturing Practice requirements.

J. Pfizer Inc. will submit to the EUA file Certificates of Analysis (CoA) for each drug product lot at least 48 hours prior to vaccine distribution. The CoA will include the established specifications and specific results for each quality control test performed on the final drug product lot.

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concurrence is required from the Preparedness and Response Team (PREP)/Office of the Center Director (OD)/CBER and the Office of Counterterrorism and Emerging Threats (OCET)/Office of the Chief Scientist (OCS).

K. Pfizer Inc. will submit to the EUA file quarterly manufacturing reports, starting in July 2021, that include a listing of all drug substance and drug product lots produced after issuance of this authorization. This report must include lot number, manufacturing site, date of manufacture, and lot disposition, including those lots that were quarantined for investigation or those lots that were rejected. Information on the reasons for lot quarantine or rejection must be included in the report.

L. Pfizer Inc. and authorized distributor(s) will maintain records regarding release of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula), Pfizer-BioNTech COVID-19 Vaccine, Bivalent, and Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) for distribution (i.e., lot numbers, quantity, release date).

M. Pfizer Inc. and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

N. Pfizer Inc. will conduct post-authorization observational studies to evaluate the association between Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula), Pfizer-BioNTech COVID-19 Vaccine (Original monovalent), and Pfizer-BioNTech COVID-19 Vaccine, Bivalent, and a pre-specified list of adverse events of special interest, including myocarditis and pericarditis, along with deaths and hospitalizations, and severe COVID-19. The study population should include individuals administered the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) (previously, but no longer authorized for use in the U.S.) as a primary series (6 months of age and older) or booster dose (5 years of age and older); individuals administered a dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (previously, but no longer authorized for use in the U.S.) (6 months of age and older), and Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) (6 months through 11 years of age) under this EUA in the general U.S. population, and populations of interest such as healthcare workers, pregnant women, immunocompromised individuals, subpopulations with specific comorbidities. The studies should be conducted in large scale databases with an active comparator. Pfizer Inc. will provide protocols and status update reports to the IND 19736 with agreed-upon study designs and milestone dates.

Vaccination Providers

O. Vaccination providers will administer the vaccine in accordance with this authorization.

P. Vaccination providers will provide the Fact Sheet for Recipients and Caregivers to each individual receiving vaccination and provide the necessary information for receiving their dose(s).

Q. Vaccination providers administering the vaccines must report the following information associated with the administration of the vaccines of which they become

aware to VAERS in accordance with the Fact Sheet for Healthcare Providers Administering Vaccine:

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events (irrespective of attribution to vaccination)
- Cases of myocarditis
- Cases of pericarditis
- Cases of Multisystem Inflammatory Syndrome
- Cases of COVID-19 that result in hospitalization or death

Complete and submit reports to VAERS online at https://vaers.hhs.gov/reportevent.html. The VAERS reports should include the words "Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) EUA", "Pfizer-BioNTech COVID-19 Vaccine, Bivalent EUA" or "Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) EUA", as appropriate, in the description section of the report. More information is available at vaers.hhs.gov or by calling 1-800-822-7967. To the extent feasible, report to Pfizer Inc. by contacting 1-800-438-1985 or by providing a copy of the VAERS form to Pfizer Inc.; Fax: 1-866-635-8337.

R. Vaccination providers will conduct any follow-up requested by the U.S government, including CDC, FDA, or other designee, regarding adverse events to the extent feasible given the emergency circumstances.

S. Vaccination providers will ensure that any records associated with this EUA are maintained until notified by FDA. Such records will be made available to CDC, and FDA for inspection upon request.

T. Vaccination providers receiving authorized Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) will ensure that appropriate storage and cold chain is maintained.

Conditions Related to Printed Matter, Advertising, and Promotion

U. All descriptive printed matter, advertising, and promotional material, relating to the use of the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in Section 502(a) and (n), as applicable, of the FD&C Act and FDA implementing regulations. In addition, such materials shall:
    - Be tailored to the intended audience.
    - Present the same risk information relating to the major side effects and contraindications concurrently in the audio and visual parts of the presentation for advertising and promotional materials in audio-visual format.
    - Be accompanied by the authorized labeling, if the promotional materials are not subject to Section 502(n) of the Act.

Pfizer Inc. must submit such materials to FDA accompanied by Form FDA-2253 by the time of initial dissemination or first use.

V. All descriptive printed matter, advertising, and promotional material relating to the use of the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) clearly and conspicuously shall state that:
   - The Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) has not been approved or licensed by FDA, but has been authorized for emergency use by FDA, under an EUA to prevent Coronavirus Disease 2019 (COVID-19) for use in individuals 6 months through 11 years of age; and
   - The emergency use of this product is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of the medical product under Section 564(b)(1) of the FD&C Act unless the declaration is terminated or authorization revoked sooner.

   If the Agency notifies Pfizer Inc. that any descriptive printed matter, advertising, or promotional materials do not meet the terms set forth in Conditions U and V of this EUA, Pfizer Inc. must cease distribution of such descriptive printed matter, advertising, or promotional materials in accordance with the Agency's notification. Furthermore, as part of its notification, the Agency may also require Pfizer Inc. to issue corrective communication(s).

Condition Related to Export

W. If the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) is exported from the United States, conditions C, D, and O through V do not apply, but export is permitted only if 1) the regulatory authorities of the country in which the vaccine will be used are fully informed that this vaccine is subject to an EUA and is not approved or licensed by FDA and 2) the intended use of the vaccine will comply in all respects with the laws of the country in which the product will be used. The requirement in this letter that the authorized labeling (i.e., Fact Sheets) be made available to vaccination providers, recipients, and caregivers in condition A will not apply if the authorized labeling (i.e., Fact Sheets) are made available to the regulatory authorities of the country in which the vaccine will be used.

   If the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) is exported from the United States, conditions C, D, and O through V do not apply, but export is permitted only if 1) the vaccine was manufactured on or before April 18, 2023, 2) the regulatory authorities of the country in which the vaccine will be used are fully informed that this vaccine is subject to an EUA and is not approved or licensed by FDA, 3) the intended use of the vaccine will comply in all respects with the laws of the country in which the product will be used, 4) the Fact Sheets that were authorized as of March 14, 2023 for the vial presentation being exported are made available, upon request, to the regulatory authorities of the countries in which the vaccine will be used, and 5) the regulatory authorities are informed that

the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and associated Fact Sheets are no longer authorized for use in the United States and that FDA is not currently revising the Fact Sheets with updated information.

If the Pfizer-BioNTech COVID-19 Vaccine, Bivalent is exported from the United States, conditions C, D, and O through V do not apply, but export is permitted only if 1) the vaccine was manufactured on or before September 11, 2023, 2) the regulatory authorities of the country in which the vaccine will be used are fully informed that this vaccine is subject to an EUA and is not approved or licensed by FDA, 3) the intended use of the vaccine will comply in all respects with the laws of the country in which the product will be used, 4) the Fact Sheets that were authorized as of April 28, 2023 (Fact Sheet for Recipients and Caregivers) and as of July 14, 2023 (Fact Sheet for Healthcare Providers Administering Vaccine) for the vial presentation being exported are made available, upon request, to the regulatory authorities of the countries in which the vaccine will be used, and 5) the regulatory authorities are informed that the Pfizer-BioNTech COVID-19 Vaccine, Bivalent and associated Fact Sheets are no longer authorized for use in the United States and that FDA is not currently revising the Fact Sheets with updated information.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

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Peter Marks, M.D., Ph.D.
Director
Center for Biologics Evaluation and Research

Enclosures

U.S. FOOD & DRUG ADMINISTRATION

September 11, 2023

ModernaTX, Inc.
Attention: Ms. Michelle Olsen
200 Technology Square
Cambridge, MA 02139

Dear Ms. Olsen:

On February 4, 2020, as amended on March 15, 2023, pursuant to Section 564(b)(1)(C) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act or the Act), the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency, or a significant potential for a public health emergency, that affects, or has a significant potential to affect, national security or the health and security of United States citizens living abroad, and that involves the virus that causes Coronavirus Disease 2019 (COVID-19).[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act (21 U.S.C. 360bbb-3), subject to the terms of any authorization issued under that section.[2]

On December 18, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of Moderna COVID-19 Vaccine (Original monovalent)[3] for the prevention of COVID-19 for individuals 18 years of age and older, pursuant to Section 564 of the Act.

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[1] U.S. Department of Health and Human Services, Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3. February 4, 2020. U.S. Department of Health and Human Services, *Amended Determination of a Public Health Emergency or Significant Potential for a Public Health Emergency Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3(b)*. March 15, 2023. 88 FR 16644 (March 20, 2023) ("Amended Determination").

[2] U.S. Department of Health and Human Services, Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3, 85 FR 18250 (April 1, 2020). See Amended Determination ("The declarations issued pursuant to section 564(b)(1) of the FD&C Act that circumstances exist justifying the authorization of emergency use of certain in vitro diagnostics, personal respiratory protective devices, other medical devices and drugs and biological products, as set forth in those declarations, and that are based on the February 4, 2020 determination, remain in effect until those declarations are terminated in accordance with section 564 of the FD&C Act.").

[3] For purposes of this letter, Moderna COVID-19 Vaccine (Original monovalent) refers to the vaccine that encodes the spike protein of only the Original SARS-CoV-2.

FDA reissued the letter of authorization on: February 25, 2021,[4] July 7, 2021,[5] August 12, 2021,[6] October 20, 2021,[7] November 19, 2021,[8] and January 7, 2022.[9] On January 31, 2022, FDA approved SPIKEVAX (COVID-19 Vaccine, mRNA)[10] and reissued the letter in its entirety for both Moderna COVID-19 Vaccine and certain uses of SPIKEVAX (COVID-19 Vaccine, mRNA).[11]

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[4] In the February 25, 2021 revision, FDA allowed flexibility on the date of submission of monthly periodic safety reports and revised the requirements for reporting of vaccine administration errors by ModernaTX, Inc.

[5] In the July 7, 2021 revision, FDA clarified terms and conditions that relate to export of Moderna COVID-19 Vaccine (Original monovalent) from the United States.

[6] In the August 12, 2021 revision, FDA authorized for emergency use a third dose of the Moderna COVID-19 vaccine (Original monovalent) administered at least 1 month following the two dose series of this vaccine in individuals 18 years of age or older who have undergone solid organ transplantation, or individuals 18 years of age or older who have been diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

[7] In the October 20, 2021 revision, FDA authorized for emergency use the administration of a single booster dose of Moderna COVID-19 Vaccine (Original monovalent) at least 6 months after completing the primary series of this vaccine in individuals: 65 years of age and older; 18 through 64 years of age at high risk of severe COVID-19; and 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2. Additionally, FDA authorized the administration of a single booster dose of the Moderna COVID-19 Vaccine (Original monovalent) as a heterologous booster dose following completion of primary vaccination with another authorized or approved COVID-19 vaccine. The eligible population(s) and dosing interval for the heterologous booster dose were the same as those authorized for a booster dose of the vaccine used for primary vaccination.

[8] In the November 19, 2021 revision, FDA authorized the use of Moderna COVID-19 Vaccine (Original monovalent) as a single booster dose in individuals 18 years of age or older at least 6 months after completing the primary series of this vaccine (i.e., as a homologous booster dose), and authorized the use of the vaccine as a single booster dose following completion of primary vaccination with another authorized or approved COVID-19 vaccine (i.e., as a heterologous booster dose) in individuals 18 years of age or older. The dosing interval for the heterologous booster dose was authorized to be the same as that authorized for a booster dose of the vaccine used for primary vaccination.

[9] In the January 7, 2022 revision, FDA revised the authorized dosing interval of the homologous booster dose to at least five (5) months after completion of the primary series of Moderna COVID-19 Vaccine (Original monovalent). In addition, FDA revised the Fact Sheets for Healthcare Providers Administering Vaccine (Vaccination Providers) and the Fact Sheet for Recipients and Caregivers to reflect this revision.

[10] SPIKEVAX (COVID-19 Vaccine, mRNA) was approved for active immunization to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older.

[11] In the January 31, 2022 revision, FDA clarified that, subsequent to the FDA approval of SPIKEVAX (COVID-19 Vaccine, mRNA) for the prevention of COVID-19 for individuals 18 years of age and older, this EUA would remain in place for the Moderna COVID-19 Vaccine (Original monovalent) for the previously-authorized uses. It also authorized SPIKEVAX (COVID-19 Vaccine, mRNA) under this EUA for certain uses that are not included in the approved Biologics License Application (BLA). In addition, the Fact Sheet for Recipients and Caregivers was updated as the Vaccine Information Fact Sheet for Recipients and Caregivers, which comprises the Fact Sheet for the authorized Moderna COVID-19 Vaccine (Original monovalent) and information about the FDA-licensed vaccine, SPIKEVAX (COVID-19 Vaccine, mRNA).

Subsequently, FDA reissued the letter of authorization on March 15, 2022,[12] March 29, 2022,[13] June 17, 2022,[14] and August 31, 2022.[15] The August 31, 2022 reissuance provided for certain emergency uses of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)[16] after either completion of primary vaccination with any FDA approved or authorized monovalent COVID-19 vaccine[17] or receipt of the most recent booster dose with any

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[12] In the March 15, 2022 revision, FDA changed the timing of periodic safety report submissions from monthly to every two months.

[13] In the March 29, 2022 revision, FDA authorized: 1) the administration of a second booster dose of SPIKEVAX (COVID-19 Vaccine, mRNA) or the Moderna COVID-19 Vaccine (Original monovalent) at least 4 months after receipt of a first booster dose of any FDA authorized or approved COVID-19 vaccine to: a) individuals 50 years of age and older; and b) individuals 18 years of age or older who have undergone solid organ transplantation, or individuals 18 years of age or older who have been diagnosed with conditions that are considered to have an equivalent level of immunocompromise; and 2) a manufacturing change to include an additional presentation of the Moderna COVID-19 Vaccine (Original monovalent) for booster vaccination doses only, supplied in multiple dose vials with dark blue caps and labels with a purple border.

[14] In the June 17, 2022 revision, FDA authorized the use of: SPIKEVAX (COVID-19 Vaccine, mRNA) or the Moderna COVID-19 Vaccine (Original monovalent) as: 1) a two-dose primary series for the prevention of COVID-19 in individuals 12 through 17 years of age; and 2) a third primary series dose at least 1 month following the second dose of this vaccine in individuals 12 through 17 years of age who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise. FDA also authorized the Moderna COVID-19 Vaccine (Original monovalent) as 1) a two-dose primary series for the prevention of COVID-19 in individuals 6 months through 11 years of age (6 months through 5 years of age, and 6 years through 11 years of age); and 2) a third primary series dose at least 1 month following the second dose of this vaccine in individuals 6 months through 11 years of age who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise. In addition, FDA authorized two new presentations of the Moderna COVID-19 Vaccine (Original monovalent): 1) multiple dose vials, with dark blue caps and labels with a magenta border, each 0.25 mL dose containing 25 mcg mRNA; and 2) multiple dose vials, with dark blue caps and labels with a teal border, each 0.5 mL dose containing 50 mcg mRNA. Finally, FDA authorized the use of the presentation of the Moderna COVID-19 Vaccine (Original monovalent) in multiple dose vials, with dark blue caps and labels with a purple border (each 0.5 mL dose containing 50 mcg mRNA), labeled "BOOSTER DOSES ONLY" to provide primary series doses in individuals 6 years through 11 years of age.

[15] In the August 31, 2022 revision, FDA authorized the use of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in multiple dose vials with dark blue caps and labels with gray borders (each 0.5 mL dose containing a total of 50 mcg mRNA) for the prevention of COVID-19 in individuals 18 years of age or older as a single booster dose administered at least 2 months after either: 1) completion of primary vaccination with any FDA authorized or approved monovalent COVID-19 vaccine, or 2) receipt of the most recent booster dose with any FDA authorized or approved monovalent COVID-19 vaccine. FDA also revised the scope of authorization for SPIKEVAX (COVID-19 Vaccine, mRNA) and Moderna COVID-19 Vaccine (Original monovalent) to remove their use as a booster dose for individuals 18 years of age and older. Finally, FDA revised the Fact Sheets for Moderna COVID-19 Vaccine (Original monovalent), as applicable, to reflect these changes and to reflect updates to the Conditions of Authorization regarding VAERS reporting.

[16] Hereinafter, this letter refers to this vaccine as the "Moderna COVID-19 Vaccine, Bivalent."

[17] For purposes of this letter, monovalent COVID-19 Vaccine refers to any COVID-19 Vaccine that contains or encodes the spike protein of only the Original SARS-CoV-2. We note that the Moderna COVID-19 Vaccine (2023-2024 Formula) is also monovalent and encodes the spike protein of SARS-CoV-2 Omicron variant lineage XBB 1.5.

FDA authorized or approved monovalent COVID-19 vaccine. Subsequently, FDA reissued the letter of authorization on October 12, 2022,[18] December 8, 2022,[19] and April 18, 2023.[20]

On September 11, 2023, FDA approved SPIKEVAX (COVID-19 Vaccine, mRNA) (2023-2024 Formula)[21] for active immunization to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

On September 11, 2023, having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the April 18, 2023 letter of authorization in its entirety with revisions to:

1. Authorize Moderna COVID-19 Vaccine (2023-2024 Formula)[22] in single dose vials with

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[18] In the October 12, 2022 revision, FDA authorized Moderna COVID-19 Vaccine, Bivalent as a single booster dose in individuals 12 through 17 years of age and 6 through 11 years of age at least 2 months after either: 1) completion of primary vaccination with any FDA authorized or approved monovalent COVID-19 vaccine, or 2) receipt of the most recent booster dose with any FDA authorized or approved monovalent COVID-19 vaccine. For both of these age groups, FDA authorized the use of the Moderna COVID-19 Vaccine, Bivalent in multiple dose vials with dark blue caps and labels with gray borders. The authorized volume of the booster dose is age dependent. A single booster dose for individuals 12 through 17 years of age is a 0.5 mL dose containing a total of 50 mcg mRNA. A single booster dose for individuals 6 through 11 years of age is a 0.25 mL dose containing a total of 25 mcg mRNA. In addition, FDA revised the Fact Sheets for Moderna COVID-19 Vaccine, Bivalent to reflect these changes.

[19] In the December 8, 2022 revision, FDA authorized the use of Moderna COVID-19 Vaccine, Bivalent in multiple dose vials with dark pink caps and labels with a yellow box (each 0.2 mL dose containing a total of 10 mcg of mRNA) in individuals 6 months through 5 years of age at least 2 months after completion of primary vaccination with Moderna COVID-19 Vaccine. In addition, because another COVID-19 vaccine's primary series for individuals 6 months through 4 years of age was revised to no longer consist of only monovalent doses, FDA revised the scope of authorization for the Moderna COVID-19 Vaccine, Bivalent for use in individuals 6 years of age and older so that it can be administered as a booster dose regardless of whether primary vaccination was completed with a monovalent COVID-19 vaccine. Specifically, FDA authorized the Moderna COVID-19 Vaccine, Bivalent in multiple dose vials with dark blue caps and labels with gray borders for use in individuals 6 through 11 years of age (each 0.25 mL booster dose containing a total of 25 mcg mRNA) and for use in individuals 12 years of age and older (each 0.5 mL booster dose containing a total of 50 mcg mRNA) as a single booster dose administered at least 2 months after either: 1) completion of primary vaccination with any FDA authorized or approved COVID-19 vaccine, or 2) receipt of the most recent booster dose with any FDA authorized or approved monovalent COVID-19 vaccine. FDA revised the applicable Fact Sheets for Moderna COVID-19 Vaccine (Original monovalent), and the Fact Sheets for Moderna COVID-19 Vaccine, Bivalent, to reflect these changes. Finally, FDA revised the Fact Sheets for Moderna COVID-19 Vaccine (Original monovalent), and the Fact Sheets for Moderna COVID-19 Vaccine, Bivalent, to convey that urticaria has been reported during post-authorization use.

[20] In the April 18, 2023 revision, FDA: 1) revised the authorized dosing regimen and schedule of the Moderna COVID-19 Vaccine, Bivalent, as described in Section II of the April 18, 2023 reissuance of this letter; 2) no longer authorized use of the Moderna COVID-19 Vaccine and certain uses of SPIKEVAX (COVID-19 Vaccine; mRNA) in the United States; 3) clarified the terms and conditions that relate to export of Moderna COVID-19 Vaccine from the United States; and 4) revised Condition G to require the inclusion of distribution data for Moderna COVID-19 Vaccine and Moderna COVID-19 Vaccine, Bivalent in the monthly periodic safety reports. FDA also revised the applicable Fact Sheets for Moderna COVID-19 Vaccine, Bivalent, to reflect these changes. In addition, the Fact Sheets for Healthcare Providers Administering Vaccine (Vaccination Providers) were consolidated into a single Fact Sheet for Healthcare Providers Administering Vaccine for all authorized presentations of Moderna COVID-19 Vaccine, Bivalent; and the Fact Sheets for Recipients and Caregivers were consolidated into a single Fact Sheet for Recipients and Caregivers for all authorized presentations of Moderna COVID-19 Vaccine, Bivalent.

[21] SPIKEVAX (COVID-19 Vaccine, mRNA) (2023-2024 Formula) encodes the spike protein of SARS-CoV-2 Omicron variant lineage XBB.1.5 (Omicron XBB.1.5).

[22] Moderna COVID-19 Vaccine (2023-2024 Formula) encodes the spike protein of SARS-CoV-2 Omicron variant lineage XBB.1.5 (Omicron XBB.1.5).

dark blue caps and labels with a green box (each 0.25 mL dose containing a total of 25 mcg of mRNA) for use in individuals 6 months through 11 years of age as described in Section II;

2. Revise the conditions related to printed matter, advertising, and promotion to add additional requirements;
3. Remove the requirement that distribution of vaccines authorized under this EUA must be distributed to emergency response stakeholders as directed by the U.S. Government and make corresponding changes to the Conditions of Authorization;
4. Remove the requirement that vaccines authorized under this EUA be administered only by vaccination providers enrolled in the CDC COVID-19 Vaccination Program and make corresponding changes to the Conditions of Authorization;
5. Revise Condition G to provide flexibility to determine a different reporting interval for periodic safety reports, if appropriate;
6. No longer authorize the use of the Moderna COVID-19 Vaccine, Bivalent in the United States; and
7. Clarify the terms and conditions that relate to export of Moderna COVID-19 Vaccine, Bivalent from the United States.

In addition, FDA also authorized Fact Sheets for Moderna COVID-19 Vaccine (2023-2024 Formula) that reflect the relevant changes.

For the December 18, 2020 authorization for individuals 18 years of age and older, FDA reviewed safety and efficacy data from an ongoing phase 3 trial (Study 1) in approximately 30,000 participants randomized 1:1 to receive Moderna COVID-19 Vaccine (Original monovalent) or saline control. Study 1 enrolled participants 18 years of age and older. FDA's review of the available safety data from 30,351 participants 18 years of age and older, who were followed for a median of 7 weeks after receiving the second dose, did not identify specific safety concerns that would preclude issuance of an EUA. Review of additional safety data from these participants with a median of 9 weeks of follow-up after receipt of the second dose did not change FDA's assessment of safety of the vaccine. FDA's analysis of the efficacy data from 28,207 participants 18 years of age and older without evidence of SARS-CoV-2 infection prior to dose 1 confirms the vaccine was 94.1% effective (95% confidence interval (CI) 89.3, 96.8) in preventing COVID-19 occurring at least 14 days after the second dose (with 11 COVID-19 cases in the vaccine group compared to 185 COVID-19 cases in the placebo group). In this final scheduled analysis participants had been followed for a median of 9 weeks following the second dose. This result is consistent with that obtained from an interim analysis of efficacy conducted after these participants had been followed for a median of 7 weeks after the second dose (vaccine efficacy 94.5%, 95% CI: 86.5, 97.8). Based on the safety and effectiveness data, and review of manufacturing information regarding product quality and consistency, it is reasonable to believe that Moderna COVID-19 Vaccine (Original monovalent) may be effective. Additionally, it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of Moderna COVID-19 Vaccine (Original monovalent) outweigh the known and potential risks of the vaccine, for the prevention of COVID-19 in individuals 18 years

of age and older. Finally, on December 17, 2020, the Vaccines and Related Biological Products Advisory Committee voted in agreement with this conclusion.

For the August 12, 2021 authorization of a third primary series dose of the Moderna COVID-19 Vaccine (Original monovalent) in individuals 18 years of age or older who have undergone solid organ transplantation, or individuals 18 years of age or older who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise[23], FDA reviewed safety and effectiveness data reported in two manuscripts on solid organ transplant recipients. The first study was a double-blind, randomized-controlled study conducted in 120 individuals who had undergone various solid organ transplant procedures (heart, kidney, kidney-pancreas, liver, lung, pancreas) a median of 3.57 years earlier (range 1.99-6.75 years). A third dose of the Moderna COVID-19 vaccine (Original monovalent) was administered to 60 individuals approximately 2 months after they had received a second dose (i.e., doses at 0, 1 and 3 months); saline placebo was given to 60 individuals or comparison. The primary outcome was anti-RBD antibody at 4 months greater than 100 U/mL. This titer was selected based on NHP challenge studies as well as a large clinical cohort study to indicate this antibody titer was possibly protective. Secondary outcome was based on a virus neutralization assay polyfunctional T cell responses. Baseline characteristics were comparable between the two study arms as were pre-intervention anti-RBD titer and neutralizing antibodies. Levels of SARS-CoV-2 antibodies indicative of a significant response occurred four weeks after the third dose in 33/60 (55.0%) of the Moderna COVID-19 vaccinated group and 10/57 (17.5%) of the placebo individuals. In the 60 individuals who received a third vaccine dose, the adverse event profile was similar to that after the second dose and no grade 3 or grade 4 adverse events were reported. A supportive secondary study describes a single arm study conducted in 101 individuals who had undergone various solid organ transplant procedures (heart, kidney, liver, lung, pancreas) a median of 97±8 months earlier. A third dose of a similar messenger RNA COVID-19 vaccine, Pfizer-BioNTech COVID-19 Vaccine (Original monovalent), was administered to 99 of these individuals approximately 2 months after they had received a second dose. Levels of SARS-CoV-2 antibodies meeting the pre-identified criteria for success occurred four weeks after the third dose in 26/59 (44.0%) of those who were initially considered to be seronegative and received a third dose of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent); 67/99 (68%) of the entire group receiving a third vaccination had an increase in antibody titers that the investigators considered significant. In those who received a third vaccine dose, the adverse event profile was similar to that after the second dose and no grade 3 or grade 4 events were reported. Despite the moderate enhancement in antibody titers, the totality of data (including the supportive paper by Kamar et al. and demonstrated efficacy of the product in the elderly and persons with co-morbidities) supports the conclusion that a third dose of the Moderna COVID-19 Vaccine (Original monovalent) may be effective in this population, and that the known and potential benefit of a third dose of Moderna COVID-19 Vaccine (Original monovalent) outweigh the known and potential risks of the vaccine for immunocompromised individuals at least 18 years of age who have received two

[23] Certain kinds of immunocompromise refers to individuals who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

doses of the Moderna COVID-19 Vaccine (Original monovalent) and who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

For the October 20, 2021 authorization of a single booster dose of the Original monovalent Moderna COVID-19 Vaccine administered at least 6 months after completing the primary series in individuals: 65 years of age or older; 18 through 64 years of age at high risk of severe COVID-19; and 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2, FDA reviewed safety and effectiveness data from an ongoing Phase 2 trial in which 171 participants aged 18 years and older received a single 50 mcg booster dose (0.25 mL) of the Moderna COVID-19 Vaccine (Original monovalent) at least 6 months (range 5.8-8.5 months) after completion of the 100 µg primary series (two 0.5 mL doses, one month apart). Following the booster dose, the median follow-up time was 5.7 months. FDA's review of the currently available safety data did not identify specific safety concerns that would preclude issuance of an EUA. The effectiveness of the 50 µg booster dose (0.25 mL) of the Moderna COVID-19 Vaccine (Original monovalent) is based on an assessment of neutralizing antibody titers (ID50) against a pseudovirus expressing the SARS-CoV-2 Spike protein from a USA_WA1/2020 isolate carrying the D614G mutation. Immunogenicity analyses compared the ID50 one month after the booster dose in 149 participants to the ID50 one month after the primary series in a random subset of 1055 participants from another study. Participants from these two studies had no serologic or virologic evidence of SARS-CoV-2 infection prior to the booster dose and prior to the first primary series dose, respectively. FDA's analyses confirmed that the immunobridging criteria for a booster response were met for a comparison of the ID50 geometric mean titers and that the immunobridging criterion for a booster response was not met for a comparison of ID50 seroresponse rates. Based on the totality of the scientific evidence available, including data from the above-referenced clinical trials, FDA concluded that a booster dose of the Moderna COVID-19 Vaccine (Original monovalent) may be effective, and that the known and potential benefits of a single booster dose at least 6 months after completing the primary series outweigh the known and potential risks for individuals 65 years of age and older, individuals 18 through 64 years of age at high risk of severe COVID-19, and individuals 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2.

For the October 20, 2021 authorization of a single booster dose of the Moderna COVID-19 Vaccine (Original monovalent) as a heterologous booster dose following completion of primary vaccination with another authorized or approved COVID-19 vaccine, FDA reviewed data from an ongoing Phase1/2 clinical trial in participants 19-85 years of age. In this study, adults who had completed primary vaccination with Moderna COVID-19 Vaccine (Original monovalent) 2-dose series (N=151), a Janssen COVID-19 Vaccine single dose (N=156), or a Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) 2-dose series (N=151) at least 12 weeks prior to enrollment and who reported no history of SARS-CoV-2 infection were randomized 1:1:1 to receive a booster dose of one of three vaccines: Moderna COVID-19 Vaccine (Original monovalent) (0.5 mL), Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine (Original monovalent). Adverse events were assessed through 28 days after the booster dose. An overall review of adverse reactions reported following the Moderna COVID-19 Vaccine (Original monovalent) heterologous booster dose (0.5 mL) did not identify any new safety

concerns, as compared with adverse reactions reported following Moderna COVID-19 Vaccine (Original monovalent) primary series doses or homologous booster dose (0.25 mL). Neutralizing antibody titers, as measured by a pseudovirus neutralization assay using a lentivirus expressing the SARS-CoV-2 Spike protein with D614G mutation, were assessed on Day 1 prior to administration of the booster dose and on Day 15 after the booster dose. A booster response to the Moderna COVID-19 Vaccine (Original monovalent) 100 mcg (0.5 mL) was demonstrated regardless of primary vaccination. FDA also considered immunogenicity data from manufacturer-conducted clinical trials that evaluated both a 0.25 mL dose and a 0.5 mL dose of the Moderna COVID-19 Vaccine (Original monovalent) for the first dose of the primary series and a 0.25 mL dose for a homologous booster dose. Based on the totality of the scientific evidence available, including data from the above-referenced clinical trial, FDA concluded that a heterologous booster dose (0.25 mL) of the Moderna COVID-19 Vaccine (Original monovalent) may be effective, and that the known and potential benefits of a heterologous booster dose of the Moderna COVID-19 Vaccine (Original monovalent) following completion of primary vaccination with another authorized or approved COVID-19 vaccine outweigh the known and potential risks.

For the November 19, 2021 authorization expanding the eligible population for the homologous and heterologous booster doses to individuals 18 years of age and older, FDA reviewed data provided by the sponsor and other data available to FDA, including real world evidence. Data previously reviewed to support the October 20, 2021, authorization of a homologous booster dose, together with new real-world data indicating increasing COVID-19 cases in the United States, including among vaccinated individuals, and suggesting a decreased risk of myocarditis following mRNA COVID-19 vaccine booster doses compared with second primary series doses, supported expansion of the population eligible for a Moderna COVID-19 Vaccine (Original monovalent) homologous booster dose to include all individuals 18 years of age and older who completed the primary series at least 6 months previously. Data previously reviewed to support the October 20, 2021, authorization of a heterologous booster dose, together with data and information to support authorization of the EUA amendment to expand the eligible population for a homologous booster dose of the Pfizer-BioNTech Vaccine (Original monovalent), support a revision to the Moderna COVID-19 Vaccine (Original monovalent) EUA such that the eligible population for a heterologous booster dose of the Moderna COVID-19 Vaccine (Original monovalent) is all adults 18 years of age and older who completed primary vaccination with another authorized or approved COVID-19 vaccine. Based on the totality of the scientific evidence available, FDA concluded that a homologous or heterologous booster dose of the Moderna COVID-19 Vaccine (Original monovalent) may be effective, and that the known and potential benefits of the booster dose of the Moderna COVID-19 Vaccine (Original monovalent) following completion of primary vaccination with Moderna COVID-19 Vaccine (Original monovalent) or another authorized or approved COVID-19 vaccine outweigh the known and potential risks in individuals 18 years of age and older.

For the January 7, 2022 authorization revising the authorized dosing interval of the homologous booster dose to at least 5 months after completion of the primary series with Moderna COVID-19 Vaccine (Original monovalent), the FDA reviewed: prepublications; accepted publications; published publications; and real world evidence on the safety of booster doses provided by the

Israeli Ministry of Health, which includes data from approximately 4.1 million third (booster) doses of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) given to individuals 16 years of age and older at least 5 months after the primary series with Pfizer-BioNTech COVID-19 Vaccine (Original monovalent), and which did not raise new safety concerns associated with the booster dose. Although the overall composition of the Moderna COVID-19 Vaccine (Original monovalent) is different than the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent), both are mRNA vaccines with safety and efficacy profiles that, though not identical, are relatively similar. Acknowledging the differences, it is reasonable to make the inference that the safety data on the 5 month interval for booster doses obtained in the population in Israel can apply to the Moderna COVID-19 Vaccine (Original monovalent). Based on the totality of the scientific evidence available, FDA concluded that a homologous booster dose of the Moderna COVID-19 Vaccine (Original monovalent) may be effective and that the known and potential benefits of the booster dose of the Moderna COVID-19 Vaccine (Original monovalent) following completion of primary vaccination with the Moderna COVID-19 Vaccine (Original monovalent) outweigh the known and potential risks in individuals 18 years of age and older when given at least 5 months following the primary series.

For the March 29, 2022 authorization of a second booster dose of the Moderna COVID-19 Vaccine (Original monovalent) for administration to individuals 50 years of age and older and to individuals 18 years of age or older with certain kinds of immunocompromise at least 4 months after receipt of a first booster dose of any FDA authorized or approved COVID-19 vaccine, the sponsor provided a publication of an ongoing, open label, non-randomized study conducted in healthcare workers at a single site in Israel. (*Gili Regev-Yochay, Tal Gonen, Mayan Gilboa, et al. 2022 DOI: 10.1056/NEJMc2202542*). In this study, 120 individuals 18 years of age and older who had received primary vaccination and a first booster dose with Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) were administered a second booster dose of Moderna COVID-19 Vaccine (Original monovalent) at least four months after the first booster dose. Among these individuals, approximately 7- to 16-fold increases in geometric mean neutralizing antibody titers against wild-type virus and Delta and Omicron variants, were reported at two weeks after the second booster as compared to 5 months after the first booster dose. No new safety concerns were reported during up to three weeks of follow up after the second booster dose. Based on the totality of the scientific evidence available, FDA concluded that a second booster dose of the Moderna COVID-19 Vaccine (Original monovalent) may be effective and that the known and potential benefits of a second booster dose of the Moderna COVID-19 Vaccine (Original monovalent) following receipt of a first booster dose of any FDA authorized or approved COVID-19 vaccine outweigh the known and potential risks in the authorized populations when given at least 4 months following the first booster dose.

For the March 29, 2022 authorization of the manufacturing change to include an additional presentation of the Moderna COVID-19 Vaccine (Original monovalent) containing 50 mcg mRNA per 0.5 mL dose in a multiple dose vial presentation (supplied in a vial with a dark blue cap and a label with a purple border), FDA reviewed data on analytical comparability, which uses laboratory testing to demonstrate that a change in product manufacturing is not expected to impact safety or effectiveness. For the additional Moderna COVID-19 Vaccine (Original monovalent) presentation, the results of multiple different tests to assess critical quality attributes

and safety were evaluated, including tests for appearance, lipid nanoparticle size, mRNA and lipid content and purity, sterility and endotoxin content. For this additional presentation, results of tests performed to assess critical safety and quality attributes and other characterization tests showed that the additional Moderna COVID-19 Vaccine (Original monovalent) presentation for use only for booster vaccination doses (supplied in a multiple dose vial with a dark blue cap and a label with a purple border) is expected to have the same safety and effectiveness as the currently authorized presentation (supplied in a multiple dose vial with a red cap and a label with a light blue border).

For the June 17, 2022 authorization of the Moderna COVID-19 Vaccine (Original monovalent) for individuals 6 months through 17 years of age, and the two new presentations of the Moderna COVID-19 Vaccine (Original monovalent), FDA reviewed safety and effectiveness data from two ongoing studies, Study 3 and Study 4. Study 3 is an ongoing Phase 2/3 trial that has enrolled 3,726 participants 12 through 17 years of age, of whom 2,486 participants received at least one dose of Moderna COVID-19 Vaccine (Original monovalent) (containing 100 mcg mRNA per dose) and 1,240 participants received saline placebo. Participants with a known history of SARS-CoV-2 infection were excluded from the study. FDA's review of the available safety data among 2,486 participants who received Moderna COVID-19 Vaccine (Original monovalent) and had a median follow-up duration of 53 days after the second dose for blinded, placebo-controlled follow-up and 312 days after the second dose including unblinded follow-up, did not identify specific safety concerns that would preclude issuance of an EUA. Effectiveness is based on a comparison of immune responses in this age group to adults 18 through 25 years of age. SARS-CoV-2 50% neutralizing antibody titers and seroresponse rates 28 days after the second dose were compared between a subset of participants 12 through 17 years of age from Study 3 and a subset of participants 18 through 25 years of age who received Moderna COVID-19 Vaccine (Original monovalent) (containing 100 mcg mRNA per dose) in the above-referenced Study 1. Participants included in these analyses had no immunologic or virologic evidence of prior SARS-CoV-2 at baseline. FDA's analyses confirm that immunobridging criteria were met for both geometric mean antibody titers and seroresponse rates. FDA's analysis of available descriptive efficacy data from 3,181 participants 12 through 17 years of age who had a negative baseline SARS-CoV-2 status confirm that the vaccine was 93.3% effective (95% confidence interval 47.9, 99.9) in preventing COVID-19 (defined as at least one symptom of COVID-19 and a positive SARS-CoV-2 test). The median length of follow up for efficacy for participants in the study was 53 days post Dose 2. Study 4 is an ongoing Phase 2/3 trial that has enrolled 4,002 participants 6 years through 11 years of age, of whom 3,007 participants received at least one dose of Moderna COVID-19 Vaccine (Original monovalent) (50 mcg mRNA per dose) and 995 participants received saline placebo. Participants with a known history of SARS-CoV-2 infection within 2 weeks of study vaccination were excluded from the study. FDA's review of the available safety data among 3,007 participants who received Moderna COVID-19 Vaccine (Original monovalent) and had a median follow-up duration of 51 days after the second dose for blinded, placebo-controlled follow-up and 158 days after the second dose including unblinded follow-up, did not identify specific safety concerns that would preclude issuance of an EUA. Effectiveness in individuals 6 years through 11 years of age is based on a comparison of immune responses in this age group to adults 18 through 25 years of age. SARS-CoV-2 50% neutralizing antibody titers and seroresponse rates 28 days after the second dose were compared between a

subset of participants 6 years through 11 years of age in this study to a subset of individuals 18 through 25 years of age who received Moderna COVID-19 Vaccine (Original monovalent) (containing 100 mcg mRNA) in Study 1. Participants included in these analyses had no immunologic or virologic evidence of prior SARS-CoV-2 at baseline. FDA's analyses confirm that immunobridging criteria were met for both geometric mean antibody titers and seroresponse rates. Safety and effectiveness of the Moderna COVID-19 Vaccine (Original monovalent) for individuals 6 months through 5 years of age were also evaluated in Study 4. In Study 4, 6,388 participants 6 months through 5 years of age were enrolled, of whom 4,792 received at least one dose of Moderna COVID-19 Vaccine (Original monovalent) (25 mcg mRNA per dose) and 1,596 received saline placebo. Among these participants, 4,038 participants (3,031 who received Moderna COVID-19 Vaccine (Original monovalent) and 1,007 who received placebo) were 2 through 5 years of age and 2,350 participants (1,761 who received Moderna COVID-19 Vaccine (Original monovalent) and 589 who received placebo) were 6 through 23 months of age. The median duration of blinded follow-up for safety was 71 days after Dose 2 for participants 2 through 5 years and 68 days after Dose 2 for participants 6 through 23 months of age. FDA's review of the available safety data among 4,038 participants 2 through 5 years of age and 2,350 participants 6 through 23 months of age did not identify specific safety concerns that would preclude issuance of an EUA. Effectiveness in individuals 6 months through 5 years of age is based on a comparison of immune responses in this age group to adults 18 through 25 years of age. SARS-CoV-2 neutralizing antibody concentrations and seroresponse rates 28 days after the second dose were compared between a subset of participants 2 through 5 years of age in Study 4 and a subset of participants 18 through 25 years of age in Study 1, and between a subset of participants 6 through 23 months in Study 4 and a subset of participants 18 through 25 years of age in Study 1. Participants included in these analyses had no immunologic or virologic evidence of prior SARS-CoV-2 infection at baseline. FDA's analyses confirm that for both age groups, 2 through 5 years and 6 through 23 months, immunobridging criteria were met for both geometric mean antibody concentrations and seroresponse rates. FDA's analysis of available descriptive efficacy data from 5,476 participants 6 months through 5 years of age show that the vaccine was 36.8% effective (95% confidence interval 12.5, 54.0) in preventing COVID-19 (defined as at least one symptom of COVID-19 and a positive SARS-CoV-2 test) in individuals 2 through 5 years of age and 50.6% effective (95% confidence interval 21.4, 68.6) in individuals 6 through 23 months of age. The median length of follow-up for efficacy post-Dose 2 was 71 days for participants 2 through 5 years of age and 68 days for participants 6 through 23 months of age. Based on these data, FDA concluded that it is reasonable to believe that Moderna COVID-19 Vaccine (Original monovalent) may be effective in individuals 6 months through 17 years of age. Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of Moderna COVID-19 Vaccine (Original monovalent) outweigh the known and potential risks of the vaccine for the prevention of COVID-19 in individuals 6 months through 17 years of age. On June 14, 2022, the Vaccines and Related Biological Products Advisory Committee voted in agreement with this conclusion for individuals 6 through 17 years. On June 15, 2022, the Vaccines and Related Biological Products Advisory Committee voted in agreement with this conclusion for individuals 6 months through 5 years of age.

For the June 17, 2022 authorization of a third primary series dose of Moderna COVID-19 Vaccine (Original monovalent) in individuals 6 months through 17 years of age who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise, safety in this population is extrapolated from the experience in children 6 months through 17 years of age who were vaccinated with a 2-dose primary series and the above mentioned safety data on a third primary series dose of the Moderna COVID-19 Vaccine (Original monovalent) in adult solid organ transplant recipients. Effectiveness in this population is extrapolated from available immunogenicity and efficacy data on a 2-dose primary series in individuals in this age group and adults and the above mentioned effectiveness data on a third primary series dose of the Moderna COVID-19 Vaccine (Original monovalent) in adult solid organ transplant recipients. Based on the totality of the scientific evidence available, FDA concluded that a third dose of the Moderna COVID-19 Vaccine (Original monovalent) may be effective and that the known and potential benefits of a third dose of the Moderna COVID-19 Vaccine (Original monovalent) outweigh the known and potential risks of the vaccine for immunocompromised individuals 6 months through 17 years of age who have received two doses of the Moderna COVID-19 Vaccine (Original monovalent) and who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

The August 31, 2022 authorization of a booster dose of the Moderna COVID-19 Vaccine, Bivalent, in individuals 18 years of age and older is based on: 1) safety and effectiveness data from clinical trials which evaluated primary and booster vaccination with Moderna COVID-19 Vaccine (Original monovalent); 2) postmarketing safety data with Moderna COVID-19 Vaccine (Original monovalent); and 3) safety and immunogenicity data from a clinical trial (Study 5) which evaluated a booster dose of Moderna's bivalent COVID-19 vaccine (Original and Omicron BA.1), not authorized or approved in the U.S., hereafter referred to as bivalent vaccine (Original and Omicron BA.1). FDA considered safety and effectiveness data previously reviewed by FDA in support of the December 18, 2020 and June 17, 2022 authorizations of primary vaccinations and the October 20, 2021, November 19, 2021, January 7, 2022, and March 29, 2022 authorizations of booster vaccinations in individuals 18 years and older with Moderna COVID-19 Vaccine (Original monovalent), as well as postmarketing safety data. Study 5 is a Phase 2/3 open-label study that evaluated the immunogenicity, safety, and reactogenicity of a booster dose of the bivalent vaccine (Original and Omicron BA.1) compared to a booster dose of Moderna COVID-19 Vaccine (Original monovalent) when administered as a second booster dose to participants 18 years of age and older who had previously received a primary series and a first booster dose with Moderna COVID-19 Vaccine (Original monovalent) at least 3 months prior. The safety analysis set included 437 participants in the bivalent vaccine (Original and Omicron BA.1) booster dose group and 377 participants in the Moderna COVID-19 Vaccine (Original monovalent) booster dose group. Following the booster dose through the cutoff date of April 27, 2022, the median follow-up time was 43 days among bivalent vaccine (Original and Omicron BA.1) recipients and 57 days among Moderna COVID-19 Vaccine (Original monovalent) recipients. FDA's review of the safety data accrued with the bivalent vaccine (Original and Omicron BA.1) together with the previously submitted safety data from clinical trials and postmarketing safety data with Moderna COVID-19 Vaccine (Original monovalent) did not identify specific safety concerns that would preclude issuance of an EUA. In Study 5,

primary immunogenicity analyses evaluated 50% inhibitory dose (ID50) neutralizing antibody geometric mean titers (GMTs) and seroresponse rates (the proportion achieving a ≥4-fold rise in ID50 from pre-dose 1 of the primary series) 28 days following a second booster dose with bivalent vaccine (Original and Omicron BA.1) relative to those following a second booster dose with Moderna COVID-19 Vaccine (Original monovalent). Primary analyses of GMTs met predefined success criteria for superiority against Omicron BA.1 and noninferiority against the Original strain. The primary analysis of seroresponse against Omicron BA.1 met the criterion for noninferiority. Post-hoc analyses evaluated seroresponse rates (the proportion achieving a ≥4-fold rise in ID50 from pre-second booster) against both the Original strain and Omicron BA.1. The lower limit of the 2-sided 97.5% CI for the percentage difference in seroresponse rate (bivalent vaccine [Original and Omicron BA.1] minus Moderna COVID-19 Vaccine (Original monovalent)) was 12.9 against Omicron BA.1 and 2.1 against the Original strain. Based on the totality of the scientific evidence available, including these data and previously submitted data on the effectiveness of primary and booster vaccination with Moderna COVID-19 Vaccine (Original monovalent) in individuals 18 years of age and older, FDA concluded that it is reasonable to believe that Moderna COVID-19 Vaccine, Bivalent may be effective as a booster dose in individuals 18 years of age and older when administered at least 2 months after completion of primary vaccination or receipt of the most recent booster dose with any FDA authorized or approved monovalent COVID-19 vaccine. Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of Moderna COVID-19 Vaccine, Bivalent outweigh the known and potential risks of the vaccine for the prevention of COVID-19 in individuals 18 years of age and older when administered at least 2 months after completion of primary vaccination or receipt of the most recent booster dose with any FDA authorized or approved monovalent COVID-19 vaccine. In addition, authorization of Moderna COVID-19 Vaccine, Bivalent was considered for the express purpose of improving protection conferred by COVID-19 vaccine booster doses against the currently circulating Omicron variant of SARS-CoV-2, resulting in a more favorable anticipated benefit/risk balance compared to Moderna COVID-19 Vaccine (Original monovalent). Consequently, revising this EUA to no longer provide for the use of the Moderna COVID-19 Vaccine (Original monovalent) as a booster dose was appropriate for the protection of public health.

The October 12, 2022 authorization of a booster dose of Moderna COVID-19 Vaccine, Bivalent in individuals 6 years through 17 years of age is based on the data that FDA relied on for the August 31, 2022 authorization of the Moderna COVID-19 Vaccine, Bivalent in individuals 18 years of age and older. In addition, FDA reviewed data regarding the use of Moderna COVID-19 Vaccine (Original monovalent) as a booster dose in individuals 6 years through 11 years of age and 12 through 17 years of age. Safety and effectiveness data for a booster dose of Moderna COVID-19 Vaccine (Original monovalent) in individuals 12 through 17 years of age were collected in Study 3, an ongoing Phase 2/3 clinical trial described above. The open-label booster portion of the study involved 1,364 participants 12 years through 17 years of age who received a booster dose of Moderna COVID-19 Vaccine (Original monovalent) at least 5 months after the second dose of the primary series. As of the data cutoff date, the median duration of follow-up for safety was 116 days after the booster dose. FDA's review of the safety data from the open-label booster portion of Study 3 did not identify specific safety concerns that would preclude

issuance of an EUA. Effectiveness of a booster dose of the Moderna COVID-19 Vaccine (Original monovalent) in participants 12 years through 17 years of age was based on a comparison of immune responses, as assessed by neutralizing antibody concentration against a pseudovirus expressing the SARS-CoV-2 Spike protein from a USA_WA1/2020 isolate carrying the D614G mutation, following the booster dose in this age group to that following the primary series in adults 18 through 25 years. The primary immunogenicity analysis population included 257 booster dose participants in Study 3 and a random subset of 295 participants 18 through 25 years from Study 1 (described above) who received two doses of Moderna COVID-19 Vaccine (Original monovalent) 1 month apart. Study 1 and 3 participants included in the analysis population had no serologic or virologic evidence of SARS-CoV-2 infection prior to the first primary series dose and prior to the booster dose, respectively. The primary immunogenicity analyses of the GMC ratio and difference in seroresponse rates following the booster dose in Study 3 compared to after the primary series in Study 1 met the pre-defined immunobridging success criteria. Seroresponse for a participant was defined as achieving a ≥4-fold rise of neutralizing antibody concentration from baseline (before the first dose of the primary series in Study 1 and Study 3). Safety and effectiveness data for a booster dose of Moderna COVID-19 Vaccine (Original monovalent) in individuals 6 years though 11 years of age were collected in Study 4, an ongoing Phase 2/3 clinical trial described above. The open-label booster portion of this study involved 1,294 participants 6 years through 11 years of age who received a booster dose of Moderna COVID-19 Vaccine (Original monovalent) at least 6 months after the second dose of the primary series. As of the data cutoff date, the median duration of follow-up for safety was 29 days after the booster dose. FDA's review of the safety data from the open-label booster portion of Study 4 did not identify specific safety concerns that would preclude issuance of an EUA. Effectiveness of a booster dose of the Moderna COVID-19 Vaccine (Original monovalent) in participants 6 years through 11 years of age was based on a comparison of immune responses, as assessed by neutralizing antibody concentration against a pseudovirus expressing the SARS-CoV-2 Spike protein from a USA_WA1/2020 isolate carrying the D614G mutation, following the booster dose in this age group to that following the primary series in adults 18 through 25 years. The primary immunogenicity analysis population included 95 booster dose participants in Study 4 and a random subset of 295 participants 18 through 25 years from Study 1 who received two doses of Moderna COVID-19 Vaccine (Original monovalent) 1 month apart. Study 1 and 4 participants included in the analysis population had no serologic or virologic evidence of SARS-CoV-2 infection prior to the first primary series dose and prior to the booster dose, respectively. The primary immunogenicity analyses of the GMC ratio and difference in seroresponse rates following the booster dose in Study 4 compared to following the primary series in Study 1 met the pre-defined immunobridging success criteria. Seroresponse for a participant was defined as achieving a ≥4-fold rise of neutralizing antibody concentration from baseline (before the first dose of the primary series in Study 4 and Study 1). Based on the totality of the scientific evidence available, FDA concluded that it is reasonable to believe that Moderna COVID-19 Vaccine, Bivalent may be effective as a booster dose in individuals 6 years through 17 years of age when administered at least 2 months after completion of primary vaccination or receipt of the most recent booster dose with any FDA authorized or approved monovalent COVID-19 vaccine. Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of Moderna COVID-19 Vaccine, Bivalent outweigh the known and potential risks of the vaccine for the prevention of

COVID-19 in individuals 6 years through 17 years of age when administered at least 2 months after completion of primary vaccination or receipt of the most recent booster dose with any FDA authorized or approved monovalent COVID-19 vaccine.

The December 8, 2022 authorization of a booster dose of Moderna COVID-19 Vaccine, Bivalent in individuals 6 months through 5 years of age is based on data that FDA relied on for the August 31, 2022 authorization of the Moderna COVID-19 Vaccine, Bivalent in individuals 18 years of age and older. In addition, FDA reviewed postmarketing safety data with Moderna COVID-19 Vaccine (Original monovalent) and Moderna COVID-19 Vaccine, Bivalent, and safety and immunogenicity data regarding the use of the Moderna COVID-19 Vaccine (Original monovalent) as a booster dose in individuals 17 months through 5 years of age collected in Study 4. Study 4 is an ongoing Phase 2/3 Study with multiple parts. The open-label booster portion of the study involved 145 participants 17 months through 5 years of age who received a booster dose of Moderna COVID-19 Vaccine (Original monovalent) (10 mcg mRNA) at least 6 months after the completion of the Moderna COVID-19 Vaccine (Original monovalent) two-dose primary series. As of the data cutoff date of August 18, 2022, the median duration of follow-up for safety after the booster dose was 99 days. The primary immunogenicity analysis population included 56 booster dose participants in Study 4 and a random subset of 295 participants 18 through 25 years from Study 1 who had completed primary vaccination with two doses of Moderna COVID-19 Vaccine (Original monovalent) (100 mcg mRNA per dose) 1 month apart. Study 1 and 4 participants included in the analysis population had no serologic or virologic evidence of SARS-CoV-2 infection prior to the first primary series dose and prior to the booster dose, respectively. The primary immunogenicity analyses of the GMC ratio and difference in seroresponse rates following the booster dose in Study 4 compared to following the primary series in Study 1 met the pre-defined immunobridging success criteria. Seroresponse for a participant was defined as achieving a ≥4-fold rise of neutralizing antibody concentration from baseline (before the first dose of the primary series in Study 4 and Study 1). In a descriptive analysis, the booster dose seroresponse rate among participants 17 months through 5 years of age with seroresponse defined as at least a 4-fold rise relative to the pre-booster concentration, was 94.6%. The difference in seroresponse rates (Study 4 participants minus Study 1 participants) in this post-hoc analysis was -4.7% (95% CI -14.0, -0.9). Based on the totality of the scientific evidence available, FDA concluded that it is reasonable to believe that Moderna COVID-19 Vaccine, Bivalent may be effective as a booster dose in individuals 6 months through 5 years of age when administered at least 2 months after completion of primary vaccination with Moderna COVID-19 Vaccine (Original monovalent). Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of Moderna COVID-19 Vaccine, Bivalent outweigh the known and potential risks of the vaccine for the prevention of COVID-19 in individuals 6 months through 5 years of age when administered at least 2 months after completion of primary vaccination with Moderna COVID-19 Vaccine (Original monovalent).

For the April 18, 2023 authorization, the effectiveness of Moderna COVID-19 Vaccine, Bivalent for individuals 6 months of age and older is based on previously reviewed data on 1) effectiveness of Moderna COVID-19 Vaccine (Original monovalent) and 2) immunogenicity of the bivalent vaccine (Original and Omicron BA.1). The effectiveness of a single dose of

Moderna COVID-19 Vaccine, Bivalent for most individuals 6 years of age and older is based on seroprevalence surveys that estimate that almost all of the U.S. population 5 years of age and older now have antibodies (from vaccination and/or infection) against SARS-CoV-2 (*Centers for Disease Control and Prevention. COVID Data Tracker. Atlanta, GA: US Department of Health and Human Services, CDC; 2023, March 31. https://covid.cdc.gov/covid-data-tracker*) and a comparison of neutralizing antibody titers against a pseudovirus expressing the original SARS-CoV-2 Spike protein (D614G) at baseline (pre-Dose 1), at 28 days after Dose 1 for participants with evidence of prior SARS-CoV-2 infection, and at 28 days after Dose 2 for participants without evidence of prior SARS-CoV-2 infection. These data are from Study 4 and Study 1 evaluating a primary series of Moderna COVID-19 Vaccine (Original monovalent) for the following age groups: 6 years through 11 years of age and 18 years of age and older, respectively. In both age groups, neutralizing antibody titers at 28 days post-Dose 1 in participants with evidence of prior infection were not statistically different from those of participants without evidence of prior infection at 28 days post-Dose 2. The safety of Moderna COVID-19 Vaccine, Bivalent in individuals 6 months of age and older is based on previously reviewed safety data from clinical studies which evaluated primary and booster vaccination with Moderna COVID-19 Vaccine (Original monovalent), and a booster dose of bivalent vaccine (Original and Omicron BA.1); and postmarketing safety data with Moderna COVID-19 Vaccine (Original monovalent) and Moderna COVID-19 Vaccine, Bivalent. FDA's review of the available safety data in individuals 6 months of age and older did not identify specific safety concerns that would preclude issuance of an EUA. Based on the totality of the scientific evidence available, FDA concluded that it is reasonable to believe that Moderna COVID-19 Vaccine, Bivalent may be effective in individuals 6 months of age and older for the prevention of COVID-19 when administered in accordance with the revised dosing regimen and schedule. Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of Moderna COVID-19 Vaccine, Bivalent when administered in accordance with the revised dosing regimen and schedule outweigh the known and potential risks of the vaccine for the prevention of COVID-19 in individuals 6 months of age and older. The revised dosing regimen and schedule are set forth in the Scope of Authorization (Section II). In addition, simplification of the vaccine composition (i.e., single vaccine composition for all doses) and schedule was considered for the express purpose of reducing complexity, decreasing vaccine administration errors due to the complexity of the number of different vial presentations, and potentially increasing vaccine uptake by allowing clearer communication. Revising the EUA to provide for a simplified vaccine composition and schedule in the United States, by no longer providing for the use of t Moderna COVID-19 Vaccine (Original monovalent) in the United States, is appropriate for the protection of the public health.

The September 11, 2023 authorization of Moderna COVID-19 Vaccine (2023-2024 Formula) for individuals 6 months through 11 years of age is based on: 1) the effectiveness of the Moderna COVID-19 Vaccine (Original monovalent) in individuals 6 months of age and older, 2) the immunogenicity of Moderna COVID-19 Vaccine (Original and Omicron BA.1) in individuals 18 years of age and older, and 3) safety data previously reviewed. FDA's review of previously submitted safety data with Moderna COVID-19 Vaccine (Original monovalent) and Moderna COVID-19 Vaccine (Original and Omicron BA.1) and postmarketing safety data with Moderna COVID-19 Vaccine (Original monovalent) and Moderna COVID-19 Vaccine, Bivalent did not

identify specific safety concerns that would preclude issuance of an EUA. The safety data accrued with the Moderna COVID-19 Vaccine (Original monovalent), bivalent vaccine (Original and Omicron BA.1) and Moderna COVID 19 Vaccine, Bivalent are relevant to Moderna COVID 19 Vaccine (2023-2024 Formula) because these vaccines are manufactured using the same process. Based on the totality of the scientific evidence available, FDA concluded that it is reasonable to believe that Moderna COVID-19 Vaccine (2023-2024 Formula) may be effective in individuals 6 months through 11 years of age for the prevention of COVID-19 when administered in accordance with the dosing regimen and schedule outlined in Section II. Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of the Moderna COVID-19 Vaccine (2023-2024 Formula) outweigh the known and potential risks of the vaccine for the prevention of COVID-19 in individuals 6 months through 11 years of age when administered according to the authorized dosing regimen and schedule.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of Moderna COVID-19 Vaccine (2023-2024 Formula), Moderna COVID-19 Vaccine, Bivalent and Moderna COVID-19 Vaccine (Original monovalent) for the prevention of COVID-19, as described in the Scope of Authorization section (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of Moderna COVID-19 Vaccine (2023-2024 Formula)[24] for the prevention of COVID-19 when administered as described in the Scope of Authorization (Section II) meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

A. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

B. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that Moderna COVID-19 Vaccine (2023-2024 Formula) may be effective in preventing COVID-19, and that, when used under the conditions described in this authorization, the known and potential benefits of Moderna COVID-19 Vaccine (2023-2024 Formula) when used to prevent COVID-19 outweigh its known and potential risks; and

[24] In this section (Section I), references to Moderna COVID-19 Vaccine (2023-2024 Formula) apply to Moderna COVID-19 Vaccine, Bivalent, and Moderna COVID-19 Vaccine (Original monovalent).

C. There is no adequate, approved, and available alternative[25] to the emergency use of Moderna COVID-19 Vaccine (2023-2024 Formula) to prevent COVID-19.[26]

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- ModernaTX, Inc. will supply Moderna COVID-19 Vaccine (2023-2024 Formula), Moderna COVID-19 Vaccine, Bivalent, and Moderna COVID-19 Vaccine (Original monovalent) either directly or through authorized distributor(s)[27] for use consistent with the terms and conditions of this EUA;
- Moderna COVID-19 Vaccine (2023-2024 Formula), Moderna COVID-19 Vaccine, Bivalent and Moderna COVID-19 Vaccine (Original monovalent) may be administered by a vaccination provider[28] without an individual prescription for each vaccine recipient; and
- The presentations of the Moderna COVID-19 Vaccine (2023-2024 Formula), Moderna COVID-19 Vaccine, Bivalent, and Moderna COVID-19 Vaccine (Original monovalent) covered by this authorization, as described in more detail under *Product Description*, will be administered by vaccination providers in accordance with the uses described in the Scope of Authorization (Section II).

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[25] There are no COVID-19 vaccines that are approved to provide additional doses to certain immunocompromised populations as described in this EUA or COVID-19 vaccination in individuals younger than 12 years of age. Although SPIKEVAX (COVID-19 Vaccine, mRNA) and Comirnaty (COVID-19 Vaccine, mRNA) are approved to prevent COVID-19 in certain individuals, available information indicates that availability of COVID-19 vaccines is needed for individuals who might not receive the approved vaccines.

[26] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

[27] "Authorized Distributor(s)" are identified by ModernaTX, Inc. as an entity or entities allowed to distribute authorized Moderna COVID-19 Vaccine (2023-2024 Formula), Moderna COVID-19 Vaccine, Bivalent or Moderna COVID-19 Vaccine (Original monovalent).

[28] For purposes of this letter, "vaccination provider" refers to the facility, organization, or healthcare provider (e.g., non-physician healthcare professionals, such as nurses, pharmacists) licensed or otherwise authorized to administer or provide vaccination services pursuant to State law. If the vaccine is exported from the United States, a "vaccination provider" is a provider that is authorized to administer this vaccine in accordance with the laws of the country in which it is administered. For purposes of this letter, "vaccination provider" also includes a person authorized by the U.S. Department of Health and Human Services (e.g., under the PREP Act Declaration for Medical Countermeasures against COVID-19) to administer FDA-authorized COVID-19 vaccine (e.g., qualified pharmacy technicians and State-authorized pharmacy interns acting under the supervision of a qualified pharmacist). See, e.g., HHS, *Eleventh Amendment to the Declaration Under the Public Readiness and Emergency Preparedness Act for Medical Countermeasures Against COVID-19 and Republication of the Declaration*. (88 FR 30769, May 12, 2023). In addition, for purposes of this letter, the term "State" includes any State or Territory of the United States, the District of Columbia, and the Commonwealth of Puerto Rico. See Section 201(a)(1) of the Act.

Table 1. Authorized Uses of Moderna COVID-19 Vaccine (2023-2024 Formula) for use in Individuals 6 Months Through 4 Years of Age

Number of Previous Doses with a Moderna COVID-19 Vaccine*	Dosing Regimen, Dose, and Schedule€
0^	2 doses¥, 0.25 mL each Dose 1: month 0 Dose 2: month 1
1	Single dose, 0.25 mL One month after receipt of a previous dose of Moderna COVID-19 vaccine*
≥ 2	Single dose, 0.25 mL ≥ 2 months after a previous dose of a Moderna COVID-19 vaccine*

* Previous doses of Moderna COVID-19 vaccine(s) refers to Moderna COVID-19 Vaccine (Original monovalent) and Moderna COVID-19 Vaccine, Bivalent. These vaccines are no longer authorized for use in the United States.
€ For individuals with certain kinds of immunocompromise previously vaccinated with a Moderna COVID-19 vaccine, see text following the tables for dosing information.
^ Not previously vaccinated with any COVID-19 vaccine
¥ Notwithstanding the age limitations for use of the vaccine, individuals turning from 4 years to 5 years of age during the vaccination series may receive both doses with Moderna COVID-19 Vaccine (2023-2024 Formula).

Table 2. Authorized Uses of the Moderna COVID-19 Vaccine (2023-2024 Formula) in Individuals 5 through 11 Years of Age Irrespective of Vaccination Status

Dosing Regimen, Dose and Schedule
Single dose, 0.25 mL If previously vaccinated, ≥ 2 months after receipt of the last previous dose of COVID-19 vaccine[a,b]

[a] For individuals with certain kinds of immunocompromise, see text below tables for dosing information.
[b] COVID-19 vaccine refers to the monovalent COVID-19 vaccines that encode the spike protein of the original SARS-CoV-2 and the bivalent COVID-19 vaccines encoding the spike protein of original SARS-CoV-2 and of the Omicron variant lineages BA.4 and BA.5 that are no longer authorized for use in the United States.

Individuals 6 Months through 11 Years of Age with Certain Kinds of Immunocompromise

The Moderna COVID-19 Vaccine (2023-2024 Formula) is authorized for use in individuals 6 months through 11 years of age with certain kinds of immunocompromise according to the following dosing regimen and schedule:

Complete at least a three-dose series with a COVID-19 vaccine, each dose one month apart,[29] in which at least 1 dose is with a COVID-19 vaccine (2023-2024 Formula).

- If previously not vaccinated, complete the three-dose series with Moderna COVID-19 Vaccine (2023-2024 Formula).
- If previously vaccinated with one or two dose(s) of Moderna COVID-19 Vaccine (Original monovalent) and/or the Moderna COVID-19 Vaccine, Bivalent, complete the remaining dose(s) in the three-dose series with Moderna COVID-19 Vaccine (2023-2024 Formula).
- If previously vaccinated with three or more doses, administer a single dose of Moderna COVID-19 Vaccine (2023-2024 Formula) at least two months following the last previous dose.[30,31]

An additional dose of Moderna COVID-19 Vaccine (2023-2024 Formula) may be administered at least 2 months following the last dose of a COVID-19 vaccine (2023-2024 Formula).[32,33] Additional doses of Moderna COVID-19 Vaccine (2023-2024 Formula) may be administered at the discretion of the healthcare provider, taking into consideration the individual's clinical circumstances. The timing of the additional doses may be based on the individual's clinical circumstances.

Moderna COVID-19 Vaccine (Original monovalent)

The Moderna COVID-19 Vaccine (Original monovalent) is no longer authorized for use in the United States. However, the authorized presentations of the Moderna COVID-19 Vaccine (Original monovalent) described in Section II of the December 8, 2022 reissuance of this Letter remain authorized when exported from the United States in accordance with Section III.X. Under Section III.X, the Fact Sheets for Moderna COVID-19 Vaccine (Original monovalent) that were authorized as of December 8, 2022 and that describe the scope of FDA's

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[29] COVID-19 vaccine, each dose of the three-doses series given one month apart, refers to Moderna COVID-19 vaccines. Individuals turning from 11 to 12 years of age during the vaccination series may complete the series with doses of Moderna COVID-19 Vaccine (2023-2024 Formula).

[30] For immunocompromised individuals 6 months through 4 years of age, the last previous dose refers to the last dose of Moderna COVID-19 Vaccine (Original monovalent) or Moderna COVID-19 Vaccine, Bivalent which are no longer authorized for use in the U.S.

[31] For immunocompromised individuals 5 years through 11 years of age, the last previous dose refers to the last dose of a COVID-19 vaccine (Original monovalent) or bivalent COVID-19 vaccine which are no longer authorized for use in the U.S.

[32] For immunocompromised individuals 6 months through 4 years of age, the last dose of a COVID-19 vaccine (2023-2024 Formula) refers to a dose with Moderna COVID-19 Vaccine (2023-2024 Formula).

[33] For immunocompromised individuals 5 years through 11 years of age, the last dose of a COVID-19 vaccine (2023-2024 Formula) refers to a dose with Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) or Moderna COVID-19 Vaccine (2023-2024 Formula).

December 8, 2022 authorization must, upon request, be made available to the regulatory authorities of the country in which the vaccine will be used.

Moderna COVID-19 Vaccine, Bivalent

The Moderna COVID-19 Vaccine, Bivalent is no longer authorized for use in the United States. However, the authorized presentations of the Moderna COVID-19 Vaccine, Bivalent described in Section II of the April 18, 2023 reissuance of this Letter remain authorized when exported from the United States in accordance with Section III.X. Under Section III.X, the Fact Sheets for Moderna COVID-19 Vaccine, Bivalent that were authorized as of April 18, 2023 and that describe the scope of FDA's April 18, 2023 authorization must, upon request, be made available to the regulatory authorities of the country in which the vaccine will be used.

Product Description

The Moderna COVID-19 Vaccine (2023-2024 Formula) is provided in single dose vials:

Single dose vials with dark blue caps and labels with a green box

Each 0.25 mL dose of Moderna COVID-19 Vaccine (2023-2024 Formula) supplied in a single-dose vial with a dark blue cap and a label with a green box contains 25 mcg mRNA encoding the pre-fusion stabilized S protein of the SARS-CoV-2 Omicron variant lineage XBB.1.5. Each dose also contains the following ingredients: a total lipid content of 0.5 mg (SM-102, polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), 0.13 mg tromethamine, 0.62 mg tromethamine hydrochloride, 0.011 mg acetic acid, 0.049 mg sodium acetate trihydrate, and 21.8 mg sucrose. The Moderna COVID-19 Vaccine (2023-2024 Formula) does not contain a preservative.

The manufacture of the authorized Moderna COVID-19 Vaccine (2023-2024 Formula), is limited to those facilities identified and agreed upon in the ModernaTX, Inc. request for authorization.

For Moderna COVID-19 Vaccine (Original monovalent), Section III.X refers to the Fact Sheets for the Moderna COVID-19 Vaccine (Original monovalent) that were authorized under the December 8, 2022 reissuance of this Letter. Those Fact Sheets describe different presentations of the vaccine that were authorized for use in the United States as of that date and that remain authorized for export in accordance with Section III.

For Moderna COVID-19 Vaccine, Bivalent Section III.X refers to the Fact Sheets for the Moderna COVID-19 Vaccine, Bivalent that were authorized under the April 18, 2023 reissuance of this Letter. Those Fact Sheets describe different presentations of the vaccine that were authorized for use in the United States as of that date and that remain authorized for export in accordance with Section III.

The Moderna COVID-19 Vaccine (2023-2024 Formula), Moderna COVID-19 Vaccine, Bivalent and Moderna COVID-19 Vaccine (Original monovalent) vial labels and carton labels are clearly marked for "Emergency Use Authorization." The Moderna COVID-19 Vaccine (2023-2024 Formula), Moderna COVID-19 Vaccine, Bivalent, and Moderna COVID-19 Vaccine (Original monovalent) are authorized to be distributed, stored, further redistributed, and administered when packaged in the authorized manufacturer packaging (i.e., vials and cartons), despite the fact that the vial and carton labels may not contain information that otherwise would be required under the FD&C Act.

The Moderna COVID-19 Vaccine (2023-2024 Formula) is authorized for emergency use with the following product-specific information required to be made available to vaccination providers and recipients, respectively (referred to as "authorized labeling"):

> Fact Sheet for Healthcare Providers Administering Vaccine: Emergency Use Authorization of the Moderna COVID-19 Vaccine (2023-2024 Formula) For Individuals 6 Months Through 11 Years of Age
>
> Fact Sheet for Recipients and Caregivers About the Moderna COVID-19 Vaccine (2023-2024 Formula) Which Has Emergency Use Authorization (EUA) to Prevent Coronavirus Disease 2019 (COVID-19) in Individuals 6 Months Through 11 Years of Age

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of Moderna COVID-19 Vaccine (2023-2024 Formula) Moderna COVID-19 Vaccine, Bivalent, and Moderna COVID-19 Vaccine (Original monovalent) when used to prevent COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh their known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that Moderna COVID-19 Vaccine (2023-2024 Formula), Moderna COVID-19 Vaccine, Bivalent, and Moderna COVID-19 Vaccine (Original monovalent) may be effective in preventing COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that Moderna COVID-19 Vaccine (2023-2024 Formula), Moderna COVID-19 Vaccine, Bivalent and the Moderna COVID-19 Vaccine (Original monovalent) (as described in this Scope of Authorization (Section II)) meet the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of Moderna COVID-19 Vaccine (2023-2024 Formula), Moderna COVID-19 Vaccine, Bivalent and Moderna COVID-19 Vaccine (Original monovalent) under this EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), Moderna COVID-19 Vaccine (2023-2024 Formula), Moderna COVID-19 Vaccine, Bivalent, and Moderna COVID-19 Vaccine (Original monovalent) are authorized to prevent COVID-19 as described in the Scope of Authorization (Section II) under this EUA, despite the fact that they do not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

ModernaTX, Inc. and Authorized Distributor(s)

A. ModernaTX, Inc. and authorized distributor(s) will ensure that for Moderna COVID-19 Vaccine (2023-2024 Formula), the authorized labeling (i.e., Fact Sheets) will be made available to vaccination providers, recipients, and caregivers consistent with the terms of this letter.

B. ModernaTX, Inc. and authorized distributor(s) will ensure that appropriate storage and cold chain is maintained until delivered to healthcare facilities or other vaccine receipt sites.

C. ModernaTX, Inc. will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., authorized distributors and vaccination providers) involved in distributing or receiving authorized Moderna COVID-19 Vaccine (2023-2024 Formula). ModernaTX, Inc. will provide to all relevant stakeholders a copy of this letter of authorization and communicate any subsequent amendments that might be made to this letter of authorization and its authorized labeling.

D. ModernaTX, Inc. may develop and disseminate instructional and educational materials (e.g., video regarding vaccine handling, storage/cold-chain management, preparation, disposal) that are consistent with the authorized emergency use of the Moderna COVID-19 Vaccine (2023-2024 Formula) as described in the letter of authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs during an emergency. Any instructional and educational materials that are inconsistent with the authorized labeling are prohibited.

E. ModernaTX, Inc. may request changes to this authorization, including to the authorized Fact Sheets. Any request for changes to this EUA must be submitted to

Office of Vaccines Research and Review (OVRR)/Center for Biologics Evaluation and Research (CBER). Such changes require appropriate authorization prior to implementation.[34]

F. ModernaTX, Inc. will report to Vaccine Adverse Event Reporting System (VAERS):
   - Serious adverse events (irrespective of attribution to vaccination);
   - Cases of myocarditis;
   - Cases of pericarditis;
   - Cases of Multisystem Inflammatory Syndrome; and
   - Cases of COVID-19 that result in hospitalization or death, that are reported to ModernaTX, Inc.

   These reports should be submitted to VAERS as soon as possible but no later than 15 calendar days from initial receipt of the information by ModernaTX, Inc.

G. ModernaTX, Inc. must submit to Investigational New Drug application (IND) number 19745 periodic safety reports monthly, or at another appropriate reporting interval determined by the Office of Biostatistics and Pharmacovigilance (OBPV)/CBER, in accordance with a due date agreed upon with OBPV/CBER beginning after the first full calendar month after authorization. Each periodic safety report is required to contain descriptive information which includes:
   - A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest;
   - A narrative summary and analysis of vaccine administration errors, whether or not associated with an adverse event, that were identified since the last reporting interval;
   - Newly identified safety concerns in the interval;
   - Actions taken since the last report because of adverse experiences (for example, changes made to Healthcare Providers Administering Vaccine (Vaccination Providers) Fact Sheet, changes made to studies or studies initiated); and

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[34] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study. All changes to the authorization require review and concurrence from OVRR. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), or (7), review and concurrence is required from the Preparedness and Response Team (PREP)/Office of the Center Director (OD)/CBER and the Office of Counterterrorism and Emerging Threats (OCET)/Office of the Chief Scientist (OCS).

- Cumulative doses distributed, and doses distributed during the reporting interval, for Moderna COVID-19 Vaccine (2023-2024 Formula).

H. No changes will be implemented to the description of the product, manufacturing process, facilities, or equipment without notification to and concurrence by FDA.

I. All manufacturing facilities will comply with Current Good Manufacturing Practice requirements.

J. ModernaTX, Inc. will submit to the EUA file Certificates of Analysis (CoA) for each drug product lot at least 48 hours prior to vaccine distribution. The CoA will include the established specifications and specific results for each quality control test performed on the final drug product lot.

K. ModernaTX, Inc. will submit to the EUA file quarterly manufacturing reports, starting in July 2021, that include a listing of all Drug Substance and Drug Product lots produced after issuance of this authorization. This report must include lot number, manufacturing site, date of manufacture, and lot disposition, including those lots that were quarantined for investigation or those lots that were rejected. Information on the reasons for lot quarantine or rejection must be included in the report.

L. ModernaTX, Inc. and authorized distributor(s) will maintain records regarding release of Moderna COVID-19 Vaccine (2023-2024 Formula), Moderna COVID-19 Vaccine, Bivalent, and Moderna COVID-19 Vaccine (Original monovalent) for distribution (i.e., lot numbers, quantity, release date).

M. ModernaTX, Inc. and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

N. ModernaTX, Inc. will conduct post-authorization observational studies to evaluate the association between Moderna COVID-19 Vaccine (Original monovalent), Moderna COVID-19 Vaccine, Bivalent, and Moderna COVID-19 Vaccine (2023-2024 Formula), and a pre-specified list of adverse events of special interest, including myocarditis and pericarditis, along with deaths and hospitalizations, and severe COVID-19. The study population should include individuals administered the Moderna COVID-19 Vaccine (Original monovalent) (previously, but no longer authorized for use in the U.S.) as a primary series (6 months of age and older) or booster dose (18 years of age and older); individuals administered a dose of the Moderna COVID-19 Vaccine, Bivalent (previously, but no longer authorized for use in the U.S.) (6 months of age and older), and Moderna COVID-19 Vaccine (2023-2024 Formula) (6 months through 11 years of age) under this EUA in the general U.S. population, and populations of interest such as healthcare workers, pregnant women, immunocompromised individuals, subpopulations with specific comorbidities. The studies should be conducted in large scale databases with an

active comparator. ModernaTX, Inc. will provide protocols and status update reports to the IND 19745 with agreed-upon study designs and milestone dates.

O. ModernaTX, Inc., working with its contract research organization, will continue to monitor the performance of its clinical investigators in ongoing clinical studies of its vaccines and will report to FDA promptly any significant deviations from the protocols.

Vaccination Providers

P. Vaccination providers will administer the vaccines in accordance with this authorization.

Q. Vaccination providers will provide the Fact Sheet for Recipients and Caregivers to each individual receiving vaccination and provide the necessary information for receiving their dose(s).

R. Vaccination providers administering the vaccines must report the following information associated with the administration of the vaccines of which they become aware to VAERS in accordance with the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers):
   - Vaccine administration errors whether or not associated with an adverse event
   - Serious adverse events (irrespective of attribution to vaccination)
   - Cases of myocarditis
   - Cases of pericarditis
   - Cases of Multisystem Inflammatory Syndrome
   - Cases of COVID-19 that result in hospitalization or death

   Complete and submit reports to VAERS online at https://vaers.hhs.gov/reportevent.html. The VAERS reports should include the words "Moderna COVID-19 Vaccine (Original monovalent) EUA" or "Moderna COVID-19 Vaccine, Bivalent EUA," or "Moderna COVID-19 Vaccine (2023-2024 Formula) EUA," as appropriate, in the description section of the report. More information is available at vaers.hhs.gov or by calling 1-800-822-7967. To the extent feasible, report to ModernaTX, Inc., by contacting 1-866-663-3762, by providing a copy of the VAERS form to ModernaTX, Inc., Fax: 1-866-599-1342 or by email; ModernaPV@modernatx.com.

S. Vaccination providers will conduct any follow-up requested by the U.S. government, including CDC, FDA, or other designee, regarding adverse events to the extent feasible given the emergency circumstances.

T. Vaccination providers will ensure that any records associated with this EUA are

maintained until notified by FDA. Such records will be made available to CDC and FDA for inspection upon request.

U. Vaccination providers receiving authorized Moderna COVID-19 Vaccine (2023-2024 Formula) will ensure that appropriate storage and cold chain is maintained.

Conditions Related to Printed Matter, Advertising, and Promotion

V. All descriptive printed matter, advertising, and promotional material relating to the use of the Moderna COVID-19 Vaccine (2023-2024 Formula) shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in Section 502(a) and (n), as applicable, of the FD&C Act and FDA implementing regulations. In addition, such materials shall:
   - Be tailored to the intended audience.
   - Present the same risk information relating to the major side effects and contraindications concurrently in the audio and visual parts of the presentation for advertising and promotional materials in audio-visual format.
   - Be accompanied by the authorized labeling, if the promotional materials are not subject to Section 502(n) of the Act.

   ModernaTX, Inc. must submit such materials to FDA accompanied by Form FDA-2253 by the time of initial dissemination or first use.

W. All descriptive printed matter, advertising, and promotional material relating to the use of the Moderna COVID-19 Vaccine (2023-2024 Formula) clearly and conspicuously shall state that:
   - The Moderna COVID-19 Vaccine (2023-2024 Formula) has not been approved or licensed by FDA, but has been authorized for emergency use by FDA, under an EUA to prevent Coronavirus Disease 2019 (COVID-19) for use in individuals 6 months through 11 years of age; and
   - The emergency use of this product is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of the medical product under Section 564(b)(1) of the FD&C Act unless the declaration is terminated or authorization revoked sooner.

   If the Agency notifies ModernaTX , Inc. that any descriptive printed matter, advertising, or promotional materials do not meet the terms set forth in Conditions V and W of this EUA, ModernaTX, Inc. must cease distribution of such descriptive printed matter, advertising, or promotional materials in accordance with the Agency's notification. Furthermore, as part of its notification, the Agency may also require ModernaTX, Inc. to issue corrective communication(s).

Condition Related to Export

X. If the Moderna COVID-19 Vaccine (2023-2024 Formula), is exported from the United States, conditions C, D, and P through W do not apply, but export is permitted only if 1) the regulatory authorities of the country in which the vaccine will be used are fully informed that this vaccine is subject to an EUA and is not approved or licensed by FDA and 2) the intended use of the vaccine will comply in all respects with the laws of the country in which the product will be used. The requirement in this letter that the authorized labeling (i.e., Fact Sheets) be made available to vaccination providers, recipients, and caregivers in condition A will not apply if the authorized labeling (i.e., Fact Sheets) are made available to the regulatory authorities of the country in which the vaccine will be used.

If the Moderna COVID-19 Vaccine (Original monovalent) is exported from the United States, conditions C, D, and P through W do not apply, but export is permitted only if 1) the vaccine was manufactured on or before April 18, 2023, 2) the regulatory authorities of the country in which the vaccine will be used are fully informed that this vaccine is subject to an EUA and is not approved or licensed by FDA, 3) the intended use of the vaccine will comply in all respects with the laws of the country in which the product will be used, 4) the Fact Sheets that were authorized as of December 8, 2022 for the vial presentation being exported are made available, upon request, to the regulatory authorities of the countries in which the vaccine will be used, and 5) the regulatory authorities are informed that the Moderna COVID-19 Vaccine (Original monovalent) and associated Fact Sheets are no longer authorized for use in the United States and that FDA is not currently revising the Fact Sheets with updated information.

If the Moderna COVID-19 Vaccine, Bivalent is exported from the United States, conditions C, D, and P through W do not apply, but export is permitted only if 1) the vaccine was manufactured on or before September 11, 2023, 2) the regulatory authorities of the country in which the vaccine will be used are fully informed that this vaccine is subject to an EUA and is not approved or licensed by FDA, 3) the intended use of the vaccine will comply in all respects with the laws of the country in which the product will be used, 4) the Fact Sheets that were authorized as of April 18, 2023 for the vial presentation being exported are made available, upon request, to the regulatory authorities of the countries in which the vaccine will be used, and 5) the regulatory authorities are informed that the Moderna COVID-19 Vaccine, Bivalent and associated Fact Sheets are no longer authorized for use in the United States and that FDA is not currently revising the Fact Sheets with updated information.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

_____

Peter Marks, M.D., Ph.D.
Director
Center for Biologics Evaluation and Research

U.S. FOOD & DRUG ADMINISTRATION

May 11, 2023

Novavax, Inc.
Attention: Ms. Kathleen Callahan
21 Firstfield Rd
Gaithersburg, MD 20878

Dear Ms. Callahan:

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act or the Act), the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes Coronavirus Disease 2019 (COVID-19).[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[2]

On July 13, 2022, the Food and Drug Administration (FDA or the Agency) issued an Emergency Use Authorization (EUA) for emergency use of the Novavax COVID-19 Vaccine, Adjuvanted for the prevention of COVID-19 for individuals 18 years of age and older pursuant to Section 564 of the Act. FDA reissued the letter of authorization on August 19, 2022,[3] September 12, 2022,[4] and October 19, 2022.[5]

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[1] U.S. Department of Health and Human Services, Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3. February 4, 2020.

[2] U.S. Department of Health and Human Services, Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3, 85 FR 18250 (April 1, 2020).

[3] In the August 19, 2022 revision, FDA authorized the use of Novavax COVID-19 Vaccine, Adjuvanted for individuals 12 through 17 years of age.

[4] In the September 12, 2022 revision, FDA revised the conditions of authorization related to Vaccine Adverse Event Reporting System (VAERS) reporting requirements for vaccination providers and Novavax, Inc. to include myocarditis and pericarditis. Because some cases of myocarditis or pericarditis following vaccine administration may not meet the definition of serious adverse events, this helps to ensure that cases are reported by Novavax, Inc. and vaccination providers.

[5] In the October 19, 2022 revision, FDA authorized the use of Novavax COVID-19 Vaccine, Adjuvanted as a first booster dose (0.5 mL) to the following individuals at least at least at 6 months after completion of primary vaccination with an authorized or approved COVID-19 vaccine:1) individuals 18 years of age and older for whom an FDA authorized mRNA bivalant COVID-19 booster vaccine is not accessible or clinically appropriate, and 2) individuals 18 years of age and older who elect to receive the Novavax COVID-19 Vaccine, Adjuvanted because they would otherwise not receive a booster dose of a COVID-19 vaccine. FDA also revised the Fact Sheets for Novavax COVID-19 Vaccine, Adjuvanted to reflect these changes.(For the purposes of this letter, bivalent refers to any authorized COVID-19 vaccine that encodes the spike protein of the Original SARS-CoV-2 and the Omicron BA.4/BA.5 SARS-CoV-2. FDA-authorized mRNA bivalent COVID-19 vaccines are: Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).)

On May 11, 2023, having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the October 19, 2022 letter of authorization in its entirety with revisions to Condition G to require the inclusion of distribution data for Novavax COVID-19 Vaccine, Adjuvanted in the monthly periodic safety reports.

In addition, the product description set forth in the Scope of Authorization (Section II) was revised to reflect the previous authorization of multiple dose vials of the Novavax COVID-19 Vaccine, Adjuvanted that contain 5 doses of 0.5 mL each, as well as multiple dose vials of the Novavax COVID-19 Vaccine, Adjuvanted that contain 10 doses of 0.5 mL each.

For the July 13, 2022 authorization for individuals 18 years of age and older, FDA reviewed safety and efficacy data from an ongoing phase 3 trial (Study 1) in which participants 18 years of age and older were randomized 2:1 to receive two doses of Novavax COVID-19 Vaccine, Adjuvanted or placebo, 3 weeks apart. This study includes pre-crossover and post-crossover periods. In the pre-crossover period, 19,735 participants received Novavax COVID-19 Vaccine, Adjuvanted and 9,847 received saline placebo. In the post-crossover period, 6,416 participants received Novavax COVID-19 Vaccine, Adjuvanted and 15,298 received saline placebo. Of participants who received two doses of Novavax COVID-19 Vaccine, Adjuvanted in the pre-crossover period (n=19,111), 78% had a follow-up duration of at least 2 months (median = 2.5 months) after Dose 2. Of the participants who received two doses of Novavax COVID-19 Vaccine, Adjuvanted in the post-crossover period (n= 6,346), 99% had a follow-up duration of at least 2 months (median = 4.4 months) after the last dose. FDA's review considered the safety and effectiveness data as they relate to the request for emergency use authorization, and did not identify specific safety concerns that would preclude issuance of an EUA. FDA's analysis of the efficacy data from 25,657 participants 18 years of age and older who did not have evidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection through 6 days after the second dose and who had a median follow-up of 2.5 months after Dose 2 during the pre-crossover period shows that the vaccine was 90.4% effective (95% confidence interval (CI): 83.8%, 94.3%) in preventing PCR-confirmed symptomatic mild, moderate, or severe COVID-19 occurring at least 7 days after Dose 2. Based on these data, and the review of manufacturing information regarding product quality and consistency, FDA concluded that it is reasonable to believe that the Novavax COVID-19 Vaccine, Adjuvanted may be effective. Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of the Novavax COVID-19 Vaccine, Adjuvanted outweigh its known and potential risks for the prevention of COVID-19 in individuals 18 years of age and older. Finally, on June 7, 2022, the Vaccines and Related Biological Products Advisory Committee voted in agreement with this conclusion.

For the August 19, 2022 authorization for individuals 12 years through 17 years of age, FDA reviewed safety and effectiveness data from the adolescent primary series expansion of Study 1, an ongoing phase 3 trial described above. In the primary series expansion, 2,232 individuals 12 to 17 years of age received at least one dose of the Novavax COVID-19 Vaccine, Adjuvanted (n=1,487) or saline placebo (n=745). Of participants who received two doses of the Novavax COVID-19 Vaccine, Adjuvanted in the pre-crossover period (n=1,468), 86% had a follow-up duration of at least 2 months (median = 71 days) after Dose 2. Of participants who received two

doses of the Novavax COVID-19 Vaccine, Adjuvanted in the post-crossover period (n=638), 43% had a follow-up duration of at least 1 month (median = 30 days) after the last dose. FDA's review considered the safety and effectiveness data as they relate to the request for EUA and did not identify specific safety concerns that would preclude issuance of an EUA. Effectiveness in adolescents 12 years through 17 years of age is based on a comparison of SARS-CoV-2 neutralizing antibody titers 14 days after dose 2 in a subset of individuals in that age group to SARS-CoV-2 neutralizing antibody titers 14 days after dose 2 in a subset of adults 18 years through 25 years of age from the main adult study. Noninferior immune responses in the subset of adolescents compared to the subset of adults, as assessed by geometric mean titers and seroconversion rates were demonstrated. FDA's analysis of available descriptive efficacy data from 1,799 participants 12 years through 17 years of age without evidence of SARS-CoV-2 infection through 6 days after the second dose and who had a median follow-up of 67 days after Dose 2 during the pre-crossover period shows that the vaccine was 78.29% effective (95% confidence interval 37.55, 92.45) in preventing PCR-confirmed symptomatic mild, moderate, or severe COVID-19 occurring at least 7 days after Dose 2. In this analysis, no cases of moderate or severe COVID-19 were reported in participants who had received the Novavax COVID-19 Vaccine, Adjuvanted or placebo. Based on these data, FDA concluded that it is reasonable to believe that the Novavax COVID-19 Vaccine, Adjuvanted may be effective in individuals 12 through 17 years of age. Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of the Novavax COVID-19 Vaccine, Adjuvanted outweigh its known and potential risks for the prevention of COVID-19 in individuals 12 through 17 years of age.

For the October 19, 2022 authorization of a first booster dose at least 6 months after completion of primary vaccination with an authorized or approved COVID-19 vaccine, in individuals 18 years of age and older for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate, and individuals 18 years of age and older who elect to receive the Novavax COVID-19 Vaccine, Adjuvanted because they would otherwise not receive a booster dose of a COVID-19 vaccine, FDA relied on 1) safety and immunogenicity data from an open-label booster vaccination portion of Study 1 (described above), and 2) safety and immunogenicity data reported from an independent Phase 2 study conducted in the United Kingdom (UK). In the open-label booster vaccination portion of Study 1, 12,738 participants 18 years of age and older received a single booster dose of Novavax COVID-19 Vaccine, Adjuvanted (0.5 mL) at least 6 months after the two-dose primary series (median of 11.0 months between completion of primary series and booster dose). Safety analyses included evaluation of solicited local and systemic adverse reactions within 7 days after a booster dose (n=238) and nonserious unsolicited adverse events within 28 days after a booster dose (n=298). Safety analysis also included evaluation of serious adverse events and adverse events of interest after a booster dose (n=12,738) with a median follow-up of 121 days post booster dose through data extraction of August 18, 2022. In the independent Phase 2 study conducted in the UK, 114 participants aged 30 years and older with no history of laboratory-confirmed SARS-CoV-2 infection received Novavax COVID-19 Vaccine, Adjuvanted administered at least 84 days (median 105 days) after completion of the Pfizer-BioNTech COVID-19 Vaccine primary series. FDA's review of the currently available safety data did not identify specific safety concerns that would preclude issuance of an EUA. Effectiveness of a booster dose of the Novavax COVID-19 Vaccine, Adjuvanted following a Novavax COVID-19 Vaccine, Adjuvanted primary series was

based on assessment of neutralizing antibody titers (MN_{50}) against the original SARS-CoV-2 strain. Immunogenicity analyses compared the MN_{50} titers following the booster dose to the MN_{50} titers following the primary series. In the open-label booster phase of Study 1, participants 18 years of age and older received a single booster dose of the Novavax COVID-19 Vaccine, Adjuvanted at least 6 months after completion of the primary series. A subset of 243 participants were included in the per-protocol immunogenicity analysis set, and did not have serologic or virologic evidence (if available) of SARS-CoV-2 infection up to 28 days post booster dose. Prespecified immunogenicity non-inferiority analyses included an assessment of MN_{50} geometric mean titer (GMT) ratio and difference in seroconversion rates. Seroconversion for a participant was defined as achieving a 4-fold rise in MN_{50} from baseline (before the booster dose and before the first dose of the primary series). The analysis of the GMT ratio of MN_{50} following the booster dose compared to the primary series met the non-inferiority criteria for a booster response and point estimate. The lower limit of the two-sided 95% CI for the difference in seroconversion rates did not meet the non-inferiority criteria for a booster response. Effectiveness of a Novavax COVID-19 Vaccine, Adjuvanted booster dose in individuals who completed primary vaccination with another authorized or approved COVID-19 vaccine is inferred from immunogenicity data reported from an independent study conducted in the United Kingdom. This multicenter, randomized, controlled Phase 2 trial investigated the immunogenicity of a single booster dose of Novavax COVID-19 Vaccine, Adjuvanted in participants who had received two doses of the Pfizer-BioNTech COVID-19 Vaccine as a primary vaccination series. Participants included adults aged 30 years and older with no history of laboratory-confirmed SARS-CoV-2 infection. The Novavax COVID-19 Vaccine, Adjuvanted was administered at least 84 days after completion of a Pfizer-BioNTech COVID-19 Vaccine primary series in 114 participants. Neutralizing antibody titers measured by a microneutralization assay were assessed prior to the booster dose and 28 days post-booster dose. A booster response to the Novavax COVID-19 Vaccine, Adjuvanted was demonstrated. Bivalent mRNA COVID-19 vaccines were authorized to improve protection conferred by COVID-19 vaccine booster doses against the currently circulating Omicron variant of SARS-CoV-2, resulting in a more favorable anticipated benefit/risk balance compared to each of the respective monovalent mRNA COVID-19 vaccines. The Novavax COVID-19 Vaccine, Adjuvanted, a vaccine based on a non-mRNA platform, could provide an alternative for a first booster dose in individuals 18 years of age and older for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate, and individuals 18 years of age and older who elect to receive the Novavax COVID-19 Vaccine, Adjuvanted because they would otherwise not receive a booster dose of a COVID-19 vaccine. Based on the totality of scientific evidence available, FDA concluded that it is reasonable to believe that the Novavax COVID-19 Vaccine, Adjuvanted may be effective as a first booster dose in such individuals. Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of the Novavax COVID-19 Vaccine, Adjuvanted outweigh its known and potential risks as a first booster dose for the prevention of COVID-19 in such individuals.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of the Novavax COVID-19 Vaccine, Adjuvanted for the prevention of COVID-19 as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of the Novavax COVID-19 Vaccine, Adjuvanted, for the prevention of COVID-19 when administered as described in the Scope of Authorization (Section II) meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

A. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

B. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that the Novavax COVID-19 Vaccine, Adjuvanted may be effective in preventing COVID-19, and that, when used under the conditions described in this authorization, the known and potential benefits of the Novavax COVID-19 Vaccine, Adjuvanted when used to prevent COVID-19 outweigh its known and potential risks; and

C. There is no adequate, approved, and available alternative[6] to the emergency use of the Novavax COVID-19 Vaccine, Adjuvanted to prevent COVID-19.[7]

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Novavax, Inc. will supply the Novavax COVID-19 Vaccine, Adjuvanted either directly or through authorized distributor(s)[8] to emergency response stakeholders[9] as directed by the U.S. government, including the Centers for Disease Control and Prevention (CDC) and/or other designee, for use consistent with the terms and conditions of this EUA;

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[6] Although Spikevax (COVID-19 Vaccine, mRNA) and Comirnaty (COVID-19 Vaccine, mRNA) are approved to prevent COVID-19 in certain individuals within the scope of the Novavax COVID-19 Vaccine, Adjuvanted authorization, there are not sufficient quantities of approved vaccine available for distribution to this population in its entirety at the time of reissuance of this EUA. In addition, this vaccine may be an alternative for individuals for whom the approved mRNA COVID-19 vaccines are contraindicated.

[7] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

[8] "Authorized Distributor(s)" are identified by Novavax, Inc. or, if applicable, by a U.S. government entity, such as the Centers for Disease Control and Prevention (CDC) and/or other designee, as an entity or entities allowed to distribute authorized Novavax COVID-19 Vaccine, Adjuvanted.

[9] For purposes of this letter, "emergency response stakeholder" refers to a public health agency and its delegates that have legal responsibility and authority for responding to an incident, based on political or geographical boundary lines (e.g., city, county, tribal, territorial, State, or Federal), or functional (e.g., law enforcement or public health range) or sphere of authority to administer, deliver, or distribute vaccine in an emergency situation. In some cases (e.g., depending on a state or local jurisdiction's COVID-19 vaccination response organization and plans), there might be overlapping roles and responsibilities among "emergency response stakeholders" and "vaccination providers" (e.g., if a local health department is administering COVID-19 vaccines; if a pharmacy is acting in an official capacity under the authority of the state health department to administer COVID-19 vaccines). In such cases, it is expected that the conditions of authorization that apply to emergency response stakeholders and vaccination providers will all be met.

- The Novavax COVID-19 Vaccine, Adjuvanted covered by this authorization will be administered by vaccination providers[10] and used only to prevent COVID-19 as a two-dose primary series given 3 weeks apart to individuals ages 12 years and older and as a first booster dose to the following individuals at least 6 months after completion of primary vaccination with an authorized or approved COVID-19 vaccine:
    - Individuals 18 years of age and older for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate, and
    - Individuals 18 years of age and older who elect to receive the Novavax COVID-19 Vaccine, Adjuvanted because they would otherwise not receive a booster dose of a COVID-19 vaccine;
- The Novavax COVID-19 Vaccine, Adjuvanted may be administered by a vaccination provider without an individual prescription for each vaccine recipient.

Product Description

The Novavax COVID-19 Vaccine, Adjuvanted is supplied as a suspension in multi-dose vials containing 10 doses of 0.5 mL each, and multi-dose vials containing 5 doses of 0.5 mL each.

Each 0.5 mL dose of the Novavax COVID-19 Vaccine, Adjuvanted is formulated to contain 5 mcg of SARS-CoV-2 recombinant spike (rS) protein and 50 mcg Matrix-M adjuvant. The Matrix M adjuvant is composed of Fraction-A (42.5 mcg) and Fraction-C (7.5 mcg) of saponin extracts from the soapbark tree, *Quillaja saponaria* Molina. Each dose of the Novavax COVID-19 Vaccine, Adjuvanted also includes the following ingredients: cholesterol (30.5 mcg), phosphatidylcholine (23 mcg), potassium dihydrogen phosphate (3.85 mcg), potassium chloride (2.25 mcg), disodium hydrogen phosphate dihydrate (14.7 mcg), disodium hydrogen phosphate heptahydrate (2.465 mg), sodium dihydrogen phosphate monohydrate (0.445 mg), sodium chloride (8.856 mg), and polysorbate 80 (0.05 mg) in sterile Water for Injection. The pH is adjusted with sodium hydroxide or hydrochloric acid. The Novavax COVID-19 Vaccine, Adjuvanted does not contain a preservative.

The manufacture of the authorized Novavax COVID-19 Vaccine, Adjuvanted is limited to those facilities identified and agreed upon in Novavax Inc.'s request for authorization.

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[10] For purposes of this letter, "vaccination provider" refers to the facility, organization, or healthcare provider licensed or otherwise authorized by the emergency response stakeholder (e.g., non-physician healthcare professionals, such as nurses and pharmacists pursuant to state law under a standing order issued by the state health officer) to administer or provide vaccination services in accordance with the applicable emergency response stakeholder's official COVID-19 vaccination and emergency response plan(s) and who is enrolled in the CDC COVID-19 Vaccination Program. If the vaccine is exported from the United States, a "vaccination provider" is a provider that is authorized to administer this vaccine in accordance with the laws of the country in which it is administered. For purposes of this letter, "healthcare provider" also refers to a person authorized by the U.S. Department of Health and Human Services (e.g., under the PREP Act Declaration for Medical Countermeasures against COVID-19) to administer FDA-authorized COVID-19 vaccine (e.g., qualified pharmacy technicians and State-authorized pharmacy interns acting under the supervision of a qualified pharmacist). See, e.g., HHS. *Fourth Amendment to the Declaration Under the Public Readiness and Emergency Preparedness Act for Medical Countermeasures Against COVID-19 and Republication of the Declaration*. 85 FR 79190 (December 9, 2020).

The Novavax COVID-19 Vaccine, Adjuvanted vial label and carton labels are clearly marked for "Emergency Use Authorization." The Novavax COVID-19 Vaccine, Adjuvanted is authorized to be distributed, stored, further redistributed, and administered by emergency response stakeholders when packaged in the authorized manufacturer packaging (i.e., vials and cartons), despite the fact that the vial and carton labels may not contain information that otherwise would be required under the FD&C Act.

The Novavax COVID-19 Vaccine, Adjuvanted is authorized for emergency use with the following product-specific information required to be made available to vaccination providers and recipients, respectively (referred to as "authorized labeling"):

- Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers): Emergency Use Authorization (EUA) of the Novavax COVID-19 Vaccine, Adjuvanted to Prevent Coronavirus Disease 2019 (COVID-19)

- Fact Sheet for Recipients and Caregivers: Emergency Use Authorization (EUA) of the Novavax COVID-19 Vaccine, Adjuvanted to Prevent Coronavirus Disease 2019 (COVID-19)

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of the Novavax COVID-19 Vaccine, Adjuvanted, when used to prevent COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh its known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that the Novavax COVID-19 Vaccine, Adjuvanted may be effective in preventing COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that the Novavax COVID-19 Vaccine, Adjuvanted (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of the Novavax COVID-19 Vaccine, Adjuvanted under this EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), the Novavax COVID-19 Vaccine, Adjuvanted is authorized to prevent COVID-19 as described in the Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

Novavax, Inc. and Authorized Distributor(s)

A. Novavax, Inc. and authorized distributor(s) will ensure that the authorized Novavax COVID-19 Vaccine, Adjuvanted is distributed, as directed by the U.S. government, including CDC and/or other designee, and the authorized labeling (i.e., Fact Sheets) is made available to vaccination providers, recipients, and caregivers, consistent with the terms of this letter.

B. Novavax, Inc. and authorized distributor(s) will ensure that appropriate storage and cold chain is maintained until delivered to emergency response stakeholders' receipt sites.

C. Novavax, Inc. will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., emergency response stakeholders, authorized distributors, and vaccination providers) involved in distributing or receiving the authorized Novavax COVID-19 Vaccine, Adjuvanted. Novavax, Inc. will provide to all relevant stakeholders a copy of this letter of authorization and communicate any subsequent amendments that might be made to this letter of authorization and its authorized labeling.

D. Novavax, Inc. may develop and disseminate instructional and educational materials (e.g., video regarding vaccine handling, storage/cold-chain management, preparation, disposal) that are consistent with the authorized emergency use of the vaccine as described in the letter of authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs during an emergency. Any instructional and educational materials that are inconsistent with the authorized labeling are prohibited.

E. Novavax, Inc. may request changes to this authorization, including to the authorized Fact Sheets for the Novavax COVID-19 Vaccine, Adjuvanted. Any request for changes to this EUA must be submitted to the Office of Vaccines Research and Review (OVRR)/Center for Biologics Evaluation and Research (CBER). Such changes require appropriate authorization prior to implementation.[11]

[11] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study. All changes to the authorization require review and concurrence from OVRR. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), or (7), review and concurrence is also required from the Preparedness and Response Team (PREP)/Office of the Center Director (OD)/CBER and the Office of Counterterrorism and Emerging Threats (OCET)/Office of the Chief Scientist (OCS).

F. Novavax, Inc. will report to VAERS:
   - Serious adverse events (irrespective of attribution to vaccination);
   - Cases of myocarditis;
   - Cases of pericarditis;
   - Cases of Multisystem Inflammatory Syndrome in adults and children; and
   - Cases of COVID-19 that result in hospitalization or death, that are reported to Novavax, Inc.

   These reports should be submitted to VAERS as soon as possible but no later than 15 calendar days from initial receipt of the information by Novavax, Inc.

G. Novavax, Inc. must submit to Investigational New Drug application (IND) number 22430 periodic safety reports at monthly intervals in accordance with a due date agreed upon with the Office of Biostatistics and Pharmacovigilance (OBPV)/CBER, beginning after the first full calendar month after authorization. Each periodic safety report is required to contain descriptive information which includes:
   - A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest;
   - A narrative summary and analysis of vaccine administration errors, whether or not associated with an adverse event, that were identified since the last reporting interval;
   - Newly identified safety concerns in the interval;
   - Actions taken since the last report because of adverse experiences (for example, changes made to Healthcare Providers Administering Vaccine (Vaccination Providers) Fact Sheet, changes made to studies or studies initiated); and
   - Cumulative doses distributed, and doses distributed during the monthly reporting interval, for Novavax COVID-19 Vaccine, Adjuvanted.

H. No changes will be implemented to the description of the product, manufacturing process, facilities, or equipment without notification to and concurrence by the Agency.

I. All manufacturing facilities will comply with Current Good Manufacturing Practice requirements.

J. Novavax, Inc. will submit to the EUA file Certificates of Analysis (CoA) for each drug product lot at least 48 hours prior to vaccine distribution. The CoA will include the established specifications and specific results for each quality control test performed on the final drug product lot.

K. Novavax, Inc. will submit to the EUA file quarterly manufacturing reports that include a listing of all drug substance and drug product lots produced after issuance of this authorization. This report must include lot number, manufacturing site, date of manufacture, and lot disposition, including those lots that were quarantined for investigation or those lots that were rejected. Information on the reasons for lot

quarantine or rejection must be included in the report. The first report is due October 13, 2022.

L. Novavax, Inc. and authorized distributor(s) will maintain records regarding release of Novavax COVID-19 Vaccine, Adjuvanted for distribution (i.e., lot numbers, quantity, release date).

M. Novavax, Inc. and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

N. Novavax, Inc. will conduct post-authorization observational studies to evaluate the association between Novavax COVID-19 Vaccine, Adjuvanted and a pre-specified list of adverse events of special interest, including myocarditis and pericarditis, along with deaths and hospitalizations, and severe COVID-19. The study population should include individuals administered the authorized Novavax COVID-19 Vaccine, Adjuvanted primary series under this EUA in the general U.S. population (12 years of age and older), individuals who received a Novavax COVID-19 Vaccine, Adjuvanted booster dose (18 years of age and older), populations of interest such as healthcare workers, pregnant women, immunocompromised individuals, subpopulations with specific comorbidities. The studies should be conducted in large scale databases with an active comparator. Novavax, Inc. will provide protocols and status update reports to the IND 22430 with agreed-upon study designs and milestone dates.

Emergency Response Stakeholders

O. Emergency response stakeholders will identify vaccination sites to receive authorized Novavax COVID-19 Vaccine, Adjuvanted and ensure its distribution and administration, consistent with the terms of this letter and CDC's COVID-19 Vaccination Program.

P. Emergency response stakeholders will ensure that vaccination providers within their jurisdictions are aware of this letter of authorization, and the terms herein and any subsequent amendments that might be made to the letter of authorization, instruct them about the means through which they are to obtain and administer the vaccine under the EUA, and ensure that the authorized labeling [i.e., Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) and Fact Sheet for Recipients and Caregivers] is made available to vaccination providers through appropriate means (e.g., e-mail, website).

Q. Emergency response stakeholders receiving authorized Novavax COVID-19 Vaccine, Adjuvanted will ensure that appropriate storage and cold chain is maintained.

Vaccination Providers

R. Vaccination providers will administer the vaccine in accordance with the authorization and will participate and comply with the terms and training required by CDC's COVID-19 Vaccination Program.

S. Vaccination providers will provide the Fact Sheet for Recipients and Caregivers to each individual receiving vaccination and provide the necessary information for receiving their second dose.

T. Vaccination providers administering the Novavax COVID-19 Vaccine, Adjuvanted must report the following information associated with the administration of the Novavax COVID-19 Vaccine, Adjuvanted of which they become aware to VAERS in accordance with the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers):
   - Vaccine administration errors whether or not associated with an adverse event
   - Serious adverse events (irrespective of attribution to vaccination)
   - Cases of myocarditis
   - Cases of pericarditis
   - Cases of Multisystem Inflammatory Syndrome in adults and children
   - Cases of COVID-19 that result in hospitalization or death

   Complete and submit reports to VAERS online at https://vaers.hhs.gov/reportevent.html. The VAERS reports should include the words "Novavax COVID-19 Vaccine, Adjuvanted EUA" in the description section of the report. More information is available at vaers.hhs.gov or by calling 1-800-822-7967. To the extent feasible, report to Novavax, Inc. by contacting 1-844-668-2829 or by providing a copy of the VAERS form to Novavax, Inc.; Fax: 1-888-988-8809.

U. Vaccination providers will conduct any follow-up requested by the U.S. government, including CDC, FDA, or other designee, regarding adverse events to the extent feasible given the emergency circumstances.

V. Vaccination providers will monitor and comply with CDC and/or emergency response stakeholder vaccine management requirements (e.g., requirements concerning obtaining, tracking, and handling vaccine) and with requirements concerning reporting of vaccine administration data to CDC.

W. Vaccination providers will ensure that any records associated with this EUA are maintained until notified by FDA. Such records will be made available to CDC, and FDA for inspection upon request.

Conditions Related to Printed Matter, Advertising, and Promotion

X. All descriptive printed matter, advertising, and promotional material, relating to the use of the Novavax COVID-19 Vaccine, Adjuvanted shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in section 502(a) and (n) of the FD&C Act and FDA implementing regulations.

Y. All descriptive printed matter, advertising, and promotional material relating to the use of the Novavax COVID-19 Vaccine, Adjuvanted clearly and conspicuously shall state that:
   - This product has not been approved or licensed by FDA, but has been authorized for emergency use by FDA, under an EUA to prevent Coronavirus Disease 2019 (COVID-19) for use in individuals 12 years of age and older; and
   - The emergency use of this product is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of the medical product under Section 564(b)(1) of the FD&C Act unless the declaration is terminated or authorization revoked sooner.

Condition Related to Export

Z. If the Novavax COVID-19 Vaccine, Adjuvanted is exported from the United States, conditions C, D, and O through Y do not apply, but export is permitted only if 1) the regulatory authorities of the country in which the vaccine will be used are fully informed that this vaccine is subject to an EUA and is not approved or licensed by FDA and 2) the intended use of the vaccine will comply in all respects with the laws of the country in which the product will be used. The requirement in this letter that the authorized labeling (i.e., Fact Sheets) be made available to vaccination providers, recipients, and caregivers in condition A will not apply if the authorized labeling (i.e., Fact Sheets) are made available to the regulatory authorities of the country in which the vaccine will be used.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

_____

Peter Marks, M.D., Ph.D.
Director
Center for Biologics Evaluation and Research

Enclosures

U.S. FOOD & DRUG ADMINISTRATION

Questions related to Paxlovid's approval or EUA

Q: Is Paxlovid FDA-approved to treat or prevent COVID-19?

A. On May 25, 2023, FDA approved a New Drug Application (NDA) for Paxlovid for the treatment of mild-to-moderate coronavirus disease (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. FDA has determined Paxlovid is safe and effective when used in accordance with the FDA-approved labeling.

Paxlovid is not FDA-approved for use as pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

Q. Now that Paxlovid is an approved drug, is the EUA continuing, and what does the EUA authorize?

A. Yes. The EUA authorizes the emergency use of Paxlovid for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death.

The EUA continues to authorize Paxlovid for emergency use to treat certain eligible pediatric patients, a patient population that is not covered under the approved NDA for Paxlovid at this time. Paxlovid also remains authorized under EUA to ensure continued access for all eligible patients to the U.S. government's supply of Paxlovid, including adult patients who are the subject of the approved NDA, pending commercial launch of the approved product.

Paxlovid is not authorized:

- for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.
- for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
- for use longer than five consecutive days.

The use of Paxlovid under the EUA must be consistent with the terms and conditions of the authorization.

Q. Does the authorized Paxlovid provide the same clinical benefit as the approved Paxlovid, once the approved Paxlovid is available?

A. Yes. The authorized Paxlovid contains the same tablets (nirmatrelvir tablets and ritonavir tablets) as the Paxlovid that is now FDA-approved. Since Paxlovid was initially authorized for emergency use, Pfizer has also been required, as a condition under the EUA, to comply with the same good manufacturing practices that apply to approved products. Based on these considerations, it is FDA's expectation that patients being treated with Paxlovid for COVID-19 will receive the same clinical benefit as long as the product is used in accordance with the labeling, regardless of whether the authorized or approved Paxlovid is dispensed.

Paxlovid is FDA-approved for the treatment of mild-to-moderate COVID-19 in certain adults. Paxlovid is authorized for emergency use, but not FDA-approved, for the treatment of mild-to-moderate COVID-19 in certain pediatric patients.

Q. Why does the EUA authorize Paxlovid for its approved patient population, specifically for the treatment of mild-to-moderate COVID-19 in high-risk adults?

A. Although different presentations of PAXLOVID are now FDA-approved for the treatment of mild-to-moderate COVID-19 in certain adults, there are not sufficient quantities of the approved PAXLOVID available for distribution to this population in its entirety at the time of reissuance of this EUA. To ensure continued access to the U.S. government's supply for Paxlovid and fully meet the public health need before commercial launch of the approved product, the EUA continues to include the patient population now approved under the NDA for Paxlovid.

The use of Paxlovid under the EUA must be consistent with the terms and conditions of the authorization.

Q. May health care providers prescribe Paxlovid for uses not authorized under EUA?

A. At this time, the U.S. government continues to oversee the distribution of Paxlovid, which consists solely of Paxlovid that is labeled and packaged in accordance with the EUA. The Letter of Authorization for the EUA provides for the use of Paxlovid only when consistent with the terms and conditions of the authorization. Paxlovid is currently authorized for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death. Although Paxlovid has been approved for use in eligible adult patients who are also included in the EUA population, the approved product has not yet commercially launched.

In certain circumstances, Paxlovid labeled and packaged in accordance with the EUA may also be accessed through an Expanded Access Investigational New Drug Application, also referred to as "compassionate use", for uses not within the scope of the EUA for Paxlovid, as appropriate. Expanded access may be considered when **all** of the following apply:

- Patient has a serious or immediately life-threatening disease or condition.
- There is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition.
- Patient enrollment in a clinical trial is not possible.
- Potential patient benefit justifies the potential risks of treatment.
- Providing the investigational medical product will not interfere with investigational trials that could support a medical product's development or marketing approval for the treatment indication.

Health care providers seeking to obtain Paxlovid under expanded access should first contact Pfizer through its website.

Once Pfizer has provided the requisite authorization, health care providers should contact FDA using the information detailed below to complete the process:

- During normal business hours (8:00 a.m. – 4:30 p.m. ET, weekdays):
  - By phone – (301) 796-3400 or (855) 543-3784

- By email – DDI.EIND@fda.hhs.gov
- Outside of normal business hours (After 4:30 p.m. ET weekdays and all day on weekends/federal holidays)
  - By phone – (301) 796-9900
  - By email – CDER-EIND@fda.hhs.gov

General information on expanded access for providers and patients, respectively, can be found on FDA's website.

Q. Paxlovid is approved and authorized only for certain patients at "high risk". What does "high risk" mean?

A. Determining whether a patient is at high risk for progression to severe COVID-19, including hospitalization or death, is based on the provider's assessment of the individual patient being considered for treatment with COVID-19 and that patient's medical history.

Resources providing information on conditions that place a patient with mild-to-moderate COVID-19 at high risk for disease progression, including hospitalization or death, can be found at the Centers for Disease Control and Prevention site: Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals and at NIH's COVID-19 Treatment Guidelines: Clinical Spectrum of SARS-CoV-2 Infection.

Q. Why is pediatric use not approved for Paxlovid and only authorized under the EUA?

A. The clinical development of Paxlovid for pediatric use is ongoing.

Q. How can Paxlovid be obtained for use under the EUA?

A. For questions on how to obtain Paxlovid, please contact COVID19therapeutics@hhs.gov. Information about Paxlovid's distribution can be found here.

Efficacy and Safety Considerations

Q. Are there data showing the benefit of Paxlovid for treatment of mild-to-moderate COVID-19 for certain patients?

A. Yes. The primary data supporting the approval as well as the EUA for Paxlovid are from EPIC-HR, a randomized, double-blind, placebo-controlled clinical trial studying Paxlovid for the treatment of non-hospitalized symptomatic adults with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Patients were adults 18 years of age and older with a prespecified risk factor for progression to severe disease or were 60 years and older regardless of prespecified chronic medical conditions. All patients had not received a COVID-19 vaccine and had not been previously infected with COVID-19. The main outcome measured in the trial was the proportion of people who were hospitalized due to COVID-19 or died due to any cause during 28 days of follow-up. Paxlovid significantly reduced the proportion of people with COVID-19 related hospitalization or death from any cause through 28 days of follow-up by 86% compared to placebo among patients treated within five days of symptom onset and who did not receive COVID-19 therapeutic monoclonal antibody treatment.

In this analysis, 977 patients received Paxlovid, and 989 patients received placebo, and among these patients, 0.9% who received Paxlovid were hospitalized due to COVID-19 or died from any cause during 28 days of follow-up compared to 6.5% of the patients who received placebo. Of the people who received Paxlovid, no patients died through 24 weeks after receipt compared to 15 people who received placebo.

Details on the clinical trial results can be found in Section 14 of the authorized Fact Sheet for Health Care Providers and approved Prescribing Information.

Q. Are there data supporting the benefit of Paxlovid for high-risk patients with mild-moderate COVID-19 regardless of prior/acquired immunity?

A. Benefit of Paxlovid was observed in patients with prior immunity to the virus that causes COVID-19. Among patients in EPIC-HR who were antibody positive at trial enrollment, the risk of COVID-19-related hospitalization or death from any cause during 28 days of follow-up was 0.2% among those treated with Paxlovid compared with 1.7% of those receiving placebo. EPIC-SR was another clinical trial that enrolled vaccinated patients with at least one risk factor for progression to severe COVID-19. Among these vaccinated patients, there was a reduction in the risk of COVID-19 related hospitalization or death from any cause with use of PAXLOVID versus placebo, although not statistically significant.

Q. Does Paxlovid retain activity against currently circulating Omicron variants?

A. Yes. Based on virology data, Paxlovid retains activity against currently circulating Omicron variants.

Q. Does Paxlovid cause COVID-19 rebound?

A. EPIC-HR, described above, and EPIC-SR, another trial that enrolled vaccinated patients with at least one risk factor for progression to severe COVID-19 or unvaccinated patients with no risk factors for progression to severe COVID-19, were both randomized placebo-controlled trials. These trials provide useful data to assess COVID-19 rebound. Data from these two trials showed that rebound in SARS-CoV-2 (RNA or virus) shedding or self-reported COVID-19 symptoms occurred in a subset of patients and happened at similar rates in both the patients receiving Paxlovid and placebo. Based on the data currently available to FDA, there is not a clear association between Paxlovid treatment and COVID-19 rebound.

Q. Are there potential side effects of Paxlovid?

A. Yes. Paxlovid consists of nirmatrelvir and ritonavir, and ritonavir interacts with many other medicines, which may lead to serious or life-threatening adverse reactions. Patients should tell their health care providers all of the medicines they are taking, including over-the-counter medications and herbal supplements, when deciding whether to take Paxlovid.

Because of the importance of reducing the risk of significant drug-drug interactions with Paxlovid, the approved Prescribing Information and authorized Fact Sheet for Health Care Providers for the Paxlovid EUA include a boxed warning with instructions for providers to review all medications taken by the patient to assess for potential drug-drug interactions and determine if other medicines that a patient may be taking require a dose adjustment, interruption and/or additional monitoring.

The most common side effects of taking Paxlovid include impaired sense of taste (for example, a metallic taste in the mouth) and diarrhea.

Liver problems have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering Paxlovid to patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis. Patients should talk with their health care provider if they have a history of liver problems.

Paxlovid is not recommended for patients with severe kidney problems, and a different dose is needed for patients with moderate kidney problems. Patients should talk with their health care provider if they have a history of kidney problems.

See Warnings and Precautions in the FDA-approved Prescribing Information and the Fact Sheet for Health Care Providers for additional information on risks associated with Paxlovid.

Q. Why was a boxed warning included in the Paxlovid prescribing information?

A. Paxlovid includes ritonavir, a strong CYP3A inhibitor, which may lead to greater exposure of certain other medications the patient may be taking, resulting in potentially severe, life-threatening, or fatal events due to drug-drug interactions. Such interactions can be avoided by appropriate handling of the patient's other medications when starting treatment with Paxlovid or, in some situations when adjustments of the patient's other medication may not be feasible, choosing an alternative COVID-19 treatment for the individual patient. Since the authorization of Paxlovid under EUA, FDA has reviewed new data related to the risk of drug-drug interactions. These data were discussed by FDA during the recent Antimicrobial Drugs Advisory Committee on March 16, 2023.

- FDA identified more than 250 cases of serious adverse events assessed as possibly or probably related to Paxlovid drug-drug interactions. Many of these cases reported hospitalization, and a fatal outcome was reported in a few cases.
- FDA determined that greater than 50% of Paxlovid-eligible Medicare and VA patients were taking medications that were identified as having a drug-drug interaction with Paxlovid. FDA noted that most of these potential drug-drug interactions could be prevented or managed with dose modification, interruption, and/or additional monitoring.
- FDA determined that most Paxlovid prescriptions were written by a broad range of health care providers, who may not be familiar with managing potential drug-drug interactions associated with ritonavir, which is more commonly prescribed by infectious disease physicians and other specialists who may have more experience managing ritonavir drug-drug interactions.

Drug-drug interactions are not unique to Paxlovid and are almost always manageable risks. Prior to prescribing Paxlovid, health care providers must: 1) review all medications taken by the patient to assess potential drug-drug interactions with a strong CYP3A inhibitor like Paxlovid and 2) determine if medications require a dose adjustment, interruption, and/or additional monitoring if taken at the same time as Paxlovid.

There are resources for health care providers to identify and manage potential drug-drug interactions with Paxlovid. These include: the approved prescribing information, the Fact Sheet for Health Care Providers and the Prescriber Patient Eligibility Screening Checklist available on the FDA EUA webpage. Other resources include: the NIH COVID-19 Treatment Guidelines, the IDSA COVID-19 Treatment Guidelines and the University of Liverpool COVID-19 Drug Interactions online checker.

U.S. FOOD & DRUG ADMINISTRATION

Provider Considerations When Prescribing Paxlovid

Q. Who may prescribe Paxlovid?

A. Paxlovid may be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs.

Paxlovid may also be prescribed for an individual patient by a state-licensed pharmacist under certain conditions that are listed in the EUA. For more information on this topic, please refer to the section titled Questions for Pharmacist Prescribers below.

Q. When should Paxlovid be administered to a patient?

A. Patients should talk to their health care provider to determine whether, based on their individual circumstances, they are eligible to receive Paxlovid. Paxlovid treatment should be initiated as soon as possible after diagnosis of COVID-19, even if symptoms are mild, and within five days after symptoms start.

More information about administration is available in the in the FDA-approved Prescribing Information and the Fact Sheet for Health Care Providers.

Q: Is a positive result from a direct SARS-CoV-2 viral test required prior to prescribing Paxlovid to a patient who is at high risk for severe COVID-19?

A: No. FDA recognizes that, in rare instances, individuals with a recent known exposure (e.g., a household contact) who develop signs and symptoms consistent with COVID-19 may be diagnosed by their health care provider as having COVID-19 even if they have a negative direct SARS-CoV-2 viral test result. In such instances, their health care provider may determine that treatment with Paxlovid for COVID-19 is appropriate if the patient reports mild-to-moderate symptoms of COVID-19 and is at high-risk for progression to severe COVID-19, including hospitalization or death, and the terms and conditions of the authorization are met, as detailed in the Letter of Authorization for Paxlovid and the authorized Fact Sheet for Healthcare Providers.

The agency continues to recommend that providers use direct SARS-CoV-2 viral testing to help diagnose COVID-19.

Q. I am traveling soon. May I receive Paxlovid under the EUA prior to travel in case I become sick with COVID-19?

A. Individuals being considered for Paxlovid treatment must meet the eligibility requirements under the EUA at the time of prescription. Providers must determine that patients have signs and symptoms consistent with mild-to-moderate COVID-19, assess risk for disease progression, assess renal and hepatic function, and review all medications taken by the patient to assess for potential drug-drug interactions and determine if other medicines that a patient may be taking require a dose adjustment, interruption and/or additional monitoring.

Q. What if I have questions about the expiration date on the Paxlovid carton or container?

A. FDA has authorized an extension to the expiration date (shelf-life) for certain lots of Paxlovid. To find the extended expiration date, enter the lot number found on the side of the carton or bottom of the blister pack at this website or talk with the pharmacist or provider.

Information on the authorized shelf-life extensions for Paxlovid may also be found on FDA's website.

Questions for pharmacist prescribers

Q. Are pharmacists permitted to prescribe Paxlovid?

A. The EUA authorizes state-licensed pharmacists to prescribe Paxlovid for an individual patient, subject to the terms and conditions of the EUA (e.g., eligible patient populations), under the following conditions:

- Sufficient information is available, such as through access to health records less than 12 months old or consultation with a health care provider in an established provider-patient relationship with the individual patient, to assess renal and hepatic function; and
- Sufficient information is available, such as through access to health records, patient reporting of medical history, or consultation with a health care provider in an established provider-patient relationship with the individual patient, to obtain a comprehensive list of medications (prescribed and non-prescribed) that the patient is taking to assess for potential drug interaction.

The state-licensed pharmacist should refer an individual patient for clinical evaluation (e.g., telehealth, in-person visit) with a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs, if any of the following apply:

- Sufficient information is not available to assess renal and hepatic function.
- Sufficient information is not available to assess for a potential drug interaction.
- Modification of other medications is needed due to a potential drug interaction.
- Paxlovid is not an appropriate therapeutic option based on the authorized Fact Sheet for Healthcare Providers or due to potential drug interactions for which recommended monitoring would not be feasible.

Q. What do state-licensed pharmacist prescribers need to do to determine whether a patient may be eligible to receive Paxlovid?

A. State-licensed pharmacist prescribers have the same requirements as all other prescribers to assess an adult or pediatric patient (12 years of age and older weighing at least 40 kg), who is being considered for treatment with Paxlovid, to determine that they have a diagnosis of mild-to-moderate COVID-19 and are at high risk for progression to severe COVID-19, including hospitalization or death.

A review of reported symptoms should be completed to determine that patients have signs and symptoms consistent with mild-to-moderate COVID-19, and not severe COVID-19. Patients reporting

shortness of breath or difficulty breathing should be immediately referred for further medical assessment to determine whether their illness has progressed to the severe stage, which may require hospitalization. Paxlovid is not authorized or approved for the treatment of severe COVID-19.

Definitions for mild and moderate illness are provided in NIH's COVID-19 Treatment Guidelines: Clinical Spectrum of SARS-CoV-2 Infection.

State-licensed pharmacist prescribers may determine whether an individual patient is at high risk for severe COVID-19 by obtaining a medical history from the patient or by accessing the patient's medical records. Resources about conditions that place a patient with mild-to-moderate COVID-19 at increased risk for disease progression or death can be found at the Centers for Disease Control and Prevention site: Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals and at NIH's COVID-19 Treatment Guidelines: Clinical Spectrum of SARS-CoV-2 Infection.

Q. How do state-licensed pharmacist prescribers assess for potential drug interactions?

A. All prescribers are expected to utilize available health records or patient history to obtain a complete list of all medications (prescribed and non-prescribed) that the patient is taking. State-licensed pharmacists may also consult with a health care provider in an established provider-patient relationship with the individual patient to obtain a comprehensive list of medications the patient is taking. Resources to identify potential drug interactions include the approved Prescribing Information, the Fact Sheet for Health Care Providers and the Prescriber Patient Eligibility Screening Checklist available on the FDA EUA webpage. Other resources include: the NIH COVID-19 Treatment Guidelines, the IDSA COVID-19 Treatment Guidelines and the University of Liverpool COVID-19 Drug Interactions.

Should an adjustment to another medication be needed due to a potential drug interaction, the state-licensed pharmacist should refer the individual patient for clinical evaluation with a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs.

Q. How do state-licensed pharmacist prescribers assess renal and hepatic function?

A. State-licensed pharmacist prescribers must have access to sufficient information from health records to assess renal and hepatic function. Health records include access to an electronic health record system containing this information in progress notes or laboratory records, reviewing a printed health record such as a laboratory report provided by the patient, or reviewing information in electronic health records the patient may have access to through a phone app or other means. Health records within the past 12 months are generally acceptable, provided there is no patient self-report or other information suggestive of kidney or liver disease. State-licensed pharmacists may also consult with a health care provider in an established provider-patient relationship with the individual patient to obtain this information. If sufficient information is not available to assess renal and hepatic function, the state-licensed pharmacist should refer the individual patient to a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs.

Physicians, advanced practice registered nurses, and physician assistants may rely on patient history and access to the patient's health records to make an assessment regarding the likelihood of renal

impairment. These providers may consider ordering a serum creatinine or calculating the estimated glomerular filtration rate (eGFR) for certain patients after assessment on a case-by-case basis.

Q. Will state-licensed pharmacists be able to prescribe both the standard and renal doses of Paxlovid?

A. Yes, the EUA authorizes state-licensed pharmacists to prescribe both the standard and renal doses of Paxlovid, subject to the terms and conditions on pharmacist prescribing as detailed in the EUA, provided the pharmacist has adequate information to assess renal function and the patient is otherwise eligible to receive Paxlovid.

General EUA-related questions

Q. What is an emergency use authorization (EUA)?

A. Under section 564 of the Federal Food, Drug & Cosmetic Act, after a declaration by the HHS Secretary based on one of four types of determinations, FDA may authorize an unapproved product or unapproved uses of an approved product for emergency use. In issuing an EUA, FDA must determine, among other things, that based on the totality of scientific evidence available to the agency, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by a chemical, biological, radiological, or nuclear agent; that the known and potential benefits of the product, when used to treat, diagnose or prevent such disease or condition, outweigh the known and potential risks of the product; and that there are no adequate, approved, and available alternatives. Emergency use authorization is NOT the same as FDA approval or licensure.

Q. Are there reporting requirements for health care facilities and providers as part of the EUA?

A. Yes. As part of the EUA, FDA requires health care providers who prescribe Paxlovid to report all medication errors and serious adverse events considered to be potentially related to Paxlovid through FDA's MedWatch Adverse Event Reporting program. Providers can complete and submit the report online; or download and complete the form, then submit it via fax at 1-800-FDA-0178. This requirement is outlined in the EUA's Fact Sheet for Health Care Providers. FDA MedWatch forms should also be provided to Pfizer.

Health care facilities and providers must report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

Q. Do patient outcomes need to be reported under the EUA?

A. No, reporting of patient outcomes is not required under the EUA. However, reporting of all medication errors and serious adverse events considered to be potentially related to Paxlovid occurring during treatment is required.

Q. FDA has issued a number of EUAs including for therapeutics. If state laws impose different or additional requirements on the medical product covered by an EUA, are those state laws preempted?

A. As stated in FDA's Emergency Use Authorization of Medical Products and Related Authorities Guidance, "FDA believes that the terms and conditions of an EUA issued under section 564 preempt state or local law, both legislative requirements and common-law duties, that impose different or additional requirements on the medical product for which the EUA was issued in the context of the emergency declared under section 564." The guidance explains the basis for FDA's views on this subject.

Q. Can health care providers share the patient/caregiver Fact Sheet electronically?

A. Under the authorization, Pfizer must make available the authorized Fact Sheets on its website at: www.COVID19oralRX.com. Health care facilities and health care providers must ensure that fact sheets are made available to patients, parents, and caregivers through "appropriate means" and electronic delivery of the Fact Sheet is an appropriate means.

Vaccines and Related Biological Products Advisory Committee Meeting
December 10, 2020

FDA Briefing Document

Pfizer-BioNTech COVID-19 Vaccine

Sponsor:
Pfizer and BioNTech

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Glossary

AE	adverse event
AIDS	acquired immunodeficiency syndrome
ARDS	acute respiratory distress syndrome
BNT162b2	Pfizer-BioNTech COVID-19 Vaccine
CBRN	chemical, biological, radiological, or nuclear
CDC	Centers for Disease Control and Prevention
CMC	Che
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
hACE2	human angiotensin converting enzyme 2
HHS	Health and Human Services
HIV	human immunodeficiency virus
IM	intramuscular
LNP	lipid nanoparticle
MERS-CoV	Middle Eastern respiratory syndrome
modRNA	nucleoside-modified messenger RNA
NAAT	nucleic acid amplification-based test
PVP	Pharmacovigilance Plan
RBD	receptor binding domain
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
VE	vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1. Executive Summary

On November 20, 2020, Pfizer and BioNTech (the Sponsor) submitted an Emergency Use Authorization (EUA) request to FDA for an investigational COVID-19 vaccine (BNT162b2) intended to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The vaccine is based on the SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA and formulated in lipid nanoparticles (LNPs). The proposed use under an EUA is "for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older." The proposed dosing regimen is 2 doses, 30 µg each, administered 21 days apart.

The EUA request includes safety and efficacy data from an ongoing phase 3 randomized, double-blinded and placebo-controlled trial of BNT162b2 in approximately 44,000 participants. The primary efficacy endpoint is incidence of COVID-19 among participants without evidence of SARS-CoV-2 infection before or during the 2-dose vaccination regimen. In a mid-November analysis of 36,621 participants randomized 1:1 to vaccine or placebo who were included in the per-protocol efficacy analysis population of participants without evidence of SARS-CoV-2 infection prior to 7 days after completion of the vaccination regimen, efficacy in preventing confirmed COVID-19 occurring at least 7 days after the second dose of vaccine was 95.0%, with 8 COVID-19 cases in the vaccine group and 162 COVID-19 cases in the placebo group. Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across age groups, genders, racial and ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19. Secondary efficacy analyses suggested benefit of the vaccine in preventing severe COVID-19, in preventing COVID-19 following the first dose, and in preventing COVID-19 in individuals with prior SARS-CoV-2 infection, although available data for these outcomes did not allow for firm conclusions.

Safety data from approximately 38,000 participants ≥16 years of age randomized 1:1 to vaccine or placebo with a median of 2 months of follow up after the second dose suggest a favorable safety profile, with no specific safety concerns identified that would preclude issuance of an EUA. Available safety data from all participants enrolled through the November 14, 2020 data cut-off (N=43,252, which includes late enrollment of additional adolescent and adult participants), was consistent with the safety profile for the approximately 38,000 participants with median follow-up of 2 months and also did not raise specific safety concerns. The most common solicited adverse reactions were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%); severe adverse reactions occurred in 0.0% to 4.6% of participants, were more frequent after Dose 2 than after Dose 1, and were generally less frequent in participants ⩾55 years of age (⩽ 2.8%) as compared to younger participants (⩽4.6%). The frequency of serious adverse events was low (<0.5%), without meaningful imbalances between study arms. Among non-serious unsolicited adverse events, there was a numerical imbalance of four cases of Bell's palsy in the vaccine group compared with no cases in the placebo group, though the four cases in the vaccine group do not represent a frequency above that expected in the general population. Otherwise, there were no notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to BNT162b2 vaccine. With the exception of more frequent, generally mild to moderate reactogenicity in participants <55 years of age, the safety profile of BNT162b2 was generally similar across age groups, genders, ethnic and racial groups, participants with or without medical comorbidities, and participants with or without evidence of prior SARS-CoV-2 infection at enrollment.

This meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) is being convened to discuss and provide recommendations on whether:

- based on the totality of scientific evidence available, it is reasonable to believe that the Pfizer-BioNTech COVID-19 Vaccine may be effective in preventing COVID-19 in individuals 16 years of age and older, and
- the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh its known and potential risks for use in individuals 16 years of age and older.

The committee will also discuss what additional studies should be conducted by the vaccine manufacturer following issuance of the EUA to gather further data on the safety and effectiveness of this vaccine.

2. Background

2.1. SARS-CoV-2 Pandemic

The SARS-CoV-2 pandemic presents an extraordinary challenge to global health and, as of November 30, 2020, has caused more than 60 million cases of COVID-19 and claimed the lives of 1.5 million people worldwide. In the United States, over 13 million cases have been reported to the Centers for Disease Control and Prevention (CDC), with over 260,000 deaths. Confirmed cases and mortality continue to rise globally. On January 31, 2020, the U.S. Secretary of Health and Human Services (HHS) declared a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS. Following the World Health Organization's declaration of the novel coronavirus pandemic on March 11, 2020, the U.S. President declared a national emergency in response to COVID-19 on March 13, 2020. Vaccines to protect against COVID-19 are critical to mitigate the current SARS-CoV-2 pandemic and to prevent future disease outbreaks.

SARS-CoV-2 is a novel, zoonotic coronavirus that emerged in late 2019 in patients with pneumonia of unknown cause.[1] The virus was named SARS-CoV-2 because of its similarity to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV, a lineage B betacoronavirus).[2] SARS-CoV-2 is an enveloped, positive sense, single stranded RNA virus sharing more than 70% of its sequence with SARS-CoV, and ~50% with the coronavirus responsible for Middle Eastern respiratory syndrome (MERS-CoV).[3] The SARS-CoV-2 spike glycoprotein (S), which is a main target for neutralizing antibody, binds to its receptor human angiotensin converting enzyme 2 (hACE2) to initiate infection.[4] SARS-CoV-2 is the cause of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome (ARDS), leading to multiorgan failure and death.

In an attempt to prevent the spread of disease and to control the pandemic, numerous COVID-19 vaccine candidates are in development. These vaccines are based on different platforms including mRNA and DNA technologies and include viral vectored, subunit, inactivated, and live attenuated vaccines. Most COVID-19 candidate vaccines express the spike protein or parts of the spike protein, i.e., the receptor binding domain (RBD), as the immunogenic determinant.

2.2. EUA Request for the Pfizer and BioNTech COVID-19 Vaccine BNT162b2

Pfizer, in partnership with BioNTech Manufacturing GmbH, is developing a vaccine to prevent COVID-19 which is based on the SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA and formulated in lipid nanoparticles (LNP). The Pfizer-BioNTech COVID-19 Vaccine (also referred to as BNT162b2) is administered intramuscularly as a 2-dose series spaced 21 days apart at a dose of 30 μg each. The vaccine is supplied as a multi-dose vial (5 doses) containing a frozen suspension (-80°C to -60°C) of BNT162b2 that must be thawed and diluted with 1.8 mL of sterile 0.9% sodium chloride, allowing for five 0.3 mL doses. The vaccine is preservative free.

A phase 3 randomized and placebo-controlled trial using BNT162b2 in approximately 44,000 participants is currently ongoing to evaluate the vaccine's safety and efficacy. Vaccine efficacy for the primary endpoint against confirmed COVID-19 occurring at least 7 days after the second dose was 95.0% with 8 COVID-19 cases in the vaccine group compared to 162 COVID-19 cases in the placebo group. Data from about 38,000 participants randomized 1:1 with a median of 2 months of follow-up after the second dose of vaccine showed a favorable safety profile at a dose of 30 μg in participants 16 years of age and older. On November 20, 2020, Pfizer and BioNTech submitted an EUA request to FDA for its investigational COVID-19 vaccine (BNT162b2) intended to prevent COVID-19 caused by SARS-CoV-2.

2.3. U.S. Requirements to Support Issuance of an EUA for a Biological Product

Based on the declaration by the Secretary of HHS that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA after determining that certain statutory requirements are met (section 564 of the FD&C Act (21 U.S.C. 360bbb-3)).[5]

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2, or to mitigate a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by SARS-CoV-2.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

If these criteria are met, under an EUA, FDA can allow unapproved medical products (or unapproved uses of approved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents. FDA has been providing regulatory advice to COVID-19 vaccine manufacturers regarding the data needed to determine that a vaccine's benefit outweigh its risks. This includes demonstrating that manufacturing information ensures product quality and consistency along with data from at least one phase 3 clinical trial demonstrating a vaccine's safety and efficacy in a clear and compelling manner.

In the event an EUA is issued for this product, it would still be considered unapproved and it would be under further investigation (under an Investigational New Drug Application) until it is licensed under a Biologics License Application (BLA). Licensure of a COVID-19 vaccine will be based on review of additional manufacturing, efficacy, and safety data, providing greater assurance of the comparability of licensed product to product tested in the clinical trials, greater assurance of safety based on larger numbers of vaccine recipients who have been followed for a longer period of time, and additional information about efficacy that addresses, among other questions, the potential for waning of protection over time.

2.4. Applicable Guidance for Industry

Risk and benefit considerations are unique for COVID-19 vaccines, given that an EUA may be requested to allow for a vaccine's rapid and widespread deployment for administration to millions of individuals, including healthy people. FDA published in October 2020 guidance for industry entitled "Emergency Use Authorization for Vaccines to Prevent COVID-19" (Appendix C, page 53) describing FDA's current recommendations regarding the manufacturing, nonclinical, and clinical data and information needed under section 564 of the FD&C Act to support the issuance of an EUA for an investigational vaccine to prevent COVID-19, including a discussion of FDA's current thinking regarding the circumstances under which an EUA for a COVID-19 vaccine would be appropriate.

2.5. Safety and Effectiveness Information Needed to Support an EUA

Effectiveness data

Issuance of an EUA requires a determination that the known and potential benefits of the vaccine outweigh the known and potential risks. For a preventive COVID-19 vaccine to be potentially administered to millions of individuals, including healthy individuals, data adequate to inform an assessment of the vaccine's benefits and risks and support issuance of an EUA would include meeting the prespecified success criteria for the study's primary efficacy endpoint, as described in the guidance for industry entitled "Development and Licensure of Vaccines to Prevent COVID-19" (i.e., a point estimate for a placebo-controlled efficacy trial of at least 50%, with a lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate of >30%).[6]

Safety data

An EUA request for a COVID-19 vaccine should include all safety data accumulated from studies conducted with the vaccine, with data from phase 1 and 2 focused on serious adverse events, adverse events of special interest, and cases of severe COVID-19 among study participants. Phase 3 safety data should include characterization of reactogenicity (common and expected adverse reactions shortly following vaccination) in a sufficient number of participants from relevant age groups and should include a high proportion of enrolled participants (numbering well over 3,000) followed for serious adverse events and adverse events of special interest for at least one month after completion of the full vaccination regimen. The phase 1 and 2 safety data likely will be of a longer duration than the available safety data from the phase 3 trial at the time of submission of an EUA request and thus, are intended to complement the available data from safety follow-up from ongoing phase 3 studies.

Phase 3 Follow-up

Data from phase 3 studies should include a median follow-up duration of at least 2 months after completion of the full vaccination regimen to help provide adequate information to assess a vaccine's benefit-risk profile. From a safety perspective, a 2-month median follow-up following completion of the full vaccination regimen will allow identification of potential adverse events that were not apparent in the immediate postvaccination period. Adverse events considered plausibly linked to vaccination generally start within 6 weeks of vaccine receipt.[7] Therefore, a 2-month follow-up period may allow for identification of potential immune-mediated adverse events that began within 6 weeks of vaccination. From the perspective of vaccine efficacy, it is important to assess whether protection mediated by early responses has not started to wane. A 2-month median follow-up is the shortest follow-up period to achieve some confidence that any protection against COVID-19 is likely to be more than short-lived. The EUA request should include a plan for active follow-up for safety (including deaths, hospitalizations, and other serious or clinically significant adverse events) among individuals administered the vaccine under an EUA in order to inform ongoing benefit-risk determinations to support continuation of the EUA.

2.6. Continuation of clinical trials following issuance of an EUA for a COVID-19 vaccine

FDA does not consider availability of a COVID-19 vaccine under EUA, in and of itself, as grounds for immediately stopping blinded follow-up in an ongoing clinical trial or grounds for offering vaccine to all placebo recipients. To minimize the risk that use of an unapproved vaccine under EUA will interfere with long-term assessment of safety and efficacy in ongoing trials, it is critical to continue to gather data about the vaccine even after it is made available under EUA. An EUA request should therefore include strategies that will be implemented to ensure that ongoing clinical trials of the vaccine are able to assess long-term safety and efficacy (including evaluating for vaccine-associated enhanced respiratory disease and decreased effectiveness as immunity wanes over time) in sufficient numbers of participants to support vaccine licensure. These strategies should address how ongoing trial(s) will handle loss of follow-up information for study participants who choose to withdraw from the study in order to receive the vaccine under an EUA.

FDA is aware that some COVID-19 vaccine developers may wish to immediately unblind their trials upon issuance of an EUA in order to rapidly provide vaccine to trial participants who received placebo. Some developers have proposed maintaining blinding in a crossover design that provides vaccine to previous placebo recipients and placebo to previous vaccine recipients. Such strategies would impact collection of longer-term placebo-controlled safety data and evaluation of the duration of vaccine efficacy. Ethical and scientific issues associated with offering vaccination to placebo recipients have been discussed in recent statements and articles.[8-10]

2.7. Previous Meetings of the VRBPAC to Discuss Vaccines to Prevent COVID-19

On October 22, 2020, the VRBPAC met in open session, to discuss, in general, the development, authorization and/or licensure of vaccines to prevent COVID-19. No specific application was discussed at this meeting. Topics discussed at the meeting included:

- FDA's approach to safety and effectiveness, and chemistry, manufacturing and control (CMC) data as outlined in the respective guidance documents

- Considerations for continuation of blinded Phase 3 clinical trials if an EUA has been issued for an investigational COVID-19 vaccine
- Studies following licensure and/or issuance of an EUA for COVID-19 vaccines to:
    - Further evaluate safety, effectiveness and immune markers of protection
    - Evaluate the safety and effectiveness in specific populations.

3. Topics for VRBPAC Discussion

The Vaccines and Related Biological Products Advisory Committee will convene on December 10, 2020, to discuss and provide recommendations on whether:

- based on the totality of scientific evidence available, it is reasonable to believe that the Pfizer-BioNTech COVID-19 Vaccine may be effective in preventing COVID-19 in individuals 16 years of age and older, and
- the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh its known and potential risks for use in individuals 16 years of age and older.

The committee will also discuss what additional studies should be conducted by the vaccine manufacturer following issuance of the EUA to gather further data on the safety and effectiveness of this vaccine.

4. Pfizer-BioNTech COVID-19 Vaccine (BNT162b2)

4.1. Vaccine Composition, Dosing Regimen

The Pfizer-BioNTech COVID-19 Vaccine is a white to off-white, sterile, preservative-free, frozen suspension for intramuscular injection. The vaccine contains a nucleoside-modified messenger RNA (modRNA) encoding the viral spike glycoprotein (S) of SARS-CoV-2. The vaccine also includes the following ingredients: lipids ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-distearoyl-sn-glycero-3-phosphocholine, and cholesterol), potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose.

The Pfizer-BioNTech COVID-19 Vaccine is supplied as a frozen [between -80°C to -60°C (-112°F to -76°F)] multi-dose (5-dose) vial. The vaccine must be thawed and diluted in its original vial with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to administration. After dilution, the vial contains 5 doses of 0.3 mL per dose. After dilution, the multiple-dose vials must be stored between 2°C to 25°C (35°F to 77°F) and used within 6 hours from the time of dilution.

The Pfizer-BioNTech COVID-19 Vaccine, BNT162b2 (30 µg), is administered intramuscularly (IM) as a series of two 30 µg doses (0.3 mL each) 21 days apart.

FDA has reviewed the CMC data submitted to date for this vaccine and has determined that the CMC information is consistent with the recommendations set forth in FDA's Guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19. As such, FDA has determined that the Sponsor has provided adequate information to ensure the vaccine's quality and consistency for authorization of the product under an EUA.

4.2. Proposed Use Under EUA

The proposed indication and use of the vaccine under an EUA is “for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.”

5. FDA Review of Clinical Safety and Effectiveness Data

5.1. Overview of Clinical Studies

Data from two ongoing clinical studies were included in the EUA request, which are summarized in Table 1 below. Study C4591001 is a multi-center, multi-national Phase 1,2,3 randomized, blinded, placebo-controlled safety, immunogenicity, and efficacy study that is the focus of the EUA review. Study BNT162-01 is a Phase 1 study that explored various vaccine candidates and dose levels and will not be discussed in detail. A brief summary of the BNT162-01 study design and results to date is found in Appendix A, page 51.

Table 1: Clinical Trials Submitted in Support of Efficacy and Safety Determinations of the Pfizer-BioNTech COVID-19 Vaccine

Study Number/ Country	Description	BNT162b2 (30 μg)* participants (N)	Placebo participants (N)	Study Status
C4591001 USA, Argentina, Brazil, Germany, S. Africa, Turkey	Phase 1,2,3 randomized, placebo-controlled, observer-blind; to evaluate safety, immunogenicity and efficacy of COVID-19 vaccine	Phase 1: 24 Phase 2/3: 21823	Phase 1: 6 Phase 2/3: 21828	Ongoing
BNT162-01 Germany	Phase 1/2 randomized, open-label; to evaluate safety and immunogenicity, dose escalation	12	0	Ongoing

N= total number of randomized participants as of November 14, 2020. Placebo: saline.
*Phase 1 studies included additional participants vaccinated with other dose levels and other mRNA vaccine candidates.
Studies C4591001 and BNT162-01 started in April 2020 (first participant, first visit).

5.2. Study C4591001

5.2.1. Design

Study C4591001 is an ongoing, randomized, placebo-controlled, phase 1/2/3 study being conducted in the US, Argentina, Brazil, Germany, South Africa and Turkey. Initially the study was designed as a phase 1/2 study in healthy adults in the US for vaccine candidate and dosage selection, immunogenicity and preliminary efficacy, but the protocol was revised to expand the study design for inclusion of a phase 2/3 portion to evaluate clinical disease endpoint efficacy in individuals 12 years of age and older in the US and additional sites outside of the US.

In phase 1, two age groups were evaluated in separate cohorts, younger participants 18 through 55 years of age (N=45) and older participants 65 through 85 years of age (N=45). The study population included healthy men and women and excluded participants at high risk of SARS-CoV-2 infection or with serological evidence of prior or current SARS-CoV-2 infection. Two different vaccine candidates were evaluated, and younger participants received escalating dose levels with progression to subsequent dose levels and evaluation of escalating dose levels in the older age group (65 through 85 years), based on recommendations from an internal review committee that reviewed safety and immunogenicity data. For each vaccine candidate and dose

level, participants were randomized 4:1, such that 12 participants received the vaccine candidate and 3 participants received placebo. Review of the safety and immunogenicity from phase 1, in combination with data from Study BNT162-01 (See Section 10), supported the final vaccine candidate and dose level (BNT162b2 at 30 µg, given 21 days apart) to proceed into phase 2/3.

In phase 2/3, participants were enrolled with stratification by age (younger adults: 18 through 55 years of age; older adults: over 55 years of age) and a goal of 40% enrollment in the older adult age group. Adolescents were added to the protocol, based on review of safety data in younger adults enrolled in the ongoing study, so the age strata were revised as follows: 12 through 15 years of age, 16 through 54 years of age, and 55 years of age and older. The study population for phase 2/3 includes participants at higher risk for acquiring COVID-19 and at higher risk of severe COVID-19 disease, such as participants working in the healthcare field, participants with autoimmune disease, and participants with chronic but stable medical conditions such as hypertension, asthma, diabetes, and infection with HIV, hepatitis B or hepatitis C. Participants were randomized 1:1 to receive 2 doses of either BNT162b2 or placebo, 21 days apart. The phase 2 portion of the study evaluated reactogenicity and immunogenicity for 360 participants enrolled early-on, and these participants also contribute to the overall efficacy and safety data in the phase 3 portion. The ongoing phase 3 portion of the study is evaluating the safety and efficacy of BNT162b2 for the prevention of COVID-19 disease occurring at least 7 days after the second dose of vaccine. Efficacy is being assessed throughout a participant's follow-up in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness, an illness visit occurs. Assessments for illness visits include a nasal (midturbinate) swab, which is tested at a central laboratory using a reverse transcription-polymerase chain reaction (RT-PCR) test (e.g., Cepheid; FDA authorized under EUA), or other sufficiently validated nucleic acid amplification-based test (NAAT), to detect SARS-CoV-2. The central laboratory NAAT result is used for the case definition, unless it is not possible to test the sample at the central laboratory. In that case, the following NAAT results are acceptable: Cepheid Xpert Xpress SARS-CoV-2Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001) Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001).

The study design includes planned interim analyses of the first primary efficacy endpoint at pre-specified numbers of COVID-19 cases (at least 62, 92, and 120 cases), and all primary and secondary efficacy endpoints were analyzed in the final efficacy analysis after at least 164 COVID-19 cases were accrued (see Statistical Analysis section, below). Participants are expected to participate for a maximum of approximately 26 months.

Primary Efficacy Endpoints

Study C4591001 has two primary endpoints:

First primary endpoint: COVID-19 incidence per 1000 person-years of follow-up in participants without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2

Second primary endpoint: COVID-19 incidence per 1000 person-years of follow-up in participants with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2

Secondary Efficacy Endpoints

Study C4591001 has secondary endpoints based on different approaches to COVID-19 case evaluation criteria as follows:

COVID-19 confirmed at least 14 days after Dose 2: COVID-19 incidence per 1000 person-years of follow up in participants either (1) without or (2) with and without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥14 days after Dose 2

Severe COVID-19: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥7 days after Dose 2 or (2) ≥14 days after Dose 2

CDC-defined COVID-19: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥7 days after Dose 2 or (2) ≥14 days after Dose 2.

For the primary efficacy endpoint, the case definition for a confirmed COVID-19 case was the presence of at least one of the following symptoms and a positive SARS-CoV-2 NAAT within 4 days of the symptomatic period:

- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhea;
- Vomiting.

For a secondary efficacy endpoint, a second definition, which may be updated as more is learned about COVID-19, included the following additional symptoms defined by CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html):

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea.

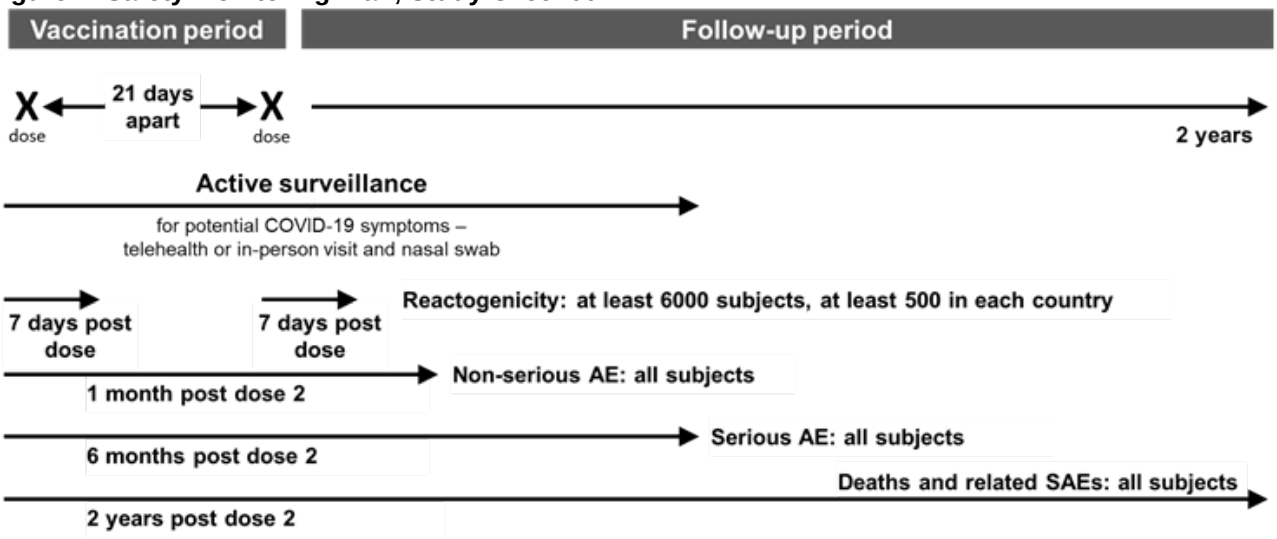
For another secondary endpoint, the case definition for a severe COVID-19 case was a confirmed COVID-19 case with at least one of the following:

- Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO2 ≤93% on room air at sea level, or PaO2/FiO2 <300 mm Hg);
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an ICU;
- Death.

Evaluation of Safety

The primary safety objective for all phases was to describe the safety of BNT162 vaccine(s) in healthy adults after 1 or 2 doses. All phase 1 participants (n=30), and then 6653 U.S. participants (360 phase 2, 6293 phase 3) and the first ~500 phase 3 participants/per country with enrollment through October 9, 2020 (Argentina, Brazil and South Africa) recorded local reactions, systemic events, and antipyretic/pain medication usage from Day 1 through Day 7 after each dose. Unsolicited adverse events (AEs) are collected from Dose 1 to 1 month after the last dose and serious AEs (SAEs) from Dose 1 to 6 months after the last dose. Figure 1 below shows the study safety monitoring plan.

Figure 1. Safety Monitoring Plan, Study C4591001



Reactogenicity assessments included solicited injection site reactions (pain, redness, swelling) and systemic AEs (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain), and antipyretic/pain medication use were recorded in an e-diary. At the data cutoff date for the EUA, reactogenicity events were not collected from adolescents 16 to 17 years of age (enrolled prior to the implementation of Protocol Amendment 9, finalized on 29 October 2020) using an e-diary but were detected and reported as unsolicited AEs. For any phase 3 participants who were not in the reactogenicity subset, local reactions and systemic events consistent with reactogenicity were detected and reported as unsolicited AEs. HIV-positive participants and adolescents 12 through 15 years of age were included in the reactogenicity subset with implementation of protocol amendment 6 (finalized on September 8, 2020) and amendment 7 (finalized on October 6, 2020), respectively. Solicited reactogenicity data in adolescents 16-17 years of age are not available for the reporting period. Reactogenicity data from a total of 100 adolescents 12 through 15 years of age enrolled in C4591001 phase 2/3 were provided in the EUA submission. However, the Sponsor did not request inclusion of this age group in the EUA because the available data, including number of participants and follow-up duration, were insufficient to support favorable a benefit-risk determination at this time. Therefore, the reactogenicity data for participants 12 through 15 years of age are not presented in this document.

Clinical laboratory tests were assessed in phase 1 at 1-week postvaccination. The planned safety follow-up for currently enrolled adolescents and adults is through 24 months after vaccination #2.

Potential COVID-19 illnesses and their sequelae were not to be reported as AEs, with the exception of illnesses that met regulatory criteria for seriousness and were not confirmed to be COVID-19. These illnesses were evaluated and reported as SAEs.

In phase 2/3, monitoring for risk of vaccine-enhanced disease was performed by an unblinded team supporting the Data Monitoring Committee that reviewed cases of severe COVID-19 as they were received and reviewed AEs at least weekly for additional potential cases of severe COVID-19. The stopping rule was triggered when the 1-sided probability of observing the same or a more extreme case split was 5% or less when the true incidence of severe disease was the same for vaccine and placebo participants, and alert criteria were triggered when this probability was less than 11%.

Analysis Populations

For the purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed informed consent document.
Randomized	All participants who are assigned a randomization number.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
All-available efficacy	1. All randomized participants who receive at least 1 vaccination. 2. All randomized participants who complete 2 vaccination doses.

Phase 2/3 safety analysis populations were as follows:

- Phase 2/3 all-enrolled population: composed of a total of 43,448 (21720 vaccine, 21728 placebo) participants ≥16 years of age, regardless of duration of follow-up, for whom written informed consent was obtained. Initial enrollment included individuals 18 years and older, then included individuals as young as 16 years of age and individuals with known HIV (protocol amendment 6; finalized on September 8, 2020). As of November 14, 2020, 43.9% and 79.5% of vaccine recipients completed at least 2 months (≥8 weeks) and at least 1 month (≥4 weeks), respectively, of safety follow-up after Dose 2. The percentages of placebo recipients completing at least 2 months (≥8 weeks) and at least 1 month (≥4 weeks) were similar to the vaccine group.

- Phase 2/3 safety population (median follow-up time of 2 months after vaccination #2): comprised of a total of 37586 (18801 vaccine,18785 placebo) participants >16 years of age enrolled by October 9, 2020 and received at least 1 dose of study vaccine or placebo; overall, 98.1% of participants completed the 2-dose series. As of November 14, 2020, 50.6% and 91.6% of vaccine recipients completed at least 2 months (>8 weeks) and at least 1 month (>4 weeks), respectively, of safety follow-up after Dose 2. The percentages of placebo recipients completing at least 2 months (>8 weeks) and at least 1 month (>4 weeks) were similar to the vaccine group. A total of 283 (138 vaccine,145 placebo) individuals were 16 to <18 years of age. HIV-positive individuals were included in the all-enrolled population, but not the phase 2/3 safety population because the number of participants enrolled by October 9, 2020 was small (n=120) and the median duration of safety follow-up was short.

5.2.2. FDA Assessment of Phase 2/3 Follow-Up Duration

Study C4591001 initially enrolled approximately 30,000 participants and then several months later began enrollment of approximately 14,000 additional participants, including adolescents and participants with chronic, stable HIV, hepatitis B, or hepatitis C infections. Because of the gap in enrollment, the entire enrolled study population had a median follow-up of less than 2 months as of the EUA submission data cut-off date of November 14, 2020. However, the analyses submitted to support this EUA request meet the expectation for median duration of follow-up time, as follows:

- Submitted safety analyses for participants enrolled through October 9, 2020, and followed through November 14, 2020 (referred to by Pfizer and in this document as the phase 2/3 safety population and including a total of 37,586 participants), represent a median follow-up of 2 months. Additionally, this safety database is larger than for the initial planned enrollment of approximately 30,000 participants.

- The date for data cut-off for the first interim analysis for efficacy was November 4, 2020, when a total of 94 confirmed COVID-19 cases were accrued. All of the participants included in the first interim efficacy analysis had at least 7 days of follow-up after Dose 2, and thus were enrolled no later than October 7, 2020. All participants in the first interim efficacy analysis were therefore included in the phase 2/3 safety population defined above. Although the median follow-up duration for participants included in the first interim efficacy analysis was slightly less than 2 months as of November 4, 2020, these participants were also included in the final efficacy analyses with data cut-off of November 14, 2020, which extended the median follow-up for these participants to greater than 2 months. The results of the final efficacy analysis on data to November 14, 2020, indicate that the conclusions from the first interim efficacy analysis would not change when including additional follow-up to November 14, 2020.

The date for data cut-off for the final efficacy analysis was November 14, 2020, when a total of 170 confirmed COVID-19 cases were accrued. As noted above, the median follow-up duration after completion of the full vaccination regimen for all participants enrolled at that time was less than 2 months for both safety and efficacy populations, due to a gap in enrollment. Because the data for the final efficacy analysis could be submitted in support of the EUA request and could provide data from a greater number of participants than from the interim analysis, FDA has focused its review on the efficacy data from the final efficacy analyses. Additional safety analyses from this larger database of all enrolled participants were also reviewed to evaluate for differences compared with the smaller phase 2/3 safety population.

5.2.3. Subject Disposition and Inclusion in Analysis Populations

Disposition tables are presented below in Table 2 (efficacy analysis populations) and Table 3 (phase 2/3 safety population). Overall, few participants were discontinued or lost to follow-up, and these and other analysis population exclusions were generally balanced between treatment groups. Of 43,448 participants in the phase 2/3 all-enrolled population, 94.2% of vaccine recipients and 94.1% of placebo recipients completed 2 doses (data not shown).

Table 2. Efficacy Populations, Treatment Groups as Randomized

	BNT162b2 (30 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Randomized[b]	21823 (100.0)	21828 (100.0)	43651 (100.0)
Dose 1 all-available efficacy population	21768 (99.7)	21783 (99.8)	43551 (99.8)
Participants without evidence of infection before Dose 1	20314 (93.1)	20296 (93.0)	40610 (93.0)
Participants excluded from Dose 1 all-available efficacy population	55 (0.3)	45 (0.2)	100 (0.2)
Reason for exclusion[c]			
Did not receive at least 1 vaccination	54 (0.2)	45 (0.2)	99 (0.2)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Dose 2 all-available efficacy population	20566 (94.2)	20536 (94.1)	41102 (94.2)
Participants without evidence of infection prior to 7 days after Dose 2	18701 (85.7)	18627 (85.3)	37328 (85.5)
Participants without evidence of infection prior to 14 days after Dose 2	18678 (85.6)	18563 (85.0)	37241 (85.3)
Participants excluded from Dose 2 all-available efficacy population	1257 (5.8)	1292 (5.9)	2549 (5.8)
Reason for exclusion[c]			
Did not receive 2 vaccinations	1256 (5.8)	1292 (5.9)	2548 (5.8)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Evaluable efficacy (7 days) population	20033 (91.8)	20244 (92.7)	40277 (92.3)
Evaluable efficacy (14 days) population	20033 (91.8)	20243 (92.7)	40276 (92.3)
Participants excluded from evaluable efficacy (7 days) population	1790 (8.2)	1584 (7.3)	3374 (7.7)
Participants excluded from evaluable efficacy (14 days) population	1790 (8.2)	1585 (7.3)	3375 (7.7)
Reason for exclusion[c]			
Randomized but did not meet all eligibility criteria	36 (0.2)	26 (0.1)	62 (0.1)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Did not receive all vaccinations as randomized or did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	1550 (7.1)	1561 (7.2)	3111 (7.1)
Had other important protocol deviations on or prior to 7 days after Dose 2	311 (1.4)	60 (0.3)	371 (0.8)
Had other important protocol deviations on or prior to 14 days after Dose 2	311 (1.4)	61 (0.3)	372 (0.9)

[a]n = Number of participants with the specified characteristic.
[b]These values are the denominators for the percentage calculations.
[c]Participants may have been excluded for more than 1 reason.
Note: 100 participants 12 through 15 years of age with limited follow-up are included in the randomized population (49 in the vaccine group and 51 in the placebo group). Some of these subjects were included in the denominators of efficacy analyses, depending on the population analyzed, but did not contribute primary endpoint cases and do not affect efficacy conclusions for ages 16 years and above.

Table 3. Disposition of All Randomized Participants, Phase 2/3 Safety Population

Treatment Group	BNT162b2 N=18904 n (%)	Placebo N=18892) n (%)	Total N=37796 n (%)
Randomized	18904 (100.0)	18892 (100.0)	37796 (100.0)
Vaccinated			
Completed 1 dose	18858 (99.8)	18849 (99.8)	37707 (99.8)
Completed 2 doses	18555 (98.2)	18533 (98.1)	37088 (98.1)
Withdrawn from Study	180 (1.0)	259 (1.4)	439 (1.2)
Reason for Withdrawal			
Adverse Event	8 (0.0)	5 (0.0)	13 (0.0)
Death	2 (0.0)	4 (0.0)	6 (0.0)
Withdrawal by Subject	84 (0.4)	157 (0.8)	241 (0.6)
Lost to Follow-up	80 (0.4)	86 (0.5)	166 (0.4)
No longer meets eligibility criteria	1 (0.0)	2 (0.0)	3 (0.0)
Refused further study procedures	0	1 (0.0)	1 (0.0)

Source: EUA 27036, amendment 3, Table 2; c4591001-safety-tables-cos-reacto.pdf, page 43.
Note: One participant was randomized but did not sign informed consent and therefore not included in any analysis population.
Note: 120 HIV-positive participants included in this table. HIV population analyses were summarized separately from analyses based on the phase 2/3 safety population, but included in the all-enrolled poplation analyses presented in this briefing document.
%:n/N. n = number of subjects with the specified characteristic. N = number of participants ≥16 years of age enrolled by October 9, 2020, including 120 HIV-positive participants, and received at least 1 dose of study vaccine or placebo. N is the denominator used for the percentage calculations.
Data analysis cutoff date: November 14, 2020

The numbers of randomized participants contributing to efficacy analyses presented in this document include 100 participants 12 through 15 years of age (49 in the vaccine group and 51 in the placebo group) who had limited follow-up at the time of the November 14, 2020 data cut-off. However, the sponsor did not include this age group in the EUA request. The numbers of participants presented and used as denominators for efficacy calculations were not adjusted to remove participants 12 through 15 years of age. Because the number of participants 12 through 15 years of age is very small relative to the overall efficacy analysis populations, and no primary endpoint COVID-19 cases occurred in this age group, the vaccine efficacy conclusions are not impacted. No participants 12 through 15 years of age are included in the safety analyses. However, the safety disposition table includes 120 HIV-positive participants who were not included in the phase 2/3 safety population analyses.

5.2.4. Demographics and Other Baseline Characteristics

Overall, the phase 2/3 evaluable efficacy population included 49.4% females, 81.9% White, 9.8% African American, 4.4% Asian participants, and <3% from other racial groups; 26.2% of participants were Hispanic/Latino; 21.4% of participants were ≥65 years of age. The median age was 51 years. The most frequently reported comorbidities were obesity (35.1%), diabetes (with and without chronic complications, 8.4%) and pulmonary disease (7.8%). Geographically, 76.7% of participants were from the US, 15.3% from Argentina, 6.1% from Brazil, and 2% from South Africa.

The demographic characteristics among vaccine and placebo participants in the all-available efficacy population were similar to the evaluable efficacy population. Please refer to the table below.

Table 4. Demographic Characteristics, Participants With or Without Evidence of Infection Prior to 7 Days After Dose 2, Evaluable Efficacy (7 Days) Population

Characteristic	BNT162b2 (N[a]=20033) N[b] (%)	Placebo (N[a]=20244) N[b] (%)	Total (N[a]=40277) N[b] (%)
Sex: Female	9794 (48.9)	10107 (49.9)	19901 (49.4)
Sex: Male	10239 (51.1)	10137 (50.1)	20376 (50.6)
Age at Vaccination: Mean years (SD)	50.3 (15.73)	50.1 (15.78)	50.2 (15.76)
Age at Vaccination: Median (years)	51.0	51.0	51.0
Age at Vaccination: Min, max (years)	(12, 89)	(12, 91)	(12, 91)
Age Group: 16 to <18 years	77 (0.4)	76 (0.4)	153 (0.4)
Age Group: 16 to 55 years	11589 (57.8)	11743 (58.0)	23332 (57.9)
Age Group: >55 years	8396 (41.9)	8454 (41.8)	16850 (41.8)
Age Group: ≥65 years	4294 (21.4)	4319 (21.3)	8613 (21.38)
Age Group: ≥75 years	860 (4.3)	852 (4.2)	1712 (4.3)
Race: American Indian or Alaska Native	131 (0.7)	122 (0.6)	253 (0.6)
Race: Asian	880 (4.4)	883 (4.4)	1763 (4.4)
Race: Black or African American	1957 (9.8)	1972 (9.7)	3929 (9.8)
Race: Native Hawaiian or Other Pacific Islander	54 (0.3)	29 (0.1)	83 (0.2)
Race: White	16387 (81.8)	16619 (82.1)	33006 (81.9)
Race: Multiracial	523 (2.6)	493 (2.4)	1016 (2.5)
Race: Not reported	101 (0.5)	126 (0.6)	227 (0.6)
Ethnicity: Hispanic or Latino	5272 (26.3)	5281 (26.1)	10553 (26.2)
Ethnicity: Not Hispanic or Latino	14652 (73.1)	14847 (73.3)	29499 (73.2)
Ethnicity: Not reported	109 (0.5)	116 (0.6)	225 (0.6)
Comorbidities[c]: Yes	9278 (46.3)	9314 (46.0)	18592 (46.2)
Comorbidities: No	10755 (53.7)	10930 (54.0)	21685 (53.8)
Comorbidity: Obesity	6934 (34.6)	7093 (35.0)	14027 (34.8)

[a].N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[b].n = number of participants with the specified characteristic.
[c]. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as patients who had at least one of the Charlson comorbidity index (Appendix B, page 52) category or obesity only (BMI ≥30 kg/m^2).

Overall, the phase 2/3 safety population included 83.1% White, 9.1% African American, 4.3% Asian participants, and <3% from other racial groups; 28.0% of participants were Hispanic/Latino; 21.6% of participants were >65 years of age. The median age was 52 years, and safety data from a total of 103 participants 16 and 17 years of age were included in this submission. The most frequently reported comorbidities were obesity (35.1%), diabetes (without chronic complications, 7.8%) and chronic pulmonary disease (7.8%). Geographically, 76.7% of participants were from the US, 15.3% from Argentina, 6.1% from Brazil, and 2.0% from South Africa.

The demographic characteristics among vaccine and placebo participants in the all-enrolled population were similar and were also enrolled from sites in Germany (1%) and Turkey (1%). There were no significant imbalances in demographic and other baseline characteristics between the all-enrolled population and phase 2/3 safety population with median 2-month follow-up.

Table 5. Demographics and Other Baseline Characteristics, Phase 2/3 Safety Population

Characteristic	BNT162b2 N=18801 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	Placebo N=18785 n (%)	Placebo n (%)	Placebo n (%)	Placebo n (%)	Total N=37586 n (%)
Age (years)	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	
Age (years)									
Mean [SD]	16.40 [0.49]	44.99 [12.66]	68.84 [2.80]	78.07 [2.78]	16.36 [0.48]	44.78 [12.72]	68.84 [2.78]	78.10 [2.81]	50.38 [15.70]
Median	16	46	68	77	16	46	69	77	52
Min, max	16-17	18-64	65-74	75-89	16-17	18-64	65-74	75-91	16-91
Sex									
Male	33 (0.2)	7385 (39.3)	1714 (9.1)	470 (2.5)	24 (0.1)	7153 (38.1)	1724 (9.2)	498 (2.7)	19001 (50.6)
Female	20 (0.1)	7305 (38.9)	1513 (8.0)	361 (1.9)	26 (0.1)	7539 (40.1)	1511 (8.0)	310 (1.7)	18585 (49.4)
Race									
White	37 (0.2)	11895 (63.3)	2908 (15.5)	775 (4.1)	38 (0.2)	11891 (63.3)	2930 (15.6)	756 (4.0)	31230 (83.1)
African American	11 (0.1)	1477 (7.9)	186 (1.0)	20 (0.1)	7 (0.0)	1505 (8.0)	189 (1.0)	21 (0.1)	3416 (9.1)
Asian	0 (0.0)	693 (3.7)	81 (0.4)	26 (0.1)	0 (0.0)	715 (3.8)	72 (0.4)	19 (0.1)	1606 (4.3)
Multiracial	3 (0.0)	417 (2.2)	21 (0.1)	7 (0.0)	3 (0.0)	379 (2.0)	18 (0.1)	5 (0.0)	853 (2.3)
Not reported	0 (0.0)	82 (0.4)	11 (0.1)	0 (0.0)	1 (0.0)	98 (0.5)	10 (0.1)	5 (0.0)	207 (0.6)
American Indian or Alaska native	0 (0.0)	84 (0.4)	15 (0.1)	2 (0.0)	1 (0.0)	83 (0.4)	11 (0.1)	2 (0.0)	198 (0.5)
Nat. HI or other Pac. Isl.	2 (0.0)	42 (0.2)	5 (0.0)	1 (0.0)	0 (0.0)	21 (0.1)	5 (0.0)	0 (0.0)	76 (0.2)
Ethnicity									
Hispanic or Latino	6 (0.0)	4595 (24.4)	549 (2.9)	103 (0.5)	5 (0.0)	4616 (24.6)	558 (3.0)	90 (0.5)	10522 (28.0)
Non-Hispanic/non-Latino	47 (0.2)	10009 (53.2)	2658 (14.1)	722 (3.8)	44 (0.2)	10004 (53.3)	2652 (14.1)	707 (3.8)	26843 (71.4)
Not reported	0 (0.0)	86 (0.5)	20 (0.1)	6 (0.0)	1 (0.0)	72 (0.4)	25 (0.1)	11 (0.1)	221 (0.6)
Baseline Body Mass Index (BMI)									
Obese	3 (0.0)	5200 (27.7)	1079 (5.7)	248 (1.3)	14 (0.1)	5242 (27.9)	1147 (6.1)	235 (1.3)	13168 (35.0)
Overweight	14 (0.1)	4901 (26.1)	1278 (6.8)	368 (2.0)	9 (0.0)	4857 (25.9)	1255 (6.7)	340 (1.8)	13022 (34.6)

Characteristic	BNT162b2 N=18801 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	Placebo N=18785 n (%)	Placebo n (%)	Placebo n (%)	Placebo n (%)	Total N=37586 n (%)
Age (years)	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	
Baseline Evidence of Prior SARS-CoV-2 Infection									
Negative	48 (0.3)	13879 (73.8%)	3109 (16.5)	805 (4.3)	47 (0.3%)	13858 (73.8%)	3115 (16.6%)	788 (4.2%)	35649 (94.8%)
Positive	3 (0.0)	473 (2.5%)	53 (0.3)	16 (0.1)	3 (0.0%)	520 (2.8%)	52 (0.3%)	5 (0.0%)	1125 (3.0%)
Missing	2 (0.0)	338 (1.8%)	65 (0.3)	10 (0.1)	0 (0.0%)	314 (1.7%)	68 (0.4%)	15 (0.1%)	812 (2.2%)
Comorbidities									
No	48 (0.3)	12353 (65.7%)	2081 (11.1)	444 (2.4)	37 (0.2%)	12412 (66.1%)	2118 (11.3%)	470 (2.5%)	29963 (79.7%)
Yes	5 (0.0)	2337 (12.4%)	1146 (6.1)	387 (2.1)	13 (0.1%)	2280 (12.1%)	1117 (5.9%)	338 (1.8%)	7623 (20.3%)
Diabetes Without Chronic Complication	0 (0.0)	814 (4.3%)	497 (2.6)	156 (0.8)	1 (0.0%)	849 (4.5%)	491 (2.6%)	132 (0.7%)	2940 (7.8%)
Chronic Pulmonary Disease	5 (0.0)	1093 (5.8%)	286 (1.5)	89 (0.5)	12 (0.1%)	1060 (5.6%)	309 (1.6%)	66 (0.4%)	2920 (7.8%)
Myocardial Infarction	0 (0.0)	82 (0.4%)	71 (0.4)	41 (0.2)	0 (0.0%)	73 (0.4%)	83 (0.4%)	31 (0.2%)	381 (1.0%)
Peripheral Vascular Disease	0 (0.0)	26 (0.1%)	67 (0.4)	31 (0.2)	0 (0.0%)	29 (0.2%)	52 (0.3%)	33 (0.2%)	238 (0.6%)
Liver Disease (mild, moderate or severe)	0 (0.0)	83 (0.4%)	34 (0.2)	7 (0.0)	0 (0.0%)	67 (0.4%)	17 (0.1%)	6 (0.0%)	214 (0.6%)
Diabetes With Chronic Complication	0 (0.0)	47 (0.2%)	36 (0.2)	15 (0.1)	0 (0.0%)	47 (0.3%)	47 (0.3%)	18 (0.1%)	210 (0.6%)
Congestive Heart Failure	0 (0.0)	44 (0.2%)	26 (0.1)	17 (0.1)	0 (0.0%)	36 (0.2%)	30 (0.2%)	16 (0.1%)	169 (0.4%)
AIDS/HIV	0 (0.0)	0 (0.0%)	0 (0.0)	0 (0.0)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)

Characteristic	BNT162b2 N=18801 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	Placebo N=18785 n (%)	Placebo n (%)	Placebo n (%)	Placebo n (%)	Total N=37586 n (%)
Age (years)	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	
Hypertension only	0 (0.0)	2569 (13.7%)	1528 (8.1)	488 (2.6)	1 (0.0%)	2621 (14.0%)	1569 (8.4%)	432 (2.3%)	9208 (24.5%)

Source: FDA-generated table.
Abbreviations: n = number of participants with the specified characteristic; N = number of participants ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo, N is denominator for the percentage calculations; SD = standard deviation; min, max = minimum, maximum; Nat. HI = Native Hawaiian; Pac. Isl. = Pacific Islander
Data analysis cutoff date: November 14, 2020.

5.2.5. Vaccine Efficacy

Primary Efficacy Analyses

Efficacy Results – Primary Endpoint (Evaluable Efficacy Population)

For the first primary efficacy endpoint, vaccine efficacy (VE) for BNT162b2 against confirmed COVID-19 was evaluated in participants without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2. For the second primary efficacy endpoint, VE for BNT162b2 against confirmed COVID-19 was evaluated in participants with and without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2. Cases were counted from 7 days after Dose 2 for both endpoints. The criterion for success was met if the posterior probability that true vaccine efficacy >30% conditioning on the available data was >99.5% at the final analysis.

For participants without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0%. The case split was 8 COVID-19 cases in the BNT162b2 group compared to 162 COVID-19 cases in the placebo group (Table 6). The 95% credible interval for the vaccine efficacy was 90.3% to 97.6%, indicating that the true VE is at least 90.3% with a 97.5% probability, which met the pre-specified success criterion.

Table 6. Final Analysis of Efficacy of BNT162b2 Against Confirmed COVID-19 From 7 Days After Dose 2 in Participants Without Evidence of Prior SARS-CoV-2 Infection - Evaluable Efficacy Population

Pre-specified Age Group	BNT162b2 N[a] = 18198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a] =18325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)	Met Predefined Success Criterion*
All participants	8 2.214 (17411)	162 2.222 (17511)	95.0 (90.3, 97.6)[e]	Yes
16 to 55 years	5 1.234 (9897)	114 1.239 (9955)	95.6 (89.4, 98.6)[f]	NA
> 55 years and older	3 0.980 (7500)	48 0.983 (7543)	93.7 (80.6, 98.8)[f]	NA

*Success criterion: the posterior probability that true vaccine efficacy > 30% conditioning on the available data is >99.5% at the final analysis

[a] N = number of participants in the specified group.

[b] n1 = Number of participants meeting the endpoint definition.

[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

[d] n2 = Number of participants at risk for the endpoint.

[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.

[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

For participants with and without evidence of SARS-CoV-2 infection before and during vaccination regimen, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 94.6%, with 9 and 169 cases in the BNT162b2 and placebo groups respectively (Table 7). The posterior probability was >99.99% for the true VE being greater than 30%. The 95% credible interval for the vaccine efficacy was 89.9% to 97.3%, indicating that the true VE is at least 89.9% with a 97.5% probability given the available data.

Table 7. Efficacy of BNT162b2 Against Confirmed COVID-19 From 7 Days After Dose 2 in Participants With And Without Evidence of Prior SARS-CoV-2 Infection, Evaluable Efficacy Population

Pre-specified Age Group	BNT162b2 N[a] = 19965 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a] =20172 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)	Met Predefined Success Criterion*
All participants	9 2.332 (18559)	169 2.345 (18708)	94.6 (89.9, 97.3)[e]	Yes
16 to 55 years	6 1.309 (10653)	120 1.317 (10738)	95.0 (88.7, 98.2)[f]	NA
>55 years and older	3 1.022 (7892)	49 1.028 (7956)	93.8 (80.9, 98.8)[f]	NA

*Success criterion: the posterior probability that true vaccine efficacy >30% conditioning on the available data is >99.5% at the final analysis
[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
[d] n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Subgroup Analyses of Vaccine Efficacy

Subgroup analyses of the second primary efficacy endpoint provide additional information about the VE for participants with and without evidence of infection prior to vaccination in specific populations enrolled, which is the endpoint considered to represent the general population who may receive the vaccine, as baseline evidence of prior infection may not be known by all people who might receive the vaccine. The results are displayed below in Table 8. The VE point estimates for the subgroup analyses were comparable to results for the first primary efficacy endpoint.

VE point estimates were uniformly high across the subgroups examined with the exception of participants identifying as multiracial and participants with evidence of prior SARS-CoV-2 infection at enrollment, for which too few COVID-19 cases occurred to interpret efficacy data for these subgroups. Additionally, the numbers of participants and cases in some other specific subgroups, such as the adolescent age group and racial subgroups, limits the interpretability of the VE results because of the wide credible intervals, but are displayed for completeness.

Table 8: Subgroup Analyses of Second Primary Endpoint: First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup, Participants With and Without Evidence of Infection Prior to 7 Days After Dose 2, Evaluable Efficacy (7 Days) Population

Efficacy Endpoint Subgroup	BNT162b2 N[a]=19965 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=20172 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
Overall	9 2.332 (18559)	169 2.345 (18708)	94.6 (89.6, 97.6)
Age group (years)			
16 to 17	0 0.003 (58)	1 0.003 (61)	100.0 (-3969.9, 100.0)
18 to 64	8 1.799 (14443)	149 1.811 (14566)	94.6 (89.1, 97.7)
65 to 74	1 0.424 (3239)	14 0.423 (3255)	92.9 (53.2, 99.8)
≥75	0 0.106 (805)	5 0.109 (812)	100.0 (-12.1, 100.0)
At risk[f]			
Yes	4 1.083 (8584)	87 1.084 (8609)	95.4 (87.8, 98.8)
No	5 1.250 (9975)	82 1.261 (10099)	93.8 (85.0, 98.1)
Age group (years) and at risk			
16-64 and not at risk	5 1.012 (8172)	75 1.019 (8239)	93.3 (83.6, 97.9)
16-64 and at risk	3 0.790 (6329)	75 0.794 (6388)	96.0 (87.8, 99.2)
≥65 and not at risk	0 0.238 (1794)	7 0.241 (1849)	100.0 (29.5, 100.0)
≥65 and at risk	1 0.293 (2250)	12 0.290 (2218)	91.7 (44.2, 99.8)
Obese[g]			
Yes	3 0.810 (6445)	68 0.832 (6582)	95.5 (86.2, 99.1)
No	6 1.522 (12108)	101 1.513 (12120)	94.1 (86.7, 97.9)
Age group (years) and obese			
16-64 and not obese	5 1.163 (9380)	89 1.162 (9422)	94.4 (86.4, 98.2)
16-64 and obese	3 0.637 (5116)	61 0.651 (5199)	95.0 (84.6, 99.0)
≥65 and not obese	1 0.358 (2715)	12 0.351 (2685)	91.8 (44.7, 99.8)
≥65 and obese	0 0.172 (1328)	7 0.180 (1382)	100.0 (27.4, 100.0)
Sex			
Female	5 1.149 (9102)	84 1.176 (9366)	93.9 (85.2, 98.1)
Male	4 1.183 (9457)	85 1.170 (9342)	95.3 (87.6, 98.8)
Ethnicity			
Hispanic or Latino	3 0.637 (5074)	55 0.638 (5090)	94.5 (83.2, 98.9)

Efficacy Endpoint Subgroup	BNT162b2 N[a]=19965 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=20172 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
Not Hispanic or Latino	6 1.681 (13380)	114 1.693 (13509)	94.7 (88.1, 98.1)
Race			
American Indian or Alaska native	0 0.011 (104)	1 0.010 (104)	100.0 (-3511.0, 100.0)
Asian	1 0.095 (796)	4 0.097 (808)	74.4 (-158.7, 99.5)
Black or African American	0 0.187 (1758)	7 0.188 (1758)	100.0 (30.4, 100.0)
Native Hawaiian or other Pacific Islander	0 0.006 (50)	1 0.003 (29)	100.0 (-2112.1, 100.0)
White	7 1.975 (15294)	153 1.990 (15473)	95.4 (90.3, 98.2)
Multiracial	1 0.047 (467)	1 0.042 (424)	10.4 (-6934.9, 98.9)
Not reported	0 0.010 (90)	2 0.013 (112)	100.0 (-581.6, 100.0)
Baseline SARS-CoV-2 Status			
Positive[h]	1 0.056 (526)	1 0.060 (567)	-7.1 (-8309.9, 98.6)
Negative[i]	8 2.237 (17637)	164 2.242 (17720)	95.1 (90.1, 97.9)
Unknown	0 0.039 (396)	4 0.043 (421)	100.0 (-68.9, 100.0)

[a.] N = number of participants in the specified group.
[b.] n1 = Number of participants meeting the endpoint definition.
[c.] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
[d.] n2 = Number of participants at risk for the endpoint.
[e.] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.
[f.] At risk is defined as having at least one of the Charlson comorbidity index (Appendix B, page 52) category or obesity (BMI ≥30 kg/m^2).
[g.] Obese is defined as BMI ≥30 kg/m^2.
[h.] Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
[i.] Negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.

The demographics of the participants with confirmed COVID-19 cases contributing to the primary efficacy analysis are displayed below in Table 9.

Table 9. Demographic Characteristics, Participants With Protocol Defined Case (Without Evidence of Infection Prior to 7 Days After Dose 2)

Characteristic	BNT162b2 (N[a]=8) N[b] (%)	Placebo (N[a]=162) N[b] (%)	Total (N[a]=170) N[b] (%)
Sex: Female	5 (62.5)	81 (50.0)	86 (50.6)
Sex: Male	3 (37.5)	81 (50.0)	84 (49.4)
Age at Vaccination: Mean years (SD)	51.4 (12.47)	47.4 (15.21)	47.6 (15.09)
Age at Vaccination: Median (years)	51	48	48
Age at Vaccination: Min, max (years)	(30, 69)	(18, 79)	(18, 79)
Age Group: 16 to < 18 years	0	0	0
Age Group: 18 to < 65 years	7 (87.5)	143 (88.3)	150 (88.2)
Age Group: ≥ 65 to < 75 years	1 (12.5)	14 (8.6)	15 (8.8)
Age Group: ≥ 75 years	0	5 (3.1)	5 (2.9)
Race: American Indian or Alaska Native	0	1 (0.6)	1 (0.6)
Race: Asian	1 (12.5)	4 (2.5)	5 (2.9)
Race: Black or African American	0	7 (4.3)	7 (4.1)
Race: Native Hawaiian or Other Pacific Islander	0	1 (0.6)	1 (0.6)
Race: White	7 (87.5)	146 (90.1)	153 (90.0)
Race: Multiracial	0	1 (0.6)	1 (0.6)
Race: Not reported	0	2 (1.2)	2 (1.2)
Ethnicity: Hispanic or Latino	3 (37.5)	53 (32.7)	56 (32.9)
Ethnicity: Not Hispanic or Latino	5 (62.5)	109 (67.3)	114 (67.1)
Ethnicity: Not reported	0	0	0
Comorbidities[c]: Yes	4 (50.0)	86 (53.1)	90 (52.9)
Comorbidities: No	4 (50.0)	76 (46.9)	80 (47.1)
Comorbidity: Obesity	3 (37.5)	67 (41.4)	70 (41.2)

[a] N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[b] n = Number of participants with the specified characteristic.
[c] Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as patients who had at least one of the Charlson comorbidity index (Appendix B, page 52) category or obesity only (BMI ≥30 kg/m^2).

Only 3% of participants had evidence of prior infection at study enrollment, and additional analyses showed that very few COVID-19 cases occurred in these participants over the course of the entire study (9 in the placebo group and 10 in the BNT162b2 group, only 1 of which occurred 7 days or more after completion of the vaccination regimen – data not shown). The placebo group attack rate from enrollment to the November 14, 2020, data cut-off date was 1.3% both for participants without evidence of prior infection at enrollment (259 cases in 19,818 participants) and for participants with evidence of prior infection at enrollment (9 cases in 670 participants). While limited, these data do suggest that previously infected individuals can be at risk of COVID-19 (i.e., reinfection) and could benefit from vaccination.

Additional analyses of the first primary efficacy endpoint were conducted to evaluate the vaccine efficacy, by comorbidity status. VE point estimates were uniformly high across the comorbidities examined, though for some interpretation of the results is limited by small numbers of participants and/or cases.

Table 10. Vaccine Efficacy: First COVID-19 Occurrence From 7 Days After Dose 2, by Comorbidity Status, Among Participants Without Evidence of Infection Prior to 7 Days After Dose 2, Evaluable Efficacy (7 Days) Population

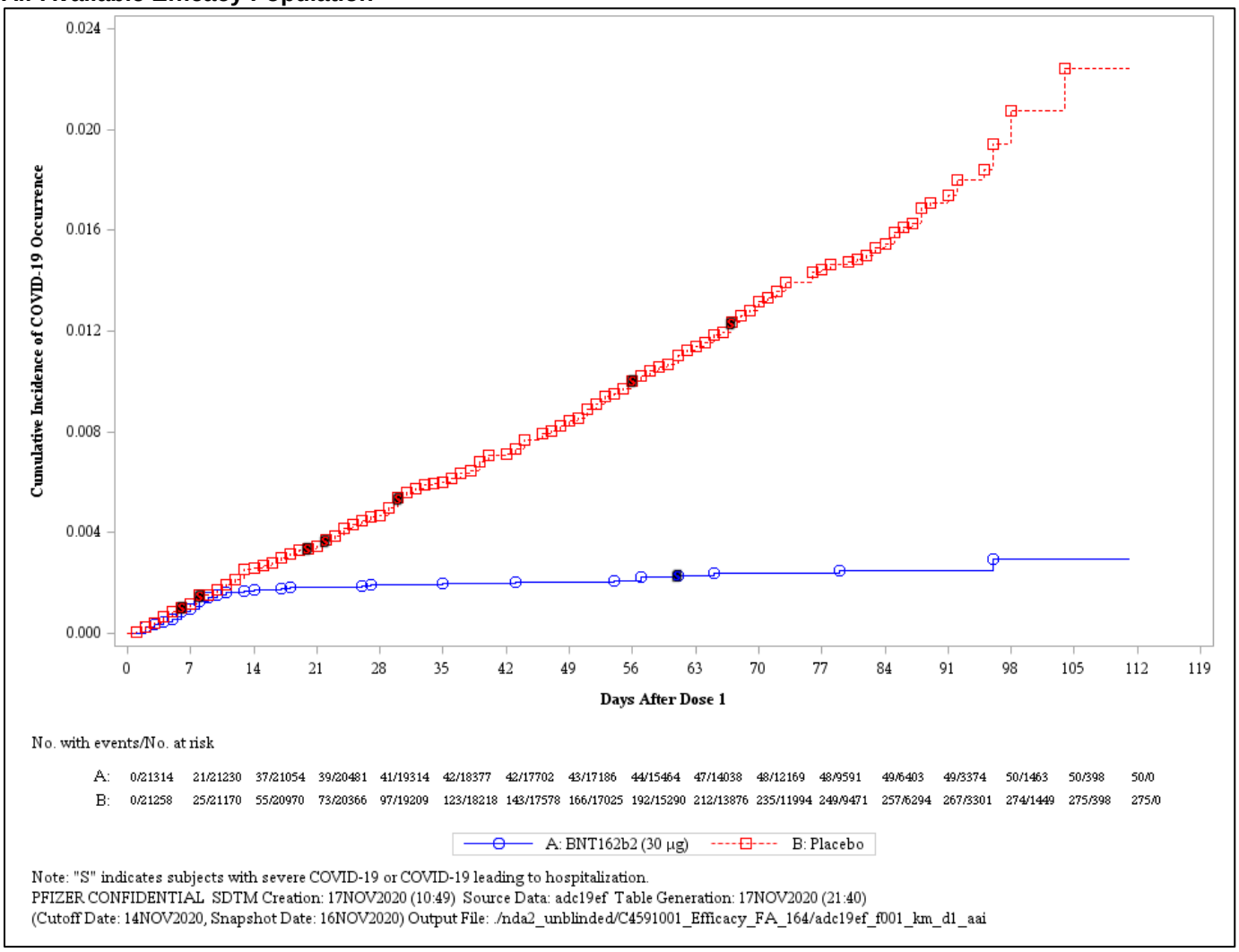
Efficacy Endpoint Subgroup	BNT162b2 (30 µg) N[a]=18198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
Overall	8 2.214 (17411)	162 2.222 (17511)	95.0 (90.0, 97.9)
Comorbidity			
No comorbidity	4 1.189 (9381)	76 1.197 (9482)	94.7 (85.9, 98.6)
Any comorbidity[f]	4 1.025 (8030)	86 1.025 (8029)	95.3 (87.7, 98.8)
Any malignancy	1 0.092 (704)	4 0.090 (681)	75.7 (-145.8, 99.5)
Cardiovascular	0 0.067 (534)	5 0.062 (492)	100.0 (-0.8, 100.0)
Chronic pulmonary disease	1 0.175 (1374)	14 0.171 (1358)	93.0 (54.1, 99.8)
Diabetes	1 0.176 (1372)	19 0.176 (1374)	94.7 (66.8, 99.9)
Obese (BMI≥30.0 kg/m^2)	3 0.763 (6000)	67 0.782 (6103)	95.4 (86.0, 99.1)
Hypertension	2 0.567 (4413)	44 0.567 (4437)	95.4 (82.6, 99.5)
Diabetes (including gestational diabetes)	1 0.177 (1381)	20 0.178 (1384)	95.0 (68.7, 99.9)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
[d] n2 = Number of participants at risk for the endpoint.
[e] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
[f] Subject who had 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least one of the Charlson comorbidity index (Appendix B, page 52) category or BMI ≥30 kg/m2.

Cumulative Incidence Curves

Based on the cumulative incidence curve for the all-available efficacy population after Dose 1, (Figure 2), COVID-19 disease onset appears to occur similarly for both BNT162b2 and placebo groups until approximately 14 days after Dose 1, at which time point, the curves diverge, with more cases accumulating in the placebo group than in the BNT162b2 group, and there does not appear to be evidence of waning protection during the follow-up time of approximately 2 months following the second dose that is being evaluated at this point in time.

Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1, Dose 1 All-Available Efficacy Population



Secondary Efficacy Analyses

The secondary efficacy endpoints evaluate the VE of BNT162b2 for the prevention of COVID-19 disease from 14 days after Dose 2 and based on the CDC's definition of COVID-19 disease from 7 and 14 days after Dose 2. The case splits and VE for each of these secondary efficacy endpoints were each similar to the primary efficacy endpoints described above.

Severe COVID-19 Cases

In the final analysis of the evaluable efficacy population (7 days), four participants had severe COVID-19 disease at least 7 days after Dose 2 (one subject who received BNT162b2 and three participants who received placebo). The vaccine recipient who had severe COVID-19 disease met the severe case definition because oxygen saturation at the COVID-19 illness visit was 93% on room air. The subject was not hospitalized, did not seek further medical care, and did not have risk factors for severe disease. The three placebo recipients who had severe COVID-19 disease met the severe case definition for the following reasons: one subject had an oxygen saturation of 92% on room air without other severe disease criteria, one subject was

hospitalized for noninvasive positive pressure ventilation with bilateral pneumonia, and one subject had an oxygen saturation of 92% and ICU admission for heart block. One of these placebo recipients with severe disease also had a body mass index > 30 kg/m^2 as a risk factor, while the other two participants did not have any risk factors for severe disease. The vaccine efficacy of this secondary efficacy endpoint is shown in Table 11.

Table 11. First Severe COVID-19 Occurrence from 7 Days after Dose 2 - Evaluable Efficacy Population

Secondary Efficacy Endpoint	BNT162b2 N[a]=18198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)	Met Predefined Success Criterion*
First severe COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection	1 2.215 (17411)	3 2.232 (17511)	66.4 (-124.8, 96.3)[e]	No

*Success criterion: the posterior probability that true vaccine efficacy > 30% conditioning on the available data is >98.6% at the final analysis.
[a.] N = number of participants in the specified group.
[b.] n1 = Number of participants meeting the endpoint definition.
[c.] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 or 14 days after Dose 2 to the end of the surveillance period depending on specified endpoint.
[d]. n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

In the all-available efficacy population, ten participants had severe COVID-19 disease after Dose 1 (one subject who received BNT162b2 and nine participants who received placebo). Five of the remaining six placebo recipients who had severe COVID-19 disease were hospitalized, two of whom were admitted to an intensive care unit. Five of these remaining six placebo recipients who had severe disease had at least one risk factor for severe disease. The total number of severe cases is small, which limits the overall conclusions that can be drawn; however, the case split does suggest protection from severe COVID-19 disease.

Table 12. First Severe COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population

Secondary Efficacy Endpoint	BNT162b2 N[a]=21669 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21686 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
First severe case occurrence after Dose 1	1 4.021 (21314)	9 4.006 (21259)	88.9 (20.1, 99.7)[f]
After Dose 1 to before Dose 2	0	4	100.0 (-51.5, 100.0)
Dose 2 to 7 days after Dose 2	0	1	100.0 (-3800.0, 100.0)
≥7 Days after Dose 2	1	4	75.0 (-152.6, 99.5)

[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 or 14 days after Dose 2 to the end of the surveillance period depending on specified endpoint.
[d] n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Additional Efficacy Analyses

Additional analyses of the first primary efficacy endpoint were conducted to evaluate the all-available efficacy population, for all participants regardless of evidence of prior infection through 7 days after Dose 2 (Table 13).

Table 13. Primary Efficacy Endpoint –All-Available Efficacy Population

Efficacy Endpoint	BNT162b2 N[a]=21669 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21686 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
First COVID-19 occurrence after Dose 1 – Dose 1	50 4.015 (21314)	275 3.982 (21258)	82.0 (75.6, 86.9)[f]
After Dose 1 to before Dose 2	39	82	52.4 (29.5, 68.4)
Dose 2 to 7 days after Dose 2	2	21	90.5 (61, 98.9)
≥7 Days after Dose 2	9	172	94.8 (89.8, 97.6)

[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 or 14 days after Dose 2 to the end of the surveillance period depending on specified endpoint.
[d] n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

VE in participants in the all-available efficacy population was similar to results in the evaluable efficacy population. The VE for the prevention of COVID-19 disease after Dose 1 is 82%, in the all-available efficacy population. Based on the number of cases accumulated after Dose 1 and before Dose 2, there does seem to be some protection against COVID-19 disease following one dose; however, these data do not provide information about longer term protection beyond 21 days after a single dose.

Efficacy Summary

The data submitted in this EUA request were consistent with the recommendations set forth in the FDA Guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19 and met the prespecified success criteria established in the protocol. In the planned interim and final analyses, vaccine efficacy after 7 days post Dose 2 was 95%, (95% CI 90.3; 97.6) in participants without prior evidence of SARS-CoV-2 infection and >94% in the group of participants with or without prior infection. Efficacy outcomes were consistently robust (⩾93%) across demographic subgroups.

Efficacy against severe COVID-19 occurring after the first dose was 88.9% (95% CI 20.1, 99.7), with an estimated VE of 75.0% (95% CI -152.6, 99.5) (1 case in BNT162b2 group and 4 cases in placebo group) against severe COVID-19 occurring at least 7 days after Dose 2.

Among all participants (regardless of evidence of infection before or during the vaccination regimen), 50 cases of COVID-19 occurred after Dose 1 in the BNT162b2 group compared with 275 cases in the placebo group, indicating an estimated VE of 82% (95% CI: 75.6%, 86.9%) against confirmed COVID-19 occurring after Dose 1, with VE of 52.4% (95% CI: 29.5%, 68.4%) between Dose 1 and Dose 2. The efficacy observed after Dose 1 and before Dose 2, from a post-hoc analysis, cannot support a conclusion on the efficacy of a single dose of the vaccine, because the time of observation is limited by the fact that most of the participants received a

second dose after three weeks. The trial did not have a single-dose arm to make an adequate comparison.

5.2.6. Safety

Overview of Adverse Events

Table 14 below presents an overview of all adverse events in the phase 2/3 safety population. A higher proportion of vaccine recipients reported adverse events compared with placebo recipients, and this imbalance was driven by reactogenicity (solicited adverse events) reported in the 7 days following vaccination and unsolicited adverse events corresponding to reactogenicity symptoms among participants not in the reactogenicity subset (see presentation of unsolicited adverse events in a later section). Proportions of participants with serious adverse events, deaths, and withdrawals due to adverse events were balanced between treatment groups.

Table 14. Study C4591001 Safety Overview- Ages 16 years and older

Participants Experiencing at Least One:	BNT162b2 n/N (%)	Placebo n/N (%)
Immediate unsolicited AE Within 30 minutes after vaccination[a]		
Dose #1	78/18801 (0.4)	66/18785 (0.4)
Dose #2	52/18494 (0.3)	39/18470 (0.2)
Solicited injection site reaction within 7 days[b]		
Dose #1	3216/4093 (78.6)	525/4090 (12.8)
Dose #2	2748/3758 (73.1)	396/3749 (10.6)
Solicited systemic AE within 7 days[b]		
Dose #1	2421/4093 (59.1)	1922/4090 (47.0)
Dose #2	2627/3758 (69.9)	1267/3749 (33.8)
From Dose 1 through 1 month after Dose 2[a]		
Unsolicited non-serious AE	5071/18801 (27.0)	2356/18785 (12.5)
SAE	103/18801 (0.5)	81/18785 (0.4)
From Dose 1 through cutoff date (safety population)		
SAE	124/18801 (0.7)	101/18785 (0.5)
From Dose 1 through cutoff date (all-enrolled)[c]		
Withdrawal due AEs	37/21621 (0.6)	30/21631 (0.5)
SAE	126/21621 (0.6)	111/21631 (0.5)
Deaths	2/21621 (0.0)	4/21631 (0.0)

Source: c4591001-safety-tables-ae3.pdf pages 216,446,459,463; c4591001-safety-tables-cos-reacto.pdf, pages 113-114.
n= number of participants with the specified reaction or AE.
[a] N: number of participants in the phase 2/3 safety population.
[b] N: number of participants in the reactogenicity subset of the phase 2/3 safety population.
[b] N: number of participants in the all-enrolled population.
Data analysis cutoff date: November 14, 2020.

Solicited Local Reactions and Systemic Adverse Events

As of the cutoff date, solicited reactogenicity data in participants 16 and 17 years of age were not collected by e-diary and are not available. Symptoms consistent with solicited reactogenicity that were reported by these participants were collected and analyzed as unsolicited adverse events and are discussed with review of those data.

Solicited Local Reactions

For each age group in the reactogenicity subset (younger: 18 to 55 years, older: >55 years) and overall (18 years and older), the median onset of local reactions in the vaccine group was 0 (day of vaccination) to 2 days after either dose and lasted a median duration between 1 and 2 days.

For both age groups, injection site pain was the most frequent solicited local adverse reaction. After dose 2, the younger age group reported any pain more frequently than the older age group (77.8% vs 66.1%) and pain characterized as moderate (27.1% vs. 18.0%); a similar pattern was observed after Dose 1. Injection site redness and swelling after each dose were generally similar for both age groups.

Subgroup analyses by age

Table 15. Frequency of Solicited Local Reactions Within 7 Days After Each Vaccination, Reactogenicity Subset of the Phase 2/3 Safety Population*, 18 to 55 Years of Age

Local Reaction	BNT162b2 Dose 1 N=2238 n (%)	Placebo Dose 1 N=2248 n (%)	BNT162b2 Dose 2 N=2045 n (%)	Placebo Dose 2 N=2053 n (%)
Pain[a]				
Any	1904 (83.1)	322 (14.0)	1632 (77.8)	245 (11.7)
Mild	1170 (51.1)	308 (13.4)	1039 (49.5)	225 (10.7)
Moderate	710 (31.0)	12 (0.5)	568 (27.1)	20 (1.0)
Severe	24 (1.0)	2 (0.1)	25 (1.2)	0 (0.0)
Redness[b]				
Any	104 (4.5)	26 (1.1)	123 (5.9)	14 (0.7)
Mild	70 (3.1)	16 (0.7)	73 (3.5)	8 (0.4)
Moderate	28 (1.2)	6 (0.3)	40 (1.9)	6 (0.3)
Severe	6 (0.3)	4 (0.2)	10 (0.5)	0 (0.0)
Swelling[b]				
Any	132 (5.8)	11 (0.5)	132 (6.3)	5 (0.2)
Mild	88 (3.8)	3 (0.1)	80 (3.8)	3 (0.1)
Moderate	39 (1.7)	5 (0.2)	45 (2.1)	2 (0.1)
Severe	5 (0.2)	3 (0.1)	7 (0.3)	0 (0.0)

Source: adapted from EUA 27034, amendment 3, Table 17.
n = number of participants with the specified reaction.
N = number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.
[b] Mild: 2.0 to ≤5.0 cm; moderate: 5.0 to ≤10.0 cm; severe: >10.0 cm.
* Participants in the reactogenicity subset of the safety population ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

Table 16. Frequency of Solicited Local Reactions Within 7 Days After Each Vaccination, Reactogenicity Subset of the Phase 2/3 Safety Population*, >55 Years of Age and Older

Local Reaction	BNT162b2 Dose 1 N=1802 n (%)	Placebo Dose 1 N=1792 n (%)	BNT162b2 Dose 2 N=1660 n (%)	Placebo Dose 2 N=1646 n (%)
Pain[a]				
Any	1282 (71.1)	166 (9.3)	1098 (66.1)	127 (7.7)
Mild	1008 (55.9)	160 (8.9)	792 (47.7)	125 (7.6)
Moderate	270 (15.0)	6 (0.3)	298 (18.0)	2 (0.1)
Severe	4 (0.2)	0 (0.0)	8 (0.5)	0 (0.0)
Redness[b]				
Any	85 (4.7)	19 (1.1)	120 (7.2)	12 (0.7)
Mild	55 (3.1)	12 (0.7)	59 (3.6)	8 (0.5)
Moderate	27 (1.5)	5 (0.3)	53 (3.2)	3 (0.2)
Severe	3 (0.2)	2 (0.1)	8 (0.5)	1 (0.1)
Swelling[b]				
Any	118 (6.5)	21 (1.2)	124 (7.5)	11 (0.7)
Mild	71 (3.9)	10 (0.6)	68 (4.1)	5 (0.3)
Moderate	45 (2.5)	11 (0.6)	53 (3.2)	5 (0.3)
Severe	2 (0.1)	0 (0.0)	3 (0.2)	1 (0.1)

Source: EUA 27036, amendment 3, Table 21.
n = number of participants with the specified reaction.
N = number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.
[b] Mild: 2.0 to ≤5.0 cm; moderate: 5.0 to ≤10.0 cm; severe: >10.0 cm.
* Participants in the reactogenicity subset of the safety population ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

Solicited Systemic AEs

For each age group in the reactogenicity subset (younger: 18 to 55 years, older: >55 years) and overall (18 years and older), the median onset of systemic AEs in the vaccine group in general was 1 to 2 days after either dose and lasted a median duration of 1 day.

The frequency and severity of systemic AEs were higher in the younger than the older age groups. Within each age group, the frequency and severity of systemic AEs was higher after Dose 2 than Dose 1, except for vomiting and diarrhea, which was generally similar regardless of dose. For both age groups, fatigue, headache and new/worsened muscle pain were most common.

Subgroup analyses by age

Table 17. Frequency of Solicited Systemic Adverse Events Within 7 Days After Each Vaccination-Reactogenicity Subset of the Phase 2/3 Safety Population*, 18 to 55 Years of Age

Adverse Event	BNT162b2 Dose 1 N=2238 n (%)	Placebo Dose 1 N=2248 n (%)	BNT162b2 Dose 2 N=2045 n (%)	Placebo Dose 2 N=2053 n (%)
Fever				
≥38.0℃	85 (3.7)	20 (0.9)	331 (15.8)	10 (0.5)
>38.0℃ to 38.4℃	64 (2.8)	10 (0.4)	194 (9.2)	5 (0.2)
>38.4℃ to 38.9℃	15 (0.7)	5 (0.2)	110 (5.2)	3 (0.1)
>38.9℃ to 40.0℃	6 (0.3)	3 (0.1)	26 (1.2)	2 (0.1)
>40.0℃	0 (0.0)	2 (0.1)	1 (0.0)	0 (0.0)

Adverse Event	BNT162b2 Dose 1 N=2238 n (%)	Placebo Dose 1 N=2248 n (%)	BNT162b2 Dose 2 N=2045 n (%)	Placebo Dose 2 N=2053 n (%)
Fatigue[a]				
Any	1085 (47.4)	767 (33.4)	1247 (59.4)	479 (22.8)
Mild	597 (26.1)	46 (20.3)	442 (21.1)	248 (11.8)
Moderate	455 (19.9)	289 (12.6)	708 (33.7)	217 (10.3)
Severe	33 (1.4)	11 (0.5)	97 (4.6)	14 (0.7)
Headache[a]				
Any	959 (41.9)	775 (33.7)	1085 (51.7)	506 (24.1)
Mild	628 (27.4)	505 (22.0)	538 (25.6)	321 (15.3)
Moderate	308 (13.4)	251 (10.9)	480 (22.9)	170 (8.1)
Severe	23 (1.0)	19 (0.8)	67 (3.2)	15 (0.7)
Chills[a]				
Any	321 (14.0)	146 (6.4)	737 (35.1)	79 (3.8)
Mild	230 (10.0)	111 (4.8)	359 (17.1)	65 (3.1)
Moderate	82 (3.6)	33 (1.4)	333 (15.9)	14 (0.7)
Severe	9 (0.4)	2 (0.1)	45 (2.1)	0 (0.0)
Vomiting[b]				
Any	28 (1.2)	28 (1.2)	40 (1.9)	25 (1.2)
Mild	24 (1.0)	22 (1.0)	28 (1.3)	16 (0.8)
Moderate	4 (0.2)	5 (0.2)	8 (0.4)	9 (0.4)
Severe	0 (0.0)	1 (0.0)	4 (0.2)	0 (0.0)
Diarrhea[c]				
Any	255 (11.1)	270 (11.7)	219 (10.4)	177 (8.4)
Mild	206 (9.0)	217 (9.4)	179 (8.5)	144 (6.8)
Moderate	46 (2.0)	52 (2.3)	36 (1.7)	32 (1.5)
Severe	3 (0.1)	1 (0.0)	4 (0.2)	1 (0.0)
New or worsened muscle pain[a]				
Any	487 (21.3)	249 (10.8)	783 (37.3)	173 (8.2)
Mild	256 (11.2)	175 (7.6)	326 (15.5)	111 (5.3)
Moderate	218 (9.5)	72 (3.1)	410 (19.5)	59 (2.8)
Severe	13 (0.6)	2 (0.1)	47 (2.2)	3 (0.1)
New or worsened joint pain[a]				
Any	251 (11.0)	138 (6.0)	459 (21.9)	109 (5.2)
Mild	147 (6.4)	95 (4.1)	205 (9.8)	54 (2.6)
Moderate	99 (4.3)	43 (1.9)	234 (11.2)	51 (2.4)
Severe	5 (0.2)	0 (0.0)	20 (1.0)	4 (0.2)
Use of antipyretic or pain medication	638 (27.8)	332 (14.4)	945 (45.0)	266 (12.6)

Source: adapted from EUA 27036, amendment 3, Table 19.
n = number of participants with the specified reaction.
N = number of participants in the reactogenicity subset reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] Mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily activity.
[b] Mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration.
[c] Mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; severe: 6 or more loose stools in 24 hours.
* Participants in the reactogenicity subset of the safety population ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

Table 18. Frequency of Solicited Systemic Adverse Events Within 7 Days After Each Vaccination-Reactogenicity Subset of the Phase 2/3 Safety Population*, >55 Years of Age and Older

Adverse Event	BNT162b2 Dose 1 N=1802 n (%)	Placebo Dose 1 N=1792 n (%)	BNT162b2 Dose 2 N=1660 n (%)	Placebo Dose 2 N=1646 n (%)
Fever				
≥38.0°C	26 (1.4)	7 (0.4)	181 (10.9)	4 (0.2)
>38.0°C to 38.4°C	23 (1.3)	2 (0.1)	131 (7.9)	2 (0.1)
>38.4°C to 38.9°C	1 (0.1)	3 (0.2)	45 (2.7)	1 (0.1)
>38.9°C to 40.0°C	1 (0.1)	2 (0.1)	5 (0.3)	1 (0.1)
>40.0°C	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue[a]				
Any	615 (34.1)	405 (22.6)	839 (50.5)	277 (16.8)
Mild	373 (20.7)	252 (14.1)	351 (21.1)	161 (9.8)
Moderate	240 (13.3)	150 (8.4)	442 (26.6)	114 (6.9)
Severe	2 (0.1)	3 (0.2)	46 (2.8)	2 (0.1)
Headache[a]				
Any	454 (25.2)	325 (18.1)	647 (39.0)	229 (13.9)
Mild	348 (19.3)	242 (13.5)	422 (25.4)	165 (10.0)
Moderate	104 (5.8)	80 (4.5)	216 (13.0)	60 (3.6)
Severe	2 (0.1)	3 (0.2)	9 (0.5)	4 (0.2)
Chills[a]				
Any	113 (6.3)	57 (3.2)	377 (22.7)	46 (2.8)
Mild	87 (4.8)	40 (2.2)	199 (12.0)	35 (2.1)
Moderate	26 (1.4)	16 (0.9)	161 (9.7)	11 (0.7)
Severe	0 (0.0)	1 (0.1)	17 (1.0)	0 (0.0)
Vomiting[b]				
Any	9 (0.5)	9 (0.5)	11 (0.7)	5 (0.3)
Mild	8 (0.4)	9 (0.5)	9 (0.5)	5 (0.3)
Moderate	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Diarrhea[c]				
Any	147 (8.2)	118 (6.6)	137 (8.3)	99 (6.0)
Mild	118 (6.5)	100 (5.6)	114 (6.9)	73 (4.4)
Moderate	26 (1.4)	17 (0.9)	21 (1.3)	22 (1.3)
Severe	3 (0.2)	1 (0.1)	2 (0.1)	4 (0.2)
New or worsened muscle pain[a]				
Any	251 (13.9)	149 (8.3)	477 (28.7)	87 (5.3)
Mild	168 (9.3)	100 (5.6)	202 (12.2)	57 (3.5)
Moderate	82 (4.6)	46 (2.6)	259 (15.6)	29 (1.8)
Severe	1 (0.1)	3 (0.2)	16 (1.0)	1 (0.1)
New or worsened joint pain[a]				
Any	155 (8.6)	109 (6.1)	313 (18.9)	61 (3.7)
Mild	101 (5.6)	68 (3.8)	161 (9.7)	35 (2.1)
Moderate	52 (2.9)	40 (2.2)	145 (8.7)	25 (1.5)
Severe	2 (0.1)	1 (0.1)	7 (0.4)	1 (0.1)

Adverse Event	BNT162b2 Dose 1 N=1802 n (%)	Placebo Dose 1 N=1792 n (%)	BNT162b2 Dose 2 N=1660 n (%)	Placebo Dose 2 N=1646 n (%)
Use of antipyretic or pain medication	358 (19.9)	213 (11.9)	625 (37.7)	161 (9.8)

Source: EUA 27036, amendment 3, Table 23.
n = number of participants with the specified reaction.
N = number of participants in the reactogenicity subset reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] Mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily activity.
[b] Mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration.
[c] Mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; severe: 6 or more loose stools in 24 hours.
* Participants in the reactogenicity subset of the safety population ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

Unsolicited (non-serious) AEs

A higher frequency of unsolicited, non-serious adverse events was reported in the vaccine group compared to placebo group and was primarily attributed to local reactions and systemic adverse events in subjects not in the reactogenicity subset and are consistent with solicited reactions/events reported by reactogenicity subset participants during the first 7 days following vaccination. Table 19 below presents unsolicited adverse events reported by at least 1% of participants in any treatment group for the phase 2/3 safety population.

Reports of lymphadenopathy were imbalanced with notably more cases in the vaccine group (64) vs. the placebo group (6), which is plausibly related to vaccination. Bell's palsy was reported by four vaccine participants and none in the placebo group. These cases occurred at 3, 9, 37, and 48 days after vaccination. One case (onset at 3 days postvaccination) was reported as resolved with sequelae within three days after onset, and the other three were reported as continuing or resolving as of the November 14, 2020 data cut-off with ongoing durations of 10, 15, and 21 days, respectively. The observed frequency of reported Bell's palsy in the vaccine group is consistent with the expected background rate in the general population, and there is no clear basis upon which to conclude a causal relationship at this time, but FDA will recommend surveillance for cases of Bell's palsy with deployment of the vaccine into larger populations. There were no other notable patterns or numerical imbalances between treatment groups for specific categories (system organ class or preferred term) of non-serious adverse events, including other neurologic, neuro-inflammatory, and thrombotic events, that would suggest a causal relationship to BNT162b2 vaccine.

Table 19. Frequency of Unsolicited AEs with Occurrence in ≥1% of Participants in any Treatment Group from Dose 1 to 1-month After Dose 2, Phase 2/3 Safety Population*, 16 Years of Age and Older

System Organ Class Preferred Term	BNT162b2 N=18801 n (%)	Placebo N=18785 n (%)	Total N=37586 n (%)
General disorders and administration site conditions	3521 (18.7)	737 (3.9)	4258 (11.3)
Injection site pain	2125 (11.3)	286 (1.5)	2411 (6.4)
Fatigue	1029 (5.5)	260 (1.4)	1289 (3.4)
Pyrexia	1146 (6.1)	61 (0.3)	1207 (3.2)
Chills	999 (5.3)	87 (0.5)	1086 (2.9)
Pain	455 (2.4)	36 (0.2)	491 (1.3)
Musculoskeletal and connective tissue disorders	1387 (7.4)	401 (2.1)	1788 (4.8)
Myalgia	909 (4.8)	126 (0.7)	1035 (2.8)
Arthralgia	212 (1.1)	82 (0.4)	294 (0.8)
Nervous system disorders	1158 (6.2)	460 (2.4)	1618 (4.3)
Headache	973 (5.2)	304 (1.6)	1277 (3.4)
Gastrointestinal disorders	565 (3.0)	368 (2.0)	933 (2.5)
Diarrhoea	194 (1.0)	149 (0.8)	343 (0.9)
Nausea	216 (1.1)	63 (0.3)	279 (0.7)

Source: FDA analysis.
Adverse events in any PT = at least one adverse event experienced (regardless of the MedDRA Preferred Term)
%: n/N. n = number of participants reporting at least 1 occurrence of the specified event.
of any event. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
* Participants ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

Subgroup analyses by age

16 and 17 years of age: the table below represents an FDA-generated summary of unsolicited AEs consistent with reactogenicity and AEs that occurred at ≥1% and higher in the BNT162b2 Vaccine Group, classified by MedDRA System Organ Class and Preferred Term.

Table 20. Frequency of Unsolicited AEs with Occurrence in ≥1% of Participants in any Treatment Group from Dose 1 to 1 Month After Dose 2, Phase 2/3 Safety Population*, 16 and 17 Years of Age

System Organ Class Preferred Term	BNT162b2 N=53 n (%)	Placebo N=50 n (%)	Total N=103 n (%)
General disorders and administration site conditions	7 (13.2)	3 (6.0)	10 (9.7)
Injection site pain	5 (9.4)	2 (4.0)	7 (6.8)
Pyrexia	5 (9.4)	0	5 (4.9)
Pain	2 (3.8)	0	2 (1.9)
Chills	1 (1.9)	0	1 (1.0)
Injury, poisoning and procedural complications	1 (1.9)	0	1 (1.0)
Concussion	1 (1.9)	0	1 (1.0)
Facial bones fracture	1 (1.9)	0	1 (1.0)
Road traffic accident	1 (1.9)	0	1 (1.0)
Investigations	1 (1.9)	0	1 (1.0)
Body temperature increased	1 (1.9)	0	1 (1.0)

Source: FDA analysis.
Adverse events in any PT = at least one adverse event experienced (regardless of the MedDRA Preferred Term)
%: n/N. n = number of participants reporting at least 1 occurrence of the specified event.
of any event. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
* Participants ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

Table 21. Frequency of Unsolicited AEs with Occurrence in ≥1% of Participants in any Treatment Group from Dose 1 to 1 Month After Dose 2, Phase 2/3 Safety Population*, 65 Years and Older

System Organ Class Preferred Term	BNT162b2 (N=4058) n (%)	Placebo (N=4043) n (%)	Total (N=8101) n (%)
General disorders and administration site conditions	577 (14.2)	118 (2.9)	695 (8.6)
Injection site pain	361 (8.9)	39 (1.0)	400 (4.9)
Fatigue	175 (4.3)	44 (1.1)	219 (2.7)
Chills	143 (3.5)	19 (0.5)	162 (2.0)
Pyrexia	148 (3.6)	10 (0.2)	158 (2.0)
Pain	60 (1.5)	7 (0.2)	67 (0.8)
Musculoskeletal and connective tissue disorders	231 (5.7)	83 (2.1)	314 (3.9)
Myalgia	125 (3.1)	23 (0.6)	148 (1.8)
Arthralgia	42 (1.0)	21 (0.5)	63 (0.8)
Pain in extremity	33 (0.8)	10 (0.2)	43 (0.5)
Nervous system disorders	179 (4.4)	87 (2.2)	266 (3.3)
Headache	127 (3.1)	45 (1.1)	172 (2.1)
Gastrointestinal disorders	127 (3.1)	72 (1.8)	199 (2.5)
Diarrhea	49 (1.2)	26 (0.6)	75 (0.9)
Nausea	40 (1.0)	13 (0.3)	53 (0.7)

Source: FDA analysis.
Adverse events in any PT = at least one adverse event experienced (regardless of the MedDRA Preferred Term)
%: n/N. n = number of participants reporting at least 1 occurrence of the specified event.
of any event. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
* Participants ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

FDA independently conducted standard MedDRA queries (SMQs) using FDA-developed software (MAED) to evaluate for constellations of unsolicited adverse event preferred terms that could represent various diseases and conditions, including but not limited to allergic, neurologic, inflammatory, and autoimmune conditions. The SMQs, conducted on the phase 2/3 all-enrolled safety population, revealed a slight numerical imbalance of adverse events potentially representing allergic reactions, with more participants reporting hypersensitivity-related adverse events in the vaccine group (137 [0.63%]) compared with the placebo group (111 [0.51%]). No imbalances between treatment groups were evident for any of the other SMQs evaluated.

Immediate AEs (phase 2/3 safety population)
The frequency of immediate AEs reported in the vaccine group was 0.4% after Dose 1 and <0.3% after Dose 2 and were mainly consistent with solicited reactogenicity events. In both study groups, the most frequently reported immediate AE was injection site pain (BNT162b2 vaccine 0.3%, placebo 0.2%).

Study Withdrawals due to an AE (all-enrolled population)
Of 43,448 enrolled participants, 37 (0.2%) vaccine recipients and 30 (0.1%) placebo recipients (0.1%), and no adolescents 16 to <18 years of age, withdrew from the study due to an AE. AEs in the SOC of General Disorders and Administration Site Conditions (7 vaccine, 3 placebo) was common, with injection site pain the most frequent (2 vaccine, 0 placebo).

Serious Adverse Events

Deaths

A total of six (2 vaccine, 4 placebo) of 43,448 enrolled participants (0.01%) died during the reporting period from April 29, 2020 (first participant, first visit) to November 14, 2020 (cutoff date). Both vaccine recipients were >55 years of age; one experienced a cardiac arrest 62 days after vaccination #2 and died 3 days later, and the other died from arteriosclerosis 3 days after vaccination #1. The placebo recipients died from myocardial infarction (n=1), hemorrhagic stroke (n=1) or unknown causes (n=2); three of the four deaths occurred in the older group (>55 years of age). All deaths represent events that occur in the general population of the age groups where they occurred, at a similar rate.

Non-fatal SAEs

In the all-enrolled population of (total N=43,448), the proportions of participants who reported at least 1 SAE during the time period from Dose 1 to the data cutoff date (November 14, 2020) were 0.6% in the BNT162b2 vaccine group and 0.5% in the placebo group. The most common SAEs in the vaccine group which were numerically higher than in the placebo group were appendicitis (0.04%), acute myocardial infarction (0.02%), and cerebrovascular accident (0.02%), and in the placebo arm numerically higher than in the vaccine arm were pneumonia (0.03%), atrial fibrillation (0.02%), and syncope (0.02%). Occurrence of SAEs involving system organ classes and specific preferred terms were otherwise balanced between treatment groups, including no imbalance overall in cardiovascular serious adverse events.

Appendicitis was reported as a SAE for 12 participants, and numerically higher in the vaccine group: 8 vaccine participants ([appendicitis [n=7], appendicitis perforated [n=1]) and 4 placebo participants (appendicitis [n=2], appendicitis perforated [n=1], complicated appendicitis [n=1]). All of the vaccine participants (n=8) and 2 placebo participants were younger than 65 years of age. The cases were considered unrelated to vaccination by the study investigators and occurred no more frequently than expected in the given age groups. FDA agrees that there is no clear basis upon which to suspect that this imbalance represents a vaccine-related risk.

Three SAEs reported in the BNT162 group were considered by the investigator as related to vaccine or vaccine administration: shoulder injury, ventricular arrhythmia, and lymphadenopathy. The investigator and the sponsor thought that the shoulder injury was related to vaccine administration. Two SAEs in the BNT162b2 group and none in the placebo group were considered by the investigator, but not the Sponsor, as related to study vaccination: shoulder injury (n=1), ventricular arrhythmia in a participant with known cardiac conditions (n=1), and lymphadenopathy temporally following vaccination (n=1). In FDA's opinion following review of the adverse event narratives, two of these events were considered as possibly related to vaccine: shoulder injury possibly related to vaccine administration or to the vaccine itself, and lymphadenopathy involving the axilla contralateral to the vaccine injection site. For lymphadenopathy, the event was temporally associated and biologically plausible.

Among participants 16 to 17 years of age, there was 1 participant in the vaccine group who experienced an SAE of facial bones fracture, which was not considered related to study intervention by the investigator.

Suspected COVID-19 Cases

As specified in the protocol, suspected cases of symptomatic COVID-19 that were not PCR-confirmed were not recorded as adverse events unless they met regulatory criteria for seriousness. Two serious cases of suspected but unconfirmed COVID-19 were reported, both in the vaccine group, and narratives were reviewed. In one case, a 36-year-old male with no medical comorbidities experienced fever, malaise, nausea, headache and myalgias beginning on the day of Dose 2 and was hospitalized 3 days later for further evaluation of apparent infiltrates on chest radiograph and treatment of dehydration. A nasopharyngeal PCR test for SARS-CoV-2 was negative on the day of admission, and a chest CT was reported as normal. The participant was discharged from the hospital 2 days after admission. With chest imaging findings that are difficult to reconcile, it is possible that this event represented reactogenicity following the second vaccination, a COVID-19 case with false negative test that occurred less than 7 days after completion of the vaccination series, or an unrelated infectious process. In the other case, a 66-year-old male with no medical comorbidities experienced fever, myalgias, and shortness of breath beginning 28 days post-Dose 2 and was hospitalized one day later with abnormal chest CT showing a small left-sided consolidation. He was discharged from the hospital 2 days later, and multiple nasopharyngeal PCR tests collected over a 10-day period beginning 2 days after symptom onset were negative. It is possible, though highly unlikely, that this event represents a COVID-19 case with multiple false negative tests that occurred more than 7 days after completion of the vaccination regimen, and more likely that it represents an unrelated infectious process.

Among 3410 total cases of suspected but unconfirmed COVID-19 in the overall study population, 1594 occurred in the vaccine group vs. 1816 in the placebo group. Suspected COVID-19 cases that occurred within 7 days after any vaccination were 409 in the vaccine group vs. 287 in the placebo group. It is possible that the imbalance in suspected COVID-19 cases occurring in the 7 days postvaccination represents vaccine reactogenicity with symptoms that overlap with those of COVID-19. Overall though, these data do not raise a concern that protocol-specified reporting of suspected, but unconfirmed COVID-19 cases could have masked clinically significant adverse events that would not have otherwise been detected.

Subgroup Analyses

There were no specific safety concerns identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection, and occurrence of solicited, unsolicited, and serious adverse events in these subgroups were generally consistent with the overall study population.

Pregnancies

Female study participants of childbearing potential were screened for pregnancy prior to each vaccination, with a positive test resulting in exclusion or discontinuation from study vaccination. The study is collecting outcomes for all reported pregnancies that occur after vaccination, or before vaccination and not detected by pre-vaccination screening tests. Twenty-three pregnancies were reported through the data cut-off date of November 14, 2020 (12 vaccine, 11 placebo). Study vaccination occurred prior to the last menstrual period (LMP) in 5 participants (4 vaccine, 2 placebo), within 30 days after LMP in 8 participants (4 vaccine, 6 placebo), >30 days after LMP in 1 participant (0 vaccine, 2 placebo), and date of LMP not known in 5 participants (4 vaccine, 1 placebo). Unsolicited AEs related to pregnancy include spontaneous abortion and retained products of conception, both in the placebo group. Pregnancy outcomes are otherwise

unknown at this time.

Clinical Laboratory Evaluations

Clinical laboratory tests (hematology, chemistries) were assessed in study BNT162-01 and C4591001 phase 1. The only common laboratory abnormality reported throughout the studies was transient decreases in lymphocytes 1-3 days after Dose 1, which increased in frequency with increasing dose, were mostly Grade 1-2, generally normalized at the next laboratory assessment 6-8 days after Dose 1 and did not occur after Dose 2. Among C4591001 phase 1 participants who received the 30 µg dose of BNT162b2, transient decreases in lymphocytes post-Dose 1 occurred in 5 of 12 participants 18-55 years of age and in 4 of 12 participants 65-85 years of age. These transient hematological changes were not associated with clinical symptoms.

Safety Summary

The information provided by the Sponsor was adequate for review and to make conclusions about the safety of BNT162b2 in the context of the proposed indication and population for intended use under EUA. The number of participants in the phase 2/3 safety population (N=37586; 18801 vaccine,18785 placebo) meets the expectations in FDA's Guidance on Development and Licensure of Vaccines to Prevent COVID-19 for efficacy, and the median duration of at least 2 months follow-up after completion of the 2-dose primary vaccination series meets the agency's expectations in FDA's Guidance on its Emergency Use Authorization for Vaccines to Prevent COVID-19. The all-enrolled population contained more participants >16 years of age, regardless of duration of follow-up (43448; 21720 vaccine, 21728 placebo). The demographic and baseline characteristics of the all-enrolled population and the safety population were similar. Although the overall median duration of follow-up in the all-enrolled population was less than 2 months, because the protocol was amended to include subpopulations such as individuals with HIV and adolescents, the data from both populations altogether provide a comprehensive summary of safety.

Local site reactions and systemic solicited events after vaccination were frequent and mostly mild to moderate. The most common solicited adverse reactions were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%); severe adverse reactions occurred in 0.0% to 4.6% of participants, were more frequent after Dose 2 than after Dose 1, and were generally less frequent in adults ≥55 years of age (≤2.8%) as compared to younger participants (≤4.6%). Among adverse events of special interest, which could be possibly related to vaccine, lymphadenopathy was reported in 64 participants (0.3%): 54 (0.5%) in the younger (16 to 55 years) age group; 10 (0.1%) in the older (>55 years) age group; and 6 in the placebo group. The average duration of these events was approximately 10 days, with 11 events ongoing at the time of the data cutoff. Bell's palsy was reported by four vaccine participants. From Dose 1 through 1 month after Dose 2, there were three reports of Bell's palsy in the vaccine group and none in the placebo group. This observed frequency of reported Bell's palsy is consistent with the expected background rate in the general population. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to BNT162b2 vaccine.

A total of six deaths occurred in the reporting period (2 deaths in the vaccine group, 4 in placebo). In the vaccine group, one participant with baseline obesity and pre-existing atherosclerosis died 3 days after Dose 1, and the other participant experienced cardiac arrest

60 days after Dose 2 and died 3 days later. Of the four deaths in the placebo arm, the cause was unknown for two of them, and the other two participants died from hemorrhagic stroke (n=1) and myocardial infarction (n=1), respectively; three deaths occurred in the older group (>55 years of age). All deaths represent events that occur in the general population of the age groups where they occurred, at a similar rate.

The frequency of non-fatal serious adverse events was low (<0.5%), without meaningful imbalances between study arms. The most common SAEs in the vaccine arm which were numerically higher than in the placebo arm were appendicitis (0.04%), acute myocardial infarction (0.02%), and cerebrovascular accident (0.02%), and in the placebo arm numerically higher than in the vaccine arm were pneumonia (0.03%), atrial fibrillation (0.02%), atrial fibrillation (0.02%) and syncope (0.02%). Appendicitis was the most common SAE in the vaccine arm. There were 12 participants with SAEs of appendicitis; 8 in the BNT162b2 group. Of the 8 total appendicitis cases in the BNT162b2 group, 6 occurred in the younger (16 to 55 years) age group and 2 occurred in the older (>55 years) age group (one of the cases in the older age group was perforated). One of the 6 participants with appendicitis in the younger age group also had a peritoneal abscess. Cases of appendicitis in the vaccine group were not more frequent than expected in the general population.

6. Sponsor's Plans for Continuing Blinded, Placebo-Controlled Follow-Up

The Sponsor plans to offer vaccination to participants ⩾16 years of age who originally received placebo and who become eligible for receipt of BNT162b2 according to local or national recommendations. The Sponsor proposes that these participants will be unblinded upon request and will have the opportunity to receive BNT162b2 as part of the study. The Sponsor also proposes that all placebo recipients ⩾16 years of age will be offered BNT162b2 after completing 6 months of follow-up after Dose 2, if they did not request and receive vaccine previously. The participants will provide consent to receive vaccination and to continue follow-up. For these participants, the Sponsor plans a total follow up period of 18 months, with one visit 1-month postvaccination and subsequent phone contacts at 1, 6, and 18 months postvaccination. Safety and efficacy monitoring during this period will include collection of AEs, SAEs, and screening and diagnosing COVID-19 cases.

7. Pharmacovigilance Activities

Pfizer submitted a Pharmacovigilance Plan (PVP) to monitor safety concerns that could be associated with Pfizer-BioNTech COVID-19 Vaccine. The Sponsor identified vaccine-associated enhanced disease including vaccine-associated enhanced respiratory disease as an important potential risk. Use in pregnancy and lactation and vaccine effectiveness are areas the Sponsor identified as missing information. In addition to the safety concerns specified by the Sponsor, FDA requested that the Sponsor update their PVP to include missing information in pediatric participants less than 16 years of age.

The Sponsor will conduct both passive and active surveillance activities for continued vaccine safety monitoring. Passive surveillance activities will include submitting spontaneous reports of the following events to the Vaccine Adverse Event Reporting System (VAERS) within 15 days:

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome in children and adults
- Cases of COVID-19 that result in hospitalization or death

The Sponsor will also conduct periodic aggregate review of safety data and submit periodic safety reports at monthly intervals. Each periodic safety report is required to contain descriptive information which includes:

- A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest
- Newly identified safety concerns in the interval
- Actions taken since the last report because of adverse experiences (e.g., changes made to Vaccination Provider fact sheets, changes made to studies or studies initiated)

Sponsor studies will include completion of long-term follow-up from ongoing clinical trials as well as the following three planned active surveillance studies. Of note, the Sponsor will submit plans for a clinical study to assess safety and immunogenicity in pregnant women and has proposed active surveillance studies designed to monitor vaccination during pregnancy within populations expected to receive the vaccine under EUA.

- Study Protocol Number C4591008. The Sponsor proposes to survey 20,000 U.S. health care workers enrolled in the COVID-19 HERO registry as well as health care workers in certain participating health care facilities about adverse events of special interest, and other clinically significant events of interest after vaccination with the Pfizer-BioNTech COVID-19 Vaccine. Incidence rates of these events in this cohort will be compared to expected rates. The respondents would receive follow-up surveys for a 30-month period.
- Study Protocol Number C4591011. This study is an active safety surveillance evaluation conducted within the Department of Defense Health System Databases using data derived from electronic health records and medical service claims among covered U.S. military and their families. Rates of safety events of interest in vaccinated participants will be compared to unvaccinated comparators. The study will be conducted for 30 months.
- Study Protocol Number C4591012. This study is an active surveillance study for adverse events of special interest and other clinically significant events associated with the Pfizer-BioNTech COVID-19 Vaccine using the Veteran's Health Administration electronic medical record database. Vaccinated participants will be compared to unvaccinated participants or to recipients of seasonal influenza vaccine. The study will be conducted for 30 months.

Currently, the primary objective of all three proposed studies above is descriptive, and the list of adverse events in the studies has not been finalized. FDA will provide feedback on these studies after further review.

Reporting to VAERS and Pfizer, Inc.

Providers administering the Pfizer-BioNTech COVID-19 Vaccine must report to VAERS (as required by the National Childhood Vaccine Injury Act) and to Pfizer the following information associated with the vaccine of which they become aware:

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome in children and adults
- Cases of COVID-19 that result in hospitalization or death

Additional VAERS Reporting

An additional source of VAERS reports will be through a program administered by the CDC known as v-safe. V-safe is a new smartphone-based opt-in program that uses text messaging and web surveys from CDC to check in with vaccine recipients for health problems following COVID-19 vaccination. The system also will provide telephone follow-up to anyone who reports medically significant (important) adverse events. Responses indicating missed work, inability to do normal daily activities, or that the recipient received care from a doctor or other healthcare professional will trigger the VAERS Call Center to reach out to the participant and collect information for a VAERS report, if appropriate.

8. Benefit/Risk Assessment in the Context of Proposed Indication and Use Under EUA

8.1. Known Benefits

The known benefits among recipients of the proposed vaccine relative to placebo are:

- Reduction in the risk of confirmed COVID-19 occurring at least 7 days after Dose 2
- Reduction in the risk of confirmed COVID-19 after Dose 1 and before Dose 2
- Reduction in the risk of confirmed severe COVID-19 any time after Dose 1

The protocol-specified 2-dose vaccination regimen was highly effective in preventing PCR-confirmed COVID-19 occurring at least 7 days after completion of the vaccination regimen. Additional primary efficacy analyses in the all-available efficacy population, including participants who had protocol violations, showed consistency with outcomes in the primary analysis population. Efficacy findings were also consistent across various subgroups, including racial and ethnic minorities, participants aged 65 years and older, and those with one or more of the following conditions: obesity, diabetes, hypertension, and chronic cardiopulmonary diseases. While limited, available data suggest that individuals with previous SARS-CoV-2 infection can be at risk of COVID-19 (i.e., re-infection) and may benefit from vaccination.

Among participants with no evidence of COVID-19 prior to vaccination, the vaccine was effective in reducing the risk of COVID-19 and severe COVID-19 after Dose 1. Fewer severe cases were also observed in the vaccine recipients relative to recipients of placebo during the follow up period after Dose 1. The findings post Dose 1, from a post-hoc analysis, cannot be the basis to assess the potential efficacy of the vaccine when administered as a single dose because the period of observation is limited by the fact that most participants received a second dose three weeks after the first one.

8.2. Unknown Benefits/Data Gaps

Duration of protection

As the interim and final analyses have a limited length of follow-up, it is not possible to assess sustained efficacy over a period longer than 2 months.

Effectiveness in certain populations at high-risk of severe COVID-19

Although the proportion of participants at high risk of severe COVID-19 is adequate for the overall evaluation of safety in the available follow-up period, the subset of certain groups such as immunocompromised individuals (e.g., those with HIV/AIDS) is too small to evaluate efficacy outcomes.

Effectiveness in individuals previously infected with SARS-CoV-2

The primary endpoint was evaluated in individuals without prior evidence of COVID-19 disease, and very few cases of confirmed COVID-19 occurred among participants with evidence of infection prior to vaccination (although more cases occurred in the placebo group compared with the vaccine group). Therefore, available data are insufficient to make conclusions about benefit in individuals with prior SARS-CoV-2 infection. However, available data, while limited, do suggest that previously infected individuals can be at risk of COVID-19 (i.e., reinfection) and could benefit from vaccination.

Effectiveness in pediatric populations

The representation of pediatric participants in the study population is too limited to adequately evaluate efficacy in pediatric age groups younger than 16 years. No efficacy data are available from participants ages 15 years and younger. Although adolescents 16 to 17 years of age were included in the overall efficacy analysis, only one confirmed COVID-19 case was reported in this age group. However, it is biologically reasonable to extrapolate that effectiveness in ages 16 to 17 years would be similar to effectiveness in younger adults. Efficacy surveillance continued beyond November 14, 2020, and the Sponsor has represented that additional data will be provided in a BLA.

Future vaccine effectiveness as influenced by characteristics of the pandemic, changes in the virus, and/or potential effects of co-infections

The study enrollment and follow-up occurred during the period of July 27 to November 14, 2020, in various geographical locations. The evolution of the pandemic characteristics, such as increased attack rates, increased exposure of subpopulations, as well as potential changes in the virus infectivity, antigenically significant mutations to the S protein, and/or the effect of co-infections may potentially limit the generalizability of the efficacy conclusions over time. Continued evaluation of vaccine effectiveness following issuance of an EUA and/or licensure will be critical to address these uncertainties.

Vaccine effectiveness against asymptomatic infection

Data are limited to assess the effect of the vaccine against asymptomatic infection as measured by detection of the virus and/or detection of antibodies against non-vaccine antigens that would indicate infection rather than an immune response induced by the vaccine. Additional evaluations will be needed to assess the effect of the vaccine in preventing asymptomatic infection, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against long-term effects of COVID-19 disease

COVID-19 disease may have long-term effects on certain organs, and at present it is not possible to assess whether the vaccine will have an impact on specific long-term sequelae of COVID-19 disease in individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 should translate to overall prevention of COVID-19-related sequelae in vaccinated populations, though it is possible that asymptomatic infections may not be prevented as effectively as symptomatic infections and may be associated with sequelae that are either late-onset or undetected at the time of infection (e.g., myocarditis). Additional evaluations will be needed to assess the effect of the vaccine in preventing long-term effects of COVID-19, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against mortality

A larger number of individuals at high risk of COVID-19 and higher attack rates would be needed to confirm efficacy of the vaccine against mortality. However, non-COVID vaccines (e.g., influenza) that are efficacious against disease have also been shown to prevent disease-associated death.[11-14] Benefits in preventing death should be evaluated in large observational studies following authorization.

Vaccine effectiveness against transmission of SARS-CoV-2

Data are limited to assess the effect of the vaccine against transmission of SARS-CoV-2 from individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 may translate to overall prevention of transmission in populations with high enough vaccine uptake, though it is possible that if efficacy against asymptomatic infection were lower than efficacy against symptomatic infection, asymptomatic cases in combination with reduced mask-wearing and social distancing could result in significant continued transmission. Additional evaluations including data from clinical trials and from vaccine use post-authorization will be needed to assess the effect of the vaccine in preventing virus shedding and transmission, in particular in individuals with asymptomatic infection.

8.3. Known Risks

The vaccine has been shown to elicit increased local and systemic adverse reactions as compared to those in the placebo arm, usually lasting a few days. The most common solicited adverse reactions were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%). Adverse reactions characterized as reactogenicity were generally mild to moderate. The number of subjects reporting hypersensitivity-related adverse events was numerically higher in the vaccine group compared with the placebo group (137 [0.63%] vs. 111 [0.51%]). Severe adverse reactions occurred in 0.0-4.6% of participants, were more frequent after Dose 2 than after Dose 1 and were generally less frequent in older adults (>55 years of age) ($\underline{\leq}$2.8%) as compared to younger participants (≤4.6%). Among reported unsolicited adverse events, lymphadenopathy occurred much more frequently in the vaccine group than the placebo group and is plausibly related to vaccination.

Serious adverse events, while uncommon (<1.0%), represented medical events that occur in the general population at similar frequency as observed in the study. Three SAEs in the BNT162b2 group were considered related by the investigator, but not the Sponsor, as related to study vaccination: shoulder injury (n=1), ventricular arrhythmia in a participant with known cardiac conditions (n=1), and lymphadenopathy temporally related following vaccination (n=1). We considered two of the events as possibly related to vaccine: the shoulder injury possibly due to vaccine administration or the vaccine itself and lymphadenopathy. Lymphadenopathy was temporally associated and biologically plausible.

No specific safety concerns were identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection. Although participants 16 to 17 years of age were enrolled in the phase 3 trial, safety data for this age group is limited. However, available data are consistent with the safety profile in the adult population, and it is biologically reasonable to extrapolate the greater safety experience in adults, in particular younger adults, to the oldest pediatric age group of 16 to 17 years.

8.4. Unknown Risks/Data Gaps

Safety in certain subpopulations

There are currently insufficient data to make conclusions about the safety of the vaccine in subpopulations such as children less than 16 years of age, pregnant and lactating individuals, and immunocompromised individuals.

Adverse reactions that are very uncommon or that require longer follow-up to be detected

Following authorization of the vaccine, use in large numbers of individuals may reveal additional, potentially less frequent and/or more serious adverse events not detected in the trial safety population of nearly 44,000 participants over the period of follow up at this time. Active and passive safety surveillance will continue during the post authorization period to detect new safety signals.

A numerically greater number of appendicitis cases occurred in the vaccine group but occurred no more frequently than expected in the given age groups and do not raise a clear concern at this time for a causal relationship to study vaccination. Although the safety database revealed an imbalance of cases of Bell's palsy (4 in the vaccine group and none in the placebo group), causal relationship is less certain because the number of cases was small and not more frequent than expected in the general population. Further signal detection efforts for these adverse events will be informative with more widespread use of the vaccine.

Vaccine-enhanced disease

Available data do not indicate a risk of vaccine-enhanced disease, and conversely suggest effectiveness against severe disease within the available follow-up period. However, risk of vaccine-enhanced disease over time, potentially associated with waning immunity, remains unknown and needs to be evaluated further in ongoing clinical trials and in observational studies that could be conducted following authorization and/or licensure.

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10. Appendix A. Study BNT162-01

Design

Study BNT162-01 is an ongoing, first-in-human, phase 1 dose-level finding study conducted in Germany to evaluate the safety and immunogenicity of several different candidate vaccines, including BNT162b2. Twelve adults 18 to 55 years of age received 30ug BNT162b2.

Secondary and exploratory objectives were specified to describe the immune response, measured by functional antibody titer, antibody binding assay, and cell-mediated immune responses (cytokines associated with Th1 and Th2 responses to assess for the induction of a balanced versus Th1 or Th2 dominant immune response) at baseline and various time points after vaccination, specifically 7 days post Dose 2. Adverse event monitoring was the same as in study C4591001.

Results

No SAEs were reported in the BNT162-01 safety database included in the EUA submission, and the safety profile for BNT162b2 in this study was similar to that in the much larger study, C4591001.

Evaluable ELISPOT data were available from 39 participants across dose levels of BNT162b2 (data cutoff date was 17 September 2020). Evaluable intracellular cytokine staining and FACS data were available from 36 participants across dose levels of BNT162b2 (cutoff date was 04 September 2020). Data for serology results for serum neutralizing titers were available for 45 participants across dose levels of BNT162b2 (data cutoff date was 18 September 2020). Most participants who received both doses of BNT162b2 had evidence of SARS-CoV-2 S protein-specific CD4+ (39/39, 100%) and CD8+ (35/39, 89.7%) T cell responses. These T cell responses were directed against different parts of the antigen, including epitopes in the RBD, indicating the induction of multi-epitope responses by BNT162b2. Functionality and polarization of S-specific BNT162b2-induced SARS-CoV-2 T cells were assessed by intracellular accumulation of cytokines IFNγ, IL-2, and IL-4 measured after stimulation with overlapping peptide pools representing the full-length sequence of the whole SARS-CoV-2 S protein. For benchmarking, PBMC fractions from 15 convalescent patients with virologically confirmed COVID-19 were used. The Th1 polarization of the T helper response was characterized by the IFNγ and IL-2 production, and only minor IL-4, production upon antigen-specific (SARS-CoV-2 S protein peptide pools) re-stimulation. The SARS-CoV-2 neutralizing geometric mean titer (GMTs) increased over baseline after Dose 1, with a boost effect after Dose 2 that was most pronounced at the 30 µg dose level.

Thus, the immunogenicity results from Study BNT162-01 showed evidence of antibody-mediated SARS-CoV-2 neutralization and a Th1 polarization in the cell-mediated cellular immune responses in healthy adults 18 to 55 years of age, which supports the final dose selection and prospect of benefit for the enrollment of larger numbers of participants in Study C4591001.

11. Appendix B. Charlson Comorbidity Index

This index is based on a list of 19 conditions identified from diagnoses in hospital and physician data. Each condition is assigned a weight from 1 to 6. The index score is the sum of the weights for all identified conditions (Charlson et al., 1987). An index score of 0 indicates no comorbid conditions, while higher scores indicate a greater level of comorbidity.

Charlson Index Diagnoses: Cancer, Chronic Pulmonary Disease, Diabetes without Complications, Congestive Heart Failure, Cerebrovascular Disease, Dementia, Renal Disease, Peripheral Vascular Disease, Myocardial Infarction, Diabetes with Complications, Paraplegia and Hemiplegia, Connective Tissue Disease-Rheumatic Disease, Peptic Ulcer Disease, Mild Liver Disease, Metastatic Carcinoma, Moderate or Severe Liver Disease, HIV/AIDS.

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12. Appendix C. Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19

Emergency Use Authorization for Vaccines to Prevent COVID-19

Vaccines and Related Biological Products Advisory Committee Meeting
December 17, 2020

FDA Briefing Document

Moderna COVID-19 Vaccine

Sponsor:
ModernaTX, Inc.

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Glossary

AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ARDS	acute respiratory distress syndrome
CBRN	chemical, biological, radiological, or nuclear
CDC	Centers for Disease Control and Prevention
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
hACE2	human angiotensin converting enzyme 2
HHS	Health and Human Services
HIV	human immunodeficiency virus
IM	intramuscular
LNP	lipid nanoparticle
MERS-CoV	Middle Eastern respiratory syndrome
mRNA	messenger RNA
NAAT	nucleic acid amplification-based test
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
VE	vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1. Executive Summary

On November 30, 2020, ModernaTX (the Sponsor) submitted an Emergency Use Authorization (EUA) request to FDA for an investigational COVID-19 vaccine (mRNA-1273) intended to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The vaccine is based on the SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA and formulated in lipid nanoparticles (LNPs). The proposed use under an EUA is for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The proposed dosing regimen is 2 doses, 100 µg each, administered 1 month apart.

The EUA request includes safety and efficacy data from an ongoing Phase 3 randomized, double-blinded and placebo-controlled trial of mRNA-1273 in approximately 30,400 participants. The primary efficacy endpoint is the reduction of incidence of COVID-19 among participants without evidence of SARS-CoV-2 infection before the first dose of vaccine in the period after 14 days post-dose 2. In an interim analysis conducted using a data cutoff of November 7, 2020, a total of 27,817 participants randomized 1:1 to vaccine or placebo with a median 7 weeks of follow-up post-dose 2 were included in the per-protocol efficacy analysis population of participants without evidence of SARS-CoV-2 infection prior to vaccination. Efficacy in preventing confirmed COVID-19 occurring at least 14 days after the second dose of vaccine was 94.5.0% (95% CI 86.5%, 97.8%) with 5 COVID-19 cases in the vaccine group and 90 COVID-19 cases in the placebo group. Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across age groups, genders, racial and ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19. Secondary efficacy analyses suggested benefit of the vaccine in preventing severe COVID-19 (11 protocol-defined severe COVID-19 cases in the placebo group vs. 0 cases in the vaccine group), in preventing COVID-19 following the first dose, and in preventing COVID-19 in individuals with prior SARS-CoV-2 infection, although available data for some of these outcomes did not allow for firm conclusions. Efficacy data from the final scheduled analysis of the primary efficacy endpoint (data cutoff of November 21, 2020, with a median follow-up of >2 months post-dose 2) demonstrated a VE of 94.1% (95% CI 89.3%, 96.8%), with 11 COVID-19 cases in the vaccine group and 185 COVID-19 cases in the placebo group and was consistent with results obtained from the interim analysis. The VE in this analysis when stratified by age group was 95.6% (95% CI: 90.6%, 97.9%) for participants 18 to <65 years of age and 86.4% (95% CI: 61.4%, 95.5%) for participants ⩾65 years of age. A final secondary efficacy analysis also supported efficacy against protocol-defined severe COVID-19, with 30 cases in the placebo group vs. 0 cases in the vaccine group.

Safety data from a November 11, 2020 interim analysis of approximately 30,350 participants ≥18 years of age randomized 1:1 to vaccine or placebo with a median of 7 weeks of follow-up after the second dose supported a favorable safety profile, with no specific safety concerns identified that would preclude issuance of an EUA. These safety data are the primary basis of FDA's safety review. On December 7, 2020, the Sponsor submitted additional follow-up data from these participants with a cutoff of November 25, 2020, which represents a median of 9 weeks (>2 months) of follow-up post-dose 2. Key safety data from this later submission, including death, other serious adverse events, and unsolicited adverse events of interest were independently verified and confirmed not to change the safety conclusions from the interim safety analysis.

The most common solicited adverse reactions associated with mRNA-1273 were injection site pain (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and

chills (43.4%); severe adverse reactions occurred in 0.2% to 9.7% of participants, were more frequent after dose 2 than after dose 1, and were generally less frequent in participants ⩾65 years of age as compared to younger participants. Among unsolicited adverse events of clinical interest, which could be possibly related to vaccine, using the November 25, 2020 data cutoff, lymphadenopathy was reported as an unsolicited event in 173 participants (1.1%) in the vaccine group and 95 participants (0.63%) in the placebo group. Lymphadenopathy (axillary swelling and tenderness of the vaccination arm) was a solicited adverse reaction observed after any dose in 21.4% of vaccine recipients <65 years of age and in 12.4% of vaccine recipients ≥65 years of age, as compared with 7.5% and 5.8% of placebo recipients in those age groups, respectively. There was a numerical imbalance in hypersensitivity adverse events across study groups, with 1.5% of vaccine recipients and 1.1% of placebo recipients reporting such events in the safety population. There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine. Throughout the safety follow-up period to date, there were three reports of facial paralysis (Bell's palsy) in the vaccine group and one in the placebo group. Currently available information is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to mRNA-1273.

The frequency of serious adverse events was low (1.0% in the mRNA-1273 arm and 1.0% in the placebo arm), without meaningful imbalances between study arms. The most common SAEs in the vaccine group which were numerically higher than the placebo group were myocardial infarction (0.03%), cholecystitis (0.02%), and nephrolithiasis (0.02%), although the small numbers of cases of these events do not suggest a causal relationship. The most common SAEs in the placebo arm which were numerically higher than the vaccine arm, aside from COVID-19 (0.1%), were pneumonia (0.05%) and pulmonary embolism (0.03%).

With the exception of more frequent, generally mild to moderate reactogenicity in participants <65 years of age, the safety profile of mRNA-1273 was generally similar across age groups, genders, ethnic and racial groups, participants with or without medical comorbidities, and participants with or without evidence of prior SARS-CoV-2 infection at enrollment.

This meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) is being convened to discuss and provide recommendations on whether, based on the totality of scientific evidence available, the benefits of the mRNA-1273 COVID-19 Vaccine outweigh its risks for use in individuals 18 years of age and older. The committee will also discuss what additional studies should be conducted by the vaccine manufacturer following issuance of the EUA to gather further data on the safety and effectiveness of this vaccine.

2. Background

2.1 SARS-CoV-2 Pandemic

The SARS-CoV-2 pandemic presents an extraordinary challenge to global health and, as of December 11, 2020, has caused more than 71 million cases of COVID-19 and claimed the lives of more than 1.6 million people worldwide. In the United States, more than 16 million cases have been reported to the Centers for Disease Control and Prevention (CDC), with over 296,000 deaths. Confirmed cases and mortality continue to rise globally. On January 31, 2020, the U.S. Secretary of Health and Human Services (HHS) declared a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS. Following the World Health Organization's declaration of the novel coronavirus pandemic on March 11, 2020, the U.S.

President declared a national emergency in response to COVID-19 on March 13, 2020. Vaccines to protect against COVID-19 are critical to mitigate the current SARS-CoV-2 pandemic and to prevent future disease outbreaks.

SARS-CoV-2 is a novel, zoonotic coronavirus that emerged in late 2019 in patients with pneumonia of unknown cause.[1] The virus was named SARS-CoV-2 because of its similarity to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV, a lineage B betacoronavirus).[2] SARS-CoV-2 is an enveloped, positive sense, single stranded RNA virus sharing more than 70% of its sequence with SARS-CoV, and ~50% with the coronavirus responsible for Middle Eastern respiratory syndrome (MERS-CoV).[3] The SARS-CoV-2 spike glycoprotein (S), which is the main target for neutralizing antibodies, binds to its receptor human angiotensin converting enzyme 2 (hACE2) to initiate infection.[4] SARS-CoV-2 is the cause of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome (ARDS), leading to multiorgan failure and death.

In an attempt to prevent the spread of disease and to control the pandemic, numerous COVID-19 vaccine candidates are in development. These vaccines are based on different platforms including mRNA and DNA technologies and include viral vectored, subunit, inactivated, and live-attenuated vaccines. Most COVID-19 candidate vaccines express the spike protein or parts of the spike protein, i.e., the receptor binding domain, as the immunogenic determinant.

2.2 EUA Request for the Moderna COVID-19 Vaccine mRNA-1273

ModernaTX, Inc. (Sponsor) is developing a vaccine to prevent COVID-19 that is based on the pre-fusion stabilized SARS-CoV-2 spike glycoprotein (S) antigen encoded by mRNA and formulated in a lipid nanoparticle (LNP). The Moderna COVID-19 Vaccine (also referred to as mRNA-1273) is a 2-dose series of 100-µg intramuscular injections administered 1 month apart. The vaccine is supplied as a multi-dose vial (10 doses) containing a frozen suspension -25º to -15ºC) of mRNA-1273 that must be thawed prior to administration. The vaccine does not contain a preservative.

A Phase 3 randomized and placebo-controlled trial using mRNA-1273 in approximately 30,000 participants is currently ongoing to evaluate the vaccine's safety and efficacy. A prespecified interim efficacy analysis from 27,817 participants using a data cutoff date of November 7, 2020, demonstrated vaccine efficacy (VE) of 94.5% (95% CI: 86.5%, 97.8%) for the prevention of symptomatic confirmed COVID-19 occurring at least 14 days after the second dose. At the time of this interim analysis, the median efficacy follow-up was 7 weeks post completion of the 2-dose series. Safety data from a November 11, 2020, interim analysis with a median of 7 weeks follow-up after the second dose of vaccine were reported to demonstrate an acceptable tolerability profile with no significant safety concerns. On November 30, 2020, ModernaTX submitted an EUA request to FDA, based on the interim analyses described above, for use of mRNA-1273 to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

On December 7, 2020, the Sponsor submitted an amendment to the EUA request with additional accrued safety data on all participants with a median of 2 months (9 weeks) follow-up after the second dose, using a data cutoff date of November 25, 2020, and data from the prespecified final efficacy analysis using a data cutoff of November 21, 2020, which met the median follow-up of 2 months after dose 2 and demonstrated vaccine efficacy of 94.1% (95%

CI: 89.3%, 96.8%) for the prevention of symptomatic confirmed COVID-19 occurring at least 14 days after the second dose. Although the complete datasets and analyses from the primary efficacy analysis and associated safety analyses submitted on December 7, 2020, have not been independently verified by the FDA to the same extent as the data for the interim efficacy analyses and associated safety analyses submitted on November 30, 2020, based on comprehensive independent review of the data from the interim analysis, and the consistency of findings across the two analysis time points, FDA considers that the totality of available data are sufficient to support an evaluation of this product for EUA.

2.3 U.S. Requirements to Support Issuance of an EUA for a Biological Product

Based on the declaration by the Secretary of HHS that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA after determining that certain statutory requirements are met (section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360bbb-3)).[5]

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2, or to mitigate a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by SARS-CoV-2.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

If these criteria are met, under an EUA, FDA can allow unapproved medical products (or unapproved uses of approved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents. FDA has been providing regulatory advice to COVID-19 vaccine manufacturers regarding the data needed to determine that a vaccine's benefit outweigh its risks. This includes demonstrating that manufacturing information ensures product quality and consistency along with data from at least one phase 3 clinical trial demonstrating a vaccine's safety and efficacy in a clear and compelling manner.

In the event an EUA is issued for this product, it would still be considered unapproved and would continue under further investigation (under an Investigational New Drug Application). Licensure of a COVID-19 vaccine will be based on review of additional manufacturing, efficacy, and safety data, providing greater assurance of the comparability of licensed product to product tested in the clinical trials, greater assurance of safety based on larger numbers of vaccine recipients who have been followed for a longer period of time, and additional information about efficacy that addresses, among other questions, the potential for waning of protection over time.

2.4 Alternatives for Prevention of COVID-19

No vaccine or other medical product is FDA approved for prevention of COVID-19. On December 11, 2020, FDA issued an EUA for the Pfizer-BioNTech COVID-19 vaccine for active immunization for prevention of COVID-19 due to SARS-CoV-2 in individuals 16 years of age and older. However, the Pfizer-BioNTech COVID-19 vaccine is not an approved product, and furthermore is not available in quantity sufficient to vaccinate all persons in the U.S. for whom the vaccine is authorized for use. On October 22, 2020, FDA approved remdesivir for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms for the treatment of COVID-19 requiring hospitalization. Several other therapies are currently available under emergency use authorization, but not FDA approved, for treatment of COVID-19. Thus, there is currently no adequate, approved, and available alternative for prevention of COVID-19.

2.5 Applicable Guidance for Industry

Risk and benefit considerations are unique for COVID-19 vaccines, given that an EUA may be requested to allow for a vaccine's rapid and widespread deployment for administration to millions of individuals, including healthy people. FDA published in October 2020 guidance for industry entitled "Emergency Use Authorization for Vaccines to Prevent COVID-19" describing FDA's current recommendations regarding the manufacturing, nonclinical, and clinical data and information needed under section 564 of the FD&C Act to support the issuance of an EUA for an investigational vaccine to prevent COVID-19, including a discussion of FDA's current thinking regarding the circumstances under which an EUA for a COVID-19 vaccine would be appropriate.[6]

2.6 Safety and Effectiveness Information Needed to Support an EUA

Effectiveness data

Issuance of an EUA requires a determination that the known and potential benefits of the vaccine outweigh the known and potential risks. For a preventive COVID-19 vaccine to be potentially administered to millions of individuals, including healthy individuals, data adequate to inform an assessment of the vaccine's benefits and risks and support issuance of an EUA would include meeting the prespecified success criteria for the study's primary efficacy endpoint, as described in the guidance for industry entitled "Development and Licensure of Vaccines to Prevent COVID-19" (i.e., a point estimate for a placebo-controlled efficacy trial of at least 50%, with a lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate of >30%).[7]

Safety data

An EUA request for a COVID-19 vaccine should include all safety data accumulated from studies conducted with the vaccine, with data from Phase 1 and 2 focused on serious adverse events, adverse events of special interest, and cases of severe COVID-19 among study participants. Phase 3 safety data should include characterization of reactogenicity (common and expected adverse reactions shortly following vaccination) in a sufficient number of participants from relevant age groups and should include a high proportion of enrolled participants (numbering well over 3,000) followed for serious adverse events and adverse events of special interest for at least one month after completion of the full vaccination regimen. The Phase 1 and 2 safety data likely will be of a longer duration than the available safety data from the Phase 3 trial at the time of submission of an EUA request and thus, are intended to complement the available data from safety follow-up from ongoing Phase 3 studies.

Phase 3 Follow-up

Data from Phase 3 studies should include a median follow-up duration of at least 2 months after completion of the full vaccination regimen to help provide adequate information to assess a vaccine's benefit-risk profile. From a safety perspective, a 2-month median follow-up following completion of the full vaccination regimen will allow identification of potential adverse events that were not apparent in the immediate postvaccination period. Adverse events considered plausibly linked to vaccination generally start within 6 weeks of vaccine receipt.[8] Therefore, a 2-month follow-up period may allow for identification of potential immune-mediated adverse events that began within 6 weeks of vaccination. From the perspective of vaccine efficacy, it is important to assess whether protection mediated by early responses has not started to wane. A 2-month median follow-up is the shortest follow-up period to achieve some confidence that any protection against COVID-19 is likely to be more than short-lived. The EUA request should include a plan for active follow-up for safety (including deaths, hospitalizations, and other serious or clinically significant adverse events) among individuals administered the vaccine under an EUA in order to inform ongoing benefit-risk determinations to support continuation of the EUA.

2.7 Continuation of Clinical Trials Following Issuance of an EUA for a COVID-19 Vaccine

FDA does not consider availability of a COVID-19 vaccine under EUA, in and of itself, as grounds for immediately stopping blinded follow-up in an ongoing clinical trial or grounds for offering vaccine to all placebo recipients. To minimize the risk that use of an unapproved vaccine under EUA will interfere with long-term assessment of safety and efficacy in ongoing trials, it is critical to continue to gather data about the vaccine even after it is made available under EUA. An EUA request should therefore include strategies that will be implemented to ensure that ongoing clinical trials of the vaccine are able to assess long-term safety and efficacy (including evaluating for vaccine-associated enhanced respiratory disease and decreased effectiveness as immunity wanes over time) in sufficient numbers of participants to support vaccine licensure. These strategies should address how ongoing trial(s) will handle loss of follow-up information for study participants who choose to withdraw from the study in order to receive the vaccine under an EUA.

FDA is aware that some COVID-19 vaccine developers may wish to immediately unblind their trials upon issuance of an EUA in order to rapidly provide vaccine to trial participants who received placebo. Regardless of when vaccination of placebo recipient would occur, there may be advantages to maintaining blinding in a crossover design that provides vaccine to previous placebo recipients and placebo to previous vaccine recipients. Such strategies would impact collection of longer-term placebo-controlled safety data and evaluation of the duration of vaccine efficacy. Ethical and scientific issues associated with offering vaccination to placebo recipients have been discussed in recent statements and articles.[9-11]

2.8 Previous Meetings of the VRBPAC to Discuss Vaccines to Prevent COVID-19

On October 22, 2020, the VRBPAC met in open session to discuss, in general, the development, authorization, and/or licensure of vaccines to prevent COVID-19. No specific application was discussed at this meeting. Topics discussed at the meeting included:

- FDA's approach to safety and effectiveness, and chemistry, manufacturing and control (CMC) data as outlined in the respective guidance documents
- Considerations for continuation of blinded Phase 3 clinical trials if an EUA has been issued for an investigational COVID-19 vaccine

- Studies following licensure and/or issuance of an EUA for COVID-19 vaccines to:
    - Further evaluate safety, effectiveness and immune markers of protection
    - Evaluate the safety and effectiveness in specific populations.

On December 10, 2020, the VRBPAC met in open session to discuss the EUA request of the Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 in individuals 16 years of age older. Topics discussed at the meeting but not voted upon included Pfizer's plan for continuation of blinded, placebo-controlled follow-up in ongoing trials in the event that the vaccine is made available under EUA and gaps in plans for further evaluation of vaccine safety and effectiveness in populations that receive the Pfizer-BioNTech Vaccine under an EUA. The committee voted in favor of a determination that, based on the totality of scientific evidence available, the benefits of the proposed vaccine outweigh its risks for use in individuals 16 years of age and older.

3. Topics for VRBPAC Discussion

The Vaccines and Related Biological Products Advisory Committee will convene on December 17, 2020, to discuss and provide recommendations on whether based on the totality of scientific evidence available, the benefits of the Moderna COVID-19 Vaccine outweigh its risks for use in individuals 18 years of age and older. The Committee will also discuss what additional studies should be conducted by the vaccine manufacturer following issuance of the EUA to gather further data on the safety and effectiveness of this vaccine.

4. Moderna COVID-19 Vaccine (mRNA-1273)

4.1 Vaccine Composition, Dosing Regimen

The Moderna COVID-19 Vaccine is a white to off-white, sterile, preservative-free frozen suspension for intramuscular injection. The vaccine contains a synthetic messenger ribonucleic acid (mRNA) encoding the pre-fusion stabilized spike glycoprotein (S) of SARS-CoV-2 virus. The vaccine also contains the following ingredients: lipids (SM-102, 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 [PEG2000-DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), tromethamine, tromethamine hydrochloride, acetic acid, sodium acetate, and sucrose.

The Moderna COVID-19 Vaccine is provided as a frozen suspension [stored between -25º to -15ºC (-13º to 5ºF)] multi-dose vial containing 10 doses. The vaccine must be thawed prior to administration. After thawing, a maximum of 10 doses (0.5 mL each) can be withdrawn from each vial. Vials can be stored refrigerated between 2° to 8°C (36° to 46°F) for up to 30 days prior to first use. Unopened vials may be stored between 8° to 25°C (46° to 77°F) for up to 12 hours. After the first dose has been withdrawn, the vial should be held between 2° to 25°C (36° to 77°F) and discarded after 6 hours.

The Moderna COVID-19 Vaccine, mRNA-1273 (100 µg) is administered intramuscularly as a series of two doses (0.5 mL each), given 28 days apart.

FDA has reviewed the CMC data submitted to date for this vaccine and has determined that the CMC information is consistent with the recommendations set forth in FDA's Guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19. FDA has determined that the Sponsor has provided adequate information to ensure the vaccine's quality and consistency for authorization of the product under an EUA.

4.2 Proposed Use Under EUA

The proposed use of the vaccine under an EUA is for the prevention of COVID-19 in adults 18 years of age and older.

5. FDA Review of Clinical Safety and Effectiveness Data

5.1 Overview of Clinical Studies

Data from three ongoing clinical studies were included in the EUA request, which are summarized in Table 1 below. Study mRNA-1273-P301 is a multi-center, Phase 3 randomized, blinded, placebo-controlled safety, immunogenicity, and efficacy study that is the focus of the EUA review. Study mRNA1273-P201 is a Phase 2 dose-confirmation study that explored 2 dose levels of mRNA-1273 and will not be discussed in detail. Study 20-0003 is a Phase 1 open label, dose-ranging, first-in-human study of mRNA-1273 and will also not be discussed in detail. A brief summary of the P201 and 20-0003 study designs and results to date is found in Appendix A, page 53.

Table 1. Clinical Trials Submitted in Support of Efficacy and Safety Determinations of the Moderna COVID-19 Vaccine mRNA-1273

Study Number	Type of Study (Efficacy, Safety, Nonclinical)	Participants randomized (N)	Study Design & Type of Control	Test Product(s); Dosing Regimens	Study Status
P301	Efficacy, Safety	30418	A Phase 3, randomized, stratified, observer-blind, placebo-controlled study	mRNA-1273 100 µg	Ongoing-vaccine efficacy demonstrated at the 1st interim analysis
P201	Safety, Immunogenicity	600	A Phase 2a, randomized, observer-blind, placebo-controlled, dose-confirmation study	mRNA-1273 50ug,100µg	Ongoing-Day 57 primary analysis have completed
20-0003*	Safety, Immunogenicity	120	A Phase 1 Open-label dose-ranging study	mRNA-1273 25ug 50ug,100ug 250ug	Ongoing-Day 119 (25ug, 100ug, 250ug), Day 57 (50ug)

*Sponsor: Division of Microbiology and Infectious Diseases (DMID), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health

5.2 Study mRNA-1273-P301

5.2.1 Design

Study mRNA-1273-P301 is an ongoing randomized, stratified, observer-blind, placebo-controlled study to evaluate the efficacy, safety and immunogenicity of mRNA-1273 administered in 2 doses 28 days apart in adults 18 years of age and older. The study took place in 99 sites in the United States. Participants (N=30,351) were randomized 1:1 to receive intramuscular injections of either 100 µg of mRNA-1273 vaccine (n=15,181) or placebo

(n=15,170) on Day 1 and Day 29. Participants were stratified by age and health risk into one of three groups: 18 to <65 years of age and not at risk for progression to severe COVID-19, 18 to <65 years of age and at risk for progression to severe COVID-19, and ≥65 years of age, with the latter two groups consisting of 41.4% of the study population. Participants were considered at risk for progression to severe COVID-19 if they had underlying comorbidities including diabetes, chronic lung disease, severe obesity, significant cardiovascular disease, liver disease, or infection with HIV. The study included 24,907 (82.1%) participants considered at occupational risk for acquiring SARS-CoV-2 infection, of whom 7,613 (25.1%) were healthcare workers. Other essential workers were also represented. The primary efficacy endpoint was efficacy of the vaccine to prevent protocol-defined COVID-19 occurring at least 14 days after the second dose in participants with negative SARS-CoV-2 status at baseline (i.e., negative RT-PCR and negative serology against SARS-CoV-2 nucleocapsid on Day 1).

Symptoms of COVID-19 experienced by participants during post-vaccination follow-up prompted an unscheduled illness visit and nasopharyngeal (NP) swab. NP samples were tested for SARS CoV-2 at a central laboratory using a reverse transcription-polymerase chain reaction (RT-PCR) test (Viracor; FDA authorized under EUA), or other sufficiently validated nucleic acid amplification-based test (NAAT). The central laboratory NAAT result is used for the case definition, unless it is not possible to test the sample at the central laboratory.

The case-driven study design required 151 COVID-19 cases to trigger the final scheduled efficacy analysis. Two interim analysis timepoints were pre-specified; the first upon accrual of 53 cases and the second upon accrual of 106 cases. The expected duration of study participation is approximately 25 months.

Primary Efficacy Endpoint

The primary efficacy endpoint was efficacy of the vaccine to prevent protocol-defined COVID-19 occurring at least 14 days after the second dose in participants with negative SARS-CoV-2 status at baseline (i.e., negative RT-PCR and negative serology against SARS-CoV-2 nucleocapsid on Day 1). The primary analysis was based on the Per-Protocol Set, defined as all randomized, baseline SARS-CoV-2 negative participants who received planned doses per schedule and have no major protocol deviations. For the primary efficacy endpoint, the case definition for a confirmed COVID-19 case was defined as:

- At least TWO of the following systemic symptoms: Fever (≥38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), or
- At least ONE of the following respiratory signs/ symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; and
- NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.

Vaccine efficacy was defined as the percent reduction (mRNA-1273 vs. placebo) in the hazard of the primary endpoint, i.e. VE =1 – Hazard Ratio (HR). A stratified Cox proportional hazard (PH) model using Efron's method to handle ties and with treatment group as the independent variable was used to estimate the HR, where the same stratification factor used for randomization was applied. The primary objective would be met if the null hypothesis of H0: VE ≤30% is rejected at any of the interim or primary analyses at the respective significance level.

The final scheduled efficacy analysis of the primary endpoint was planned when a total of 151 adjudicated cases occurring at least 14 days after the second injection had been accrued. In addition, two interim analyses were planned when 35% (53 cases) and 70% (106 cases) of the

total target number of cases had been accrued. The Lan-DeMets spending function was used for approximating O'Brien-Fleming efficacy bounds to preserve the overall Type I error rate at a one-sided α =0.025, yielding nominal one-sided α of 0.0002, 0.0073, and 0.0227 at the first and second interim and the primary analyses, respectively. As conducted, the first and only interim analysis in the study occurred at 95 adjudicated cases of the primary endpoint, where the null hypothesis of H0: VE ≤30% was evaluated at a one-sided alpha of 0.0047.

Secondary Efficacy Endpoints

Secondary endpoints based on the Per-Protocol Set included the VE of mRNA-1273 to prevent the following:

- Severe COVID-19 (as defined below)
- COVID-19 based on a less restrictive definition of disease (defined below) occurring at least 14 days after the second dose of vaccine
- Death due to COVID-19
- COVID-19 occurring at least 14 days after the first dose of vaccine (including cases that occurred after the second dose)

One additional secondary endpoint was based on the Full Analysis Set (FAS): VE of mRNA-1273 to prevent COVID-19 occurring at least 14 days after the second dose, regardless of prior SARS-CoV-2 infection.

One of the secondary efficacy endpoints assessed COVID-19 as defined by a less restrictive definition: a positive NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) for SARS-CoV-2 by RT-PCR **and** one of the following systemic symptoms:

- fever (temperature ≥38ºC), or
- chills,
- cough,
- shortness of breath or difficulty breathing,
- fatigue,
- muscle aches or body aches,
- headache,
- new loss of taste or smell,
- sore throat,
- nasal congestion or rhinorrhea,
- nausea or vomiting, or diarrhea

Another secondary endpoint assessed cases of severe COVID-19, defined as a case of confirmed COVID-19 plus at least one of the following:

- Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO2≤93% on room air at sea level, or PaO2/FiO2<300 mm Hg);
- Respiratory failure or Acute Respiratory Distress Syndrome, (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an ICU;
- Death

Vaccine efficacy of secondary endpoints was estimated from the Cox proportional-hazards model when the primary endpoint reached statistical significance. Estimates based on the Per-Protocol Set were presented with nominal two-sided 95% confidence intervals.

Analysis Populations

For the purposes of analysis, the following populations are defined:

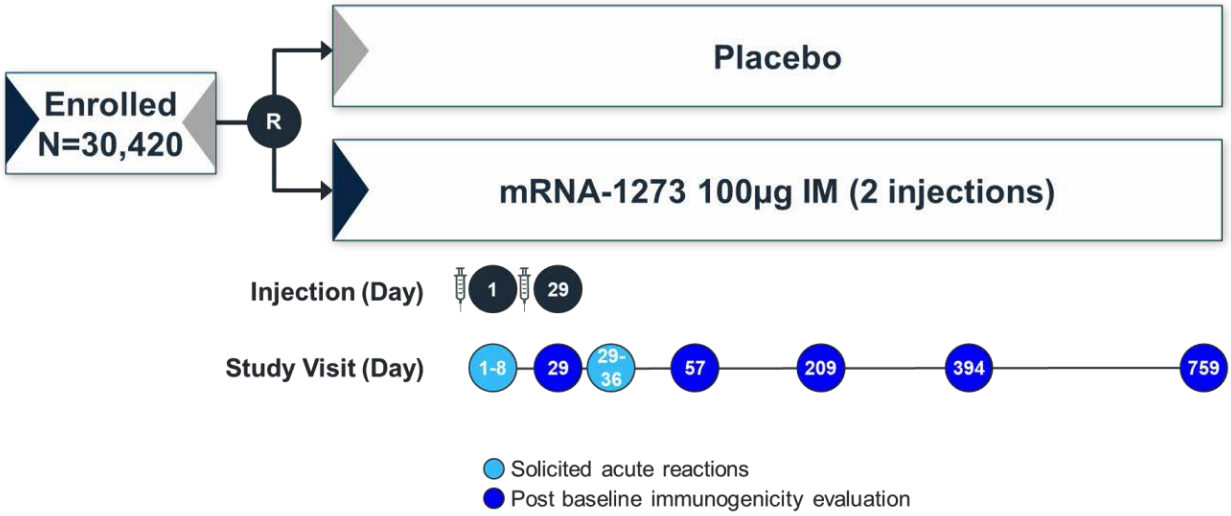
Table 2. Efficacy Set Definitions

Population	Description
Randomized	All participants who are randomized, regardless of the participants' treatment status in the study.
Full Analysis Set	All randomized participants who received at least one dose of Investigational Product (IP).
mITT Set	All participants in the FAS who had no immunologic or virologic evidence of prior COVID-19 (i.e., negative NP swab test at Day 1 and/or bAb against SARS-CoV-2 nucleocapsid below limit of detection [LOD] or lower limit of quantification [LLOQ]) at Day 1 before the first dose of IP.
Per Protocol Set	All participants in the mITT Set who received planned doses of IP per schedule and have no major protocol deviations, as determined and documented by Sponsor prior to DBL and unblinding, that impact critical or key study data.
Safety Set	All randomized participants who received at least one dose of IP.
Solicited Safety Set	All randomized participants who received at least one dose of IP and contributed any solicited adverse reaction data.

Evaluation of Safety

The primary safety objective for all phases was to describe the safety of mRNA-1273 after 1 or 2 doses. In all studies, participants recorded local reactions, systemic events, and antipyretic/pain medication usage from Day 1 through Day 7 after each dose. Unsolicited adverse events (AEs) are collected from dose 1 to 28 after the last dose and medically attended adverse events (MAAEs) and serious AEs (SAEs) from dose 1 to the end of the study. Figure 1 below shows the study safety monitoring plan.

Figure 1. Safety Monitoring Plan, Study 301



Safety assessments included the following:

- Solicited local and systemic adverse reactions (AR) that occurred during the 7 days following each dose (i.e., the day of vaccination and 6 subsequent days). Solicited ARs were recorded daily using eDiaries.
- Unsolicited AEs observed or reported during the 28 days following each dose (i.e., the day of vaccination and 27 subsequent days). Unsolicited AEs are those not included in the protocol-defined solicited AR.
- AEs leading to discontinuation from vaccination and/or study participation from Day 1 through Day 759 or withdrawal from the study.
- Medically Attended Adverse Events (MAAE) from Day 1 through Day 759 or withdrawal from the study.
- Serious Adverse Events (SAEs) from Day 1 through Day 759 or withdrawal from the study.
- Abnormal vital sign measurements.
- Physical examination findings.
- Pregnancy and accompanying outcomes.

Safety laboratory evaluations were not assessed in Study P301 but were collected in the phase 2 Study P201. See Appendix A on page 53.

Potential COVID-19 illnesses and their sequelae were not to be reported as AEs, with the exception of illnesses that met regulatory criteria for seriousness and were not confirmed to be COVID-19. Such illnesses were evaluated and reported as SAEs.

Monitoring for risk of vaccine-enhanced disease was performed by an unblinded team supporting the Data Monitoring Committee that reviewed cases of severe COVID-19 as they were received and reviewed AEs at least weekly for additional potential cases of severe COVID-19. The stopping rule was triggered when the 1-sided probability of observing the same or a more extreme case split was 5% or less when the true incidence of severe disease was the same for vaccine and placebo participants.

The table below shows the Phase 3 safety analyses populations that were used to determine the proportions of study participants who experienced adverse events, including solicited adverse reactions after each dose, unsolicited adverse events, medically attended adverse events, and serious adverse events.

Table 3. Safety Set Definitions

Population	Description
Randomized Set	All participants who are randomized, regardless of the participants treatment status in the study.
Safety Set	All randomized participants who received at least one dose of investigational product. The safety set was used for all analyses of safety except solicited adverse reactions. Participants were included in the treatment group corresponding to the investigational product they received.
Solicited Safety Set	All randomized participants who received at least one dose of investigational product and contributed any solicited adverse reaction data. The solicited safety set was used for the analyses of solicited adverse reactions. Participants were included in the treatment group corresponding to the investigational product they received.
Solicited Safety Set-1st Injection	All randomized participants who received the 1st dose and provided any solicited reaction data.

Population	Description
Solicited Safety Set-2nd Injection	All randomized participants who received the 2nd dose and provided any solicited reaction data.

5.2.2 FDA Assessment of Phase 3 Follow-Up Duration

As of the interim analysis cutoff (November 7, 2020, for efficacy, November 11, 2020, for safety), the proportion of participants across groups who received one dose of vaccine or placebo was 100%, and the proportion of participants who received two doses was 91.9% (92.1% vaccine, 91.7% placebo). The median follow-up after dose 2 was 7 weeks across groups. (For participants who did not receive a second dose of vaccine or placebo, follow-up after dose 2 was zero. Among participants who received dose 2, the median follow-up after the second dose was 50.0 days.) The proportion of participants with at least 1 month of follow-up after dose 2 was 76.7% (77.2% vaccine, 76.2% placebo) and with at least 2 months follow-up after dose 2 was 25.3% (25.7% vaccine, 24.9% placebo). FDA has completed its independent validation and evaluation of the datasets from which the Sponsor's interim safety and efficacy analyses were derived.

A second safety data cutoff was performed on November 25, 2020, and final efficacy analysis performed with a data cutoff of November 21, 2020, when 196 primary endpoint cases accrued. These data include a median follow-up of 2 months (9 weeks) for both efficacy and safety. The proportion of participants with at least 1 month of follow-up after dose 2 was 87.9% (88.2% vaccine, 87.7% placebo) and with at least 2 months follow-up after dose 2 was 53.6% (53.8% vaccine, 53.5% placebo). The Sponsor submitted analyses from the final efficacy analysis (Tables, Figures and Listings) on December 4, 2020, and safety analyses (Tables, Figures and Listings) on December 7, 2020, for FDA review under the EUA. Datasets were also submitted on December 7, 2020 and validated by FDA by December 8, 2020. The review of the second dataset submission for the final scheduled efficacy analysis and safety data through November 25, 2020, was not as comprehensive as that of the interim efficacy data and safety data first submitted in support of the EUA. However, preliminary assessments of safety and efficacy data and analyses from second data cutoff do not demonstrate any notable differences compared with the efficacy and safety analyses from November 7, 2020, and November 11, 2020, respectively, and key safety and efficacy data (e.g., the primary analysis, cases of severe COVID-19, and serious adverse events) from the December 7, 2020, submission were verified. FDA therefore considers the totality of submitted data to satisfy the expectation of a median of 2 months follow-up after completion of the full vaccination regimen.

5.2.3 Participant Disposition and Inclusion in Analysis Populations

Disposition tables are presented below in Table 4 (Per-Protocol Set) and Table 5 (Safety Set). The proportion of participants excluded from the Per-Protocol Set was balanced between treatment groups, with the majority of those excluded due to positive or unknown baseline SARS-CoV-2 status. Overall, few participants were discontinued or lost to follow-up, and these and other analysis population exclusions were generally balanced between treatment groups. In the per protocol population, 26.3% of vaccine recipients and 25.7% of placebo recipients completed at least 2 months follow-up after dose 2.

Table 4. Efficacy Analysis Population Study Disposition[a], mRNA-1273-P301

Disposition	Vaccine Group (N=15208) n (%)	Placebo Group (N=15210) n (%)	Total (N=30418) n (%)
Randomized	15208	15210	30418
Full Analysis Set	15180 (99.8)	15170 (99.7)	30350 (99.8)
Modified Intent-to-Treat Set	14312 (94.1%)	14370 (94.5%)	28682 (94.3)
Participants excluded from PP set	1274 (8.4%)	1327 (8.7%)	2601 (8.6%)
Randomized but received no Investigational Product (IP)	28 (0.2%)	40 (0.3%)	68 (0.2%)
Baseline SARS-CoV-2 status was positive or not known	868 (5.7%)	800 (5.3%)	1668 (5.5)
Received IP other than what the participant was randomized to	5 (<0.1)	7 (<0.1)	12 (<0.1)
Discontinued study or study vaccine without receiving the second dose	136 (0.9)	203 (1.3)	339 (1.1)
Did not receive second dose of IP	144 (0.9)	155 (1.0)	299 (1.0)
Received vaccine out of window	81 (0.5)	98 (0.6)	179 (0.6)
Major protocol deviation	12 (<0.1)	24 (0.2)	36 (0.1)
Per Protocol Set	13934 (91.6)	13883 (91.3)	27817 (91.4)
Completed 1 dose**	13934 (100)	13883 (100)	27817 (100)
Completed 2 doses**	13218 (94.9)	13164 (94.8)	26382 (94.8)
Completed at least 7 weeks follow-up after dose 2**	7293 (52.3)	7304 (52.6)	14597 (52.5)
Completed at least 2 months follow-up after dose 2**	3669 (26.3)	3568 (25.7)	7237 (26.0)
Discontinued from Study**	24 (0.2)	34 (0.2)	58 (0.2)
Reason for Discontinuation**			
Adverse Event	0	0	0
Death	0	1 (<0.1)	1 (<0.1)
Withdrawal by Participant	18 (0.1)	22 (0.2)	40 (0.1)
Lost to Follow-up	2 (<0.1)	9 (<0.1)	11 (<0.1)
Protocol Deviation	0	0	0
Physician Decision	2 (<0.1)	0	2 (<0.1)
Other	2 (<0.1)	2 (<0.1)	4 (<0.1)

Source: Sponsor's Table 14.1.1.1.1.1, Table 4.1.2.1, Table 14.1.1.1.3.2, Table 14.1.6.2
[a] EUA request (interim analysis): November 11, 2020 cutoff
*Percentage based on number of participants in the Safety Set
**Percentage based on number of participants in the Per-Protocol Set

Based on the November 11, 2020 safety data cutoff, an overview of participant disposition is presented in the table below. The proportion of randomized participants who discontinued from the study was 0.9% (288 participants) across study groups, with a greater number in the placebo group (168) compared with the vaccine group (120). The most frequently reported reason was withdrawal of consent (67 participants in the vaccine group, 120 in the placebo group). In addition, 51 participants were lost to follow-up (20 in the vaccine group, 31 in the placebo group). In the vaccine group, 3 participants withdrew due to an adverse event (<0.1%, including 1 participant who withdrew due to a SAE) and 3 participants died during the study. In the placebo group, no participants withdrew due to an adverse event, and 4 participants died during the study.

Table 5. Safety Analysis Population Study Disposition[a], mRNA-1273-P301

Disposition	Vaccine Group (N=15208) n (%)	Placebo Group (N=15210) n (%)	Total (N=30418) n (%)
Randomized	15208	15210	30418
Completed 1 dose	15180 (99.8)	15170 (99.7)	30350 (99.8)
Completed 2 doses	13982 (91.9)	13916 (91.5)	27898 (91.7)
Exposed (Safety Set)	15184	15166	30350 (99.8)
Discontinued from Study	120 (0.8)	168 (1.1)	288 (0.9)
Reason for Discontinuation			
Adverse Event	3 (<0.1)	0	3 (<0.1)
Death	3 (<0.1)	4 (<0.1)	7 (<0.1)
Withdrawal by Participant	67 (0.4)	120 (0.8)	187 (0.6)
Lost to Follow-up	20 (0.1)	31 (0.2)	51 (0.2)
Protocol Deviation	1 (<0.1)	1 (<0.1)	2 (<0.1)
Physician Decision	17 (0.1)	2 (<0.1)	19 (<0.1)
Other	9 (<0.1)	10(<0.1)	19 (<0.1)
Completed ≥1 month f/up*	14354 (94.5)	14345 (94.6)	28700 (94.6)
Completed ≥2 months f/up*	12021 (79.2)	11974 (79.0)	23995 (79.1)
Completed ≥1 month f/up after dose 2*	11717 (77.2)	11559 (76.2)	23276 (76.7)
Completed ≥2 months f/up after dose 2*	3894 (25.7)	3773 (24.9)	7667 (25.3)

Source: Sponsor's Table 14.1.1.1.1.1, Table 4.1.2.1, Table 14.1.1.1.3.2, Table 14.1.6.2.
[a] EUA request (interim analysis): November 11, 2020 cutoff

5.2.4 Demographics and Other Baseline Characteristics

The Per-Protocol Set included 47.4% females and 25.3% of individuals ≥65 years of age. There were 36.5% of participants considered as representing communities of color with 9.7% African American, 4.7% Asian, and <3% from other racial groups; 20% of participants were Hispanic/Latino. A majority of the participants (82%) were considered at occupational risk for SARS-CoV-2 exposure, with 25.4% of participants being healthcare workers. At least one protocol-defined high-risk condition for severe COVID-19 was present in 22.3% of participants, and 4% of participants had two or more high risk conditions. The protocol-specified risk factors were those conditions that placed an individual at increased risk for severe complications of COVID-19 and were selected based on CDC recommendations[12] from March 2020. These conditions included the following:

- Chronic lung disease (e.g., emphysema and chronic bronchitis), idiopathic pulmonary fibrosis and cystic fibrosis) or moderate to severe asthma
- Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
- Severe obesity (body mass index ≥40 kg/m2)
- Diabetes (Type 1, Type 2 or gestational)
- Liver disease
- HIV infection

There was a similar distribution of demographic characteristics between the treatment groups as well as between the all randomized population, Full Analysis Set, and the Per-Protocol Set.

Table 6. Demographic Characteristics[a], Per-Protocol Set

Characteristic	Vaccine Group (N=13934) n (%)	Placebo Group (N=13883) n (%)	Total (N=27817) n (%)
Sex			
Female	6661 (47.8)	6514 (46.9)	13175 (47.4)
Male	7273 (52.2)	7369 (53.1)	14642 (52.6)
Age (years)			
Mean (SD)	51.6 (15.45)	51.5 (15.55)	51.6 (15.50)
Median	53.0	52.0	53.0
Min, max	18, 95	18, 95	18, 95
Age- subgroups (years)			
18 to <65	10407 (74.7)	10384 (74.8)	20791 (74.7)
65 and older	3527 (25.3)	3499 (25.2)	7026 (25.3)
Race			
American Indian or Alaska Native	107 (0.8)	110 (0.8)	217 (0.8)
Asian	616 (4.4)	684 (4.9)	1300 (4.7)
Black or African American	1369 (9.8)	1338 (9.6)	2707 (9.7)
Native Hawaiian or Other Pacific Islander	33 (0.2)	30 (0.2)	63 (0.2)
White	11078 (79.5)	11005 (79.3)	22083 (79.4)
Other	298 (2.1)	293 (2.1)	591 (2.1)
Ethnicity			
Hispanic or Latino	2783 (20.0)	2769 (19.9)	5552 (20.0)
Not Hispanic or Latino	11019 (79.1)	10987 (79.1)	22006 (79.1)
Race and Ethnicity			
Non-Hispanic white	8858 (63.6)	8755 (63.1)	17613 (63.3)
Communities of color	5054 (36.3)	5102 (36.7)	10156 (36.5)
Occupational Risk*	11397 (81.8)	11408 (82.2)	22805 (82.0)
Healthcare worker	3541 (25.4)	3531 (25.4)	7072 (25.4)
High Risk Condition**			
No high risk condition	11820 (77.9)	11788 (77.7)	23608 (77.8)
One high risk condition present	3116 (22.4)	3075 (22.1)	6191 (22.3)
Two or more high risk conditions present	561 (4.0)	554 (4.0)	1115 (4.0)
Age and Health Risk for Severe COVID-19***			
18 to <65 years and not at risk	8309 (59.6)	8323 (60.0)	16632 (59.8)
18 to <65 years and at risk	2098 (15.1)	2061 (14.8)	4159 (15.0)
≥65 years	3527 (25.3)	3499 (25.2)	7026 (25.3)

Source: Sponsor's Table14.1.3.4.2. [a] EUA request (interim analysis): November 11, 2020 data cutoff.
Occupational risk includes: Healthcare Workers, Emergency Response, Retail/Restaurant Operations, Manufacturing and Production Operations, Warehouse Shipping and Fulfillment centers, Transportation and Delivery Services, Border Protection and Military Personnel, and Personal care and in-home services, Hospitality and Tourism Workers, Pastoral, Social or Public Health Workers, Educators and Students.
[**] High risk is defined as patients who meet at least one of the following criteria (protocol-defined): Chronic lung disease (eg, emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma; Significant cardiac disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension); Severe obesity (body mass index ≥40 kg/m2); Diabetes (Type 1, Type 2 or gestational); Liver disease; Human Immunodeficiency Virus (HIV) infection
[***] Age and health risk for severe COVID-19 is used as stratification factor for randomization.

The demographic characteristics among vaccine and placebo participants in the safety population were similar. There were no significant imbalances in demographic and other baseline characteristics between the per-protocol population and the safety population, with median 7-week follow-up.

Table 7. Demographic Characteristics[a], Safety Set

Characteristic	Vaccine Group (N=15184) n (%)	Placebo Group (N=15165) n (%)	Total (N=30350) n (%)
Sex			
Female	7255 (47.8)	7100 (46.8)	14355 (47.3
Male	7929 (52.2)	8065 (53.2)	15995 (52.7)
Age (years)			
Mean (SD)	51.4 (15.50)	51.3 (15.60)	51.4 (15.55)
Median	53.0	52.0	52.0
Min, max	18, 95	18, 95	18, 95
Age – Subgroups (years)			
≥18 to <65	11414 (75.2)	11415 (75.3)	22830 (75.2)
65 and older	3770 (24.8)	3750 (24.7)	7520 (24.8)
Race			
American Indian or Alaska Native	110 (0.7)	120 (0.8)	230 (0.8)
Asian	653 (4.3)	732 (4.8)	1385 (4.6)
Black or African American	1562 (10.3)	1528 (10.1)	3090 (10.2)
Native Hawaiian or other Pacific islander	34 (0.2)	32 (0.2)	66 (0.2)
White	12032 (79.2)	11990 (79.1)	24023 (79.2)
Other	321 (2.1)	315 (2.1)	636 (2.1)
Multiracial	315 (2.1)	319 (2.1)	634 (2.1)
Ethnicity			
Hispanic or Latino	3121 (20.6)	3112 (20.5)	6234 (20.5)
Not Hispanic or Latino	11920 (78.5)	11914 (78.6)	23834 (78.5)
Race and Ethnicity			
Non-Hispanic White	9534 (62.8)	9458 (62.4)	18992 (62.6)
Communities of color	5624 (37.0)	5680 (37.5)	11305 (37.2)
Occupational Risk*	12420 (81.8)	12487 (82.3)	24907 (82.1)
Healthcare worker	3787 (24.9)	3826 (25.2)	7613 (25.1)
High Risk Condition**			
One high risk condition present	3360 (22.1)	3382 (22.3)	6742 (22.2)
No high risk condition	11824 (77.9)	11783 (77.7)	23608 (77.8)
Age and Health Risk for Severe COVID-19***			
≥18 to <65 years and not at risk	8889 (58.5)	8884 (58.6)	17773 (58.6)
≥18 to <65 years and at risk	2530 (16.7)	2534 (16.7)	5065 (16.7)
≥65 years	3765 (24.8)	3747 (24.7)	7512 (24.8)

Characteristic	Vaccine Group (N=15184) n (%)	Placebo Group (N=15165) n (%)	Total (N=30350) n (%)
Baseline SARS CoV-2 status****			
Negative	14316 (94.3%)	14366 (94.7)	26862 (94.5%)
Positive	341 (2.2%)	334 (2.2%)	675 (2.2%)
Missing	527 (3.5%)	465 (3.5%)	993 (3.3%)

Source: Sponsor's Table 14.1.3.2.2 [a] EUA request (interim analysis): November 11 2020 cutoff.
* Occupational risk includes: Healthcare Workers, Emergency Response, Retail/Restaurant Operations, Manufacturing and Production Operations, Warehouse Shipping and Fulfillment centers, Transportation and Delivery Services, Border Protection and Military Personnel, and Personal care and in-home services, Hospitality and Tourism Workers, Pastoral, Social or Public Health Workers, Educators and Students.**
**High risk is defined as patients who meet at least one of the following criteria (protocol-defined): Chronic lung disease (eg, emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma; Significant cardiac disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension); Severe obesity (body mass index ≥40 kg/m2); Diabetes (Type 1, Type 2 or gestational); Liver disease; Human immunodeficiency virus (HIV) infection

The following table provides the proportions of participants randomized to each of the protocol-specified strata based on presence or absence of protocol-defined risk factors for severe COVID-19 disease, including age ⩾65 years. The presence of these risk factors was assessed at screening via review of the participants medical history. The protocol specified that at least 25% (and up to 50%) of enrolled participants were to be either ⩾65 years of age or 18 through <65 years of age with a protocol-defined risk factor. As of the November 11, 2020 cutoff, ~25% of participants were age ⩾65 years, and 16.7% of participants were age 18 to <65 years with a protocol-defined risk factor. The remainder of participants (58.6%) were age 18 to <65 years without risks. The proportions of participants in each of these three strata randomized to vaccine or placebo are shown in the table below.

Table 8. Protocol-Defined Risk for Severe COVID-19 Disease, Safety Seta

Participants Risk Categories	Vaccine Group (N=15184) n (%)	Placebo Group (N=15165) n (%)	Total (N=30350) n (%)
Without Any Protocol Risk for Severe COVID-19	11824 (77.9)	11783 (77.7)	23608 (77.8)
With Any Protocol Risk for Severe COVID-19	3360 (22.1)	3382 (22.3)	6742 (22.2)
Chronic Lung Disease	707 (4.7)	741 (4.9)	1448 (4.8)
Significant Cardiac Disease	742 (4.9)	741 (4.9)	1483 (4.9)
Severe Obesity	986 (6.5)	978 (6.4)	1964 (6.5)
Diabetes	1427 (9.4)	1431 (9.4)	2858 (9.4)
Liver Disease	100 (0.7)	96 (0.6)	196 (0.6)
HIV Infection	90 (0.6)	86 (0.6)	176 (0.6)

Source: Sponsor's Table 14.1.3.2.2. [a] EUA request (interim analysis): November 11, 2020 cutoff

5.2.5 Vaccine Efficacy

Interim Primary Efficacy Analysis

The interim primary efficacy analysis was based on the Per-Protocol Set, which consisted of all participants with negative baseline SARS-CoV-2 status (i.e., negative RT-PCR for SARS-CoV-2 at Day 1 and/or negative serology against SARS-CoV-2 nucleocapsid) and who received 2 doses of investigational product per schedule with no major protocol deviations. The primary efficacy endpoint was vaccine efficacy (VE) in preventing protocol defined COVID-19 occurring at least 14 days after dose 2. Cases were adjudicated by a blinded committee. The primary

efficacy success criterion would be met if the null hypothesis of VE ≤30% was rejected at the O'Brien Fleming boundary at either the interim or primary analysis. The efficacy analysis presented is based on the data at the first pre-specified interim analysis timepoint consisting of 95 adjudicated cases. As shown in Table 9, in participants ≥18 years of age, there were 5 COVID-19 cases in the vaccine group and 90 COVID-19 cases in the placebo group, with a VE of 94.5%, a lower bound of the 95% CI of 86.5%, and a one-sided p-value of <0.0001 for testing H0: VE ≤30%, which met the pre-specified success criterion. In participants ≥65 years of age in the Per-Protocol Set, there were no COVID-19 cases in the vaccine group and 15 COVID-19 cases in the placebo group.

Table 9. Interim Analysis[a] for Primary Efficacy Endpoint, COVID-19 Starting 14 Days After the 2nd Dose, Per-Protocol Set

Primary Endpoint: COVID-19 (per adjudication committee assessment)	Vaccine Group N=13934 Cases n (%) (Incidence rate per 1,000 person-years)	Placebo Group N=13883 Cases n (%) (Incidence rate per 1,000 person-years)	Vaccine Efficacy (VE) % (95% CI)*	Met Predefined Success Criterion**
All participants	5 (<0.1) 1.840	90 (0.6) 33.365	94.5% (86.5%, 97.8%)	Yes
18 to <65	5 / 10407 (<0.1) 2.504	75 / 10384 (0.7) 37.788	93.4% (83.7%, 97.3%)	NA
65 and older	0 / 3527	15 / 3499 (0.4) 21.046	100%	NA

Source: Sponsor's Table 14.2.2.1.1.1.1, Table 14.2.2.1.1.6.1.1.
COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the 2nd dose. All potential COVID-19 cases starting 14 days after the 2nd dose in the clinical database as of 07-Nov-2020 have been sent to adjudication committee, and have been adjudicated for this analysis (07-Nov-2020 is the data cutoff date for efficacy). One case (in the placebo group) was assessed as a case by the adjudication committee but did not meet case definition based on statistical analysis plan (participant had body aches, nasal congestion, rhinorrhea, which were not protocol defined symptoms).
* VE is calculated as 1-ratio of incidence rates (mRNA-1273/placebo) and 95% CI from the stratified Cox proportional hazard model.
**The one-sided p-value is <0.0001 from the stratified Cox proportional hazard model to test the null hypothesis of VE ≤30%, achieving the pre-specified efficacy boundary: the one-sided nominal alpha of 0.0049 based on 95 cases using the Lan-DeMets O'Brien-Fleming spending function.

There were an additional 18 COVID-19 cases which met the protocol-defined primary efficacy endpoint but were not able to be adjudicated in time for the interim analysis. Of these 18 cases, one was in the vaccine group, and 17 were in the placebo group. Vaccine efficacy for the primary efficacy endpoint including these unadjudicated cases was similar to the results presented above.

Interim Subgroup Analyses of Vaccine Efficacy

Subgroup analyses for the primary efficacy endpoint include VE based on age, sex, race and ethnicity, risk factor, and baseline SARS-CoV-2 status and provide additional information on the applicability of these results across the general population. In general, VE among the subgroups are similar to the VE seen in the overall study population. The small number participants and cases in some subgroups, such as participants ≥75 years of age and participants in certain racial subgroups, limits the interpretability of the individual VE results, but are displayed for completeness.

Table 10. Subgroup Analyses of Vaccine Efficacy[a], COVID-19 14 Days After Dose 2 Per Adjudication Committee Assessments, Per-Protocol Set

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
Age (years)			
18 to <65	5 / 10407 (<0.1) 2.504	75 / 10384 (0.7) 37.788	93.4% (83.7%, 97.3%)
65 to <75	0 / 2904	12/ 2823 (0.4) 20.883	100%
75 and older	0 / 623	3 / 676 (0.4) 21.726	100%
Age and risk for severe COVID-19**			
18 and <65 and not at risk	4 / 8309 (<0.1) 2.524	57 / 8323 (0.7) 36.034	93.0% (80.8%, 97.5%)
18 and <65 and at risk	1 / 2098 (<0.1) 2.428	18 / 2061 (0.9) 44.673	94.6% (59.4%, 99.3%)
≥65	0 / 3527	15 / 3499 (0.4) 21.046	100%
Sex			
Female	3 / 6661 (<0.1) 2.271	45 / 6514 (0.7) 34.991	93.5% (79.2%, 98.0%)
Male	2 / 7273 (<0.1) 1.433	45 / 7369 (0.6) 31.883	95.5% (81.5%, 98.9%)
Race and Ethnicity			
Non-Hispanic white	5 / 8858 (<0.1) 2.657	70 /8755 (0.8) 37.721	93.0% (82.6%, 97.2%)
Communities of color	0 / 5054	20 / 5102 (0.4) 23.892	100%
Ethnicity			
Hispanic or Latino	0 / 2783	12 / 2769 (0.4) 26.346	100%
Not Hispanic or Latino	5 / 11019 (<0.1) 2.243	77 / 10987 (0.7) 34.729	93.6% (84.1%, 97.4%)
Race			
American Indian or Alaska Native	0 / 107	0 / 110	
Asian	0 / 616	3 / 684 (0.4) 26.549	100%
Black or African American	0 / 1,369	4 / 1338 (0.3) 18.566	100%
Native Hawaiian or Other Pacific Islander	0 / 33	0 / 30	
White	5 /11078 (<0.1) 2.215	80 / 11005 (0.7) 35.821	93.8% (84.8%, 97.5%)
Multiple	0 / 293	1 / 304 (0.3)	100%

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
Other	0 / 298	2 / 293 (0.7) 45.645	100%

Source: Sponsor's Table 14.2.2.1.1.6.1.1, Table 14.2.2.1.1.6.3.1, Table 4.2.2.1.1.6.7.1, Table 14.2.2.1.1.6.10.1, Table 14.2.2.1.1.6.4.1, Table 14.2.2.1.1.6.2.1, Table 14.2.2.1.1.6.5.1, Table 14.2.2.1.1.6.6.1
[a] EUA request (interim analysis): November 7, 2020 data cutoff.
* VE is calculated as 1-ratio of incidence rates (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented for subgroups for which the lower bound was not evaluable by the statistical methods used for the analysis.
At risk for severe COVID-19 due to comorbidity, regardless of age. High risk is defined as patients who meet at least one of the following criteria (protocol-defined): Chronic lung disease (eg, emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic f ibrosis) or moderate to severe asthma; Significant cardiac disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension); Severe obesity (body mass index ≥40 kg/m2); Diabetes (Type 1, Type 2 or gestational); Liver disease; Human Immunodeficiency Virus (HIV) infection
**used as stratification factor for randomization

The demographics of the participants with confirmed COVID-19 cases contributing to the primary efficacy analysis are displayed below in Table 11.

Table 11. Demographic Characteristics[a], Participants With COVID-19 Starting 14 Days After Dose 2, Per Adjudication Committee Assessments, Per-Protocol Set

Characteristic	Vaccine (N[a] =5) N[b] (%)	Placebo (N[a] =90) N[b] (%)	Total (N[a] =95) N[b] (%)
Sex			
Female	3 (60)	45 (50)	48 (50.5)
Male	2 (40)	45 (50)	47 (49.5)
Age group			
18 to <65 years	5 (100)	75 (83.3)	80 (84.2)
≥65 to <75 years	0	12 (13.3)	12 (12.6)
≥75 years	0	3 (3.3)	3 (3.2)
Race			
American Indian or Alaska Native	0	0	0
Asian	0	3 (3.3)	3 (3.2)
Black or African American	0	4 (4.4)	4 (4.2)
Native Hawaiian or Other Pacific Islander	0	0	0
White	5 (100)	80 (88.9)	80 (84.2)
Multiracial	0	1 (1.1)	1 (1.1)
Other	0	2 (2.2)	2 (2.1)
Ethnicity			
Hispanic or Latino	0	12 (13.3)	12 (12.6)
Not Hispanic or Latino	5 (100)	77 (85.6)	82 (86.3)
Not reported	0	1 (1.1)	1 (1.1)
At risk for severe COVID-19			
Yes	1 (20)	24 (26.7)	25 (26.3)
No	4 (80)	66 (73.3)	70 (73.7)

[a] N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations. [a] EUA request (interim analysis): November 07 2020 efficacy data cutoff. [a] EUA request (interim analysis): November 07 2020 cutoff.
[b] n = Number of participants with the specified characteristic.

Only 2.2% of participants had evidence of prior infection at study enrollment, and there was only one COVID-19 case starting 14 days after dose 2 reported from this subgroup, which was in a participant in the placebo group. There is insufficient data to conclude on the efficacy of the vaccine in previously infected individuals.

Table 12. Vaccine Efficacy by Baseline SARS-CoV-2 Status[a]: First COVID-19 From 14 Days After Dose 2 Per Adjudication Committee Assessment, Full Analysis Set

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
Baseline SARS-CoV-2			
Regardless of baseline SARS-CoV-2 status	6/15180	92/15170	93.5% (85.2, 97.2)
Positive	0/341	1/334 (0.3) 17.038	100%
Negative	6/14312 (<0.1) 2.154	90/14370 (0.6) 32.298	93.4% (84.8%, 97.1%)
Unknown or missing	0/527	1/465 (0.2)	100%

* VE is calculated as 1-ratio of incidence rates (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented for subgroups for which the lower bound was not evaluable by the statistical methods used for the analysis.

Additional subgroup analyses of the interim primary efficacy analysis were conducted to evaluate the vaccine efficacy, by risk factor for severe COVID-19. VE point estimates were consistent with the efficacy observed for the overall study population, though interpretation of the results is limited by small numbers of participants and cases.

Table 13. Vaccine Efficacy by Risk Factor: First COVID-19 Occurrence From 14 Days After Dose 2, Per Adjudication Committee Assessment, Per-Protocol Set

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
At risk for severe COVID-19 due to comorbidity, regardless of age			
Yes	1 / 3116 (<0.1) 1.604	24 / 3075 (0.8) 39.177	95.9% (69.7%, 99.4%)
Chronic Lung Disease	0/661	6/673 (0.9) 42.950	100%
Significant Cardiac Disease	0/686	3/678 (0.4) 21.463	100%
Severe Obesity (BMI $\geq$40 kg/m^2)	1/901 (0.1) 5.524	11/884 (1.2) 62.851	91.2% (32.0%, 98.9%)
Diabetes	0/1338	7/1309 (0.5) 27.148	100%
Liver Disease	0/93	0/90	
HIV infection	0/80	1/76 (1.3) 91.108	100%
No	4 / 10818 (<0.1) 1.911	66 / 10808 (0.6) 31.657	94.0% (83.5%, 97.8%)
Obesity (BMI >30 kg/m^2)**	2/5269 (<0.1%)	46/5207 (0.9)	95.8% (82.6, 99.0)

[a] EUA request (interim analysis): November 7, 2020 efficacy data cutoff
* VE is calculated as 1-ratio of incidence rates (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented for subgroups for which the lower bound was not evaluable by the statistical methods used for the analysis.
** Post hoc analysis.

Interim Secondary Efficacy Analyses

Severe COVID-19 Cases

All 11 cases of severe COVID-19 at least 14 days after second dose as assessed by the adjudication committee were in the placebo group. Of these 11 participants, 5 had risk factors for severe COVID-19 and 6 did not. Three severe COVID-19 cases resulted in hospitalization and 8 did not. Nine of these cases met the severe COVID-19 case definition based on low oxygen saturation ≤93% on room air without any other severe disease criteria. One participant had low oxygen saturation as well as systolic blood pressure <90 mmHg. One participant had low oxygen saturation and missing data on whether other criteria were met. The vaccine efficacy of this secondary efficacy endpoint is shown in Table 14.

Table 14. Severe COVID-19 Cases Starting 14 Days After Second Dose Based on Adjudication Committee Assessment, Per-Protocol Set

	Vaccine Group N=13934 Cases n (%)	Placebo Group N=13883 Cases n (%) Incidence rate per 1,000 person-years	Vaccine Efficacy (VE) % (95% CI)*
Severe COVID-19	0	11 (<0.1); 4.072	100%

[a] EUA request (interim analysis): Novemer 07 2020 efficacy data cutoff.
* VE is calculated as 1-ratio of incidence rates (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented when the lower bound was not evaluable by the statistical methods used for the analysis.

One participant in the mRNA-1273 group, a participant >65 years of age who had risk factors for severe COVID-19, was hospitalized due to oxygen saturation of 88% on room air 2 months after receiving the second dose of vaccine. There was a verbal report of a positive SARS-CoV-2 RT-PCR test 3 days prior to hospitalization; however, NP swab collected during hospitalization was negative for SARS-CoV-2. Due to absence of a confirmed RT-PCR result at the time of data snapshot, this case was not referred for adjudication and not captured. The pre-hospitalization RT-PCR result was later reported to be positive from an external CLIA-certified laboratory and may represent a severe COVID-19 case with hospitalization in the vaccine group.

There were 4 additional severe COVID-19 cases which met the protocol-defined severe COVID-19 endpoint but were not able to be adjudicated in time for the interim analysis. All 4 cases were in the placebo group.

Other Secondary Efficacy Endpoints

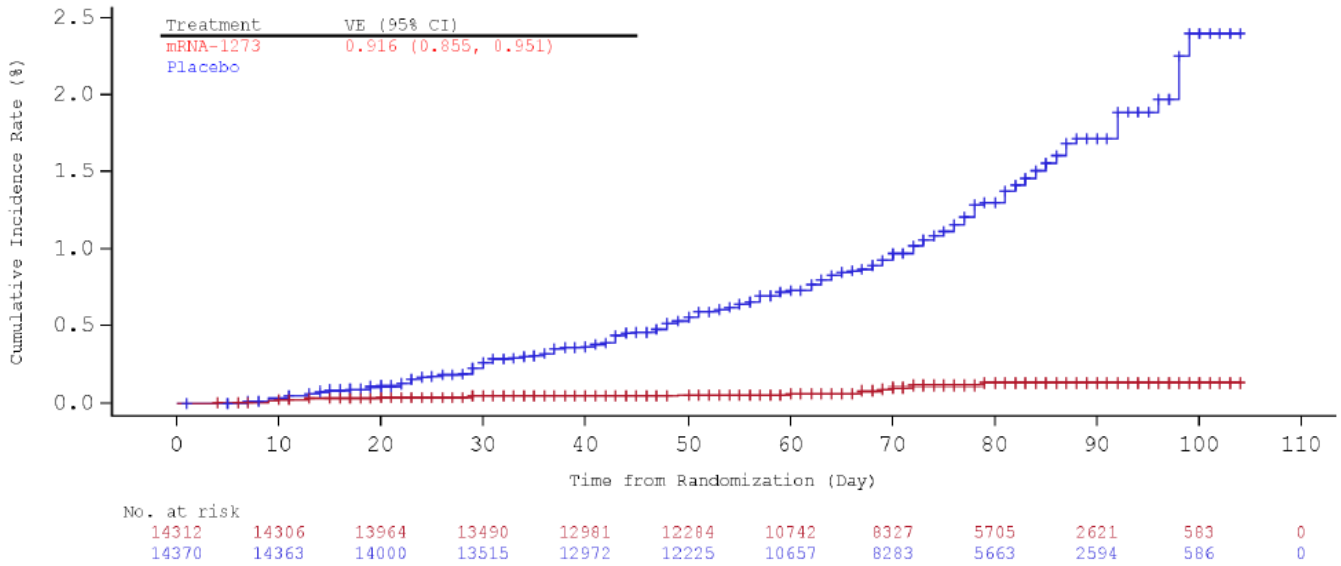
The secondary efficacy endpoint of VE of mRNA-1273 for the prevention of COVID-19 disease based on a less restrictive definition of COVID-19 disease from 14 days after dose 2 showed similar case splits and VE to the primary efficacy endpoints described above. Efficacy against COVID-19 occurring at least 14 days after the first dose of vaccine, including cases that occurred after the second dose, was also similar to the primary endpoint. There were no deaths due to COVID-19 at the time of the interim analysis to enable an assessment of vaccine efficacy against death due to COVID-19.

Cumulative Incidence Curves – Interim Efficacy Analysis

Based on the cumulative incidence curve for cases in the mITT efficacy population after randomization (same as date of dose 1), COVID-19 cases appear to have occurred similarly at low rates for both the mRNA-1273 and placebo groups until around Day 14 after dose 1. The

curves then diverge, with more cases accumulating in the placebo group than the mRNA-1273 group.

Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Randomization, mITT Set



Additional Interim Efficacy Analyses

Additional analyses were done to assess efficacy against COVID-19 after one dose of mRNA-1273. In participants in the mITT set who only received one dose of the vaccine at the time of the interim analysis, VE after one dose was 80.2% (95% CI 55.2%, 92.5%). These participants had a median follow-up time of 28 days (range: 1 to 108 days). The small, non-random sample and short median follow-up time limits the interpretation of these results. There appears to be some protection against COVID-19 disease following one dose; however, these data do not provide sufficient information about longer term protection beyond 28 days after a single dose.

Table 15. Vaccine Efficacy[a] of mRNA-1273 to Prevent COVID-19 From Dose 1 by Time Period in Participants Who Only Received One Dose, mITT Set

First COVID-19 Occurrence After Dose 1	Vaccine Group N=996 Case n (%)	Placebo Group N=1079 Case n (%)	VE (%) (95% CI)*
After dose 1	7/996 (87.5)	39/1079 (96.7)	80.2% (55.2%, 92.5%)
After dose 1 to 14 days after dose 1	5/996 (38.0)	11/1079 (41.1)	50.8% (-53.6%, 86.6%)
>14 days after dose 1**	2/983 (87.2)	28/1059 (96.2)	92.1% (68.8%, 99.1%)

Surveillance time in person years for given endpoint across all participants within each group at risk for the endpoint
* VE is calculated as 1-ratio of incidence rates (mRNA-1273/Placebo). The 95% CI of VE is calculated using the exact method conditional upon the total number of cases, adjusting for person-years
**Participants who were not at risk (cases or censored at prior time period) are excluded from this analysis
[a] Based on interim analysis: Novemer 7, 2020 efficacy data cutoff.

A similar analysis was conducted to look at vaccine efficacy against severe COVID-19 after one dose. In participants in the mITT group who received only one vaccine, 2 participants in the mRNA-1273 group and 4 participants in the placebo group developed severe COVID-19. Both participants in the vaccine group met the case definition for severe COVID-19 based on oxygen saturation ≤93% on room air. These results should be interpreted cautiously given the small sample size and case number and the short follow-up duration.

Table 16. Vaccine Efficacy[a] of mRNA-1273 to Prevent Severe COVID-19 After Dose 1 in Participants Who Only Received One Dose in mITT Set

	Vaccine Group N=996 Case n (%)	Control Group N=1079 Case n (%)	Vaccine Efficacy (95% CI)
Number of participants with severe COVID-19 starting after dose 1	2 (0.2)	4 (0.4)	42.6% (-300.8, 94.8)

[a] Based on interim analysis : EUA request (interim efficacy analysis): November 7, 2020 efficacy data cutoff.

Final Scheduled Efficacy Analysis

Data from the final scheduled efficacy analysis were submitted as an amendment to the EUA request on December 7, 2020. Analyses of efficacy endpoints beyond those presented below have not been independently verified by the FDA. The median efficacy and safety follow-up for participants in the study at of the time of the final scheduled efficacy analysis (November 21, 2020 efficacy data cutoff) was 9 weeks. Vaccine efficacy against COVID-19 starting 14 days after the second dose was 94.1% (95% CI 89.3%, 96.8%) and was consistent with results obtained from the interim analysis. The VE in participants ≥65 years of age appears to be lower than in younger adults 18 to <65 years (86.4% compared to 95.6%) and lower than observed in the interim analysis (100% based on a total of 15 cases).

Table 17. Final Scheduled Efficacy Analysis, Primary Endpoint, COVID-19 Starting 14 Days After the Second Dose per Adjudication Committee Assessments, Per-Protocol Set

Primary Endpoint: COVID-19 (per adjudication committee assessment)	Vaccine Group N=13934 Cases n (%) (Incidence Rate per 1,000 person-years)*	Placebo Group N=13883 Cases n (%) (Incidence Rate per 1,000 person-years)*	Vaccine Efficacy (VE) % (95% CI)**	Met Predefined Success Criterion***
All participants	11 (<0.1) 3.328	185 (1.3) 56.510	94.1% (89.3%, 96.8%)	Yes
18 to <65 years[1]	7/10551 (<0.1) 2.875	156/10521 (1.5) 64.625	95.6%; (90.6%, 97.9%)	NA
65 years and older[2]	4/3583 (0.1); 4.595	29/3552 (0.8); 33.728	86.4%; (61.4%, 95.5%)	NA

Source: Sponsor's Table 14.2.2.1.1.1.1, Table 14.2.2.1.1.6.1.1
COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the second dose. All potential COVID-19 cases starting 14 days after the second dose in the clinical database as of 21-Nov-2020 have been sent to adjudication committee, and have been adjudicated for this analysis (21-Nov-2020 is the data cutoff date for efficacy). One case (in the vaccine group) was adjudicated as a COVID-19 case by the committee but did was meet the case definition per statistical analysis plan due to documented symptoms and positive PCR being more than 14 days apart.
21-Nov-2020 have been sent to adjudication committee, and have been adjudicated for this analysis (21-Nov-2020 is the data cutoff date for efficacy).
* Incidence rate is defined as the number of participants with an event divided by the number of participants at risk and adjusted by person-years (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years.
**VE and 95% CI from the stratified Cox proportional hazard model
***The one-sided p-value is <0.0001 from the stratified Cox proportional hazard model to test the null hypothesis of VE ≤30%, achieving the pre-specified efficacy boundary.
[1] Percentage based on number of participants in the 18 to <65 years of age group.
[2] Percentage based on number of participants in the ≥65 years of age group.

Severe COVID-19 Cases

In the primary efficacy analysis, there were an additional 19 cases of severe COVID-19 (one of which resulted in death from COVID-19), for a total of 30 severe COVID-19 cases starting 14 days after dose 2, per adjudication committee assessment. All 30 cases were in the placebo group. Nine of the total 30 severe COVID-19 cases resulted in hospitalization. Of the 19 additional severe cases since the interim analysis, 12 cases met the severe case definition due to low oxygen saturation ≤93% with no other criteria met. The remaining participants met the definition based on the following reasons: death (1 participant), ARDS requiring ECMO (1 participant), low oxygen saturation and renal and neurologic dysfunction (1 participant), low oxygen saturation and low blood pressure (2 participants), need for high flow oxygen (1 participant), low blood pressure only (1 participants). The COVID-19 case which resulted in death was in a 54-year-old participant with diabetes. The possible severe COVID-19 case in a mRNA-1273 vaccine recipient described with the interim efficacy analysis (negative SARS-CoV-2 PCR per the study central laboratory but reported positive PCR per a CLIA-certified external lab) is not included in the per-protocol analysis below.

Table 18. Secondary Efficacy Analysis, Severe COVID-19 Starting 14 Days After the Second Dose per Adjudication Committee Assessments, Per-Protocol Set

Severe Cases 14 Days After Dose 2 Based on Adjudication Committee Assessments	Vaccine Group N=13934 Cases n (%) (Incidence rate per 1,000 person-years)	Placebo Group N=13883 Cases n (%) (Incidence rate per 1,000 person-years)	Vaccine Efficacy (VE) % (95% CI)*
All participants	0	30 (0.2) 9.138	100%

[a] EUA request (primary analysis): November 21, 2020 efficacy data cutoff.

Efficacy Summary

The data from the planned interim efficacy analysis, with a cutoff date of November 7, 2020, and median follow-up for efficacy of 7 weeks post-dose 2, met the prespecified success criteria established in the study protocol. Efficacy of the vaccine to prevent COVID-19 occurring at least 14 days after dose 2 was 94.5%, (95% CI 86.5%; 97.8%) in participants without prior evidence of SARS-CoV-2 infection. VE was >93% in the group of participants with or without prior infection, although interpretation of data in participants with positive SARS-CoV-2 status at baseline is limited by the small sample size and case numbers in this subgroup. Efficacy outcomes across demographic subgroups were consistent with the efficacy seen in the overall study population. All 11 cases of severe COVID-19 occurring 14 days after the second dose

were in the placebo group, although one severe COVID-19 may have occurred in the vaccine group but did not meet criteria for the protocol-specified case definition. Among participants in the mITT set who only received one dose of vaccine or placebo at the time of the interim analysis, efficacy against COVID-19 starting after dose 1 was 80.2% (95% CI: 55.2%, 92.5%). The efficacy observed after dose 1 and before dose 2, from a post-hoc analysis, cannot support a conclusion on the efficacy of a single dose of the vaccine, because the numbers of participants and time of observation are limited. The trial did not have a single-dose arm to make an adequate comparison.

Data from a final efficacy analysis (data cutoff November 21, 2020) was submitted as an amendment after the initial EUA request. The FDA has not independently verified the complete efficacy data from this dataset, beyond those analyses presented above. The final scheduled efficacy analysis on the primary endpoint, demonstrating a VE point estimate of 94.1% (95% CI: 89.3%, 96.8%), appear to align with the data obtained from the interim analysis, except for a lower efficacy observed in participants ≥65 years of age compared to that in younger adults 18 to <65 years of age and compared to the efficacy estimate from the interim analysis.

5.2.6 Safety

The safety analyses presented in this review are largely derived from the November 11, 2020 dataset that was the basis for the November 30, 2020 EUA request. FDA has not independently verified the complete safety dataset and analyses from the cutoff date of November 25, 2020. However, all new deaths, SAEs, unsolicited adverse events of interest, and pregnancies were reviewed using the cutoff date of November 25, 2020. No additional safety concerns were raised based on the additional data reviewed by FDA or analyses presented by the Sponsor. The safety analyses from the November 25, 2020 cutoff date, as presented by the Sponsor, appear to align with results from the interim analysis in terms of overall rates and types of solicited and unsolicited adverse events.

Adverse events were reported in a higher proportion of vaccine recipients than placebo recipients, and this imbalance was driven by reactogenicity (solicited AEs) reported in the 7 days following each dose of vaccine. The proportions of participants with SAEs, death, and withdrawals due to adverse events were balanced across the study groups. Overall, rates of AEs were lower in participants with baseline positive SARS-CoV-2 status compared with those with baseline negative SARS-CoV-2 status. The tables below provide an overview of the rates of AEs by treatment groups and baseline SARS-CoV-2 status.

Table 19. Participants Reporting at Least One Adverse Event, Among All Participants and by Baseline SARS-COV2 Status (Safety Set)[a]

Adverse Event Type	Vaccine Group n/N (%)	Placebo Group n/N (%)
Solicited Safety Set	**N=15176**	**N=15162**
Solicited adverse reactions after any injection	14338/15176 (94.5)	9027/15162 (59.5)
Baseline SARS-COV-2 negative	13566/14309 (94.8%)	8576/14363 (59.7)
Baseline SARS-COV-2 positive	279 /340 (82.1%)	151/334 (45.2)
Solicited local adverse reaction	13,962/15176 (92.0)	4,381/15161 (28.9)
Baseline SARS-COV-2 negative	13211/14309 (92.3)	4147/14362 (28.9)
Baseline SARS-COV-2 positive	268/340 (78.8)	74/334 (22.2)
Grade 3 solicited injection site reaction[a]	1386/15176 (9.1)	143/15161 (0.9)
Baseline SARS-COV-2 negative	1307/14309 (9.1)	131/14362 (0.9)
Baseline SARS-COV-2 positive	23/340 (6.8)	5/334 (1.5)
Solicited systemic adverse reaction	12553/15176 (82.7)	8032/15,162 (53.0)
Baseline SARS-COV-2 negative	11893/14309 (83.1)	7628/14363(53.1)
Baseline SARS-COV-2 positive	237/340 (69.7)	137/334 (41.0)
Grade 3 or 4 solicited systemic adverse reaction	2,501/15,176 (16.5)	560/15,162 (3.7)
Baseline SARS-COV-2 negative	2383/14309 (16.7)	529/14363 (3.7)
Baseline SARS-COV-2 positive	37/340 (10.9)	13/334 (3.9)
Safety Set	**N=15184**	**N=15165**
Unsolicited adverse event up to 28 days after any injection	3325/15184 (21.9)	2949/15165 (19.4)
Baseline SARS-COV-2 negative	3204/14316 (22.4)	2846/14366 (19.8)
Baseline SARS-COV-2 positive	49/341 (14.4)	56/334 (16.8)
Unsolicited adverse event	3283/15184 (21.6)	2902/15165 (19.1)
Grade 3 unsolicited adverse event	187/15184 (1.2)	148/15165 (1.0)
Related** unsolicited adverse events	1127/15184 (7.4)	609/15165 (4.0)
Baseline SARS-COV-2 negative	1095/14316 (7.6)	585/14366 (4.1)
Baseline SARS-COV-2 positive	16/341 (4.7)	14/334 (4.2)
Related** Grade 3 unsolicited adverse event	69/15184 (0.5)	28/15165 (0.2)
Medically attended adverse Event	1215/15184 (8.0)	1276/15165 (8.4)
Baseline SARS-COV-2 negative	1167/14316 (8.2)	1243/14366 (8.7)
Baseline SARS-COV-2 positive	19/341 (5.6)	18/334 (5.4)
Related** medically attended adverse events	122/15184 (0.8)	73/15165 (0.5)
Baseline SARS-COV-2 negative	118/14316 (0.8)	68/14366 (0.5)
Baseline SARS-COV-2 positive	0/341	5/334 (1.5)
Serious adverse event	82/15184 (0.5)	86/15165 (0.6)
Baseline SARS-COV-2 negative	79/14316 (0.6)	82/14366 (0.6)
Baseline SARS-COV-2 positive	0/341	3/334 (0.9)
Related** serious adverse event	5/15184 (<0.1)	4/15165 (<0.1)
Baseline SARS-COV-2 negative	5/14316 (<0.1)	4/14366 (<0.1)
Baseline SARS-COV-2 positive	0/341	0/334
Death*	4/15184 (<0.1)	4/15165 (<0.1)
Related** deaths	0	0
AE leading to discontinuation of the vaccine	41/15184 (0.3)	71/15165 (0.5)
Baseline SARS-COV-2 negative	34/14316 (0.2)	68/14366 (0.5)
Baseline SARS-COV-2 positive	4/341 (1.2)	3/334 (0.9)

Source**:** Sponsor's Table 14.3.1.1.3, Table 14.3.1.7.1, Table 14.3.1.7.3, Table 14.3.1.7.7

[a] There were no reports of Grade 4 injection site adverse reactions

[a] EUA request (interim analysis)-November 11, 2020

**Related as assessed by investigator

In subgroup analyses of adults ≥65 years of age, rates of solicited reactions (any, Grade 3 or higher) and all other unsolicited adverse events (AEs) (all and related) were comparable to those observed in all participants. Table 20 below summarizes AEs in participants ≥65 years of age, irrespective of baseline serostatus (as less than 1% of ≥65-year-olds were seropositive at baseline).

Table 20. Adverse Events Among Adults ≥65 Years of Age (Safety Set)[a]

Participants Reporting at Least One	Vaccine Group n/N (%)	Placebo Group n/N (%)
Solicited Safety Set		
Solicited adverse reactions after any injection	3497/3766 (92.9)	2010/3750 (53.6)
Solicited local adverse reaction	3337/3766 (88.6)	859/3750 (22.9)
Grade 3 solicited local adverse reaction	279/3766 (7.4)	66/3750 (1.8)
Solicited systemic adverse reaction	2922/3766 (77.6)	1754/3750 (46.8)
Grade 3 or 4 solicited systemic adverse reaction	444/3766 (11.8)	119/3750 (3.2)
Safety Set		
Unsolicited Adverse Event up to 28 days after any	872/3770 (23.1)	734/3750 (19.6)
Related** unsolicited adverse events	261/3770 (6.9)	138/3750 (3.7)
Medically Attended Adverse Event	336/3770 (8.9)	376/3750 (10.0)
Related** medically attended adverse events	22/3770 (0.6)	13/3750 (0.3)
Serious Adverse Event	36/3770 (1.0)	42/3750 (1.1)
Related** serious adverse event	2/3770 (<0.1)	1/3750 (<0.1)
Death	1/3768 (<0.1)	2/3752 (<0.1)
Related** deaths	0	0
AE leading to discontinuation of the vaccine	12/3770 (0.3)	17/3750 (0.5)
Related** AE leading to discontinuation of the vaccine	3/3370 (<0.1)	4/3750 (0.1)

Source: Sponsor's Table 14.3.1.1.3, Table 14.3.1.7.1, Table 14.3.1.7.3, Table 14.3.1.7.7. [a] EUA request (interim analysis)-November 11 2020. Data provided in response to Information Request (IR),- received December 7 2020
**Related as assessed by investigator

Solicited Adverse Reactions

Solicited local and systemic adverse reactions with onset within 7 days after each dose were assessed across groups and are presented in the tables below stratified by age (18 to 64 years; ≥65 years) for all participants. Solicited adverse reactions (AR) were recorded daily by study participants using eDiaries and included the assessment of local injection site reactions (pain, erythema, swelling, and lymphadenopathy) and systemic reactions (fever, headache, fatigue, myalgia, arthralgia, chills, and nausea/vomiting).

Local Adverse Reactions

Solicited local AR were reported by the majority of vaccine recipients and at higher rates than placebo recipients. Vaccine recipients reported higher rates of local reactions after dose 1 than dose 2. The proportions of participants reporting any local AR were 84.2% and 88.8% after dose 1 and dose 2 in vaccine recipients, compared to 19.8% and 18.8% after dose 1 and dose 2 in placebo recipients, respectively. The proportions reporting at least one grade 3 local AR were 3.5% and 7.0% after dose 1 and dose 2, respectively in vaccine recipients and 0.5% after any dose in placebo recipients. There were no reports of Grade 4 local reactions after any dose across groups. The majority of vaccine recipients (57.6%) reported onset of local AR on Day 1 while at home, and the median duration was 2 days after dose and 3 days after dose 2.

Overall across both age cohorts, the most frequently reported local AR was pain, reported by 83.7% vs 19.8% of vaccine/placebo recipients after the first dose (2.8% vs 0.4% reported as Grade 3) and 88.4% vs 17.0% of vaccine/placebo recipients after dose 2 (4.1% vs 0.3% reported as Grade 3). The median durations for pain were 2 days and 3 days after dose 1 and dose 2, respectively. The highest rates of pain were in participants 18 to <64 years after dose 2, with 90.1% reporting any pain and 4.6% reporting Grade 3 pain.

Axillary lymphadenopathy (vaccination arm) was the second most frequently reported local AR overall. It was reported in 10.2% vs 4.8% of vaccine/placebo recipients after dose 1 and 14.0% vs 3.9% of vaccine/placebo recipients after dose 2 respectively. Grade 3 axillary lymphadenopathy was reported in 0.3% vs 0.2% vaccine/placebo recipients after dose 1 and in 0.5% vs 0.1% of vaccine/placebo recipients after dose 2. The median duration after dose 1 was 1 day and after dose 2 was 2 days. The highest rates of axillary lymphadenopathy were reported by participants 18 to 64 years of age after dose 2, with 16.0% reporting any severity lymphadenopathy and 0.4% reporting Grade 3 lymphadenopathy.

Local reactions that persisted beyond 7 days after any dose were reported by both vaccine recipients and placebo recipients. Local reactions that persisted were reported by 3.7% of vaccine recipients and 1.3% of placebo recipients across both age cohorts. In the younger age cohort, 4.2% of vaccine recipients and 1.4% of placebo recipients reported a local reaction that persisted beyond 7 days, of which 0.6% of vaccine recipients and <0.1% of placebo recipients reported a Grade 3 reaction that persisted. In the older age cohort, 2.3% of vaccine recipients compared to 1.1% of placebo recipients reported a local reaction that persisted, including 0.5% of vaccine recipients, and <0.1% of placebo recipients reporting Grade 3 local reactions. Frequently reported local reactions persisting beyond 7 days in the younger age cohort in vaccine/placebo recipients were pain (1.5%/0.6%) and axillary lymphadenopathy (2.5%/0.7%), and in the older age cohort pain (1.2%/0.6%) and erythema (0.7%/<0.1%).

Table 21. Frequency of Solicited Local Adverse Reactions Within 7 Days Following Either the First or Second Dose of Vaccine, Participants Age 18 to <64 years, Solicited Safety Set*[a]

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Any Local	9960/11401 (87.4)	2432/11404 (21.3)	9371/10357 (90.5)	2134/10317 (20.7)
Grade 3	452/11401 (4.0)	39/11404 (0.3)	766/10357 (7.4)	41/10317 (0.4)
Pain[a]	9908/11401 (86.9)	2179/11404 (19.1)	9335/10357 (90.1)	1942/10317 (18.8)
Grade 3	367/11401 (3.2)	23/11404 (0.2)	479/10357 (4.6)	21/10317 (0.2)
Erythema[b] (Redness)	345/11401 (3.0)	46/11404 (0.4)	928/10357 (9.0)	42/10317 (0.4)
Grade 3	34/11401 (0.3)	11/11404 (<0.1)	206/10357 (2.0)	12/10317 (0.1)
Swelling[b] (Hardness)	768/11401 (6.7)	33/11404 (0.3)	1309/10357 (12.6)	35/10317 (0.3)
Grade 3	62/11401 (0.5)	3/11404 (<0.1)	176/10357 (1.7)	4/10317 (<0.1)

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Lymphadenopathy[c]	1322/11401 (11.6)	567/11404 (5.0)	1654/10357 (16.0)	444/10317 (4.3)
Grade 3	36/11401 (0.3)	13/11404 (0.1)	45/10357 (0.4)	10/10317 (<0.1)

Source: Sponsor's Table 14.3.1.1.4, Table 14.3.1.1.5
*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose
[a] EUA request (interim analysis)-November 11 2020
Note: Adverse reaction data were collected on the electronic diary (eDiary) by participants and those collected on the eCRF indicated as solicitated adverse reactions.
n= # of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N.
a: Pain- Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization
b: Erythema and Swelling/Induration- Grade 3: >100mm/>10cm; Grade 4: necrosis/exfoliative dermatitis
c: Axillary Swelling/Tenderness collected as solicited local adverse reaction (i.e. lymphadenopathy: localized axillary swelling or tenderness ipsilateral to the vaccination arm) - Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization
Note: No grade 4 solicited local adverse reactions were reported.

Table 22. Frequency of Solicited Local Adverse Reactions Within 7 Days Following Either the First or Second Dose of Vaccine, Participants Age ≥65 years, Solicited Safety Set*[a]

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Any Local	2805/3762 (74.6)	566/3746 (15.1)	3010/3587 (83.9)	473/3549 (13.3)
Grade 3	77/3762 (2.0)	39/3746 (1.0)	212/3587 (5.9)	29/3549 (0.8)
Pain[a]	2782/3762 (74.0)	481/3746 (12.8)	2990/3587 (83.4)	421/3549 (11.9)
Grade 3	50/3762 (1.3)	32/3746 (0.9)	96/3587 (2.7)	17/3549 (0.5)
Erythema[b] (Redness)	86/3761 (2.3)	19/3746 (0.5)	265/3587 (7.4)	13/3549 (0.4)
Grade 3	8/3761 (0.2)	2/3746 (<0.1)	75/3587 (2.1)	3/3549 (<0.1)
Swelling[b] (Hardness)	166/3761 (4.4)	19/3746 (0.5)	386/3587 (10.8)	13/3549 (0.4)
Grade 3	20/3761 (0.5)	3/3746 (<0.1)	69/3587 (1.9)	7/3549 (0.2)
Lymphadenopathy[c]	231/3761 (6.1)	155/3746 (4.1)	302/3587 (8.4)	90/3549 (2.5)
Grade 3	12/3761 (0.3)	14/3746 (0.4)	21/3587 (0.6)	8/3549 (0.2)

Source: Sponsor's Tables 14.3.1.1.4 and 14.3.1.1.5]
*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose.
[a] EUA request (interim analysis)-November 11 2020.
Note: Adverse reaction data were collected on the electronic diary by participants and those collected on the eCRF indicated as solicitated adverse reactions.
n= # of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N.
a: Pain- Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization
b: Erythema and Swelling/Induration- Grade 3: >100mm/>10cm; Grade 4: necrosis/exfoliative dermatitis
c: Axillary Swelling/Tenderness collected as solicited local adverse reaction (i.e. lymphadenopathy: localized axillary swelling or tenderness ipsilateral to the vaccination arm) - Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization
Note: No grade 4 solicited local adverse reactions were reported.

Systemic Adverse Reactions

Solicited systemic AR were reported for the majority of vaccine recipients and at higher rates than for placebo recipients. Vaccine recipients had higher rates of systemic reactions after the second dose than the first dose. The proportions of vaccine and placebo participants reporting systemic AR were as follows: reporting any grade was 54.9% vs 42.2% after dose 1 and 79.3% vs 36.5% after dose 2, and reporting Grade 3 was 2.9% vs. 2.0% after dose 1 and 15.7% vs. 2.0% after dose 2, respectively. Across groups and doses <0.1% reported a Grade 4 systemic reaction (mainly fever > 104 ºF). The majority of vaccine recipients reported onset of systemic AR while at home either on Day 1 (33.7%) or on Day 2 (37.0%), and the median duration after any dose was 2 days.

Overall, the most frequently reported systemic AR was fatigue, reported by 68.5% of vaccine recipients and 36.1% of placebo recipients. After any dose, Grade 3 fatigue was reported by 9.6% of vaccine participants and 1.3% of placebo recipients. Grade 4 fatigue was reported by 1 participant in the vaccine group and none in the placebo group. After dose 1, any/Grade 3 fatigue was reported by 37.2%/1.0% of vaccine recipients and after dose 2 any/Grade 3 fatigue was reported by 65.2%/9.7% of vaccine recipients. The median duration for fatigue in vaccine recipients was 2 days after any dose. The highest rates of fatigue were reported by participants 18 to 64 years after the 2nd dose, with 67.6% reporting any fatigue, 10.6% reporting Grade 3, and 1 participant reporting Grade 4 (after Dose 1).

Rates of other solicited systemic AR were: headache 63.0% vaccine group vs. 36.5% placebo group; myalgia 59.6% vaccine group vs. 20.1% placebo group; arthralgia 44.8% vaccine group vs. 17.2% placebo group; and chills 43.4% vaccine group vs. 9.5% placebo group. The rates of Grade 3 AR were: headache 5.5% vaccine group vs. 2.2% placebo group; myalgia 8.6% vaccine group vs. 0.6% placebo group; arthralgia 5.1% vaccine group vs. 0.5% placebo group; and chills 1.3% vaccine group vs. 0.2% of placebo group. The median duration was 1 day after dose 1 and 1 to 2 days after dose 2. The highest rates of solicited reactions were observed in participants 18 to 64 years after dose 2 and included the following: headache 62.8% (5.0% reported Grade 3), myalgia 61.3% (10.0% Grade 3), arthralgia 45.2% (5.8% Grade 3), and chills 45.8% (1.5% Grade 3). There was one vaccine recipient in the younger age cohort who also reported Grade 4 arthralgia after dose 1.

Fever was reported after any dose by 14.8% of vaccine participant and 0.6% of placebo recipients. Fever was reported after dose 1 in 0.8% of vaccine recipients and 15.6% of vaccine recipients after dose 2. Grade 3 (≥102.1 ºF) was reported by <0.1% (11 participants) of vaccine recipients after Dose 1 and 1.3% (186 participants) of vaccine recipients after dose 2. Grade 4 (≥104.0 ºF) fever were reported by 4 vaccine recipients after dose 1 and 11 vaccine recipients after dose 2. In participants 18 to 64 years after dose 2, any fever, Grade 3 fever, and Grade 4 fever were reported in 1,806 participants (17.4%), 168 participants (1.6%), and 10 participants (<0.1%), respectively.

Systemic reactions persisting longer than 7 days were reported in both age cohorts of vaccine and placebo recipients after any dose. In the vaccine group, 11.9% of participants reported a solicited reaction that persisted beyond 7 days compared to 9.5% of placebo participants. In the younger age cohort, 9.8% of vaccine recipients and 8.9% of placebo recipients reported a systemic reaction that persisted beyond 7 days; and 2.0% of vaccine recipients and 1.2% of placebo recipients reported Grade 3 or 4 systemic reaction that persisted beyond 7 days. In the older age cohort, 9.4% of vaccine recipients and 8.1% of placebo recipients reported a systemic reaction that persisted; 1.7% of vaccine recipients (63 participants) and 0.8% of placebo

recipients (31 participants) reported a Grade 3 or 4 reaction that persisted. The most frequently reported systemic reactions that persisted beyond 7 days in vaccine recipients/placebo recipients 18 to 64 years were fatigue (5.7%/5.0%), headache (4.8%/4.0%), myalgia (2.7%/2.7%), and arthralgia (2.6%/2.8%); in the older cohort were fatigue (5.8%/4.5%), arthralgia (3.7%/3.8%), myalgia (2.9%/2.7%), and headache (2.8%/2.7%).

Fever persisted beyond 7 days in 7 vaccine recipients and 4 placebo recipients, all of whom were in the younger age cohort. There were 2 vaccine recipients who reported grade 3 fever that persisted, and none in the placebo group.

Table 23. Frequency of Solicited Systemic Adverse Reactions Within 7 Days Following Either the First or Second Dose of Vaccine, Participants Age 18-64 years, Solicited Safety Set*[a]

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Any Systemic	6503/11405 (57.0)	5063/11406 (44.4)	8484/10358 (81.9)	3967/10320 (38.4)
Grade 3	363/11405 (3.2)	248/11406 (2.2)	1801/10358 (17.4)	215/10320 (2.1)
Grade 4	5/11405 (<0.1)	4/11406 (<0.1)	10/10358 (<0.1)	2/10320 (<0.1)
Fever	105/11403 (0.9)	39/11404 (0.3)	1806/10352 (17.4)	38/10315 (0.4)
Grade 3	10/11403 (<0.1)	1/11404 (<0.1)	168/10352 (1.6)	1/10315 (<0.1)
Grade 4	4/11403 (<0.1)	4/11404 (<0.1)	10/10352 (<0.1)	2/10315 (<0.1)
Headache	4031/11401 (35.4)	3303/11404 (29.0)	6500/10357 (62.8)	2617/10317 (25.4)
Grade 3	219/11401 (1.9)	162/11404 (1.4)	515/10357 (5.0)	124/10317 (1.2)
Fatigue	4384/11401 (38.5)	3282/11404 (28.8)	7002/10357 (67.6)	2530/10315 (24.5)
Grade 3	120/11401 (1.1)	83/11404 (0.7)	1099/10357 (10.6)	81/10315 (0.8)
Grade 4	1/11401 (<0.1)	0	0	0
Myalgia	2698/11401 (23.7)	1626/11404 (14.3)	6353/10357 (6.1)	1312/10316 (12.7)
Grade 3	73/11401 (0.6)	38/11404 (0.3)	1032/10357 (10.0)	39/10316 (0.4)
Arthralgia	1892/11401 (16.6)	1327/11404 (11.6)	4685/10357 (45.2)	1087/10315 (10.5)
Grade 3	47/11401 (0.4)	29/11404 (0.3)	603/10357 (5.8)	36/10315 (0.3)
Grade 4	1/11401 (<0.1)	0	0	0
Nausea/Vomiting	1069/11401 (9.4)	908/11404 (8.0)	2209/10357 (21.3)	754/10315 (7.3)
Grade 3	6/11401 (<0.1)	8/11404 (<0.1)	8/10357 (<0.1)	8/10315 (<0.1)

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Chills	1051/11401 (9.2)	730/11404 (6.4)	5001/10357 (48.3)	611/10315 (5.9)
Grade 3	17/11401 (0.1)	8/11404 (<0.1)	151/10357 (1.5)	14/10315 (0.1)

Source: Sponsor's Tables 14.3.1.1.4 and 14.3.1.1.5
[a] EUA request (interim analysis)-November 11 2020
*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose.
Note: Adverse reaction data were collected on the electronic diary (e-Diary) by participants and those collected on the eCRF indicated as solicitated adverse reactions.
n=# of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N a: Fever - Grade 3: ⩾39.0 – ⩽40.0°C or ⩾102.1 – ⩽104.0° F; Grade 4: >40.0°C >104.0°F
b: Headache – Grade 3: Significant; any use of Rx pain reliever or prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
c: Fatigue, Myalgia, Arthralgia – Grade 3: Significant; prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
d: Nausea/Vomiting – Grade 3: Prevents daily activity, requires outpatient intravenous hydration; Grade 4: Requires E.R. visit or hospitalization for hypotensive shock
e: Chills – Grade 3: Prevents daily activity and requires medical intervention; Grade 4: Requires E.R. visit or hospitalization

Table 24. Frequency of Solicited Systemic Adverse Reactions Within 7 Days Following Either the First or Second Dose of Vaccine, Participants Age ≥65 Years, Solicited Safety Set*[a]

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Any Systemic	1818/3761 (48.3)	1335/3748 (35.6)	2580/3589 (71.9)	1102/3549 (31.1)
Grade 3	84/3761 (2.2)	63/3748 (1.7)	387/3589 (10.8)	58/3549 (1.6)
Grade 4	0	0	2/3589 (<0.1)	1/3549 (<0.1)
Fever	10/3760 (0.3)	7/3748 (0.2)	366/3587 (10.2)	5/3549 (0.1)
Grade 3	1/3760 (<0.1)	1/3748 (<0.1)	18/3587 (0.5)	0
Grade 4	0	2/3748 (<0.1)	1/3587 (<0.1)	1/3549 (<0.1)
Headache	921/3761 (24.5)	724/3745 (19.3)	1665/3587 (46.4)	635/3549 (17.9)
Grade 3	52/3761 (1.4)	34/3745 (0.9)	107/3587 (3.0)	32/3549 (0.9)
Fatigue	1251/3761 (33.3)	851/3745 (22.7)	2094/3587 (58.4)	695/3549 (19.6)
Grade 3	30/3761 (0.8)	23/3745 (0.6)	248/3587 (6.9)	20/3549 (0.6)
Myalgia	743/3761 (19.8)	443/3745 (11.8)	1683/3587 (46.9)	385/3549 (10.8)
Grade 3	17/3761 (0.5)	9/3745 (0.2)	201/3587 (5.6)	10/3549 (0.3)
Arthralgia	618/3761 (16.4)	456/3745 (12.2)	1252/3587 (34.9)	381/3549 (10.7)
Grade 3	13/3761 (0.3)	8/3745 (0.2)	122/3587 (3.4)	7/3549 (0.2)

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Nausea/Vomiting	194/3761 (5.2)	166/3745 (4.4)	425/3587 (11.8)	129/3549 (3.6)
Grade 3	4/3761 (0.1)	4/3745 (0.1)	10/3587 (0.3)	3/3549 (<0.1)
Grade 4	0	0	1/3587 (<0.1)	0
Chills	202/3761 (5.4)	148/3745 (4.0)	1099/3587 (30.6)	144/3549 (4.1)
Grade 3	7/3761 (0.2)	6/3745 (0.2)	27/3587 (0.8)	2/3549 (<0.1)

Source: Sponsor's Tables 14.3.1.1.4 and 14.3.1.1.5
[a] EUA request (interim analysis) November 11 2020
*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose.
Note: Adverse reaction data were collected on the electronic diary (e-Diary) by participants and those collected on the eCRF indicated as solicitated adverse reactions.
n=# of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N a: Fever - Grade 3: ≥39.0 – ≤40.0°C or ≥102.1 – ≤104.0°F; Grade 4: >40.0°C >104.0°F
b: Headache – Grade 3: Significant; any use of Rx pain reliever or prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
c: Fatigue, Myalgia, Arthralgia – Grade 3: Significant; prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
d: Nausea/Vomiting – Grade 3: Prevents daily activity, requires outpatient intravenous hydration; Grade 4: Requires E.R. visit or hospitalization for hypotensive shock
e: Chills – Grade 3: Prevents daily activity and requires medical intervention; Grade 4: Requires E.R. visit or hospitalization

Unsolicited AEs

Unsolicited AEs from the November 11, 2020 data cutoff include safety data from participants who had at least 1 month of follow-up after dose 2 (76.7% of all participants) those who had at least 2 months of follow-up after dose 2 (25.3% of all participants). The median study duration following dose 2 was 7 weeks across study groups. Table 25 below shows unsolicited AEs reported through the first data cutoff. Treatment emergent adverse events (AEs) were defined as any event that occurred during the study and was not present before exposure (study vaccine or placebo), any event that occurred during the study and was not present before exposure, or any event already present that worsened after exposure. The following unsolicited adverse events were specified in the protocol:

- Unsolicited AEs observed or reported during the 28 days following each vaccine or placebo dose
- AEs leading to discontinuation from vaccination and/or study participation through Day 759 (study completion) or withdrawal from the study
- Serious adverse events and medically attended adverse events through Day 759 (study completion) or withdrawal from study

Determination of severity for all unsolicited AE were made by the investigators based on medical judgement and definitions of severity as mild, moderate, or severe.

The overall proportions of participants who reported an unsolicited adverse event were generally similar, with numerically slightly higher rates of unsolicited AEs in the vaccine group compared to placebo group for some categories of unsolicited nonserious AEs.

Table 25. Summary of Unsolicited AEs Regardless of Relationship to the Investigational Vaccine, Through 28 Days After Any Vaccination, Study 301, Safety Set

Event Type	Nov 11 Dataset[a] mRNA-1273 (N=15184) n (%)	Nov 11 Dataset[a] Placebo (N=15165) n (%)	Nov 25 Dataset[b] mRNA-1273 (N=15185) n (%)	Nov 25 Dataset[b] Placebo (N=15166) n (%)
All unsolicited AEs	3325 (21.9)	2949 (19.4)	3632 (23.9)	3277 (21.6)
Medically-attended	1215 (8.0)	1276 (8.4)	1372 (9.0)	1465 (9.7)
Severe unsolicited AEs	216 (1.4)	190 (1.3)	234 (1.5)	202 (1.3)
Leading to discontinuation from study vaccine	41 (0.3)	71 (0.5)	50 (0.3)	80 (0.5)
Serious	82 (0.5)	86 (0.6)	93 (0.6)	89 (0.6)
Death	2 (<0.1)	3 (<0.1)	2 (<0.1)	3 (<0.1)

Source:
Abbreviation: AE = adverse event.
Note: An AE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. Percentages were based on the number of safety participants.
[a] EUA request (interim analysis)-November 11 2020
[b] Primary efficacy analysis-November 25, 2020

Unsolicited Adverse Events

The table below shows rates of unsolicited AEs that occurred within 28 days of any vaccination and at rates of ≥1% in the vaccine group through the November 11, 2020 data cutoff. The proportion of vaccine recipients who reported an unsolicited AE was 21.9% (3325 participants) compared to 19.4% of placebo participants. A higher frequency of unsolicited adverse events was reported in the vaccine group compared to placebo group and was primarily attributed to local and systemic reactogenicity following vaccination.

Table 26. Unsolicited Adverse Events Occurring in ≥1% of Vaccine Group Participants, by MedDRA Primary System Organ Class and Preferred Term (Safety Analysis Set)[a]

System Organ Class Preferred Term	Vaccine N=15184 n (%) Any	Vaccine N=15184 n (%) Severe	Placebo N=15165 n (%) Any	Placebo N=15165 n (%) Severe
Infections and infestations	521 (3.4)	13 (<0.1)	621 (4.1)	25 (0.2)
Vascular disorders	149 (1.0)	28 (0.2)	138 (0.9)	39 (0.3)
Nervous system disorders	624 (4.1)	27 (0.2)	552 (3.6)	21 (0.1)
Headache	435 (2.9)	19 (0.1)	409 (2.7)	13 (<0.1)
Respiratory, thoracic and mediastinal disorders	480 (3.2)	8 (<0.1)	522 (3.4)	9 (<0.1)
Cough	148 (1.0)	1 (<0.1)	143 (0.9)	1 (<0.1)
Oropharyngeal pain	137 (0.9)	1 (<0.1)	184 (1.2)	3 (<0.1)
Gastrointestinal disorders	426 (2.8)	14 (<0.1)	387 (2.6)	16 (0.1)
Diarrhea	178 (1.2)	2 (<0.1)	147 (1.0)	1 (<0.1)
Skin and subcutaneous tissue disorders	213 (1.4)	4 (<0.1)	158 (1.0)	2 (<0.1)
Musculoskeletal and connective tissue disorders	586 (3.9)	24 (0.2)	521 (3.4)	18 (0.1)
Arthralgia	174 (1.1)	10 (<0.1)	152 (1.0)	2 (<0.1)
Myalgia	172 (1.1)	11 (<0.1)	138 (0.9)	0

System Organ Class Preferred Term	Vaccine N=15184 n (%)	Vaccine N=15184 n (%)	Placebo N=15165 n (%)	Placebo N=15165 n (%)
General disorders and administration site	894 (5.9)	43 (0.3)	560 (3.7)	13 (<0.1)
Fatigue	344 (2.3)	12 (<0.1)	307 (2.0)	7 (<0.1)
Injection site pain	147 (1.0)	6 (<0.1)	49 (0.3)	1 (<0.1)
Injury, poisoning and procedural complications	238 (1.6)	16 (0.1)	262 (1.7)	13 (<0.1)

Source: Sponsor's Tables 14.3.1.8.1 and 14.3.1.17.1
n (%)=number (percentage) of participants reporting the adverse event at least once
[a] EUA request (interim analysis): Novemer 11, 2020 data cutoff.

Unsolicited AEs considered related by the investigator to study vaccination were reported by 7.4% of vaccine recipients and 4.0% of placebo recipients. The proportion of participants who reported severe unsolicited AEs was 1.4% following any vaccine dose (275 participants) and 1.3% following any placebo dose (225 participants). The most frequently reported severe AEs that occurred in greater numbers of vaccine than placebo recipients were headache, myalgia, arthralgia, injection site erythema, and injection site pain (Table 26).

Medically attended adverse events (MAAE) from dose 1 through 28 day following any dose were reported for 8.0% of participants in the vaccine group (1,839 events in 1,215 participants) and 8.4% of those in the placebo group (1,837 events in 1,276 participants). The majority of these events were considered not related to study vaccinations and were primarily attributed to local and systemic reactogenicity following vaccinations.

FDA conducted standard MedDRA queries (SMQs) using FDA-developed software to evaluate for constellations of unsolicited adverse events with onset following dose 1 through the November 11, 2020 cutoff. The SMQs were conducted on adverse event Preferred Terms that could represent various conditions, including but not limited to allergic, neurologic, inflammatory, and autoimmune disorders. FDA assessment of additional safety data accrued through the November 25, 2020 cutoff is ongoing, though specific SMQ of adverse events of clinical interest were assessed.

A SMQ evaluating lymphadenopathy-related events (including injection site lymphadenopathy, lymph node pain, and lymphadenitis) through the November 25, 2020 data cut demonstrated a numerical imbalance across study groups, with 1.1% of vaccine recipients (191 events in 173 vaccine recipients) compared to 0.63% of placebo recipients (109 events in 95 participants) reporting such events in the Safety Set. The rates reported in the older cohort (≥65 years) were 0.74% (28 events in 28 participants) in vaccine recipients compared to 0.35% (16 events in 13 participants) in placebo recipients. The rates reported in the younger cohort (18-64 years) were 1.3% (163 events in 145 participants) in vaccine recipients and 0.72% (93 events in 82 participants) in placebo recipients. These events support a plausible relationship to study vaccination and were also reported in the evaluation of solicited local adverse reactions. Local axillary swelling/tenderness was reported in approximately 19% of participants during the 7 days following any dose in the Solicited Safety Set. The median duration following any dose was 1 to 2 days, and <1% reported Grade 3 axillary swelling/tenderness.

A SMQ evaluating hypersensitivity-related adverse events through the November 25, 2020 data cutoff demonstrated a numerical imbalance across study groups, with 1.5% of vaccine recipients (258 events in 233 participants) and 1.1% of placebo recipients (185 events in 166 participants) reporting such events in the Safety Set. In the older cohort (age ≥65 years) which

comprised 24.8% of the Safety Set, the rates of hypersensitivity were 1.8% (74 events in 68 participants) in vaccine recipients and 1% (45 events in 38 participants) in placebo recipients. In the younger age cohort (18-64 years), the rates were 1.5% (184 events in 165 participants) in vaccine recipients compared to 1.1% (140 events in 128 participants). Overall, the most frequently reported AEs in the hypersensitivity SMQ were injection site rash (0.24% vaccine, 0.01% placebo), injection site urticaria (0.1% vaccine, 0% placebo), and rash maculo-papular (0.07% vaccine, 0.01% placebo). There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine.

A query of specific adverse events of clinical interest in the Safety Set through November 25, 2020 demonstrated a small imbalance in the number of participants reporting Bell's palsy (facial paralysis), with 3 vaccine recipients and 1 placebo recipient reporting this MAAE. One case of Bell's palsy in the vaccine group was considered a SAE; a 67-year-old female with diabetes was hospitalized for stroke due to new facial paralysis 32 days after vaccination. This case was reported as resolving. Another Bell's palsy case in the vaccine group occurred 28 days after vaccination in a 30-year-old female who reported an upper respiratory infection 27 days prior to onset of her facial paralysis. This case was reported as resolved. An additional case of Bell's palsy in the vaccine group was reported with the primary analysis safety data (November 25, 2020 data cutoff) and occurred 22 days after vaccination in a 72-year-old female; this event was still ongoing at the time of safety report. The case in the placebo group, reported as resolving, occurred 17 days post injection in a 52-year-old-male. Causality assessment is confounded by predisposing factors in these participants. However, considering the temporal association and biological plausibility, a potential contribution of the vaccine to the manifestations of these events of facial palsy cannot be ruled out. FDA will recommend surveillance for cases of Bell's palsy with deployment of the vaccine into larger populations. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse events, including other neurologic, neuro-inflammatory, and thrombotic events, that would suggest a causal relationship to the Moderna COVID-19 vaccine.

Immediate Adverse Events

Immediate solicited reactions occurring within 30 minutes of vaccination were infrequent and there does not appear to be an imbalance between the treatment groups. Review of unsolicited AEs that occurred within 30 minutes of vaccination demonstrated comparable rates across study groups (0.6% vaccine, 0.6% placebo), and none of the events reported in the vaccine group were considered serious.

Study Withdrawals due to an Adverse Event (Safety Set)

Adverse events that led to discontinuation of vaccination were reported in 0.3% in the vaccine group and 0.5% in the placebo group. Following the November 25, 2020 cutoff, 4 participants were withdrawn from the study due to an adverse event (2 vaccine recipients and 2 placebo recipients). The two AEs reported in the vaccine group were acute pancreatitis and road traffic accident, and the two AEs reported in the placebo group were incarcerated hernia and duodenal ulcer hemorrhage. FDA's review of data through this latter time point is ongoing.

Serious Adverse Events

Deaths

As of December 3, 2020, 13 deaths were reported (6 vaccine, 7 placebo). Two deaths in the vaccine group were in participants >75 years of age with pre-existing cardiac disease; one

participant died of cardiopulmonary arrest 21 days after dose 1, and one participant died of myocardial infarction 45 days after dose 2. Another two vaccine recipients were found deceased at home, and the cause of these deaths is uncertain: a 70-year-old participant with cardiac disease was found deceased 57 days after dose 2, and a 56-year-old participant with hypertension, chronic back pain being treated with opioid medication died 37 days after dose 1 (The official cause of death was listed as head trauma). One case was a 72-year-old vaccine recipient with Crohn's disease and short bowel syndrome who was hospitalized for thrombocytopenia and acute kidney failure due to obstructive nephrolithiasis 40 days after dose 2 and developed complications resulting in multiorgan failure and death. One vaccine recipient died of suicide 21 days after dose 1. The placebo recipients died from myocardial infarction (n=3), intra-abdominal perforation (n=1), systemic inflammatory response syndrome in the setting of known malignancy (n=1), COVID-19 (n=1), and unknown cause (n=1). These deaths represent events and rates that occur in the general population of individuals in these age groups.

Non-fatal Serious Adverse Events

Among participants who received at least one dose of vaccine or placebo (N=30,351), the proportion of participants who reported at least one SAE from dose 1 to the primary analysis cutoff date (November 25, 2020) was 1% in the mRNA-1273 group and 1% in the placebo group. The most common SAEs occurring at higher rates in the vaccine group than the placebo group were myocardial infarction (0.03% in vaccine group, 5 cases vs. 3 cases in placebo group), cholecystitis (0.02% in vaccine group, 3 cases vs. 0 cases in placebo group), and nephrolithiasis (0.02% in vaccine group, 3 cases vs. 0 cases in placebo group). The small numbers of cases of these events do not suggest a causal relationship. The most common SAEs occurring at higher rates in the placebo arm than the vaccine arm, aside from COVID-19 (0.1% in placebo group), were pneumonia (0.05% in placebo group) and pulmonary embolism (0.03% in placebo group). Occurrence of other SAEs, including cardiovascular SAEs, were otherwise balanced between treatment groups.

As of November 25, 2020, 7 SAEs (4.8%) in the mRNA-1273 group and 5 (3.3%) in the placebo group were assessed by the investigator as related to study vaccination (Table 27). Of the 7 SAEs in the mRNA-1273 group, the Sponsor assessed 4 as related and 3 as unrelated to the vaccine.

Table 27. SAEs Considered Related by Investigator

Investigational Product	SAE	Onset (days after last dose)	Demographics/ Risk factors	Resolution	Related per Investigator/ Moderna
mRNA-1273	Intractable nausea and vomiting	1	65 F; history of headaches and severe nausea requiring hospitalization	Resolved	Yes/Yes
mRNA-1273	Facial swelling	1	46 F; dermal filler cosmetic injection 6 months prior	Resolved	Yes/Yes
mRNA-1273	Facial swelling	2	51 F; dermal filler cosmetic injection 2 weeks prior	Resolved	Yes/Yes
mRNA-1273	Rheumatoid arthritis	14	57 M; hypothyroid	Unresolved	Yes/Yes
mRNA-1273	Dyspnea with exertion, peripheral edema	8	66 F; diabetes, hypertension	Resolving	Yes/No

Investigational Product	SAE	Onset (days after last dose)	Demographics/ Risk factors	Resolution	Related per Investigator/ Moderna
mRNA-1273	Autonomic dysfunction	24	46 F; hypothyroid; possible sinus infection	Unresolved	Yes/No
mRNA-1273	B-cell lymphocytic lymphoma	31	75 F; history of metastatic lung cancer, breast cancer	Unresolved	Yes/No
Placebo	Polymyalgia rheumatica	15	83 M; chronic low back pain	Resolving	Yes/Yes
Placebo	Facial swelling, paresthesia, anxiety	7	41 F; dental procedure 2 weeks prior	Resolved	Yes/No
Placebo	Procedural hemorrhage	16	52 M; aortic stenosis, hyperlipidemia; aspirin intake	Resolved	Yes/No
Placebo	Pulmonary embolism	24	59 M; smoking	Unresolved	Yes/No
Placebo	Pneumonia and myocardial infarction	29	70 M; coronary artery disease, chronic kidney disease, diabetes	Resolved	Yes/No

There was one event of lip angioedema 2 days after vaccination in a 29-year-old female participant in the vaccine group which was classified as medically significant but not considered an SAE. The participant has a history of dermal filler injection in the lips (unknown how long prior to vaccination). She reported having a similar reaction after receipt of an influenza vaccine in the past. Taken in context with the SAEs of facial swelling which occurred in 2 participants who had previous history of cosmetic filler injections, it is possible the localized swelling in these cases is due to an inflammatory reaction from interaction between the immune response after vaccination and the dermal filler. This phenomenon has been reported after natural infection (e.g., after an influenza-like illness).

In FDA's opinion following review of the narratives, 3 SAEs are considered likely related, including the one report of intractable nausea/vomiting and 2 reports of facial swelling. The possibility that the vaccine contributed to the SAE reports of rheumatoid arthritis, peripheral edema/dyspnea with exertion, and autonomic dysfunction cannot be excluded. The vaccine was unlikely to have contributed to the other SAEs assessed by the investigator as related. As described in detail in a previous section, there was one report of Bell's palsy in the vaccine arm which occurred 32 days after vaccination; both the investigator and the Sponsor assessed this event as unrelated to the study vaccine, but in FDA's assessment a causal relationship cannot be definitively excluded.

Subgroup Analyses

There were no specific safety concerns identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection, and occurrence of solicited, unsolicited, and serious adverse events in these subgroups were generally consistent with the overall study population.

Pregnancies

Study participants of childbearing potential were screened for pregnancy prior to each vaccination, with a positive test resulting in exclusion or discontinuation from study vaccination. The study is collecting outcomes for all reported pregnancies that occur after vaccination, or

before vaccination and not detected by pre-vaccination screening tests. Thirteen pregnancies were reported through December 2, 2020 (6 vaccine, 7 placebo). Study vaccination occurred prior to the last menstrual period (LMP) in 5 participants (2 vaccine, 3 placebo), within 30 days after LMP in 5 participants (2 vaccine, 3 placebo), >30 days after LMP in 2 participants (1 vaccine, 1 placebo), and date of LMP not known in 1 participant (1 vaccine, 0 placebo). Unsolicited AEs related to pregnancy include a case of spontaneous abortion and a case of elective abortion, both in the placebo group. One participant in the placebo group is lost to follow-up. Pregnancy outcomes are otherwise unknown at this time.

A combined developmental and perinatal/postnatal reproductive toxicity study of mRNA-1273 in rats was submitted to FDA on December 4, 2020. FDA review of this study concluded that mRNA1273 given prior to mating and during gestation periods at dose of 100 µg did not have any adverse effects on female reproduction, fetal/embryonal development, or postnatal developmental except for skeletal variations which are common and typically resolve postnatally without intervention.

Safety Summary

The information provided by the Sponsor was adequate for review and to make conclusions about the safety of the mRNA-1273 vaccine in the context of the proposed indication and population for intended use under EUA. The number of participants in the Phase 3 safety population (N=30,350; 15,184 vaccine,15,165 placebo) meets the expectations described in FDA's Guidance on Development and Licensure of Vaccines to Prevent COVID-19 for efficacy. The initial EUA request was based on data from the pre-specified interim analysis (November 11, 2020 data cutoff) with a median follow-up duration of 7 weeks after dose 2; this interim analysis data is the primary basis of this EUA review and conclusions. Data and analyses from a November 25, 2020 data cut with a median duration of at least 2 months follow-up after completion of the 2-dose primary vaccination series was submitted as an amendment to the EUA request on December 7, 2020. The FDA has not independently verified the complete safety data from the primary analysis, aside from all new deaths (including those reported through December 3, 2020) and SAEs. No new safety concerns have been identified. The rates and types of solicited adverse reactions and unsolicited adverse events are unlikely to change significantly with an additional 2 weeks of follow-up. The totality of the data package submitted in the EUA request meets the Agency's expectations on the minimum duration of follow-up.

Local site reactions and systemic solicited events after vaccination were frequent and mostly mild to moderate. The most common solicited adverse reactions were injection site pain (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and chills (43.4%); 0.2% to 9.7% were reported as severe, with severe solicited adverse reactions being more frequent after dose 2 than after dose 1 and generally less frequent in adults ≥65 years of age as compared to younger participants. Among adverse events of clinical interest, lymphadenopathy was reported in 173 participants (1.14%) in the vaccine group and 95 participants (0.63%) in the placebo group. There was a numerical imbalance in hypersensitivity adverse events across study groups, with 1.5% of vaccine recipients and 1.1% of placebo recipients reporting such events in the Safety Set. There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine. Throughout the safety follow-up period to date, there has been three reports of Bell's palsy in the vaccine group and one in the placebo group. Currently available information is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to mRNA-

1273.

As of December 3, 2020, there were a total of 13 deaths reported in the study (6 vaccine, 7 placebo). These deaths represent events and rates that occur in the general population of individuals in these age groups. The frequency of non-fatal serious adverse events was low and without meaningful imbalances between study arms (1% in the mRNA-1273 group and 1% in the placebo group). The most common SAEs in the vaccine group which were numerically higher than the placebo group were myocardial infarction (0.03%), cholecystitis (0.02%), and nephrolithiasis (0.02%), although the small numbers of cases of these events do not suggest a causal relationship. The most common SAEs in the placebo arm which were numerically higher than the vaccine arm, aside from COVID-19 (0.1%), were pneumonia (0.05%) and pulmonary embolism (0.03%).

6. Sponsor's Plans for Continuing Blinded, Placebo-Controlled Follow-Up

ModernaTX expects that participants, including approximately 25% who are healthcare workers, may request unblinding to receive mRNA-1273 or another vaccine potentially available under EUA external to the trial. More extensive participant-driven crossover would be expected to alter the composition of the trial population, with greatly increased participant dropout due to a large proportion of participants belonging to priority vaccination groups desiring to be vaccinated with vaccine made available under EUA. ModernaTX is evaluating the opportunity to amend the protocol to proactively reconsent participants who received placebo to be offered mRNA-1273 vaccination and to remain in the trial, enabling ModernaTX to continue to collect the relevant safety and effectiveness data over the entire two years of follow-up while increasing the likelihood of retaining participants on trial. Adverse events among those vaccinated within the trial will be captured, regardless of the treatment group to which the participants were originally allocated, over the entire follow-up period of 24 months.

7. Pharmacovigilance Activities

The Sponsor submitted a Pharmacovigilance Plan to monitor safety concerns that could be associated with the Moderna COVID-19 Vaccine. The Sponsor identified vaccine-associated enhanced disease (which includes but is not limited to vaccine-associated enhanced respiratory disease) and anaphylactic reactions (including anaphylaxis) as important potential risks. Use in the pediatric population, use in pregnant and breast-feeding women, immunogenicity in participants with immunosuppression, concomitant administration with non-COVID vaccines, long-term safety and long-term effectiveness are areas the Sponsor identified as missing information.

The Sponsor will conduct both passive and active surveillance activities for continued vaccine safety monitoring. Passive surveillance activities will include submitting spontaneous reports of the following events to the Vaccine Adverse Event Reporting System (VAERS) within 15 days:

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome in adults
- Cases of COVID-19 that result in hospitalization or death

The Sponsor will also conduct periodic aggregate review of safety data and proposed to submit periodic safety reports at quarterly intervals, or at another interval specified by FDA. FDA has

requested that periodic reports be submitted monthly. Each periodic safety report is required to contain descriptive information which includes:

- A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest
- Newly identified safety concerns in the interval
- Actions taken since the last report because of adverse experiences (e.g., changes made to Vaccination Provider fact sheets, changes made to studies or studies initiated)

Sponsor studies will include completion of long-term follow-up from ongoing clinical trials as well as the following three planned surveillance studies.

- Pregnancy Cohort: The Sponsor plans to establish a passive pregnancy registry to monitor vaccination during pregnancy within populations expected to receive the vaccine under EUA, and to submit a protocol for FDA review and approval.

- Active Follow-up for Safety: This study is an active safety surveillance activity conducting retrospective analyses of medical and pharmacy claims data to address three objectives; estimation of background rates of 23 prespecified adverse events of special interest (AESI), descriptive analyses of observed versus expected rates, and self-controlled risk interval analyses that will be conducted if certain criteria are met from the descriptive analyses. The planned study duration is through December 2022.

- Real World Effectiveness Study: This study is a prospective cohort study to be conducted at Kaiser Permanente Southern California to evaluate vaccine effectiveness in preventing the following outcomes: laboratory confirmed and clinical COVID-19 infection, hospitalization, and mortality for COVID-19. Vaccinated participants will receive Moderna COVID-19 Vaccine between January 1, 2021 and December 31, 2021, and the comparator group will be age matched, unvaccinated KPSC members. The planned study duration is through December 31, 2023.

FDA will provide feedback on these studies after further review of protocols once submitted by the Sponsor.

Reporting to VAERS and ModernaTX, Inc.

Providers administering the Moderna COVID-19 Vaccine must report to VAERS (as required by the National Childhood Vaccine Injury Act) and to ModernaTX the following information associated with the vaccine of which they become aware:

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome in adults
- Cases of COVID-19 that result in hospitalization or death

Additional VAERS Reporting

An additional source of VAERS reports will be through a program administered by the CDC known as v-safe. V-safe is a smartphone-based opt-in program that uses text messaging and web surveys from CDC to check in with vaccine recipients for health problems following COVID-19 vaccination. The system also will provide telephone follow-up to anyone who reports

medically significant (important) adverse events. Responses indicating missed work, inability to do normal daily activities, or that the recipient received care from a doctor or other healthcare professional will trigger the VAERS Call Center to reach out to the participant and collect information for a VAERS report, if appropriate.

8. Benefit/Risk Assessment in the Context of Proposed Indication and Use Under EUA

8.1 Known Benefits

The known benefits among recipients of the proposed vaccine relative to placebo are:

- Reduction in the risk of confirmed COVID-19 occurring at least 14 days after the second dose of vaccine
- Reduction in the risk of confirmed severe COVID-19 occurring at least 14 days after the second dose of vaccine

The 2-dose vaccination regimen was highly effective in preventing PCR-confirmed COVID-19 occurring at least 14 days after receipt of the second dose. Secondary efficacy analyses showed consistency with outcomes in the primary efficacy analysis; the vaccine was effective in preventing COVID-19 using a less restrictive definition of the disease and considering all cases starting 14 days after the first injection. Efficacy findings in the interim analysis were also consistent across various subgroups, including racial and ethnic minorities, participants ages 65 years and older, and those at risk for severe COVID-19 disease due to obesity, diabetes, cardiac disease, liver disease, chronic lung disease, mild to severe asthma, and infection with HIV, although the efficacy estimate in participants ages 65 years and older was slightly lower in the primary efficacy analysis.

8.2 Unknown Benefits/Data Gaps

Duration of protection

As the interim and final analyses have a limited length of follow-up, it is not possible to assess sustained efficacy over a period longer than 2 months.

Effectiveness in certain populations at high-risk of severe COVID-19

Although the proportion of participants at high risk of severe COVID-19 is adequate for the overall evaluation of safety in the available follow-up period, the subsets of certain groups such as immunocompromised individuals (e.g., those with HIV/AIDS) are too small to evaluate efficacy outcomes.

Effectiveness in individuals previously infected with SARS-CoV-2

Limited data suggest that individuals with prior SARS-CoV-2 infection can be at risk of COVID-19 (i.e., re-infection) and may benefit from vaccination. Regarding the benefit of the mRNA-1273 for individuals with prior infection with SARS-CoV2, participants with a known history of SARS-CoV-2 infection were excluded from the Phase 3 study, and there was only one case of COVID-19 among study participants with positive SARS-COV-2 infection status at baseline. Thus, the study was not designed to assess the benefit in individuals with prior SARS-CoV-2 infection.

Effectiveness in pediatric populations

No efficacy data are available from participants ages 17 years and younger.

Future vaccine effectiveness as influenced by characteristics of the pandemic, changes in the virus, and/or potential effects of co-infections

The study enrollment and follow-up occurred during the period of July 27, 2020 to November 21, 2020, in sites across the United States. The evolution of the pandemic characteristics, such as increased attack rates, increased exposure of subpopulations, as well as potential changes in the virus infectivity, antigenically significant mutations to the S protein, and/or the effect of co-infections may potentially limit the generalizability of the efficacy conclusions over time. Continued evaluation of vaccine effectiveness following issuance of an EUA and/or licensure will be critical to address these uncertainties.

Vaccine effectiveness against asymptomatic infection

Data are limited to assess the effect of the vaccine in preventing asymptomatic infection as measured by detection of the virus and/or detection of antibodies against non-vaccine antigens that would indicate infection rather than an immune response induced by the vaccine. Additional evaluations will be needed to assess the effect of the vaccine in preventing asymptomatic infection, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against long-term effects of COVID-19 disease

COVID-19 disease may have long-term effects on certain organs, and at present it is not possible to assess whether the vaccine will have an impact on specific long-term sequelae of COVID-19 disease in individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 should translate to overall prevention of COVID-19-related sequelae in vaccinated populations, though it is possible that asymptomatic infections may not be prevented as effectively as symptomatic infections and may be associated with sequelae that are either late-onset or undetected at the time of infection (e.g., myocarditis). Additional evaluations will be needed to assess the effect of the vaccine in preventing long-term effects of COVID-19, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against mortality

A larger number of individuals at high risk of COVID-19 and higher attack rates would be needed to confirm efficacy of the vaccine against mortality. However, non-COVID vaccines (e.g., influenza) that are efficacious against disease have also been shown to prevent disease-associated death.[13-16] Benefits in preventing death should be evaluated in large observational studies following authorization.

Vaccine effectiveness against transmission of SARS-CoV-2

Data are limited to assess the effect of the vaccine against transmission of SARS-CoV-2 from individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 may translate to overall prevention of transmission in populations with high enough vaccine uptake, though it is possible that if efficacy against asymptomatic infection were lower than efficacy against symptomatic infection, asymptomatic cases in combination with reduced mask-wearing and social distancing could result in significant continued transmission. Additional evaluations including data from clinical trials and from vaccine use post-authorization will be needed to assess the effect of the vaccine in preventing virus shedding and transmission, in particular in individuals with asymptomatic infection.

8.3 Known Risks

The vaccine elicited increased local and systemic adverse reactions as compared to those in the placebo arm, usually lasting a few days. The most common solicited adverse reactions were pain at injection site (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and chills (43.4%). Adverse reactions characterized as reactogenicity were generally mild to moderate; 0.2% to 9.7% of these events were reported as severe, with severe solicited adverse reactions being more frequent after dose 2 than after dose 1 and generally less frequent in older adults (≥65 years of age) as compared to younger participants. Among reported unsolicited adverse events, lymphadenopathy occurred much more frequently in the vaccine group than the placebo group and is plausibly related to vaccination. The number of participants reporting hypersensitivity-related adverse events was numerically higher in the vaccine group compared with the placebo group (258 events in 233 participants [1.5%] vs. 185 events in 166 participants [1.1%]). There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine.

Serious adverse events, while uncommon (1.0% in both treatment groups), represented medical events that occur in the general population at similar frequency as observed in the study. Of the 7 SAEs in the mRNA-1273 group that were considered as related by the investigator, FDA considered 3 as related: intractable nausea and vomiting (n=1), facial swelling (n=2). For the serious adverse events of rheumatoid arthritis, peripheral edema/dyspnea with exertion, and autonomic dysfunction, a possibility of vaccine contribution cannot be excluded. For the event of B-cell lymphoma, an alternative etiology is more likely. An SAE of Bell's palsy occurred in a vaccine recipient, for which a causal relationship to vaccination cannot be concluded at this time.

No specific safety concerns were identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection.

8.4 Unknown Risks/Data Gaps

Safety in certain subpopulations

There are currently insufficient data to make conclusions about the safety of the vaccine in subpopulations such as children less than 18 years of age, pregnant and lactating individuals, and immunocompromised individuals.

FDA review of a combined developmental and perinatal/postnatal reproductive toxicity study of mRNA-1273 in female rats concluded that mRNA1273 given prior to mating and during gestation periods at dose of 100 µg did not have any effects on female reproduction, fetal/embryonal development, or postnatal developmental except for skeletal variations which are common and typically resolve postnatally without intervention

Adverse reactions that are very uncommon or that require longer follow-up to be detected

Following authorization of the vaccine, use in large numbers of individuals may reveal additional, potentially less frequent and/or more serious adverse events not detected in the trial safety population of approximately 30,000 participants over the period of follow-up at this time. Active and passive safety surveillance will continue during the post-authorization period to detect new safety signals.

Although the safety database revealed an imbalance of cases of Bell's palsy (3 in the vaccine group and 1 in the placebo group), causal relationship is less certain because the number of cases was small and not more frequent than expected in the general population. Further signal detection efforts for these adverse events will be informative with more widespread use of the vaccine.

Vaccine-enhanced disease

Available data do not indicate a risk of vaccine-enhanced disease, and conversely suggest effectiveness against severe disease within the available follow-up period. However, risk of vaccine-enhanced disease over time, potentially associated with waning immunity, remains unknown and needs to be evaluated further in ongoing clinical trials and in observational studies that could be conducted following authorization and/or licensure.

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10. Appendix A. Phase 1 and 2 Studies

Study DMID Protocol 20-0003

Study Design

DMID Protocol 20-0003 is an ongoing Phase 1, open-label, first-in-human, dose-ranging study to evaluate the safety and immunogenicity of mRNA-1273 in healthy adults 18 years of age and older. A total of 120 participants without risk factors for progression to severe COVID-19 were enrolled into one of 10 age and dose cohorts to receive 2 injections of 25 µg, 50 µg, 100 µg, or 250 µg of mRNA-1273 given 28 days apart. The study included 60 participants 18 through 55 years of age, 30 participants 56 through 70 years of age, and 30 participants 71 years and older. Participants will be followed safety and immunogenicity for 12 months after last vaccination.

Study Objectives/Endpoints Relevant to the EUA

The immunogenicity objectives are to evaluate the binding antibody (bAb) concentrations for spike IgG as measured by ELISA and neutralizing antibody (nAb) titers as measured by PsVNA for all dose levels at baseline and at various time points after vaccination. The study also evaluated T-cell responses elicited by the mRNA-1273 vaccine as assessed by an intracellular cytokine stimulation assay. All participants are followed for solicited adverse reactions through 7 days post each vaccination. Unsolicited AEs are collected through 28 days after each vaccination. All SAEs and medically attended adverse events are collected through the end of the study.

Statistical Analysis

No formal statistical hypothesis was tested in this study, and all results were descriptive.

Study Results

The study showed a dose response in participants across all age groups as measured by both binding and neutralizing antibodies after 2 doses. There was a comparable response between the 100-µg and 250-µg dose groups, and both were greater compared to the 25-µg group. The bAb and nAb levels seen after 2 doses of 100 µg or 250 µg of mRNA-1273 were similar in magnitude compared to those seen in pooled convalescent sera from patients recovered from COVID-19. All dose levels elicited CD4+ T-cell responses that were strongly biased toward expression of Th1 cytokines, with minimal Th2 cytokine expression. This Th1-dominant profile was clinically reassuring in terms of risk of developing vaccine-induced disease. These results, along with the interim safety data showing a lower incidence of reactogenicity in the 100ug group compared to the 250ug group, led to the selection of the 100ug dose to advance to Phase 2 and 3. Preliminary safety data from this Phase 1 study show a similar profile to that observed in the Phase 3 study. No SAEs or severe COVID-19 cases have been reported from this study as of November 16, 2020.

Study mRNA-1273-P201

Study Design

Study mRNA-1273-P201 is an ongoing phase 2a, randomized, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 in healthy adults 18 years and older. The study enrolled 600 participants, consisting of 300 participants 18 to <55 years old and 300 participants 55 years and older, who

were randomized equally to receive either 2 doses of 50ug of mRNA-1273, 100ug of mRNA-1273, or saline placebo given 28 days apart. Participants will be followed for safety and immunogenicity for 12 months post last vaccination.

Study Objectives/Endpoints Relevant to the EUA
The immunogenicity objectives are to evaluate the immunogenicity of 2 doses of mRNA-1273 at the 2 dose levels (50 µg and 100 µg) administered 28 days apart as assessed by level of bAb and by nAb titers at baseline and at various time points after vaccination. All participants are followed for solicited adverse reactions through 7 days post each vaccination. Unsolicited AEs are collected through 28 days after each vaccination. All SAEs and medically attended adverse events are collected through the end of the study.

Statistical Analysis

No formal statistical hypothesis was tested in this study and all results were descriptive.

Study Results

The immune response as assessed by bAb and nAb after 2 doses were comparable in the 50-µg and 100-µg dose groups, with an overall geometric mean fold rise (GMFR)>20-fold in bAB as measured by ELISA and >50-fold in nAb as measured by microneutralization assay at 28 days post-dose 2. In the 100-µg dose group, the older age cohort (≥55 years) had slightly lower bAb response when compared to the younger age cohort (18 to <55 years) at 28 days post-dose 2, but the nAb response was similar between both age groups

Safety profile was similar to that reported in the Phase 3 study. Laboratory evaluations (including complete blood count, liver function tests, kidney functions tests, and coagulation studies) were conducted for participants ≥55 years of age (N=100) at baseline and at 1 month after the second dose (Day 29, Day 57). According to narratives that the Sponsor provided to FDA on December 6, 2020, there were 2 participants in the 100-µg group who experienced Grade 3 decreases in hemoglobin (Grade 0 reported at baseline), but both Grade 3 values were within normal range and not clinically significant. The overall event rates were not provided.

As of December 6, 2020, there were 3 SAEs reported in the vaccine group: a 65-year-old participant with community acquired pneumonia 25 days after vaccination, a 72-year-old participant with arrhythmia after being struck by lightning 28 days after vaccination, and an 87-year-old participant with worsening of chronic bradycardia 45 days after vaccination. On FDA review of the narratives, none of these SAEs are assessed as related. There were no cases of severe COVID-19 reported in the study.

Vaccines and Related Biological Products Advisory Committee Meeting
June 7, 2022

FDA Briefing Document
Novavax COVID-19 Vaccine

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1. Executive Summary

On February 1, 2022, FDA received a request from Novavax (the Sponsor) for emergency use authorization (EUA) of the Novavax COVID-19 Vaccine. The vaccine, also referred to as NVX-CoV2373, is a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) with Matrix-M1 Adjuvant. The proposed use under an EUA is for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The proposed primary series dosing regimen is two intramuscular injections at the dose level of 5 µg recombinant spike protein (rS) and 50 µg of Matrix-M adjuvant.

The EUA request includes safety and efficacy data from an ongoing multinational Phase 3 randomized, double-blind, placebo-controlled trial (study 301) and additional safety data from three additional studies. In study 301, approximately 30,000 adults ≥18 years of age were randomized 2:1 to receive NVX-CoV2373 (NVX) or placebo. The primary efficacy objective was to evaluate a 2-dose primary series of NVX-CoV2373 compared to placebo against polymerase chain reaction (PCR)-confirmed symptomatic COVID-19 illness diagnosed ≥7 days after completion of the second dose. During the course of the study, COVID-19 vaccines authorized for emergency use became available, and participants (when eligible for vaccination per national and local public health prioritization recommendations) were offered the opportunity to cross over from the originally assigned study treatment to the other study treatment (vaccine or placebo) in a blinded fashion ("blinded crossover"). The primary efficacy endpoint was assessed until a participant received the first blinded, crossover vaccination or until the data cutoff of September 27, 2021, whichever came first. During the period of collection of COVID-19 efficacy cases in early 2021, the B.1.1.7 (Alpha) variant was the predominant circulating COVID-19 strain. The per-protocol efficacy analysis population was defined as participants who were randomized, received both doses as assigned, had no evidence of SARS-CoV-2 infection prior to Dose 1, and did not have a COVID-19 event at any time before 7 days after the second injection.

As of September 27, 2021, the per-protocol efficacy analysis population included 17,272 NVX-CoV2373 recipients and 8,385 placebo recipients with a median of 2.5 months of follow-up post-Dose 2 during the blinded pre-crossover period. Vaccine efficacy (VE) against PCR-confirmed mild, moderate or severe COVID-19 was 90.4% (95% CI 83.8, 94.3). All COVID-19 cases in the NVX arm were mild; in the placebo arm, 11% of cases were moderate and 5% were severe. In a subgroup analysis of VE by age, VE was 91.1% (95% CI 84.4, 94.9) in participants 18-64 years of age and 78.6% (95% CI -16.6, 96.1) in participants ≥65 years of age. Vaccine effectiveness in participants ≥65 years of age was further supported by a post-hoc immunogenicity analysis showing that SARS-CoV-2 neutralizing antibody titers in participants ≥65 years of age were comparable to those in participants 50-64 years of age (for whom the age subgroup-specific VE estimate was 90.7% [95% CI 72.9, 96.8]). Subgroup analyses of VE by risk for severe COVID-19, ethnicity and race were comparable to the overall study population, except for VE in Hispanic or Latino participants (77.0% [95% CI 48.7, 89.7]).

The safety analysis population included participants who received at least 1 dose of NVX-CoV2373 in the pre-crossover period (N=29,582; 19,735 NVX-CoV2373, 9,847 placebo) or post-crossover period (N=21,714; 6,416 NVX-CoV2373 crossover, 15,298 placebo crossover). In the pre-crossover period, the median follow-up post-Dose 2 was 2.5 months; 77.6% of participants in the NVX arm and 72.8% of participants in the placebo arm were followed for at least 2 months post-Dose 2. In the post-crossover period, the median follow-up post-Dose 4 was 4.4 months; 99% of participants in each treatment arm were followed for at least 2 months

post-Dose 4. At FDA's request, the Sponsor provided additional safety data through an extraction date of February 17, 2022, for evaluation of clinically important adverse events. As of this later extraction date, the median post-crossover follow-up duration for participants in the Safety Analysis Set was 8.4 months after the completion of the 2-dose crossover series.

Solicited adverse reactions (ARs) were reported by a higher proportion of NVX-CoV2373 recipients than placebo recipients, were reported more frequently after NVX-CoV2373 Dose 2 than Dose 1 (local*:* 57.9% post-Dose 1, 78.7% post-Dose 2; systemic: 47.5% post-Dose 1, 69.3% post-Dose 2), and were reported more frequently by younger adult (18-64 years) than older adult (≥65 year of age) NVX-CoV2373 recipients. In participants 18-64 years of age, the most common solicited ARs associated with any dose of NVX-CoV2373 in participants were injection site pain/tenderness (82.2%), fatigue (62.0%), headache (52.9%), and muscle pain (54.1%). In participants ≥65 years of age, the most common solicited ARs associated with any dose of NVX-CoV2373 in participants were injection site pain/tenderness (63.4%), fatigue (39.2%), headache (29.2%), and muscle pain (30.2%). Severe local and systemic ARs occurred in 1.2-7.2% and 2.4%-12.1% of NVX recipients, respectively, and were more frequent after Dose 2 than after Dose 1 participants. Most solicited reactions were mild to moderate and lasted 1-3 days.

In the pre-and post-crossover period, all unsolicited adverse events (AEs) and medically attended adverse events (MAAEs) were collected through 49 days post-Dose 1, and MAAEs attributed to study vaccine, serious AEs (SAEs), and AEs of special interest (AESIs, defined as COVID-related AEs and potential immune mediated medical conditions [PIMMCs]) were collected for the duration of the study in all participants. In the blinded, placebo-controlled pre-crossover period, the proportions of participants reporting unsolicited AEs, MAAEs, and SAEs were comparable between the NVX and placebo arms. Multiple events of myocarditis/ pericarditis were reported in temporal relationship to NVX-CoV2373 administration, similar to myocarditis following mRNA COVID-19 vaccines and raising concern for a causal relationship to NVX-CoV2373. Events of lymphadenopathy were infrequent but reported by a higher proportion of participants in the NVX arm, with the highest rate observed after Dose 2 (0.2%). Review of the data also identified small imbalances in certain thromboembolic events, including cardiac and neurovascular events, hypersensitivity events, cholecystitis, uveitis, cardiac failure, and cardiomyopathy. However, a causal association between vaccination and these events cannot be concluded based on available data. Subgroup analyses of safety data did not reveal any notable differences across demographic groups. A review of additional safety data consisting of selected clinically important adverse events reported in three other clinical trials evaluating the NVX-CoV2373 vaccine manufactured at a different facility and by a different process identified an event of Guillain Barre syndrome with temporal relationship to vaccination and with no clear alternative etiology identified; otherwise, no other safety concerns were identified from the additional safety data.

The Vaccines and Related Biological Products Advisory Committee is being convened to discuss and provide recommendations on whether, based on the totality of scientific evidence available, the benefits of the Novavax COVID-19 Vaccine 2-dose primary series outweigh its risks for use in individuals 18 years of age and older.

2. SARS-CoV-2 Pandemic

SARS-CoV-2 is a zoonotic coronavirus that emerged in late 2019 and was identified in patients with pneumonia of unknown cause. SARS-CoV-2 is the causative agent of COVID-19, an

infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome (ARDS), leading to multiorgan failure and death. For some adults, COVID-19 symptoms may continue for weeks to months after their initial illness (Chen et al, 2022).

The SARS-CoV-2 pandemic continues to present a challenge to global health and, as of May 26, 2022, has caused over 527 million cases of COVID-19, including 6.3 million deaths worldwide (WHO, 2022). In the US, approximately 83 million cases and 1 million deaths have been reported to the Centers for Disease Control and Prevention (CDC, 2022a). From March 7, 2020, to May 14, 2022, adults 18 years of age and older accounted for 82.4% of COVID-19-associated hospitalizations and 99.8% of deaths from COVID-19 (CDC, 2022c).

Following emergency use authorization (EUA) of the first COVID-19 vaccines in December 2020, COVID-19 cases and deaths in the US declined sharply during the first half of 2021. The emergence of the Omicron variant, variable implementation of public health measures designed to control spread, and continued transmission among unvaccinated individuals were major factors in the resurgence of COVID-19 in the US. As of the week ending May 14, 2022, Omicron variant sub-lineages (predominantly BA.2 and BA2.12.1) comprised 98.8% of the tested strains in the US (CDC, 2022b).

3 Authorized and Approved Vaccines and Therapies for COVID-19

3.1 Comirnaty and Pfizer-BioNTech COVID-19 Vaccine

Comirnaty (COVID-19 Vaccine, mRNA) contains a nucleoside-modified messenger RNA (mRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2 that is formulated in lipid particles. The vaccine is administered intramuscularly as two doses 3 weeks apart, with each 0.3 mL dose of the approved formulation containing 30 µg mRNA. Under Emergency Use Authorization (EUA), the vaccine is called the Pfizer-BioNTech COVID-19 Vaccine, and the formulation authorized for use in individuals 12 years of age and older contains 30 µg mRNA in each 0.3 mL dose. The Pfizer-BioNTech COVID-19 Vaccine formulation authorized for use in children 5-11 years of age contains 10 µg mRNA in each 0.2 mL dose. During clinical development, the vaccine was called BNT162b2.

Comirnaty is approved as a 2-dose primary series for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. The Pfizer-BioNTech COVID-19 Vaccine is authorized under EUA as: a 2-dose primary series for individuals 5 years of age and older; a third primary series dose for individuals 5 years of age and older with certain immunocompromising conditions; a homologous first booster dose administered at least 5 months after completion of primary vaccination to individuals 5 years of age and older; a heterologous first booster dose administered after completion of primary vaccination to individuals 18 years of age and older (the dosing interval is the same as that authorized for a booster dose of the vaccine used for primary vaccination); and a second booster dose administered at least 4 months after a first booster dose with any FDA authorized or approved COVID-19 vaccine to individuals 50 years of age and older and individuals 12 years of age and older with certain immunocompromising conditions.

The Pfizer-BioNTech COVID-19 Vaccine safety and effectiveness data supporting approval of Comirnaty and emergency use authorization of Pfizer-BioNTech COVID-19 Vaccine are detailed in the decision memoranda available on the FDA website.

3.2 Spikevax and Moderna COVID-19 Vaccine

Spikevax, manufactured by Moderna, is approved for active immunization to prevent COVID-19 in individuals 18 years of age and older. The primary immunization series consists of 2 doses administered 1-month apart. The vaccine is authorized for emergency use (as the Moderna COVID-19 Vaccine) as: a 2-dose primary series for individuals 18 years of age and older; a third primary series dose for individuals 18 years of age and older with certain immunocompromising conditions; a homologous or heterologous first booster dose administered after completion of primary vaccination to individuals 18 years of age and older (the authorized dosing interval for a homologous booster is at least 5 months after completion of a primary series, and the authorized interval for a heterologous booster is the same as that authorized for a booster dose of the vaccine used for primary vaccination); and a homologous or heterologous second booster dose administered at least 4 months after the first booster dose to individuals 50 years of age and older and individuals 18 years of age and older with certain immunocompromising conditions. Safety and effectiveness data supporting approval of Spikevax and authorization of Moderna COVID-19 Vaccine are detailed in the decision memoranda available on the FDA website.

3.3 Janssen COVID-19 Vaccine

The Janssen COVID-19 Vaccine is authorized for use in individuals 18 years of age and older for whom other FDA-authorized or approved COVID-19 vaccines are not accessible or clinically appropriate, or who elect to receive the Janssen COVID-19 Vaccine because they would otherwise not receive a COVID-19 vaccine. The vaccine is authorized for use in these individuals as a single primary vaccination dose and as a single homologous or heterologous booster dose (the dosing interval for a homologous booster is at least 2 months after the single primary vaccination dose, and the dosing interval for a heterologous booster is the same as that authorized for a booster dose of the vaccine used for primary vaccination). Safety and effectiveness data supporting emergency use authorization of the Janssen COVID-19 Vaccine are detailed in the decision memorandum on the FDA website.

3.4 Therapies for COVID-19

The antiviral remdesivir is currently approved by the FDA for the treatment of COVID-19 in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) with positive results of direct SARS-CoV-2 testing who are hospitalized, or who are not hospitalized and have mild-to-moderate COVID-19 and are at high risk for severe COVID-19. Additionally, the immune modulator baricitinib is approved by the FDA for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

Other pharmacological products for pre-exposure prophylaxis of COVID-19, post-exposure prophylaxis and/or treatment of COVID-19 that have received emergency use authorization are as follows:

Antivirals: Paxlovid (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use) is authorized under EUA for the treatment of mild-to-moderate COVID-19 in adults and pediatric

patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Molnupiravir is authorized under EUA for the treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by the FDA are not accessible or clinically appropriate.

SARS-CoV-2-targeting monoclonal antibodies: Bebtelovimab is authorized under EUA for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients 12 years of age and older weighing at least 40 kg with positive results of direct SARS-CoV-2 testing, who are at high risk for progression to severe COVID-19 and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate. Tixagevimab co-packaged with cilgavimab is authorized under EUA as pre-exposure prophylaxis for prevention of COVID-19 in certain adults and pediatric individuals (12 years of age and older weighing at least 40 kg).

Immune modulators: Baricitinib is authorized for the treatment of COVID-19 in hospitalized patients 2 to less than 18 years of age who require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). Tocilizumab is authorized for the treatment of COVID-19 in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

COVID-19 convalescent plasma with high antibody titer is authorized for emergency use as a treatment for patients with COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment, in inpatient or outpatient settings.

4. EUA Request for the Novavax COVID-19 Vaccine in Adults 18 Years of Age and Older

On February 1, 2022, FDA received Novavax, Inc's. EUA request for authorization of Novavax COVID-19 vaccine (also referred as NVX-CoV2373), to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older. The vaccine is constructed from a recombinant full-length, wild-type SARS-CoV-2 S protein of Wuhan-Hu-1 sequence, assembled into nanoparticles co-formulated with the saponin-based Matrix-M adjuvant. The adjuvant contains Fraction-A and Fraction-C of *Quillaja saponaria* Molina extract. The primary vaccination series consists of two doses (5 µg of SARS-CoV-2 recombinant spike (rS) protein with 50 µg Matrix-M adjuvant per dose, administered 3 weeks apart).

Testing and submission of manufacturing and product information for the NVX-CoV2373 product intended for use under EUA were still in process at the time of this review. Emergency use authorization of the Novavax COVID-19 Vaccine would depend on manufacturing and product information consistent with the recommendations set forth in FDA's Guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19 to ensure the vaccine's quality and consistency for authorization of the product under an EUA. This information would include a comprehensive analytical comparability assessment supporting quality comparability of the vaccine product intended for use under EUA to the vaccine product evaluated in clinical trial that provide the key data to support the vaccine's safety and effectiveness.

The primary source of clinical data to support the EUA request is from Study 2019nCoV-301, which provides safety, immunogenicity, and efficacy data from a total of approximately 30,000 adult participants (including from the United States) randomized 2:1 to receive 2 intramuscular injections of either NVX-CoV2373 (n=19,735) or placebo. NVX-CoV2373 vaccine drug product (DP) administered in this study was manufactured at Par Sterile Products, LLC. Emergency use authorization of the Novavax COVID-19 Vaccine would depend on manufacturing and product information consistent with the recommendations set forth in FDA's Guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19 to ensure the vaccine's quality and consistency for authorization of the product under an EUA. This information would include a comprehensive analytical comparability assessment supporting quality comparability of the vaccine manufactured at Par Sterile Products, LLC (used in Study 301) to the vaccine product intended for use under EUA.

Additional safety data from a total of 10,323 additional NVX-CoV2373 recipients are provided from international studies (2019nCoV-302, 2019nCoV-501, 2019nCoV-101) with vaccine produced by an earlier manufacturing process than the vaccine product evaluated in study 301. The vaccine product lots used in the other three studies were manufactured at Emergent BioSolutions. Due to differences in manufacturing process and product testing, FDA could not conclude that vaccine lots manufactured at Emergent BioSolutions are comparable to those manufactured at Par Sterile Products, LLC, and available manufacturing and product information will not allow for a conclusion of comparability between vaccine manufactured at Emergent BioSolutions and vaccine intended for use under EUA. Therefore, efficacy and immunogenicity data from these three other studies are not considered supportive of the EUA request and are not discussed in this briefing document.

5. EUA Requirements, Guidance, and Considerations Pertaining to COVID-19 Vaccines

5.1 US Requirements to Support Issuance of an EUA for a Biological Product

Based on the declaration by the Secretary of the US Department of Health and Human Services (HHS) that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA after determining that certain statutory requirements are met (Section 564 of the FD&C Act (21 U.S.C. 360bbb-3)).

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020, EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2, or to mitigate a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by SARS-CoV-2.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

If these criteria are met, under an EUA, FDA can authorize unapproved medical products (or unapproved uses of approved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents.

5.2 Regulatory Considerations for EUA for COVID-19 Vaccines

An EUA allowing for rapid and widespread deployment of the vaccine to millions of individuals, including healthy people, would need to be supported by clear and compelling evidence of effectiveness and adequate safety follow-up to make a determination of favorable benefit/risk (see guidance for industry Emergency Use Authorization for Vaccines to Prevent COVID-19 originally issued October 2020 and last updated March 2022).

Effectiveness Data

Data adequate to inform an assessment of the vaccine's benefits and risks, and thus support issuance of an EUA, would include meeting the prespecified success criteria for the study's primary efficacy endpoint (i.e., a point estimate for a placebo-controlled efficacy trial of at least 50%, with a lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate of >30%).

Safety Data

An EUA request for a COVID-19 vaccine should include all safety data accumulated from studies conducted with the vaccine, with data from Phase 1 and 2 focused on serious adverse events, adverse events of special interest, and cases of severe COVID-19 among study participants. Phase 3 safety data should include characterization of reactogenicity (common and expected adverse reactions shortly following vaccination) in a sufficient number of participants from relevant age groups and should include a high proportion of enrolled participants (numbering well over 3,000) followed for serious adverse events and adverse events of special interest for at least one month after completion of the full vaccination regimen. The Phase 1 and 2 safety data likely will be of a longer duration than the available safety data from the Phase 3 trial at the time of submission of an EUA request and thus, are intended to complement the available data from safety follow-up from ongoing Phase 3 studies.

Phase 3 Follow-Up

Data from Phase 3 studies should include a median follow-up duration of at least 2 months after completion of the full vaccination regimen to provide adequate information to assess a vaccine's benefit-risk profile. From a safety perspective, a 2-month median follow-up following completion of the full vaccination regimen will allow identification of potential adverse events that were not apparent in the immediate postvaccination period. Adverse events considered plausibly linked to vaccination generally start within 6 weeks of vaccine receipt. From the perspective of vaccine efficacy, a 2-month median follow-up is the shortest follow-up period to achieve some confidence that any protection against COVID-19 is likely to be more than short-lived. The EUA request should include a plan for active follow-up for safety (including deaths, hospitalizations, and other serious or clinically significant adverse events) among individuals administered the vaccine under an EUA in order to inform ongoing benefit-risk determinations to support continuation of the EUA.

6. FDA Review of Clinical Safety and Effectiveness Data

6.1 Overview of Clinical Studies

The EUA request included data from four ongoing clinical studies summarized in Table 1. As discussed in Section 4 above, due to differences in manufacturing process between the vaccine lots used in the studies and the vaccine product intended for use under EUA, the primary source of clinical evidence to support safety and efficacy of NVX-CoV2373 is study 2019nCoV-301. Efficacy and immunogenicity data from the other studies is not included in this review, and safety data from these studies was reviewed as relevant information to further inform the safety of the vaccine product intended for use under EUA.

Table 1. Clinical Trial Overview: Data Considered in Support of Safety and Effectiveness of Novavax COVID-19 Vaccine Primary Series in Adults 18 Years and Older

Study Number/ Country	Description	NVX-CoV2373[1] Number[2]	Vaccine Manufacturing Site[3]	Comparator Number[2]	Study Status
Main study	--	--	--	--	--
2019nCoV-301 USA, Mexico (Study 301)	Phase 3, randomized, observer-blinded, placebo-controlled study to evaluate the safety, efficacy, and immunogenicity of NVX-CoV2373 vaccine	19735	Par Sterile Products, LLC	9847	Ongoing
Supporting studies (safety)	--	--	--	--	--
2019nCoV-302 United Kingdom (Study 302)	Phase 3, multicenter, randomized, observer-blinded, placebo-controlled study to evaluate safety, efficacy, and immunogenicity of NVX-CoV2373 vaccine; concomitant vaccine evaluation of NVX-CoV2373 and seasonal influenza vaccine	7570	Emergent BioSolutions	7564	Ongoing
2019nCoV-501 South Africa (Study 501)	Phase 2, randomized, observer-blinded, placebo-controlled in healthy HIV-negative adults ≥18 to ≤84 years of age and in medically stable HIV-positive adults ≥18 to ≤64 years of age.	2211	Emergent BioSolutions	2197	Ongoing

Study Number/ Country	Description	NVX-CoV2373[1] Number[2]	Vaccine Manufacturing Site[3]	Comparator Number[2]	Study Status
2019nCoV-101, Part 1 Australia (Study 101 pt1)	Phase 1, randomized, observer-blinded, placebo-controlled in healthy adults ≥18 to ≤59 years of age	29	Emergent BioSolutions	23	Completed
2019nCoV-101, Part 2 Australia USA (Study 101 pt2)	Phase 2, randomized, observer-blinded, placebo-controlled in adults ≥18 to ≤84 years of age	514	Emergent BioSolutions	255	Ongoing

Source: adapted from EUA 28237, amendment 0, page 35, Table 10.
Abbreviations: COVID-19=coronavirus disease-2019; HIV=human immunodeficiency virus; rS=recombinant spike; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2
1. 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant.
2. Number is the total number of participants in the Safety Analysis Set in the pre-crossover period.
3. Pre-crossover period (from randomization to the time of cross-over): NVX-CoV2373 vaccine was manufactured at Par Sterile Products, LLC (study 301) and at Emergent BioSolutions (studies 302, -502, and -101). Blinded cross-over period (cross-over to the time of data cutoff): NVX-CoV2373 vaccine was manufactured at Par Sterile Products, LLC (studies 301, -302, and 501). There was no blinded cross-over period in study 101.
Cutoff Dates: Study 101: December 19, 2020 (part 1) and December 15, 2020 (part 2), Study 501: February 23,2021, Study 302: February 23, 2021, Study 301: September 27. 2021.

6.2 Study 2019nCoV-301

6.2.1 Design

Study 2019nCoV-301 (referred to as Study 301) is an ongoing randomized, observer-blind, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of NVX-CoV2373 in adults ≥18 years of age. The study is being conducted at 119 sites in the US and Mexico. Study 301 also included an adolescent primary series expansion substudy and a booster dose substudy; however, with the exception of several adverse events reported in these substudies, this briefing document includes only the study design and pertinent vaccine efficacy (VE), safety and immunogenicity analyses of the primary series in adults.

The study was initiated on December 27, 2020 (first participant screened) and completed enrollment on February 18, 2021. Participants are being followed for up to 24 months after the second dose for safety and efficacy assessments.

A total of 29,945 participants were randomized 2:1 to receive 2 intramuscular injections (Dose 1 and Dose 2) of either NVX-CoV2373 (containing 5 µg of SARS-CoV-2 rS with 50 µg Matrix-M adjuvant) or saline placebo, administered 21 days apart, at Day 0 and Day 21 (vaccination window of up to +7 days). Participants were stratified by age group (18 to ≤64 years of age and ≥65 years of age). A target enrollment of 25% of the study population was to consist of participants ≥65 years of age. Prioritization for enrollment was to be given to individuals at high risk for COVID-19 by virtue of Black/African American or Native American race, Hispanic or Latino ethnicity, co-morbid conditions (e.g., obesity [BMI >30 kg/m^2], chronic kidney or lung disease, cardiovascular disease, or diabetes mellitus type 2), and life circumstances (living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated

circumstances [e.g., factory or meat packing plants, essential retail workers, etc.]). Eligible participants included subjects with clinically stable chronic conditions (such as well-controlled HIV infection) who had no previous history of laboratory confirmed SARS-CoV-2 infection or COVID-19 prior to randomization. The study excluded participants with immunodeficiency conditions, those who received immunosuppressive therapy, or immunoglobulin or blood derived products within 90 days, were pregnant or breastfeeding, or had a history of laboratory-confirmed COVID-19.

In response to evolving public health recommendations for and availability of COVID-19 vaccines authorized for Emergency Use Authorization (EUA), the Sponsor modified the study plan after the EUA-required safety data had been accrued (median duration of 2 months safety follow-up after the second vaccination) to offer crossover from the originally assigned study treatment to the other study treatment (vaccine or placebo) in a blinded fashion (Dose 3 and Dose 4 “blinded crossover”). Novavax planned for future analyses of efficacy after the blinded crossover period to evaluate efficacy of immediate versus delayed vaccination, though these have not been submitted for FDA review.

The primary efficacy objective was to evaluate a 2-dose primary series regimen of NVX-CoV2373 compared to placebo against polymerase chain reaction (PCR)-confirmed symptomatic COVID-19 illness diagnosed ≥7 days after completion of the second vaccination in participants ≥18 years of age. Efficacy was assessed through daily surveillance of symptoms suggestive of COVID-19 throughout the study follow-up. Symptoms of COVID-19 experienced by participants during post-vaccination follow-up prompted an unscheduled illness visit and nasopharyngeal swab. Additionally, subjects are given an at-home test to use for 3 days (3-Day Self-Collection Kit). For the diagnosis of SARS-CoV-2 infection, FDA-authorized PCR tests were used, irrespective whether the test was performed by participant with 3-Day Self-Collection Kit or at study sites, and swabs are sent to a central laboratory. Molecular confirmation of SARS-CoV-2 infection (using the Abbott Real Time SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) assay) by the central laboratory was required to meet the primary and secondary efficacy endpoint case definitions.

The primary efficacy endpoint was assessed with data collected up to the blinded crossover period. Participants who were unblinded with an intention to receive a COVID-19 vaccine under EUA were censored past the time of unblinding. Due to the changing landscape of the field regarding availability of emergency use COVID-19 vaccines, Novavax removed the planned interim efficacy analyses based on accumulation of approximately 66.7% of the targeted total number of cases. Consequently, only one protocol-specified primary efficacy analysis comparing the vaccine arm relative to placebo for this study was conducted using all pre-crossover blinded follow up data.

The study will remain blinded at the participant level for study site personnel and study participants until the end of the study (24 months after the first vaccination) while the Sponsor was unblinded at the participant level to prepare for regulatory submissions. An unblinded statistician and programmer from study personnel prepared data analyses.

Case Definitions

The COVID-19 case definitions for mild, moderate, and severe Covid-19 were specified as indicated in Table 2.

Table 2. COVID-19 Case Definitions

Severity	Case Definition
Mild	• Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) • New onset cough OR ≥2 additional COVID-19 symptoms: • New onset or worsening of shortness of breath or difficulty breathing compared to baseline • New onset fatigue • New onset generalized muscle or body aches • New onset headache • New loss of taste or smell • Acute onset of sore throat, congestion, and runny nose • New onset nausea, vomiting, or diarrhea
Moderate	• High fever (≥38.4°C) for ≥3 days (regardless of use of anti-pyretic medications, need not be contiguous days) • Any evidence of significant LRTI: o Shortness of breath (or breathlessness or difficulty breathing) with or without exertion (greater than baseline) o Tachypnea: 24 to 29 breaths per minute at rest o SpO_2: 94% to 95% on room air o Abnormal chest X-ray or chest computerized tomography consistent with pneumonia or LRTI o Adventitious sounds on lung auscultation crackles/rales, wheeze, rhonchi, pleural rub, stridor)
Severe	• Tachypnea: ≥30 breaths per minute at rest • Resting heart rate ≥125 beats per minute • Oxygen saturation ≤93% on room air or ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen <300 mm Hg • High flow oxygen therapy or non-invasive ventilation/non-invasive positive pressure ventilation (e.g., continuous positive airway pressure or bilevel positive airway pressure) • Mechanical ventilation or extracorporeal membrane oxygenation • One or more major organ system dysfunction or failure (e.g., cardiac/circulatory, pulmonary, renal, hepatic, and/or neurological, to be defined by diagnostic testing/clinical syndrome/interventions), including any of the following: o Acute respiratory distress syndrome o Acute renal failure o Acute hepatic failure o Acute right or left heart failure o Septic or cardiogenic shock (with shock defined as systolic blood pressure <90 mm Hg OR diastolic blood pressure <60 mm Hg) o Acute stroke (ischemic or hemorrhagic) o Acute thrombotic event: acute myocardial infarction, deep vein thrombosis, pulmonary embolism o Requirement for: vasopressors, systemic corticosteroids, or hemodialysis. o Admission to an intensive care unit o Death

Source: Study 301, version 9.0, dated May 14, 2021.
Abbreviations: COVID-19=coronavirus disease-2019; LRTI=lower respiratory tract infection

All cases meeting the severe/critical criteria were adjudicated by a blinded clinical severity adjudication committee to determine if the case was severe/critical in their judgement.

Primary Efficacy Endpoint and Statistical Criteria

- The primary endpoint was first episode of PCR-positive mild, moderate, or severe COVID-19, where severity is defined as listed in the case definitions above.
  - The relative risk (RR) of incidence rates was estimated by exponentiating the treatment group coefficient from a Poisson regression analysis with robust error variance. To assess incident rates rather than absolute counts of cases accounting for differences in follow-up times among participants, an offset was utilized in the Poisson regression. A 2-sided 95% CI was constructed around the estimate.
  - The statistical success criteria for the primary endpoint were evaluated with a 2-sided 0.05 α hypothesis test for the following hypothesis:
    H1: VE ≥50% efficacy AND lower bound of 95% CI >30% (RR ≤70%), where Vaccine Efficacy% = [1-Relative Risk] x 100

Secondary Efficacy Objectives/Endpoints

To assess:

- First episode of PCR-positive COVID-19, as defined under the primary endpoint, shown by gene sequencing to represent a variant not considered as a “variant of concern / interest” according to the CDC Variants Classification.
- First episode of PCR-positive moderate or severe COVID-19, as defined under the primary endpoint and efficacy
- VE against any symptomatic SARS-CoV-2 infection
- VE according to race and ethnicity
- VE in high-risk adults versus non-high-risk adults (high-risk is defined by age ⩾65 years with or without co-morbidities or age <65 years with co-morbidities (e.g., obesity [body mass index (BMI) >30 kg/m^2], chronic kidney or lung disease, cardiovascular disease and diabetes mellitus type 2) and/or by life circumstance [living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances (e.g., factory or meat packing plants, essential retail workers, etc.)]).

Evaluation of Safety

Safety follow-up evaluations are planned through 24 months post-last dose of the primary series. For purposes of this EUA request, participants were to have a median duration of safety follow-up of at least 2 months post-last dose of the primary series, collected during the blinded controlled period before crossover. Additional safety follow-up post crossover was also collected and submitted for review, although the comparator group for these analyses was comprised of previously vaccinated participants.

Safety assessments included the following:

- Solicited local and systemic adverse reactions (ARs) during the 7 days following vaccination, pre-crossover (also described as reactogenicity symptoms)
- Unsolicited adverse events (AEs), both pre- and post-crossover, during the 28 days following the second vaccination in the safety subset
- Medically attended AEs (MAAEs), both pre- and post-crossover, up to 28 days following the second vaccination in all participants

- MAAEs attributed to study vaccine, serious AEs (SAEs), and AEs of special interest (AESIs, defined as COVID-related AEs and potential immune mediated medical conditions [PIMMCs]), both pre- and post-crossover, for the duration of the study in all participants
- Vital sign measurements at specified clinic visits in all participants
- Physical examination findings at specified clinic visits in all participants
- Pregnancy and accompanying outcomes in all participants

The Data Safety Monitoring Committee, consisting of external experts, monitored safety and advised the Sponsor at scheduled and *ad hoc* meetings. An unblinded statistician monitored data for the pre-specified stopping boundary, which would indicate that the vaccine causes harm by increasing the rate of mild, moderate or severe COVID-19.

Datasets Reviewed

The Sponsor submitted cleaned and validated safety and efficacy data for independent FDA analysis through September 27, 2021 (cutoff date), and additional safety data as requested by FDA through a February 17, 2022 extraction date for assessment of clinically important safety events (e.g., SAEs, AESIs) collected after the September 27, 2021 data cutoff date. These additional safety data had not been cleaned up to the later extraction date.

Evaluation of Immunogenicity

Assessment of humoral antibody responses to SARS-CoV-2 protein was included as a secondary study objective. Blood samples were collected at Days 0, 21, and 35 from approximately 1,200 participants randomly selected by biostatisticians who were blinded to the vaccine assignment. The random selection included approximately 600 participants from each age cohort (18-64 years, 65 years and older), each of which included approximately 400 NVX recipients and 200 placebo recipients.

Analysis Populations

The definition of each analysis population is included in Table 3.

Table 3. Analysis Sets

Population	Description
Full Analysis Set (FAS)	Participants who were randomized and received at least 1 dose of study vaccine/placebo, regardless of protocol violations or missing data.
Per-Protocol Efficacy	Participants who were randomized, received both doses as assigned, had no immunologic or virologic evidence of prior COVID-19 at the time of vaccination, and no major protocol deviations that would impact the efficacy outcomes (e.g., baseline seropositivity for anti-SARS-CoV-2 nucleoprotein, baseline positivity for SARS-CoV-2 RNA RT-PCR from nasal swab, COVID-19 event at any time before 7 days after the second injection, participants were censored at the time of protocol deviation).
Per-Protocol Efficacy Set 2	Allows for evaluation of baseline serostatus analyses on impact of vaccine efficacy. (i.e., includes those with COVID-19 serostatus positive at time of enrollment)
Per-Protocol Immunogenicity	Participants that have at least a baseline and 1 serum sample result available after vaccination and have no major protocol violations that would impact immunological measures at the specified timepoint.
Safety	Participants who were randomized and received at least 1 dose of study vaccine/placebo. For participants who received both active and placebo vaccine during the initial or crossover period, the participant was analyzed as part of the active group.

Source: Study 301 protocol version 9.0, dated May 14, 2021.
Abbreviations: SARS-CoV-2=severe acute respiratory syndrome coronavirus; RT-PCR=reverse transcription polymerase chain reaction; COVID-19=coronavirus disease-2019.

At the time of the data cutoff date of September 27, 2021, the median pre-crossover follow-up duration for participants in the Safety Analysis Set was 2.5 months after the completion of primary series (Dose 2). At the time of the data cutoff date of February 17, 2022, the median post-crossover follow-up duration for participants in the Safety Analysis Set was 8.4 months after the completion of the crossover series (Dose 4).

HI6.2.2 Participant Disposition and Inclusion in Analysis Populations

Table 4 describes the disposition of participants among all randomized participants (data cut off September 27, 2021). A larger percentage of participants in the placebo group discontinued from the pre-crossover period (22.2% in the placebo group versus 12.2% in the vaccine group). A major reason for discontinuation is withdrawal by subject (16.3% in the placebo group versus 7.9% in the vaccine group). Table 5 describes the analysis populations and the reasons for exclusion from each (data cut off September 27, 2021). The proportion of participants excluded from the Per-Protocol Efficacy Set was balanced between treatment groups, with the majority excluded due to positive baseline SARS-CoV-2 status (either positive anti-NP or PCR result). Other participants were excluded because they did not complete the vaccine schedule or were censored prior to observation period (7 days post dose 2). In the Per-Protocol Efficacy Set, during the pre-crossover period, 21.7% of the participants who received placebo were additionally unblinded with the intention to receive a COVID-19 vaccine under EUA as compared to 13.2% of the participants who received NVX-CoV2373. Participants who were unblinded to receive a COVID-19 vaccine under EUA were censored in the efficacy analyses at the time of unblinding. In the Per-Protocol Efficacy Set, 78.0% of vaccine recipients and 73.1% of placebo recipients completed at least 2 months of pre-crossover follow-up after Dose 2. This difference in follow-up may be the result of more placebo recipients being censored at the time of unblinding to receive a COVID-19 vaccine under EUA. The Disposition (Table 4 below) was done in all randomized subjects “as randomized” (FAS population). Some differences may be

observed in percentages of unblinded subjects and those who withdrew from the study when other analysis populations are used.

Table 4. Disposition, All Randomized Participants (FAS), Study 301, September 27, 2021 cutoff

Disposition	NVX-CoV2373 N=19963	Placebo N=9882	Total N=29945
Randomized, n (%)	19963	9982	29945
Treated, n (%)	19714 (100)	9868 (100)	29582 (100)
Blinded, placebo-controlled follow-up period, n (%)	--	--	--
Completed 1 dose	19714 (100)	9868 (100)	29582 (100)
Completed 2 doses	19087 (96.8)	9440 (95.7)	28527 (96.4)
Discontinued from original blinded vaccination period	2407 (12.2)	2192 (22.2)	4599 (15.5)
Reason for discontinuation	--	--	--
Withdrawal by subject	1563 (7.9)	1604 (16.3)	3167 (10.7)
Lost to follow up	741 (3.8)	501 (5.1)	1242 (4.2)
Other	74 (0.4)	75 (0.8)	149 (0.5)
Adverse event	18 (<0.1)	6 (<0.1)	24 (<0.1)
Death	11 (<0.1)	6 (<0.1)	17 (<0.1)
Blinded crossover period, n (%)	--	--	--
Did not receive NVX-CoV2373 or placebo	4395 (22.3)	3473 (35.2)	7868 (26.6)
Crossed over to receive NVX-CoV2373 or placebo	15319 (77.7)	6395 (64.8)	21714 (73.4)
Completed dose 3	15319 (77.7)	6395 (64.8)	21714 (73.4)
Completed dose 4	15103 (76.6)	6327 (64.1)	21431 (72.4)
Discontinued prior to dose 3	0	0	0
Discontinued after dose 3 but before dose 4	175 (0.9)	56 (0.6)	231 (0.8)
Discontinued after dose 4	491 (2.5)	138 (1.4)	629 (2.1)
Discontinued from blinded crossover vaccine period	666 (3.4)	194 (2.0)	860 (2.9)
Reason for discontinuation	--	--	--
Withdrawal by subject	433 (2.2)	104 (1.1)	537 (1.8)
Lost to follow up	185 (0.9)	74 (0.7)	259 (0.9)
Other	24 (0.1)	4 ((<0.1)	28 ((<0.1)
Adverse event	1 (<0.1)	2 (<0.1)	3 (<0.1)
Death	23 (0.1)	10 (0.1)	33 (0.1)

Source: EUA 28237 Amendment 24, Clinical Summary for Clinical Study 2019nCoV-301, Table 1.
Data cutoff September 27, 2021
n=number of participants with indicated disposition. Denominators for percentages are the number of treated participants.
N= number of randomized participants.

Table 5. Disposition, Efficacy Analysis Population, Study 301 Population

Disposition	NVX-CoV2373	Placebo	Total
ITT Set[1,2], N	19963	9982	29945
Excluded from all analysis sets, n (%)	--	--	363
Sponsor exclusion[3]	--	--	289
Not dosed	--	--	74
FAS Set[4,5], n (%)	19714 (98.8)	9868 (98.9)	29582 (98.8)

Disposition	NVX-CoV2373	Placebo	Total
PP-EFF[4,5], n (%)	17272 (87.6)	8385 (85.0)	25657 (86.7)
Excluded from PP-EFF	2442 (12.4)	1483 (15.0)	3925 (13.3)
Reason for exclusion	--	--	--
Baseline positive anti-NP result	1100 (5.6)	622 (6.3)	1722 (5.8)
Censored prior to observation period	652 (3.3)	405 (4.1)	1057 (3.6)
Unblinded	339 (1.7)	194 (2.0)	533 (1.8)
Protocol deviation	173 (0.9)	170 (1.7)	343 (1.2)
Post-baseline positive PCR result	109 (0.6)	70 (0.7)	179 (0.6)
Withdrawal from Study	104 (0.5)	76 (0.8)	180 (0.6)
Death	0	1 (<0.1)	1 (<0.1)
Did not complete vaccination schedule	627 (3.2)	428 (4.3)	1055 (3.6)
Baseline positive PCR result	228 (1.2)	109 (1.1)	337 (1.1)
PP-EFF-2[6,7], n (%)	18438 (93.5)	9035 (91.6)	27473 (92.9)
Excluded from PP-EFF-2[8]	1276 (6.5)	833 (8.4)	2109 (7.1)
Reason for exclusion	--	--	--
Censored prior to observation period	652 (3.3)	405 (4.1)	1057 (3.6)
Unblinded	339 (1.7)	194 (2.0)	533 (1.8)
Protocol deviation[9]	173 (0.9)	170 (1.7)	343 (1.2)
Post-baseline positive PCR result	109 (0.6)	70 (0.7)	179 (0.6)
Withdrawal from study	104 (0.5)	76 (0.8)	180 (0.6)
Death	0	1 (<0.1)	1 (<0.1)
Did not complete vaccination schedule	627 (3.2)	428 (4.3)	1055 (3.6)

Source: EUA 28237, Amendment 26. Response-request28.pdf, Table 4, page 3.
Abbreviations: FAS=Full Analysis Set; ITT=intent-to-treat; N=number of subjects in indicated analysis set; n=number of subjects with indicated disposition; NP-nucleocapsid protein; PCR=polymerase chain reaction; PP-EFF=Per-Protocol Efficacy Set
1. Intent-to Treat: all participants randomized into the study.
2. Percentages were calculated based on randomized participants.
3. Sponsor exclusion included all participants excluded from Site US151 due to source data inadequate to verify clinical data and other Good Clinical Practice violations, and some participants excluded from Site US076 that received a second dose between February 5, 2021, and February 12, 2021 using an incorrect lot number.
4. FAS: all participants randomized who received at least 1 dose of study vaccine/placebo and tabulated with randomized treatment.
5. Percentages were calculated based on randomized (ITT Analysis Set) in each column.
6. PP-EFF Analysis Set: all participants who received the full prescr bed regimen of study vaccine/ placebo, had no major protocol deviations prior to first COVID-19 positive episode or administrative censoring, with no confirmed infection or prior infection due to SARS-CoV-2 at baseline and not censored prior to the start of the observation period.
7. Percentages were calculated based on the FAS in each column.
8. PP-EFF-2 Analysis Set followed the same method described in the PP-EFF Analysis Set except that it included all participants regardless of baseline SARS-CoV-2 serostatus.
9. Includes additional protocol deviations that did not result in censoring prior to observation period.
Note: Participants may be excluded for more than 1 reason.

6.2.3 Demographics and Other Baseline Characteristics

Table 6 and Table 7 describe the demographics and other baseline characteristics of participants included in the Safety Analysis Set and the Per-Protocol Efficacy set.

Table 6. Demographics and Other Baseline Characteristics, Safety Analysis Set, Study 301

Characteristic	NVX-CoV2373 N=19735	Placebo N=9847	Total N=29945
Sex, n (%)	--	--	--
Male	10367 (52.5)	5019 (51.0)	15386 (52.0)
Female	9368 (47.5)	4828 (49.0)	14196 (48.0)
Age (years)	--	--	--
Mean (SD)	46.5 (15.05)	46.8 (14.95)	46.6 (15.02)
Median	47.0	47.0	47.0
Minimum, maximum	18, 95	18, 90	18, 95

Characteristic	NVX-CoV2373 N=19735	Placebo N=9847	Total N=29945
Age subgroups, n (%)	--	--	--
18 to <65 years	17255 (87.4)	8612 (87.5)	25867 (87.4)
≥65 years	2480 (12.6)	1235 (12.5)	3715 (12.6)
Race, n (%)	--	--	--
White	14794 (75.0)	7381 (75.0)	22175 (75.0)
Black or African American	2323 (11.8)	1164 (11.8)	3487 (11.8)
American Indian or Alaska Native[1]	1309 (6.6)	661 (6.7)	1970 (6.7)
Asian	810 (4.1)	416 (4.2)	1226 (4.1)
Multiple	325 (1.6)	159 (1.6)	484 (1.6)
Native Hawaiian or Other Pacific Islander	56 (0.3)	12 (0.1)	68 (0.2)
Not reported	110 (0.6)	47 (0.5)	157 (0.5)
Missing	8 (<0.1)	7 (<0.1)	15 (<0.1)
Ethnicity, n (%)	--	--	--
Not Hispanic or Latino	15345 (77.8)	7669 (77.9)	23014 (77.8)
Hispanic or Latino	4334 (22.0)	2155 (21.9)	6489 (21.9)
Not reported	32 (0.2)	19 (0.2)	51 (0.2)
Missing or unknown	24 (0.1)	4 (<0.1)	28 (<0.1)
Country, n (%)	--	--	--
Mexico	1176 (6.0)	588 (6.0)	1764 (6.0)
United States	18559 (94.0)	9259 (94.0)	27818 (94.0)
Occupational risk, n (%)	--	--	--
Work requires close proximity to others	7796 (39.5)	3798 (38.6)	11594 (39.2)
Comorbidities, n (%)	--	--	--
Obesity (BMI >30 kg/m^2)	7289 (36.9)	3668 (37.2)	10957 (37.0)
Chronic kidney disease	149 (0.8)	64 (0.6)	213 (0.7)
Chronic lung disease	2776 (14.1)	1446 (14.7)	4222 (14.3)
Cardiovascular disease	226 (1.1)	126 (1.3)	352 (1.2)
Diabetes mellitus type 2	1525 (7.7)	814 (8.3)	2339 (7.9)
High-risk adults[2], n (%)	--	--	--
Yes	18811 (95.3)	9378 (95.2)	28189 (95.3)
No	924 (4.7)	469 (4.8)	1393 (4.7)
Baseline SARS-CoV-2 status (anti-NP or PCR)	--	--	--
Negative	18462 (93.5)	9156 (93.0)	27618 (93.4)
Positive	1273 (6.5)	691 (7.0)	1964 (6.6)

Source: EUA 28237 Amendment 24, Table 19.
N=number of participants in cohort; n=number of participants with indicated characteristic.
Abbreviations: BMI=body mass index; NP=nucleocapsid protein; PCR=polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus; SD=standard deviation
1. American Indians were denoted as Native Americans in the eCRF; approximately 60% of Native Americans were enrolled at sites in Mexico, while ~40% were American Indians enrolled at sites in the United States.
2. High-risk adults were defined as 1) age ≥65 years with or without comorbidities and/or living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances; 2) age <65 years with comorbidities and/or living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances.

Table 7. Demographics and Other Baseline Characteristics, Per-Protocol Efficacy Set, Study 301

Characteristic	NVX-CoV2373 N=17272	Placebo N=8385	Total N=25657
Sex, n (%)	--	--	--
Male	8989 (52.0)	4227 (50.4)	13216 (51.5)
Female	8283 (48.0)	4158 (49.6)	12441 (48.5)
Age (years)	--	--	--
Mean (SD)	46.3 (14.90)	46.7 (14.74)	46.4 (14.85)
Median	47.0	47.0	47.0
Minimum, maximum	18, 95	18, 90	18, 95

Characteristic	NVX-CoV2373 N=17272	Placebo N=8385	Total N=25657
Age subgroups, n (%)	--	--	--
18 to <65 years	15228 (88.2)	7417 (88.5)	22645 (88.3)
≥65 years	2044 (11.8)	968 (11.5)	3012 (11.7)
Race, n (%)	--	--	--
White	13124 (76.0)	6350 (75.7)	19474 (75.9)
Black or African American	1881 (10.9)	947 (11.3)	2828 (11.0)
American Indian or Alaska Native[1]	1068 (6.2)	522 (6.2)	1590 (6.2)
Asian	757 (4.4)	375 (4.5)	1132 (4.4)
Multiple	296 (1.7)	137 (1.6)	433 (1.7)
Native Hawaiian or Other Pacific Islander	47 (0.3)	10 (0.1)	57 (0.2)
Not reported	92 (0.5)	39 (0.5)	131 (0.5)
Missing	7 (<0.1)	5 (<0.1)	12 (<0.1)
Ethnicity, n (%)	--	--	--
Not Hispanic or Latino	13526 (78.3)	6572 (78.4)	20098 (78.3)
Hispanic or Latino	3707 (21.5)	1801 (21.5)	5508 (21.5)
Not reported	21 (0.1)	10 (0.1)	31 (0.1)
Missing or unknown	18 (0.1)	2 (<0.1)	20 (<0.1)
Country, n (%)	--	--	--
Mexico	1011 (5.9)	498 (5.9)	1509 (5.9)
United States	16261 (94.1)	7887 (94.1)	24148 (94.1)
Occupational risk, n (%)	--	--	--
Work requires close proximity to others	6787 (39.3)	3177 (37.9)	9964 (38.8)
Comorbidities, n (%)	--	--	--
Obesity (BMI >30 kg/m^2)	6344 (36.7)	3157 (37.7)	9501 (37.0)
Chronic kidney disease	125 (0.7)	56 (0.7)	181 (0.7)
Chronic lung disease	2461 (14.2)	1264 (15.1)	3725 (14.5)
Cardiovascular disease	199 (1.2)	101 (1.2)	300 (1.2)
Diabetes mellitus type 2	1308 (7.6)	698 (8.3)	2006 (7.8)
High-risk adults[2], n (%)	--	--	--
Yes	16455 (95.3)	7972 (95.1)	24427 (95.2)
No	817 (4.7)	413 (4.9)	1230 (4.8)

Source: EUA 28237 Amendment 24, Table 4.
Abbreviations: BMI=body mass index; eCRF=electronic case report form; N=number of participants in cohort; n=number of participants with indicated characteristic; NP=nucleocapsid protein; PCR=polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus; SD=standard deviation
1. American Indians were denoted as Native Americans in the eCRF; approximately 60% of Native Americans were enrolled at sites in Mexico, while ~40% were American Indians enrolled at sites in the United States.
2. High-risk adults were defined as 1) age ≥65 years with or without comorbidities and/or living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances; 2) age <65 years with comorbidities and/or living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances.

In the Per-Protocol Efficacy Set and the Safety Analysis Set, participants in the NVX and placebo arms were similar with respect to demographic and baseline characteristics. There were no significant imbalances in demographic or other baseline characteristics between the Safety Analysis Set and Per-Protocol Efficacy Set. Overall, 6.5% of NVX-CoV2373 vaccine recipients and 8.4% of placebo recipients in the pre-crossover period had evidence of previous infection with SARS-CoV-2 at baseline, as assessed by serology prior to vaccination. These participants were excluded in the Per-Protocol Efficacy Set dataset but were included in the Per-Protocol Efficacy Set 2 dataset. Participants in the Safety Analysis Set were enrolled from 119 sites in 2 countries (US and Mexico). Nine NVX recipients from one site were excluded from safety and efficacy analyses due to vaccine error. The post-crossover demographic and baseline characteristics for the Safety Analysis Set were generally similar to the pre-crossover set.

6.2.4 Vaccine Efficacy

6.2.4.1 Primary Efficacy Analysis

The primary endpoint was the first episode of PCR-confirmed mild, moderate, or severe COVID-19. The analysis was based on the Per-Protocol Efficacy Set.

A total of 96 cases of PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after second vaccination accrued for the September 27, 2021, updated analysis of the primary efficacy endpoint (Table 8). Of the 96 cases, 17 occurred in the NVX arm and 79 occurred in the placebo arm. All 17 cases of COVID-19 in the NVX arm were mild in severity. Of the 79 COVID-19 cases in the placebo arm, 66 were mild (84%), 9 were moderate (11%), and 4 cases were severe (5%). There were no hospitalizations or deaths due to COVID-19 among the 96 primary endpoint COVID-19 cases in this study. However, one death due to COVID-19 was reported in a placebo recipient; however, it was not a primary endpoint COVID-19 case due to receipt of another COVID-19 vaccine (which was available under EUA) prior to the event.

As shown in Table 8, vaccine efficacy (VE) against mild to severe COVID-19 with onset at least 7 days after the second dose was 90.4% (95% CI 83.8, 94.3), which met the pre-specified statistical success criteria. VE in participants 18 to <65 years of age was comparable to overall VE; however, for participants ≥65 years of age, the VE was lower at 78.6%, with wide 95% confidence intervals.

Table 8. Vaccine Efficacy in Protecting Against PCR-Confirmed Mild, Moderate, or Severe COVID-19 With Onset From 7 Days After Second Injection, Per-Protocol Efficacy Set, Study 301

Age Group	NVX-CoV2373 Cases[1] n/N (%) (Mean Incidence Rate/ 1000 Person-Years)	Placebo Cases[1] n/N (%) (Mean Incidence Rate/ 1000 Person-Years)	Vaccine Efficacy[2] (95% CI)
All participants	17/17272 (0.098) (4.34)	79/8385 (0.942) (45.25)	90.41 (83.81, 94.32)
18 to <65 years	15/15228 (0.099) (5.70)	75/7417 (1.011) (63.69)	91.06 (84.44, 94.87)
≥65 years	2/2044 (0.098) (5.76)	4/968 (0.413) (26.52)	78.63 (-16.64, 96.08)

Source: EUA 28237 Amendment 17, Table 16.
Abbreviations: CI=confidence interval; COVID-19=coronavirus disease-2019; NP=nucleocapsid protein; PCR=polymerase chain reaction; RR=relative risk.
N=number of participants in cohort; n=number of cases[1]
1. Case defined as first occurrence of PCR-confirmed mild, moderate or severe COVID-19 disease with onset from 7 days after second injection within the surveillance period.
2. VE(%) =100 × (1-RR) in SARS-CoV-2-naive (confirmed seronegative by anti-NP and no active COVID-19 infection by PCR test at baseline) adults who received both doses of study vaccine (NVX-CoV2373 or placebo) in the pre-crossover period. RR is ratio of incidence rates of active group relative to the placebo arm (NVX-CoV2373/placebo) with first occurrence of event with onset during a surveillance period from 7 days after second injection up to censor date. Participants were censored at the earliest of (i) cutoff date (September 27, 2021), (ii) date of major protocol deviation, (iii) date of death, (iv) date of unblinding (including for intended receipt of alternative COVID-19 vaccine), (v) early withdrawal, or (vi) first dose of crossover. PCR-positive participants who did not meet mild, moderate, or severe COVID-19 disease criteria were censored at date of the PCR-positive.
Note: RR based on log-linear model of occurrence using modified Poisson regression with logarithmic link function, treatment group and strata (age-group and pooled region) as fixed effects and robust error variance (Zou, 2004) fitted separately to each subgroup.

An additional supportive analysis of the primary efficacy endpoint by baseline SARS-CoV-2 status was performed using the PP-EFF-2 Analysis Set. Among the 300 participants with positive baseline SARS-CoV-2 as determined by PCR (n=204 in the NVX arm and n=96 in the

placebo arm) there were no COVID-19 cases that occurred at least 7 days after Dose 2. The VE, regardless of baseline SARS-CoV-2 status, was 89.8% (95% CI 83.0, 93.9).

Vaccine Efficacy by Age

The limited number of cases (n=6) in participants ≥65 years of age precluded a conclusive assessment of efficacy in this subgroup, with very wide confidence intervals noted. To provide supportive data for effectiveness in the elderly population, a post-hoc analysis vaccine efficacy among participants 50-64 years of age was conducted at FDA's request, and neutralizing antibody titers in participants 50-64 years of age were compared descriptively to those in participants ≥65 years of age. In the subgroup of participants 50-64 years of age, 4 primary endpoint cases were reported in the NVX arm, and 20 primary endpoint cases were reported in the placebo arm, resulting in a VE estimate for this age subgroup (90.7% [95% CI 72.9, 96.8]) that was comparable to the overall VE for ages 18 years and older (90.4% [95% CI 83.8, 94.3]) and for ages 18-64 years (91.1% [95% CI 84.4, 94.9]).

Table 9 summarizes the results of the immunogenicity comparison between the age groups, showing that the Day 35 neutralizing antibody GMT was slightly lower for ages 65 years and older compared with ages 50-64 years, with a GMT ratio of 0.91 and a lower bound of the associated 95% confidence interval that would have met FDA's usual success criterion for immunobridging non-inferiority (>0.67).

Table 9. SARS-CoV-2 Neutralizing GMTs at Baseline (Day 0) and 14 Days After Second Vaccination in Participants 50-64 Years of Age, Per Protocol Immunogenicity Analysis Set, Study 301

Timepoint	NVX-CoV2373 Participants 50-64 Years N=144	NVX-CoV2373 Participants ≥65 Years N=358	GMR
Day 0 (baseline)	--	--	--
GMT	10.2	10.4	--
95% CI	9.8, 10.7	10.0, 10.9	--
Day 35	--	--	--
GMT	978.6	899.8	--
95% CI	770.5, 1243.0	762.9, 1061.3	--
GMR ($GMT_{\geq 65\ Years}/GMT_{50\text{-}64\ Years}$)	--	--	0.91
95% CI	--	--	0.68, 1.2

Source: adapted from EUA 28237, amendment 32, t_imm_50to64_and65_updated.docx.
Abbreviations: CI=confidence interval; GMR=geometric mean ratio; GMT=geometric mean titer; MN=microneutralization assay, SARS-CoV-2 strain: Wuhan-Hu-1.
N=number of SARS-CoV2 baseline seronegative 50-64 and ≥65-year-olds. Baseline defined as the last non-missing assessment prior to the study vaccine administration.

6.2.4.2 Secondary Efficacy Analyses

PCR-Confirmed COVID-19 Cases Any Time After the First or Second Dose

A supportive analysis of PCR-confirmed COVID-19 cases any time after the first or second dose and any time after Dose 1 and before Dose 2 was performed using the Full Analysis Set. A total of 289 cases of PCR-confirmed symptomatic mild, moderate, or severe COVID-19 occurred with onset from first vaccination, including 133 participants in the NVX arm and 156 participants in the placebo arm. This analysis is presented in Table 10.

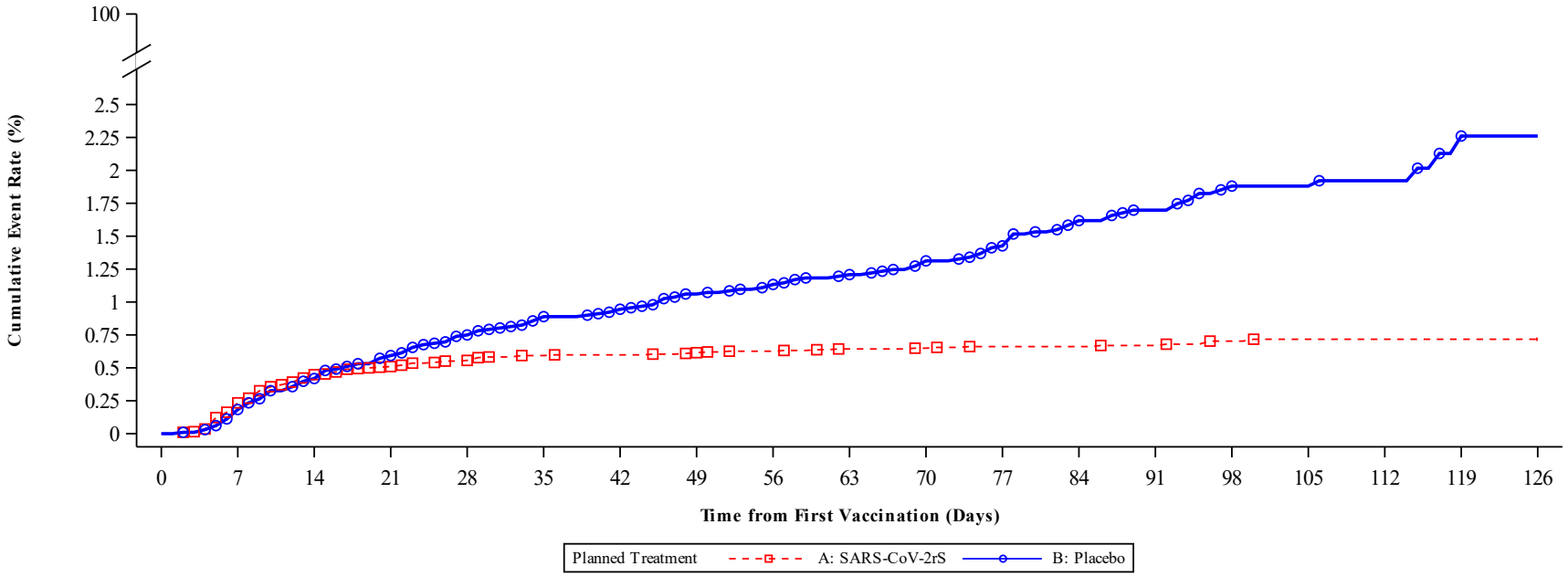
Table 10. COVID-19 Cases From Randomization, Full Analysis Set, Study 301

First COVID-19 Occurrence	NVX-CoV2373 Cases/N (%) (Mean Incidence Rate/ 1,000 Person-Years)	Placebo Cases/N (%) (Mean Incidence Rate/ 1,000 Person-Years)	Vaccine Efficacy (VE)%[1] (95% CI)
After Dose 1	133/19714 (0.67) (23.28)	156/9868 (1.58) (56.70)	58.95% (48.24, 67.44)
Any time after Dose 1 to before Dose 2	106/19714 (0.54) (70.71)	64/9868 (0.65) (85.03)	16.85% (-13.43, 39.05)
Any time after Dose 2	27/18934 (0.14) (5.89)	92/9374 (0.98) (42.26)	86.07% (78.61, 90.93)

Source: EUA 28237 Amendment 17, Table 7.
Abbreviations: CI=confidence interval; COVID-19=coronavirus disease-2019; VE=vaccine efficacy.
N=number of subjects in cohort.
1. VE and 95% CI calculated using Modified Poisson regression with logarithmic link function and treatment group and age strata as fixed effects and robust error variance (Zou, 2004).

Cumulative incidence of mild to severe COVID-19 in the FAS was similar in both the vaccine and placebo arms until approximately Day 21 after the first vaccination, at which time more cases began accumulating in the placebo arm (Figure 1).

Figure 1. Cumulative Incidence Curve of PCR-Confirmed Mild, Moderate, or Severe COVID-19 with Onset from First Vaccination in Adult Participants Who Received at Least 1 Dose of Study Vaccine Regardless of Baseline Serostatus, Full Analysis Set, Study 301



	No of cumulative events																		
Placebo	0	18	41	58	73	86	91	101	107	113	121	129	141	145	152	152	153	156	156
SARS-CoV-2 rS	0	46	88	100	109	116	117	120	122	125	126	128	128	129	132	133	133	133	133
	No at risk																		
Placebo	9868	9800	9720	9653	9410	9180	8773	8421	8082	7790	7482	6730	5654	4513	3445	2544	1500	739	524
SARS-CoV-2 rS	19714	19609	19483	19372	19000	18755	18311	17931	17568	17239	16863	15389	13015	10532	7925	5808	3181	1335	753

Source: EUA 28237 Amendment 24, Figure 1.
Abbreviations: COVID-19=coronavirus disease-2019; PCR=polymerase chain reaction

Efficacy Against COVID-19 Among Variants

Although secondary efficacy endpoints included efficacy against variants that were and were not considered variants of concern (VOC) or variants of interest (VOI) at the time, in the interim the circulating variants and CDC classification of VOC/VOI have changed. Therefore, this analysis is less relevant to the current epidemiology of SARS-CoV-2. Of the 96 cases in the primary efficacy analysis through September 27, 2021, 75 had sequence data available. Of the 75 cases with sequence data, the majority were Alpha (53%), Iota (11%), or Epsilon (7%). As of the time of this writing, none of the variants identified in the primary efficacy analysis are considered VOC/VOI.

Vaccine Efficacy in Protecting Against PCR-Confirmed Moderate to Severe COVID-19

A total of 13 moderate to severe COVID-19 cases were reported in the placebo arm, and none were reported in the NVX arm, resulting in VE of 100% (95% CI 85.4, 100.0).

Subgroup Analyses of Vaccine Efficacy

The point estimate of VE across the subgroups was comparable to the overall study population; however, lower efficacy rates were observed for participants of Hispanic or Latino ethnicity (77.0% [95% CI 48.7, 90.0]). Due to the small numbers of participants in some subgroups, the confidence intervals around the point estimate of VE are wide, which limits the interpretability of the analysis.

Table . Analysis of Efficacy by Demographics and COVID-19 Risk Conditions, COVID-19 Starting 7 Days After Dose 2, Per-Protocol Efficacy Set, Study 301

Characteristic	NVX-CoV2373 Cases[1] /N (%) (Mean Incidence Rate/ 1,000 person-years)	Placebo Cases[1] /N (%) (Mean Incidence Rate/ 1,000 person-years)	Vaccine Efficacy[2] (VE)% (95% CI)
Age (years)	--	--	--
18 to <65	15/15228 (0.099) (5.70)	75/7417 (1.011) (63.79)	91.06 (84.44, 94.87)
65 to <75	2/1764 (0.113) (6.56)	3/835 (0.359) (23.33)	71.86 (-68.37, 95.30)
75 and older	0/280 (0) (0.00)	1/133 (0.752) (44.93)	100.00 (-1699.39, 100.00)[4]
Sex	--	--	--
Male	7/8989 (0.078) (3.88)	29/4227 (0.686) (37.29)	89.60 (76.26, 95.44)
Female	10/8283 (0.121) (4.84)	50/4158 (1.203) (52.47)	90.77 (81.80, 95.32)

Characteristic	NVX-CoV2373 Cases[1] /N (%) (Mean Incidence Rate/ 1,000 person-years)	Placebo Cases[1] /N (%) (Mean Incidence Rate/ 1,000 person-years)	Vaccine Efficacy[2] (VE)% (95% CI)
Race	--	--	--
White	13/13124 (0.099) (4.98)	59/6350 (0.929) (51.65)	90.36 (82.43, 94.71)
Black or African American	1/1881 (0.053) (3.01)	8/947 (0.845) (49.56)	93.93 (51.48, 99.24)
American Indian or Alaska Native[4]	1/1068 (0.094) (4.45)	6/522 (1.149) (54.75)	91.88 (32.63, 99.02)
Native Hawaiian or Other Pacific Islander	0/47 (0) (0.00)	0/10 (0) (0.00)	NE[3]
Asian	0/757 (0) (0.00)	5/375 (1.333) (85.72)	100.00 (51.90, 100.00)[3]
Multiple	2/296 (0.676) (38.44)	0/137 (0) (0.00)	NE[3]
Ethnicity	--	--	--
Hispanic or Latino	9/3707 (0.243) (13.09)	18/1801 (0.999) (56.80)	76.96 (48.72, 89.65)
Not Hispanic or Latino	8/13526 (0.059) (2.93)	61/6572 (0.928) (50.63)	94.22 (87.93, 97.23)
Age (years) and risk for severe COVID-19[5]	--	--	--
18 to <65 and not at risk	9/8271 (0.109) (6.32)	37/3966 (0.933) (60.02)	89.47 (78.19, 94.92)
18 to <65 and at risk	6/6957 (0.086) (4.97)	38/3451 (1.101) (67.94)	92.68 (82.69, 96.91)
≥65 and not at risk	1/919 (0.109) (6.50)	1/388 (0.258) (16.56)	60.75 (-2981.22, 99.50)[3]
≥65 and at risk	1/1125 (0.089) (5.02)	3/580 (0.517) (33.17)	84.85 (-88.66, 99.71)[3]

Characteristic	NVX-CoV2373 Cases[1] /N (%) (Mean Incidence Rate/ 1,000 person-years)	Placebo Cases[1] /N (%) (Mean Incidence Rate/ 1,000 person-years)	Vaccine Efficacy[2] (VE)% (95% CI)
High-risk condition[6]	--	--	--
Yes	16/16455 (0.097) (4.24)	78/7972 (0.978) (46.42)	90.87 (84.38, 94.67)
No	1/817 (0.122) (7.15)	1/413 (0.242) (15.55)	54.02 (-3509.45, 99.41)[3]
BMI >30 kg/m^2	6/6344 (0.095) (3.63)	36/3157 (1.140) (46.11)	92.13 (81.31, 96.69)

Source: EUA 28237 Amendment 24, Table 7.
Abbreviations: BMI=body mass index; CI=confidence interval; COVID-19=coronavirus disease-2019; eCRF=electronic case report form; NE=not estimable in the event the test for exact binomial proportion cannot be conducted; NP=nucleocapsid protein; PCR=polymerase chain reaction; RR=relative risk; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; VE=vaccine efficacy
1. Case defined as first occurrence of PCR-confirmed mild, moderate or severe COVID-19 disease with onset from 7 days after second injection within the surveillance period.
2. VE (%)=100 × (1-RR) in SARS-CoV-2-naive (confirmed seronegative by anti-NP and no active COVID-19 infection by PCR test at baseline) adults who received both doses of study vaccine (NVX-CoV2373 or placebo) in the pre-crossover period. RR is ratio of incidence rates of active group relative to the placebo arm (NVX-CoV2373/placebo) with first occurrence of event with onset during a surveillance period from 7 days after second injection up to censor date. Participants were censored at the earliest of (i) cutoff date (September 27, 2021), (ii) date of major protocol deviation, (iii) date of death, (iv) date of unblinding (including for intended receipt of alternative COVID-19 vaccine), (v) early withdrawal, or (vi) first dose of crossover. PCR-positive participants who did not meet mild, moderate, or severe COVID-19 disease criteria were censored at date of the PCR-positive.
3. In case when there are zero cases in either treatment group or the total number of cases in both treatment groups combined <5, VE and 95% CI is calculated using the Clopper-Pearson exact binomial method that conditions on the total number of cases and is adjusted for total surveillance time.
4. American Indians were denoted as Native Americans in the eCRF; approximately 60% of Native Americans were enrolled at sites in Mexico, while ~40% were American Indians enrolled at sites in the United States.
5. High-risk adults were defined as 1) age ≥65 years with or without comorbidities and/or living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances; 2) age <65 years with comorbidities and/or living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances.
6. Health risks include obesity (BMI >30 kg/m^2), chronic lung disease, diabetes mellitus type 2, cardiovascular disease, and/or chronic kidney disease.
Note: RR based on log-linear model of occurrence using modified Poisson regression with logarithmic link function, treatment group and strata (age-group and pooled region) as fixed effects and robust error variance (Zou, 2004) fitted separately to each subgroup.

6.2.5 Safety

6.2.5.1 Safety Overview

Pre-specified safety analyses presented in this review are derived from safety data available from both the pre- and post-crossover periods of the study, with a database cutoff date of September 27, 2021. To provide additional safety data from longer-term follow up, data on MAAEs, SAEs, AESIs were provided through a database extraction date of February 17, 2022 (data cleaning not completed by the Sponsor). As described in Section 6.2.1, participants could cross over to receive either placebo or NVX-CoV2373 in a blinded fashion. Therefore, data collected in the pre-crossover period provides placebo-controlled data, whereas data collected in the post-crossover period are only from participants who received NVX-CoV2373 at some point during the study, limiting comparisons between the treatment arms. Additionally, based on whether participants crossed over and when, the duration of follow up in the pre-crossover period varied by individual participant, which complicated the interpretation of analyses.

The duration of safety follow-up for the pre- and post-crossover periods, as of the September 27, 2021, data cutoff date, is described in the table below.

Table 11. Study Safety Analyses Populations, Safety Analysis Set, Study 301

Population	Initial Randomization to NVX-CoV2373 N=19735	Initial Randomization to Placebo N=9847	Initial Randomization Total N=29582	Blinded Crossover NVX-CoV2373 to Placebo N=15298	Blinded Crossover Placebo to NVX-CoV2373 N=6371	Blinded Crossover Total N=21669
First vaccination series	--	--	--	--	--	--
Completed 2 doses, n	19111	9416	28527	NA	NA	NA
Median follow up post-Dose 2, months	2.5	2.5	2.5	NA	NA	NA
Completed at least 1 month follow up post Dose 2[1], n (%)	18630 (97.5)	8869 (94.2)	27499 (96.4)	NA	NA	NA
Completed at least 2 months follow up post-Dose 2[1], n (%)	14825 (77.8)	6852 (72.8)	21677 (76.0)	NA	NA	NA
Crossover vaccination series	--	--	--	--	--	--
Completed 4 doses, n	NA	NA	NA	15084	6303	21387
Median follow up post-Dose 4, months	NA	NA	NA	4.4	4.4	4.4
Completed at least 1 month follow up post-Dose 4[2], n (%)	NA	NA	NA	15027 (99.6)	6278 (99.6)	21305 (99.6)
Completed at least 2 months follow up post-Dose 4[2], n (%)	NA	NA	NA	14934 (99.0)	6244 (99.1)	21178 (99.0)

Source: EUA 28237 Amendment 17.
1. Denominator based on number of participants who completed 2 doses.
2. Denominator based on number of participants who completed 4 doses.
Abbreviations: n=number of participants with indicated completion; N=number of participants in cohort; NA=not applicable
Note: Follow up post Dose 2 is defined as the time from initial Dose 2 date to the earliest date of early termination, date of death and date of first crossover dose and date of data extract (September 27, 2021). Follow up post Dose 4 is defined as the time from second crossover dose date to the earliest date of early termination, date of death and date of data extract (September 27, 2021).
Note: Safety Analysis Set included all participants who received at least 1 dose of study vaccine/placebo. Participants in the Safety Analysis Set were analyzed according to the treatment actually received. In cases where information was available that indicated that a participant received both active and placebo vaccine during the initial period, the participant was analyzed as part of the active group.
NA: not applicable.

Table 12 provides an overview of the safety data reported as of the September 27, 2021, data cutoff date.

Table 12. Safety Overview, Safety Analysis Set, Study 301

Subjects Reporting at Least One	NVX-CoV2373	Placebo
Solicited injection site reaction within 7 days[1], n/N (%)	--	--
Dose #1	10494/18135 (57.9)	1900/8982 (21.2)
Grade 3	196/18135 (1.1)	22/8982 (0.2)
Grade 4	0/18135 (0)	0/8982 (0)
Dose #2	13524/17196 (78.6)	1802/8339 (21.6)
Grade 3	1141/17196 (6.6)	24/8339 (0.3)
Grade 4	5/17196 (<0.1)	1/8339 (<0.1)
Solicited systemic adverse reaction within 7 days[1], n/N (%)	--	--
Dose #1	8614/18135 (47.5)	3593/8982 (40.0)
Grade 3	419/18135 (2.3)	187/8982 (2.1)
Grade 4	15/18135 (<0.1)	4/8982 (<0.1)
Dose #2	11920/17196 (69.3)	2990/8339 (35.9)
Grade 3	2058/17196 (12.0)	170/8339 (2.0)
Grade 4	18/17196 (0.1)	5/8339 (<0.1)
Unsolicited adverse event[2], n/N (%)	--	--
Non-serious unsolicited AE	--	--
Pre-crossover period	2285/19735 (11.6)	1101/9847 (11.2)
Post-crossover period	522/6416 (8.1)	850/15298 (5.6)
Related non-serious unsolicited AE		
Pre-crossover period	481/19735 (2.4)	148/9847 (1.5)
Post-crossover period	131/6416 (2.0)	54/15298 (0.4)
Grade 3 non-serious unsolicited AE	--	--
Pre-crossover period	88/19735 (0.4)	37/9847 (0.4)
Post-crossover period	18/6416 (0.3)	20/15298 (0.1)
Related Grade 3 non-serious unsolicited AE		
Pre-crossover period	18/19735 (<0.1)	5/9847 (<0.1)
Post-crossover period	3/6416 (<0.1)	1/15298 (<0.1)
Medically attended adverse event, n/N (%)	--	--
Pre-crossover period	1144/19735 (5.8)	558/9847 (5.7)
Post-crossover period	299/6416 (4.7)	610/15298 (4.0)
Related MAAE		
Pre-crossover period	95/19735 (0.5)	29/9847 (0.3)
Post-crossover period	22/6416 (0.3)	23/15298 (0.2)
SAE, n/N (%)	--	--
Pre-crossover period	199/19735 (1.0)	108/9847 (1.1)
Post-crossover period	88/6416 (1.4)	178/15298 (1.2)
Related SAE	--	--
Pre-crossover period	5/19735 (<0.1)	3/9847 (<0.1)
Post-crossover period	2/6416 (<0.1)	3/15298 (<0.1)
AESI (PIMMCs)[3], n/N (%)	--	--
Pre-crossover period	25/19735 (0.1)	11/9847 (0.1)
Post-crossover period	10/6416 (0.2)	5/15298 (<0.1)
AESI (PIMMCs)[4], n/N (%)	--	--
Pre-crossover period	24/19735 (0.1)	14/9847 (0.1)
Post-crossover period	6/6416 (<0.1)	14/15298 (<0.1)

Subjects Reporting at Least One	NVX-CoV2373	Placebo
AESI (PIMMCs)[5]	--	--
Pre-crossover period	35/19735 (0.2)	19/9847 (0.2)
Post-crossover period	11/6416 (0.2)	15/15298 (<0.1)
AESI (related to COVID-19), n/N (%)	--	--
Pre-crossover period	7/19735 (<0.1)	6/9847 (<0.1)
Post-crossover period	3/6416 (<0.1)	3/15298 (<0.1)
Deaths, n/N (%)	--	--
Pre-crossover period	11/19735 (<0.1)	5/9847 (<0.1)
Post-crossover period	6/6416 (<0.1)	10/15298 (<0.1)
AE leading to discontinuation of the vaccine, n/N (%)	--	--
Pre-crossover period	67/19735 (0.3)	22/9847 (0.2)
Post-crossover period	4/6416 (<0.1)	13/15298 (<0.1)

Source: EUA 28237 Amendment 35. Response to information request 34, page 2, Table 21.
Abbreviations: AE=adverse event; AESI=adverse event of special interest; COVID-19=coronavirus disease-2019; MAAE=medically attended adverse event; PIMMC=potential immune-mediated medical condition; SAE=serious adverse event.
N=number of participants in cohort; n=number of participants with indicated event.
1. Reported as of the data cutoff date of September 27, 2021.
2. Reported within 28 days of any dose.
3. Based on investigator reporting.
4. Based on protocol-defined criteria.
5. Based on investigator reporting and protocol-defined criteria.

AEs Leading to Discontinuation

In the pre-crossover period, the proportion of participants reporting AEs leading to discontinuation of the vaccine were comparable between the NVX (0.3%) and placebo (0.2%) arms. The most common event leading to discontinuation in the NVX arm was COVID-19 (n=5; 0.03%). Of the most frequently reported events leading to discontinuation of vaccine (occurring in ≥3 participants) in the NVX arm, most were consistent with systemic reactogenicity (diarrhea, pyrexia, headache, and nausea). The remaining events (cardiovascular accident, acute kidney injury, cardiac arrest, and cough) are discussed in detail in the safety review below.

In the post-crossover period, the proportion of participants reporting AEs leading to discontinuation of the vaccine were comparable between the participants who crossed over to receive NVX-CoV2373 (0.06%) and participants who crossed over to receive placebo (0.08%). A total of 4 participants who crossed over to receive NVX-CoV2373 reported 5 events leading to discontinuation of the vaccine, including acute myocardial infarction, COVID-19, costochondritis, mental status changes, and overdose.

AEs Leading to Study Withdrawal

In the pre-crossover period, the proportion of participants AEs leading to study withdrawal were comparable between the NVX (0.2%) and placebo (0.1%) arms. The most common event leading to discontinuation in the NVX arm was COVID-19 (n=5; 0.03%). Of the most frequently reported events leading to discontinuation of vaccine (≥3 participants) in the NVX arm, most were consistent with systemic reactogenicity (diarrhea, pyrexia, headache, and nausea). The remaining events (cardiovascular accident, acute kidney injury, cardiac arrest, and cough) are discussed in detail in the safety review below.

In the post-crossover period, proportion of participants reporting AEs leading to discontinuation of the vaccine were comparable between the participants who crossed over to receive NVX (0.2%) and participants who crossed over to receive placebo (0.1%). For participants who crossed over to receive NVX-CoV2373, there were no events leading to study withdrawal

reported by more than one participant. The only event leading to withdrawal reported by more than one participant who crossed over to receive placebo was death (n=2).

6.2.5.2 Solicited Adverse Reactions

Solicited local and systemic ARs with onset within 7 days after vaccination were collected and are presented in the tables below for all participants and stratified by age (18 to 64 years; ≥65 years) for participants in the Safety Analysis Set. These data were only collected in the pre-crossover period. Solicited ARs were recorded daily by study participants using eDiaries and included the assessment of local injection site reactions (pain, tenderness, erythema, and swelling) and systemic reactions (fatigue, headache, myalgia, nausea, and fever). In the NVX arm, data on solicited local ARs and systemic ARs were provided by 92.0% of participants after Dose 1 and by 87.1% after Dose 2. In the placebo arm, data on solicited local ARs and systemic ARs were provided by 91.2% of participants after Dose 2 and 84.7% after Dose 2.

Local Adverse Reactions

All solicited local ARs were reported by a higher proportion of participants in the NVX arm than in the placebo arm, and the proportion of participants reporting solicited local reactions increased after the second dose of NVX-CoV2373. The most frequently reported local AR was injection site pain/tenderness. Grade 3 ARs were reported by a higher proportion of participants in the NVX arm than in the placebo arm and increased in frequency following the second dose of NVX-CoV2373. Grade 4 ARs were reported following the second dose of NVX-CoV2373 and after the second dose of placebo, and occurred in <0.1% of participants in each study group.

For any solicited local AR, the median time to onset was 2 days (range 1-7) for Doses 1 and 2 in the NVX arm and 2 and 1 days (range 1-7 days) for Dose 1 and 2, respectively, in the placebo arm. The median time to onset for each event was between 1 and 3 days. The median duration of any solicited local AR was 2 and 3 days (range 1-7) for Doses 1 and 2, respectively, in the NVX arm and 1 day (range 1-7) for Doses 1 and 2 in the placebo arm. For each local AR, the median duration within the reactogenicity period of 7 days was between 1 and 2 days in the NVX arm and 1 day in the placebo arm. The median duration of any solicited local reaction (including events persisting beyond the 7-day period) was 2 and 3 days in the NVX arm after Dose 1 (range 1-112 days) and 3 days after Dose 2, respectively (range 1-252 days) and 1 day in the placebo arm for both Dose 1 (range 1-19 days) and Dose 2 (range 1-55 days).

Solicited local ARs persisting beyond the 7-day reactogenicity period were reported by a higher proportion of participants in the NVX arm (0.1% after Dose 1 and 0.2% after Dose 2) compared with the placebo arm (0.02% after Dose 1 and Dose 2). Of the local solicited ARs persisting beyond 7 days, pain/tenderness events were the most common.

In an analysis of local ARs by age group, all local ARs were reported more frequently among participants 18-64 years of age compared to participants ≥65 years of age. Overall rates of each local AR and Grade 3 ARs were lower in participants ≥65 years of age, and Grade 4 were only reported in the younger participants. Table 13 provides rates of local ARs by treatment group and age group.

Table 13. Frequency of Solicited Local Reactions Within 7 Days After Each Dose, by Age Group, Safety Analysis Set, Study 301

Event	NVX-CoV2373 Dose 1	Placebo Dose 1	NVX-CoV2373 Dose 2	Placebo Dose 2
Participants 18 to <65 years	N=15884	N=7868	N=15148	N=7361
Any solicited local reaction, n (%)	--	--	--	--
Any (Grade ≥1)	9633 (60.7)	1722 (21.9)	12261 (80.9)	1637 (22.2)
Grade 3	182 (1.2)	19 (0.2)	1084 (7.2)	22 (0.3)
Grade 4	0	0	5 (<0.1)	1 (<0.1)
Pain/tenderness, n (%)	--	--	--	--
Any (Grade ≥1)	9604 (60.5)	1706 (21.7)	12234 (80.8)	1623 (22.1)
Grade 3	174 (1.1)	17 (0.2)	951 (6.3)	20 (0.3)
Grade 4	0	0	5 (<0.1)	1 (<0.1)
Erythema, n (%)	--	--	--	--
Any (Grade ≥1)	151 (1.0)	21 (0.3)	1040 (6.9)	26 (0.4)
Grade 3	3 (<0.1)	0	134 (0.9)	2 (<0.1)
Grade 4	0	0	0	0
Swelling, n (%)	--	--	--	--
Any (Grade ≥1)	137 (0.9)	24 (0.3)	943 (6.2)	22 (0.3)
Grade 3	6 (<0.1)	3 (<0.1)	82 (0.5)	1 (<0.1)
Grade 4	0	0	0	0
Participants ≥65 years	N=2251	N=1114	N=2048	N=978
Any solicited local reaction, n (%)	--	--	--	--
Any (Grade ≥1)	861 (38.3)	178 (16.0)	1263 (61.7)	165 (16.9)
Grade 3	14 (0.6)	3 (0.3)	57 (2.8)	2 (0.2)
Grade 4	0	0	0	0
Pain/tenderness, n (%)	--	--	--	--
Any (Grade ≥1)	854 (37.9)	175 (15.7)	1258 (61.4)	161 (16.5)
Grade 3	13 (0.6)	3 (0.3)	43 (2.1)	1 (0.1)
Grade 4	0	0	0	0
Erythema, n (%)	--	--	--	--
Any (Grade ≥1)	16 (0.7)	5 (0.5)	99 (4.8)	4 (0.4)
Grade 3	0	0	7 (0.3)	0
Grade 4	0	0	0	0
Swelling, n (%)	--	--	--	--
Any (Grade ≥1)	18 (0.8)	1 (0.1)	111 (5.4)	4 (0.4)
Grade 3	1 (<0.1)	0	8 (0.4)	1 (0.1)
Grade 4	0	0	0	0

Source: EUA 28237 Amendment 24 Table Shells, Table 25.
Abbreviation: ER=emergency room; n=number of participants experiencing the adverse event
Note: At each level of summarization, a participant is counted once if they indicated the event occurred and provided a severity during the reactogenicity period. The highest severity experienced during the reactogenicity period is summarized in this table. Two adverse reactions were re-characterized: tenderness to pain and muscle swelling to swelling.
Pain: Grade 1: Does not interfere with activity; Grade 2: Repeated use of nonnarcotic pain reliever >24 hours or interferes with activity; Grade 3: Any use of narcotic pain reliever or prevents daily activity; and Grade 4: Emergency room visit or hospitalization.
Tenderness: Grade 1: Mild discomfort to touch; Grade 2: Discomfort with movement; Grade 3: Significant discomfort at rest; and Grade 4: ER visit or hospitalization.
Erythema: Grade 1: 2.5 to 5 cm; Grade 2: 5.1 to 10 cm; Grade 3: >10 cm; and Grade 4: Necrosis or exfoliative dermatitis.
Swelling/induration (should be evaluated and graded using the functional scale as well as the actual measurement): Grade 1: 2.5 to 5 cm and does not interfere with activity; Grade 2: 5.1 to 10 cm or interferes with activity; Grade 3: >10 cm or prevents daily activity; and Grade 4: Necrosis.

Solicited Systemic Adverse Reactions

Solicited systemic ARs were reported by a higher proportion of participants in the NVX arm compared to the placebo arm, overall and for each solicited AR. The proportion of participants with systemic solicited ARs after Dose 2 increased in the NVX arm but remained comparable to

after Dose 1 in the placebo arm. After Dose 1, the proportion of participants with Grade 3 and 4 solicited systemic ARs was comparable between the treatment arms and generally low (<1.5% and <0.1%, respectively). After Dose 2, the proportion of participants with Grade 3 and 4 solicited systemic ARs (overall and for each event) increased in the NVX arm but remained comparable to after Dose 1 in the placebo arm. In the NVX arm, 12% of participants reported Grade 3 events.

In both treatment groups and for both Dose 1 and 2, fatigue/malaise, headache, and muscle pain (myalgia) were the most commonly reported solicited systemic ARs.

For any solicited systemic AR, the median time to onset was 2 days (range 1-7) for Doses 1 and 2 in both treatment arms. The median time to onset for each event was between 2 and 4 days for each event, with the longest latency observed for fever following Dose 1 in both treatment arms. For each systemic AR, the median duration within the reactogenicity period of 7 days was 1 day in both treatment arms. For any systemic AR, the median duration (including events persisting beyond the 7-day period) was 2 days both treatment arms for both doses (range 1-370 days and 1- 93 days for Dose 1 and 2, respectively in the NVX arm and 1-186 and 1-239 days for Dose 1 and 2, respectively, in the placebo arm).

Any solicited systemic AR persisting beyond the 7-day reactogenicity period was reported by a comparable proportion of participants in the NVX arm (0.3% after Dose 1 and 0.2% after Dose 2) and the placebo arm (0.2% after Dose 1 and Dose 2). Of the solicited systemic ARs persisting beyond 7 days, headache events were the most common in both treatment arms.

In a subgroup analysis by age, all systemic ARs were reported more frequently by participants 18-64 years of age compared to participants ≥65 years of age.

Table 14. Frequency of Solicited Systemic Reactions Within 7 Days After Each Dose, Safety Analysis Set, Participants 18 to <65 Years of Age, Study 301

Solicited Systemic Reaction	NVX-CoV2373 Dose 1 N=15884	Placebo Dose 1 N=7868	NVX-CoV2373 Dose 2 N=15148	Placebo Dose 2 N=7361
Any solicited systemic reaction, n (%)	--	--	--	--
Any (Grade ≥1)	7889 (49.7)	3242 (41.2)	10922 (72.1)	2714 (36.9)
Grade 3	383 (2.4)	175 (2.2)	1968 (13.0)	155 (2.1)
Grade 4	14 (0.1)	4 (0.1)	16 (0.1)	5 (0.1)
Fever, n (%)	--	--	--	--
Any (Grade ≥1)	56 (0.4)	31 (0.4)	941 (6.2)	16 (0.2)
Grade 1	32 (0.2)	16 (0.2)	620 (4.1)	11 (0.2)
Grade 2	13 (0.1)	7 (0.1)	259 (1.7)	3 (<0.1)
Grade 3	7 (<0.1)	7 (0.1)	60 (0.4)	2 (<0.1)
Grade 4	4 (<0.1)	1 (<0.1)	2 (<0.1)	0
Headache, n (%)	--	--	--	--
Any (Grade ≥1)	4158 (26.2)	1866 (23.7)	7128 (47.1)	1492 (20.3)
Grade 1	3153 (19.9)	1437 (18.3)	3777 (24.9)	1102 (15.0)
Grade 2	869 (5.5)	370 (4.7)	2854 (18.8)	352 (4.8)
Grade 3	132 (0.8)	58 (0.7)	492 (3.3)	36 (0.5)
Grade 4	4 (<0.1)	1 (<0.1)	5 (<0.1)	2 (<0.1)

Solicited Systemic Reaction	NVX-CoV2373 Dose 1 N=15884	Placebo Dose 1 N=7868	NVX-CoV2373 Dose 2 N=15148	Placebo Dose 2 N=7361
Fatigue/malaise, n (%)	--	--	--	--
Any (Grade ≥1)	4892 (30.8)	2095 (26.6)	8825 (58.3)	1889 (25.7)
Grade 1	2396 (15.1)	1031 (13.1)	2565 (16.9)	890 (12.1)
Grade 2	2239 (14.1)	950 (12.1)	4662 (30.8)	882 (12.0)
Grade 3	249 (1.6)	113 (1.4)	1591 (10.5)	114 (1.6)
Grade 4	8 (0.1)	1 (<0.1)	7 (0.1)	3 (<0.1)
Muscle pain (myalgia), n (%)	--	--	--	--
Any (Grade ≥1)	3827 (24.1)	1073 (13.6)	7682 (50.7)	900 (12.2)
Grade 1	2831 (17.8)	756 (9.6)	3471 (22.9)	613 (8.3)
Grade 2	915 (5.8)	285 (3.6)	3401 (22.5)	255 (3.5)
Grade 3	79 (0.5)	31 (0.4)	805 (5.3)	28 (0.4)
Grade 4	2 (<0.1)	1 (<0.1)	5 (<0.1)	4 (0.1)
Joint pain (arthralgia), n (%)	--	--	--	--
Any (Grade ≥1)	1260 (7.9)	522 (6.6)	3542 (23.4)	504 (6.9)
Grade 1	776 (4.9)	323 (4.1)	1487 (9.8)	317 (4.3)
Grade 2	434 (2.7)	174 (2.2)	1657 (10.9)	163 (2.2)
Grade 3	49 (0.3)	25 (0.3)	393 (2.6)	22 (0.3)
Grade 4	1 (<0.1)	0	5 (<0.1)	2 (<0.1)
Nausea/vomiting, n (%)	--	--	--	--
Any (Grade ≥1)	1069 (6.7)	466 (5.9)	1822 (12.0)	417 (5.7)
Grade 1	850 (5.4)	364 (4.6)	1305 (8.6)	317 (4.3)
Grade 2	197 (1.2)	93 (1.2)	484 (3.2)	91 (1.2)
Grade 3	18 (0.1)	7 (0.1)	26 (0.2)	7 (0.1)
Grade 4	4 (<0.1)	2 (<0.1)	7 (0.1)	2 (<0.1)

Source: EUA 28237 Amendment 24 Table Shells, Table 32
Abbreviations: ER=emergency room; IV=intravenous.
n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm who received the first dose (Dose 1) and second dose (Dose 2) and completed at least 1 day of the reactogenicity diary.
Note: At each level of summarization, a participant is counted once if they indicated the event occurred and provided a severity during the reactogenicity period. The highest severity experienced during the reactogenicity period is summarized in this table.
Fever: Grade 1: 38.0 to 38.4°C/100.4 to 101.1°F; Grade 2: 38.5 to 38.9°C/101.2 to 102.0°F; Grade 3: 39.0 to 40°C/102.1 to 104°F; and Grade 4: >40°C/>104°F.
Headache: Grade 1: No interference with activity; Grade 2: Repeated use of nonnarcotic pain reliever >24 hours or some interference with activity; Grade 3: Significant; any use of narcotic pain reliever or prevents daily activity; and Grade 4: ER visit or hospitalization.
Fatigue/malaise: Grade 1: No interference with activity; Grade 2: Some interference with activity; Grade 3: Significant; prevents daily activity; and Grade 4: ER visit or hospitalization.
Myalgia/arthralgia: Grade 1: No interference with activity; Grade 2: Some interference with activity; Grade 3: Significant; prevents daily activity; and Grade 4: ER visit or hospitalization.
Nausea/vomiting: Grade 1: No interference with activity or 1 to 2 episodes/24 hours; Grade 2: Some interference with activity or >2 episodes/24 hours; Grade 3: Prevents daily activity, requires outpatient IV hydration; and Grade 4: ER visit or hospitalization for hypotensive shock.

Grade 4 solicited systemic reactions in ≥65 included 1 grade 4 headache with both injections in the vaccine group, and 1 grade 4 arthralgia with the second vaccine.

Table 15. Frequency of Solicited Systemic Reactions Within 7 Days After Each Dose, Safety Analysis Set Participants ≥65 Years of Age, Study 301

Solicited Systemic Reaction	NVX-CoV2373 Dose 1 N=2251	Placebo Dose 1 N=1114	NVX-CoV2373 Dose 2 N=2048	Placebo Dose 2 N=978
Any solicited systemic reaction, n (%)	--	--	--	--
Any (Grade ≥1)	725 (32.2)	351 (31.5)	998 (48.7)	276 (28.2)
Grade 3	36 (1.6)	12 (1.1)	90 (4.4)	15 (1.5)
Grade 4	1 (<0.1)	0	2 (0.1)	0
Fever, n (%)	--	--	--	--
Any (Grade ≥1)	8 (0.4)	3 (0.3)	40 (2.0)	7 (0.7)
Grade 1	4 (0.2)	2 (0.2)	30 (1.5)	5 (0.5)
Grade 2	3 (0.1)	1 (0.1)	8 (0.4)	1 (0.1)
Grade 3	1 (<0.1)	0	2 (0.1)	1 (0.1)
Grade 4	0	0	0	0
Headache, n (%)	--	--	--	--
Any (Grade ≥1)	344 (15.3)	184 (16.5)	502 (24.5)	144 (14.7)
Grade 1	292 (13.0)	153 (13.7)	378 (18.5)	117 (12.0)
Grade 2	39 (1.7)	27 (2.4)	105 (5.1)	25 (2.6)
Grade 3	12 (0.5)	4 (0.4)	18 (0.9)	2 (0.2)
Grade 4	1 (<0.1)	0	1 (0.1)	0
Fatigue/malaise, n (%)	--	--	--	--
Any (Grade ≥1)	444 (19.7)	202 (18.1)	714 (34.9)	182 (18.6)
Grade 1	246 (10.9)	105 (9.4)	295 (14.4)	96 (9.8)
Grade 2	175 (7.8)	92 (8.3)	351 (17.1)	73 (7.5)
Grade 3	23 (1.0)	5 (0.5)	68 (3.3)	13 (1.3)
Grade 4	0	0	0	0
Muscle pain (myalgia), n (%)	--	--	--	--
Any (Grade ≥1)	284 (12.6)	125 (11.2)	561 (27.4)	102 (10.4)
Grade 1	222 (9.9)	88 (7.9)	344 (16.8)	68 (7.0)
Grade 2	59 (2.6)	33 (3.0)	185 (9.0)	32 (3.3)
Grade 3	3 (0.1)	4 (0.4)	32 (1.6)	2 (0.2)
Grade 4	0	0	0	0
Joint pain (arthralgia), n (%)	--	--	--	--
Any (Grade ≥1)	139 (6.2)	71 (6.4)	271 (13.2)	63 (6.4)
Grade 1	86 (3.8)	39 (3.5)	141 (6.9)	34 (3.5)
Grade 2	49 (2.2)	28 (2.5)	113 (5.5)	27 (2.8)
Grade 3	4 (0.2)	4 (0.4)	16 (0.8)	2 (0.2)
Grade 4	0	0	1 (0.1)	0

Solicited Systemic Reaction	NVX-CoV2373 Dose 1 N=2251	Placebo Dose 1 N=1114	NVX-CoV2373 Dose 2 N=2048	Placebo Dose 2 N=978
Nausea/vomiting, n (%)	--	--	--	--
Any (Grade ≥1)	81 (3.6)	32 (2.9)	108 (5.3)	35 (3.6)
Grade 1	69 (3.1)	26 (2.3)	84 (4.1)	28 (2.9)
Grade 2	12 (0.5)	6 (0.5)	21 (1.0)	7 (0.7)
Grade 3	0	0	3 (0.2)	0
Grade 4	0	0	0	0

Source: EUA 28237 Amendment 24 Table Shells, Table 33.
Abbreviations: ER=emergency room; IV=intravenous.
n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm who received the first dose (Dose 1) and second dose (Dose 2) and completed at least 1 day of the reactogenicity diary.
Note: At each level of summarization, a participant is counted once if they indicated the event occurred and provided a severity during the reactogenicity period. The highest severity experienced during the reactogenicity period is summarized in this table.
Fever: Grade 1: 38.0 to 38.4°C/100.4 to 101.1°F; Grade 2: 38.5 to 38.9°C/101.2 to 102.0°F; Grade 3: 39.0 to 40°C/102.1 to 104°F; and Grade 4: >40°C/>104°F.
Headache: Grade 1: No interference with activity; Grade 2: Repeated use of nonnarcotic pain reliever >24 hours or some interference with activity; Grade 3: Significant; any use of narcotic pain reliever or prevents daily activity; and Grade 4: ER visit or hospitalization.
Fatigue/malaise: Grade 1: No interference with activity; Grade 2: Some interference with activity; Grade 3: Significant; prevents daily activity; and Grade 4: ER visit or hospitalization.
Myalgia/arthralgia: Grade 1: No interference with activity; Grade 2: Some interference with activity; Grade 3: Significant; prevents daily activity; and Grade 4: ER visit or hospitalization.
Nausea/vomiting: Grade 1: No interference with activity or 1 to 2 episodes/24 hours; Grade 2: Some interference with activity or >2 episodes/24 hours; Grade 3: Prevents daily activity, requires outpatient IV hydration; and Grade 4: ER visit or hospitalization for hypotensive shock.

Immediate Adverse Events

The Sponsor did not categorize AEs that were immediate adverse events. In general, other than reactogenicity events, no pattern of concern was identified.

6.2.5.3 Unsolicited Adverse Events

The determination of severity for all unsolicited AE was made by study investigators based on protocol-specified definitions of severity mild to potentially life threatening. Causal relationship to study vaccine was determined by study investigators and classified as “related” or “not related.”

Unsolicited Adverse Events (Pre-Crossover)

In the pre-crossover period through the September 27, 2021, data cutoff, the proportions of participants reporting any non-serious unsolicited AE were comparable between the NVX (11.6%) and placebo (11.2%) arms. There was no adverse event preferred term (PT) reported by more than 1% of participants in either group; therefore, Table 16 summarizes unsolicited AEs occurring in ≥1% of participants for specific system organ classes (SOCs). The overall frequency of unsolicited adverse events by SOC were similar between groups, although imbalances in the SOC of General disorders and administration site conditions and Blood and lymphatic system disorders were noted, largely due to AEs associated with reactogenicity (including chills, injection site pruritis, and influenza-like illness) and lymphadenopathy, respectively. Events of lymphadenopathy were reported by a higher proportion of participants in the NVX arm for Dose 1 and Dose 2 (0.06% and 0.2%, respectively) than in the placebo arm (0.03% and 0.02%, respectively). All events were mild to moderate in severity, and the most common locations were axillary and cervical lymph nodes.

Severe non-serious unsolicited AEs were infrequent and reported by a comparable proportion of participants in each treatment arm (0.4% in each). The most commonly reported (≥0.1% of participants) severe unsolicited event in the NVX arm was fatigue (n=10, 0.1%). Related severe events were reported by a higher proportion of participants in the NVX arm (0.1%) compared to the placebo arm (0.05%). Of the Grade 3 related events in the NVX arm, fatigue was the only event reported by more than one participant (n=3).

Unsolicited AEs considered related by the investigator were reported by 2.4% of participants in the NVX arm and 1.5% of participants in the placebo arm. The most frequently reported related AEs in the NVX arm included chills, injection site pruritis, and lymphadenopathy.

Table 16. Pre-Crossover Period: Frequency of Unsolicited AEs Reported Within 49 Days With Occurrence in ≥1% of Participants, Safety Analysis Set, Study 301

Primary System Organ Class/ Preferred Term[1]	NVX-CoV2373 Any n/N (%)	NVX-CoV2373 Severe n/N (%)	Placebo Any n/N (%)	Placebo Severe n/N (%)
Infections and infestations	520/19735 (2.6)	25/19735 (0.1)	301/9847 (3.1)	20/9847 (0.2)
General disorders and administration site conditions	330/19735 (1.7)	19/19735 (0.1)	109/9847 (1.1)	7/9847 (0.1)
Nervous system disorders	328/19375 (1.7)	12/19735 (0.1)	171/9847 (1.7)	10/9847 (0.1)
Respiratory, thoracic and mediastinal disorders	356/19735 (1.8)	12/139735 (0.1)	175/9847 (1.8)	3/9847 (<0.1)
Gastrointestinal disorders	291/19375 (1.5)	12/19735 (0.1)	148/9847 (1.5)	6/9847 (0.1)
Musculoskeletal and connective tissue disorders	239/19375 (1.2)	16/19735 (0.1)	128/9847 (1.3)	2/9847 (<0.1)
Skin and subcutaneous tissue disorders	194/19375 (1.0)	3/19735 (<0.1)	69/9847 (0.7)	1/9847 (<0.1)
Injury, poisoning and procedural complications	189/19735 (1.0)	20/19735 (0.1)	95/9847 (1.0)	11/9847 (0.1)

Source: EUA 28237 Amendment 25 Table Shells, Table 38.
Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities.
n=number of participants reporting the adverse event at least once; N=number of participants included in the considered cohort in each group
1. Adverse Events coded using MedDRA version 24.0.
Note: AEs were classified as treatment-emergent adverse events (TEAEs) or post-treatment and defined as any AE that was newly developed at or after the first dosing date of study vaccine.
Note: Follow-up time for the pre-crossover period is defined as time from first dose to the earliest date of early termination, date of first crossover dose, date of death and date corresponding to the Day 49 assessment. Follow-up time for the post-crossover period is defined as time from first crossover dose to the earliest date of early termination, date corresponding to the post-crossover Day 49 assessment, date of death and date of data cutoff (September 27, 2021).

Unsolicited Adverse Events (Post-Crossover)

In the post-crossover period through the September 27, 2021, data cutoff, the proportion of participants reporting any non-serious unsolicited AE was higher for participants who crossed over to receive NVX (8.1%) compared to participants who crossed over to receive placebo (5.6%). There was no PT reported by more than 1% of participants in either group; therefore, Table 17 summarizes unsolicited AEs occurring in ≥1% of participants for specific SOCs. The overall frequency of unsolicited adverse events by SOC were similar between groups, although imbalances in the SOC of General disorders and administration site conditions and Nervous System disorders were noted, largely due to AEs associated with reactogenicity (including fatigue, injection site pain/erythema/pruritis/swelling, pain, headache, pyrexia, and chills).

Severe non-serious unsolicited AEs were infrequent and reported by a higher proportion of participants who crossed over to receive NVX (0.3%) compared to participants who crossed

over to receive placebo (0.1%). There were no severe unsolicited events reported by >0.1% of participants. Related severe events were reported by a higher proportion of participants in the who crossed over to receive NVX (0.05%) compared to participants who crossed over to receive placebo (0.01%). Grade 3 related events in the NVX arm included diarrhea, headache, and neuralgic amyotrophy (4 days after NVX). Please see Section 6.2.5.4 for additional discussion of the event of neuralgic amyotrophy (Parsonage-Turner syndrome).

Unsolicited AEs considered related by the investigator to study vaccination post-crossover were reported by 2.0% of participants who crossed over to receive NVX compared to 0.4% of participants who crossed over to receive placebo. This imbalance was largely due to events of injection site pain, fatigue, pyrexia, myalgia, pain, and headache.

Table 17. Post-Crossover Period: Frequency of Unsolicited AEs Reported Within 49 Days With Occurrence in ≥1% of Participants, Safety Analysis Set, Study 301

Primary System Organ Class/ Preferred Term[1]	NVX-CoV2373 Any n/N (%)	NVX-CoV2373 Severe n/N (%)	Placebo Any n/N (%)	Placebo Severe n/N (%)
General disorders and administration site conditions	138/6416 (2.2)	5/6416 (0.1)	82/15298 (0.5)	3/15298 (<0.1)
Infections and infestations	109/6416 (1.7)	2/6416 (<0.1)	243/15298 (1.6)	10/15298 (0.1)
Nervous system disorders	77/6416 (1.2)	4/6416 (0.1)	102/15298 (0.7)	7/15298 (<0.1)
Respiratory, thoracic and mediastinal disorders	73/6416 (1.1)	6/6416 (0.1)	130/15298 (0.8)	4/15298 (<0.1)
Gastrointestinal disorders	62/6416 (1.0)	2/6416 (<0.1)	108/15298 (0.7)	7/15298 (<0.1)
Musculoskeletal and connective tissue disorders	65/6416 (1.0)	2/6416 (<0.1)	107/15298 (0.7)	5/15298 (<0.1)

Source: EUA 28237 Amendment 25 Table Shells, Table 38
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities,
n=number of participants reporting the adverse event at least once; N=number of participants included in the considered cohort in each group.
1. Adverse Events coded using MedDRA version 24.0.
Note: AEs were classified as treatment-emergent adverse events (TEAEs) or post-treatment and defined as any AE that was newly developed at or after the first dosing date of study vaccine.
Note: Follow-up time for the pre-crossover period is defined as time from first dose to the earliest date of early termination, date of first crossover dose, date of death and date corresponding to the Day 49 assessment. Follow-up time for the post-crossover period is defined as time from first crossover dose to the earliest date of early termination, date corresponding to the post-crossover Day 49 assessment, date of death and date of data cutoff (September 27, 2021).

6.2.5.4 Unsolicited Adverse Events of Clinical Interest

Adverse Events of Special Interest

AESIs for Trial 301 included PIMMCs (Potential Immune-Mediated Medical Conditions) and AEs representing complications specific to COVID-19. The AEs representing complications specific to COVID-19 were reviewed, and no concerns for vaccine enhanced disease were identified. PIMMCs are defined in Appendix B and are intended to capture potential autoimmune-mediated conditions that could be associated with adjuvanted vaccines. Three approaches were used to assess AESIs of PIMMCs in the study: 1) investigator reporting; 2) protocol-defined criteria; and 3) investigator reporting and protocol-defined criteria combined. The analyses that follow discuss only PIMMCs identified using protocol-defined criteria.

The proportion of participants with PIMMCs was comparable in the NVX and placebo arms (0.1% each) during the pre-crossover period through September 27, 2021. A total of 25 PIMMCs were reported by 24 participants in the NVX arm, and 14 PIMMCs were reported by 14 participants in the placebo arm. The proportions of participants reporting each event was

comparable between the treatment arms, although the numbers of each event were small. No pattern of events to suggest a specific autoimmune phenomenon associated with vaccination was observed.

Table 18. Potential Immune-Mediated Medical Conditions Reported in the Pre-Crossover Period, Study 301

Preferred Term	NVX-CoV2373 N=19735 Number of Subjects (%)	Placebo N=9847 Number of Subjects (%)
Alopecia areata	1 (0.005)	0 (0)
Ankylosing spondylitis	1 (0.005)	0 (0)
Autoimmune thyroiditis	1 (0.005)	1 (0.01)
Basedow's disease	2 (0.01)	0 (0)
Bell's palsy	3 (0.015)	1 (0.01)
Crohn's disease	1 (0.005)	0 (0)
Erythema nodosum	1 (0.005)	0 (0)
Lichen planus	0 (0)	1 (0.01)
Neuropathy peripheral	3 (0.015)	3 (0.03)
Polymyalgia rheumatica	1 (0.005)	1 (0.01)
Psoriasis	1 (0.005)	1 (0.01)
Rheumatoid arthritis	2 (0.01)	1 (0.01)
Seizure	3 (0.015)	2 (0.02)
Thrombocytopenia	2 (0.01)	1 (0.01)
Uveitis	2 (0.01)	2 (0.02)

Source: Source: EUA 28237 Amendment 15, ADAE dataset generated using MAED.
N=number of subjects in cohort

Of the 25 PIMMCs in the NVX arm, 12 events reported by 11 participants were considered related to vaccination by the investigator, including alopecia areata, Basedow's disease, Bell's palsy, psoriasis, and thrombocytopenia (n=1 each); neuropathy peripheral, rheumatoid arthritis (n=2 each); and uveitis (n=3). In the placebo arm, 2 events reported by 2 participants were considered related to vaccination by the investigator, including peripheral neuropathy and seizure. The following are descriptions of minor imbalances, related events, or PIMMCs of specific clinical interest reported by multiple participants:

- Two events of Basedow's disease and 1 event of autoimmune thyroiditis were reported in the NVX arm compared to 1 event of autoimmune thyroiditis in the placebo arm. Although 1 case of Basedow's disease was considered related by the investigator, all participants in the NVX arm had evidence of thyroid antibodies in baseline study laboratories, indicating that the conditions were pre-existing.
- Three events of Bell's palsy were reported in the NVX arm compared to one event in the placebo arm. One event was reported 25 days following Dose 2 of NVX-CoV2373 and was considered related by the investigator and Sponsor. The remaining 2 events in the NVX arm were reported 175 and 144 days post-Dose 2, respectively, and 1 event was attributed to herpes labialis. One event of Bell's palsy was reported in the placebo arm 29 days post-Dose 2.
- Two events of thrombocytopenia were reported in the NVX arm compared to 1 event in the placebo arm. One event was reported 13 days post-Dose 1 of NVX-CoV2372 in a participant hospitalized for surgical repair of a fracture with one abnormal platelet count (57 K/mm^3) that was preceded by normal values (229 K/mm^3) with a subsequent normal value on repeat 45 minutes later (307 K/mm^3). One event (platelet count 8 K/mm^3) was reported

32 days post-Dose 2 of NVX-CoV2373 in a participant on losartan with positive findings on a platelet antibody profile and positive losartan potassium IgG platelet antibody. The participant was treated with steroids and multiple platelet transfusions, and losartan was discontinued. The platelet count recovered to 122 K/mm^3 within one month but was noted to be decreased ~8 months later (82 K/mm^3). This case was considered related by the investigator, and as discussed in Section 6.2.5.5, FDA's opinion is that losartan-induced thrombocytopenia is a plausible alternative etiology for this event. One event in the placebo arm was reported 57 days post-Dose 2 and was associated with COVID-19.

- Events of peripheral neuropathy were reported by a higher proportion of participants in the placebo arm, including events with onset within 2 weeks of vaccination. Of the 3 events in the NVX arm, 1 event involved bilateral numbness and paresthesia with onset the same day as Dose 1 and was ongoing and being treated with gabapentin as of the data extraction date, one event occurred 26 days post-Dose 1 and included bilateral upper and lower weakness and neuropathy, with a normal lumbar puncture and electromyelogram, and the remaining event was reported 1-day post-Dose 2 (no information on the details of this case were provided). The latter 2 events were considered related by the investigator.
- Events of uveitis were reported by a higher proportion of participants in the placebo arm, including events with onset within 2 months of vaccination. Two participants in the placebo arm reported events of uveitis 6 and 50 days following the most recent placebo dose; the participant with onset 6 days after the placebo dose had a history of uveitis. In the NVX arm, 1 participant had the onset of left-sided panuveitis 15 days post-Dose 1 of NVX-CoV2373; ophthalmologic exam revealed chronic changes that were thought to have preceded vaccination and he was treated with antivirals for presumed herpetic disease as well as steroids, after which his condition resolved. Attribution of this case is confounded by a potential infectious etiology and chronic ocular changes that may have preceded onset of symptoms, although the close temporal relationship to vaccination precludes exclusion of NVX-Co2373 as a contributor. One participant reported right eye panuveitis 7 days post-Dose 1 of NVX-CoV2373 that resolved after initiation of steroids, but then recurred 16 days post-Dose 2. An extensive workup was unrevealing, and the symptoms resolved after a second course of steroids. Both cases of uveitis in the NVX arm were considered related by the investigator. An additional case of iridocyclitis (bilateral anterior uveitis) was reported 18 days post-Dose 2 of NVX-CoV2373; however, this case did not meet protocol-defined criteria for a PIMMC based on the coding of the event term and was therefore not included in case counts. This 36-year-old male participant had a history of immune thrombocytopenic purpura and a family history of autoimmune disease; he was diagnosed with anterior uveitis with positive beta-2 microglobulin in the urine and evidence of acute kidney injury concerning for tubular intestinal nephritis with uveitis (TINU), although review of prior creatinine laboratories did show previously elevated values. After treatment with steroids, the uveitis resolved.
- Remaining events in the NVX arm considered related by the investigator included alopecia areata 41 days post-Dose 2, without a specific alternative etiology, which was ongoing and resolving; worsening of pre-existing psoriasis 8 days post-Dose 1; and 2 events of seronegative rheumatoid arthritis with onset 1- and 3-days post-Dose 2, respectively, both of which occurred in participants with prior history of joint pain. The onset of symptoms in temporal relationship to vaccination may suggest an inflammatory response manifesting as persistent joint pain, although the prior history of joint pain may also suggest an exacerbation of an underlying condition either precipitated by or unrelated to vaccination.

In the post-crossover period through September 27, 2021, a total of 20 PIMMCs were reported by 6 (<0.1%) participants who crossed over to receive NVX-CoV2373 and 14 (<0.1%) participants who crossed over to receive placebo.

Table 19. Potential Immune-Mediated Medical Conditions Reported in the Post-Crossover Period, Study 301

Preferred Term	NVX-CoV2373 N=6416 Number of Subjects (%)	Placebo N=15298 Number of Subjects (%)
Ankylosing spondylitis	0 (0)	2 (0.013)
Bell's palsy	1 (0.016)	2 (0.013)
Dermatitis herpetiformis	0 (0)	1 (0.007)
Neuropathy peripheral	0 (0)	1 (0.007)
Polymyalgia rheumatica	0 (0)	1 (0.007)
Psoriasis	1 (0.016)	0 (0)
Rheumatoid arthritis	2 (0.031)	1 (0.007)
Seizure	1 (0.016)	1 (0.007)
Systemic lupus erythematosus	0 (0)	1 (0.007)
Thrombocytopenia	0 (0)	2 (0.013)
Type 1 diabetes mellitus	0 (0)	1 (0.007)
Vitiligo	1 (0.016)	1 (0.007)

Source: Source: EUA 28237 Amendment 15, ADAE dataset generated using MAED.
Abbreviation: PIMMC=Potential Immune-Mediated Medical Condition.
N=number of subjects in cohort.

Of the 20 PIMMCs, 2 were considered related by the investigator, including worsening of pre-existing dermatitis herpetiformis 85 days after the last dose of NVX-CoV2373 in the pre-crossover period and 1 day after placebo in the post-crossover period and vitiligo 26 days after the last dose of NVX-CoV2373 in the post-crossover period, confounded by administration of Pfizer COVID-19 vaccine 10 days prior to onset of symptoms. Events reported by multiple participants included 2 events of ankylosing spondylitis (72 and 88 days after the last dose of NVX-CoV2373 administered in the pre-crossover period) and 16 and 11 days after the first dose of placebo in the post-crossover period, respectively, 3 events of Bell's palsy reported 20, 88 and 221 days after the last dose of NVX-CoV2373, and 2 events of thrombocytopenia, both of which occurred >60 days following the most recent dose of NVX-CoV2373 in participants with multiple co-morbidities, including alcohol abuse and liver disease.

Additional safety data provided at FDA's request in a dataset with an extraction date of February 17, 2022, identified an additional 2 participants with PIMMCs in the pre-crossover period, including an event of polymyalgia rheumatica in the NVX arm and an event of coeliac disease in the placebo arm. In the post-crossover period, 8 additional PIMMCs were reported by 8 participants, all of which were reported in the post-crossover period, including rheumatoid arthritis and seizures (n=2 each); psoriatic arthropathy, systemic lupus erythematosus, scleroderma, and lichen planus (n=1 each). Only the event of scleroderma, reported 129 days after the last dose of NVX-CoV2373, was considered related by the investigator. This participant presented with myalgia and arthralgia and was diagnosed on the basis of laboratory testing.

Cumulatively, in all 26,106 participants who received NVX-CoV2373 in the pre- and post-crossover periods, rheumatoid arthritis was the most commonly reported PIMMC following NVX-CoV2373 (n=7). There was no specific trend of temporality, with time to onset of events at 1, 3, 11, 92, 106, 149, 286, and 299 days after the most recent dose of NVX-CoV2373. In the absence of a long-term placebo comparator, it is uncertain whether this represents an excess of

cases or the expected background rate of a common medical condition in the study population. Additionally, there were three events of uveitis/iridocyclitis with onset within 21 days of NVX-CoV2373, including one case of suspected TINU and one event that recurred upon re-challenge with Dose 2 of NVX-CoV2373. Although there was no imbalance in cases in the placebo-controlled pre-crossover period, FDA considers this cluster of similar events of uveitis with no potential alternative etiology, close temporal association to vaccination, and biologic plausibility for a potential autoimmune mechanism, to be possibly related to NVX-CoV2373. Surveillance for further evaluation of uveitis events would be conducted with deployment of the vaccine into larger populations.

In summary, there were overall few events of PIMMCs, no imbalances noted in the placebo-controlled period, with generally comparable types of events and time to onset. In the absence of a longer term, placebo-controlled safety data collection period, it is difficult to discern background rates of relatively common medical conditions (e.g., rheumatoid arthritis) from potentially immune-mediated events related to vaccination with a long latency. Some PIMMCs were reported in closer temporal association to vaccination and with no clear alternative etiology identified (including Bell's palsy and peripheral neuropathy), and for these events a relationship to NVX-CoV2373 cannot be definitively excluded. Other than events of uveitis described above, there was no pattern of events to suggest a specific causal association between vaccine and a particular autoimmune spectrum of disease.

Selected Safety Analyses

The following section includes analyses of medical concepts for which imbalances were identified as well as search results from selected broad and narrow Standardized MedDRA Queries (SMQs) using FDA-developed software to evaluate unsolicited adverse events of clinical interest by searching preferred terms (PTs) that could together represent various medical concepts.

Myocarditis/Pericarditis

Of particular interest were events of myocarditis and pericarditis. Postmarketing data from individuals receiving mRNA vaccines have demonstrated increased risks of myocarditis and pericarditis, particularly within 7 days following the second primary series dose. The observed risk has been highest in adolescent and young adult males. Available data from short-term follow-up suggest that most individuals have had resolution of symptoms, although information is not yet available about potential long-term sequelae. The Spike protein antigen can induce antibodies to SARS-CoV-2 spike glycoproteins that cross-react with myocardial contractile proteins, including myocardial α-myosin heavy chain (Vojdani and Kharrazian, 2020). It has been postulated that the effect of these antibodies, influenced by hormonal differences, immune–genetic background, age, and sex are potential mechanisms of myocardial injury associated with SARS-CoV-2 infection or COVID-19 vaccination (Heymans and Cooper, 2022).

Over the course of the clinical development program, events of myocarditis and pericarditis were identified from in multiple studies, as well as from the adolescent expansion substudy and booster dose substudy of 301. Therefore, an evaluation of cases of myocarditis and pericarditis was undertaken, incorporating data from across the clinical development program to provide the most robust assessment. Table 20 describes the 6 cases occurring after NVX-CoV2373 and 1 case occurring after placebo.

Table 20. Myocarditis and/or Pericarditis Cases (In Order of Time to Onset From Vaccination)

Study	Age/ Sex	Preferred Term	Dose Number, Days to Onset	Comments	Seriousness/Outcome	FDA Opinion
301	16/M	Myocarditis	NVX CO Dose 2, 2 days	Preceding nonspecific viral illness and concomitant methylphenidate use. (Peak troponin ~32,000 ng/L)	Serious event. Hospitalized 4 days and treated with IVIG. Event recovered/resolved.	Temporal relationship and lack of clear alternative etiology supports a concern for causal relationship to vaccine
302	19/M	Myocarditis	NVX Dose 2, 2 days	MRI consistent with myocarditis (peak troponin ~7,800 ng/L) Pharyngitis and lymphadenopathy 11 days later	Serious event. Hospitalized 5 days. Event resolved after approximately 1 month.	Temporal relationship and lack of clear alternative etiology supports a concern for causal relationship to vaccine
301	28/M	Non-ST elevation MI Initial report: atypical chest pain	NVX Booster, 3 days	Adverse event described as acute MI but myocarditis in differential, with chest pain and elevated troponin (~300 ng/L). Unclear rationale for diagnosis of non-ST-elevation myocardial infarction versus myocarditis. Cardiac MRI scheduled.	Serious event. Hospitalized 2 days. Event recovered/ resolved.	Temporal relationship and lack of clear alternative etiology supports a concern for causal relationship to vaccine
302	60/F	Pericarditis	NVX CO Dose 2, 8 days	With fever, elevated WCC and neutrophils, ECG consistent with pericarditis. Troponin normal.	Serious event. Hospitalized 2 days. Event recovered/ resolved.	Temporal relationship and lack of clear alternative etiology supports a concern for causal relationship to vaccine
301	20/M	Pericarditis and myocarditis	NVX CO Dose 1, 10 days	History of sore throat and fever 8 days prior to events, with exposure to streptococcal pharyngitis, and elevated anti streptolysin O titers. Troponin normal.	Non-serious event. Participant was not hospitalized. Second CO dose not administered. Participant lost to follow-up.	Although temporally related to vaccination, ARF and nonrheumatic streptococcal myocarditis are also plausible alternative etiologies.

Study	Age/ Sex	Preferred Term	Dose Number, Days to Onset	Comments	Seriousness/Outcome	FDA Opinion
301	67/M	Myocarditis	NVX Dose 1, 28 days	Concomitant COVID-19 infection and acute kidney injury. Maximum troponin: 5329 ng/L.	Serious event. Hospitalized for 5 days. Second NVX dose not administered. Event resolved with sequelae.	Relatively longer latency and diagnosis of COVID-19 support an alternative etiology, although association with vaccine cannot be definitively excluded.
301	31/F	Myocarditis	Placebo Dose 2, 72 days	Diarrhea and social history of alcohol intake. Maximum troponin 0.33 ng/mL (normal <0.04)	Serious event. Hospitalized for 2 days. Event recovered/resolved.	Long time to onset, unrelated to placebo vaccination

Source: EUA 28237 Amendment 20, May 2, 2022, Table 1.
Abbreviations: ARF=acute rheumatic fever; CO=crossover; COVID-19=coronavirus disease-2019; ECG=electrocardiogram; MI=myocardial infarction; NA=not applicable (non-serious event); NVX=NVX-CoV2373; WCC=white cell count.

In summary, the events of myocarditis/pericarditis are concerning for a causal association with NVX-CoV2373 for the following reasons: 1) five events were reported within 2 weeks of vaccination, 2) only 1 event had a clearly identified alternative etiology (COVID-19) strongly associated with myocarditis, and other events had only circumstantial evidence of potentially plausible alternative etiologies, and 3) four of the events occurred in young men, a subject population known to be at higher risk for mRNA COVID-19 vaccine-associated myocarditis. Additionally, identification of multiple potential vaccine-associated cases in a premarket safety database of ~40,000 vaccine recipients raises concern that if causally associated, the risk of myocarditis following NVX-CoV2373 could be higher than reported during post-authorization use of mRNA COVID-19 vaccines (for which no cases were identified in pre-authorization evaluation).

All Cardiac Events

In the pre-crossover period through September 27, 2021, the proportion of participants with adverse events in the Cardiac disorders SOC was comparable across the treatment arms (0.3% in each). Of the 76 events reported in the NVX-CoV2373 treatment arm, 40 (51%) were serious. Of the 34 events reported in the placebo arm, 17 (50%) were serious. The proportion of participants reporting each PT in the cardiac SOC was comparable across the treatment arms. A total of 10 fatal cardiac events were reported, including 4 (3 cardiac arrests and 1 myocardial infarction) in the placebo arm (0.04%) and 6 (5 cardiac arrests and 1 myocardial infarction) in the NVX arm (0.03%). The time to onset of the fatal events was 6, 7, 8, and 14 days after the last dose of placebo and 12, 21, 23, 40, 58, and 64 days after the last dose of NVX. For those events reported in both treatment arms, the time to onset of the events following the most recent dose of NVX-CoV2373 or placebo was comparable. A total of 3 fatal events in the NVX arm (arrhythmia, tachycardia, and sinus bradycardia) and 2 fatal events in the placebo arm (myocarditis and myocardial infarction) were considered related by the investigator.

A search for events with PTs consistent with the medical concept of myocardial infarction, myocarditis, and cardiac arrest yielded 17 events in the NVX arm (0.1%) and 11 events in the placebo arm (0.1%). The time to onset for the events in the placebo arm was within 30 days (n=8), 31-60 days (n=1), and 60-90 days (n=2). Of these events, 2 events in the placebo arm were considered related by the investigator (myocarditis and myocardial infarction). The time to onset for the events in the NVX arm was within 30 days (n=8), 31-60 days (n=5), and 61-90 days (n=2), and >91 days (n=2). The time to onset for the events in the placebo arm was 30 days (n=8), 31-60 days (n=1), and 61-90 days (n=2).

The following SMQs were also used to assess for imbalances across the treatment arms in the pre-crossover period: Ischemic heart disease, Cardiac failure, Cardiac arrhythmias, and Cardiomyopathy.

The proportion of participants with events retrieved using the SMQ Ischemic heart disease (broad and narrow) was comparable between the NVX-CoV2373 (0.1%) and placebo (0.1%) arms. Of the 16 events in the NVX arm, 4 (25%) had onset within 2 weeks of the most recent vaccination. Of the 8 events in the placebo arm, 6 (75%) had onset within about 2 weeks of vaccination. Serious adverse events with onset within 7 days of vaccination are described in detail in Section 6.2.5.7.

Table 21. Events from Standard MedDRA Query *Ischemic Heart Disease*, Pre-Crossover Period, Scope: Narrow + Broad, Safety Analysis Set, Study 301

MedDRA Preferred Term	NVX-CoV2373 N=19735	Placebo N=9847
Total, n (%)	15 (0.1)	7 (0.1)
Acute myocardial infarction, n (%)	2 (0.01)	4 (0.04)
Angina pectoris, n (%)	2 (0.01)	0 (0.00)
Coronary artery disease, n (%)	3 (0.02)	1 (0.01)
Myocardial infarction, n (%)	5 (0.03)	3 (0.03)
Acute coronary syndrome, n (%)	1 (0.01)	0 (0.00)
Coronary artery occlusion, n (%)	1 (0.01)	0 (0.00)
Stress cardiomyopathy, n (%)	1 (0.01)	0 (0.00)
Ischemic cardiomyopathy, n (%)	1 (0.01)	0 (0.00)

Source: Source: EUA 28237 Amendment 15, ADAE2 dataset generated using MAED.
Abbreviations: CI=confidence interval; SMQ=Standardized Medical Dictionary for Regulatory Activities Query.
n=number of subjects with indicated parameter; N=number of subjects in cohort.

The proportion of participants with events retrieved using the SMQ Cardiomyopathy (broad and narrow) was comparable between the NVX-CoV2373 (0.5%) and placebo (0.4%) arms. In general, the proportion of participants reporting each type of event was comparable across treatment groups. However, terms specific for events of cardiomyopathy or cardiac failure were reported by nine participants in the NVX arm (0.05%) compared to two participants in the placebo arm (0.02%). The time to onset was within ~2 weeks for 5 events (56%) in the NVX arm and within 2 weeks for 1 event (50%) in the placebo arm. Both events in the placebo arm and 6 of 9 events in the NVX arm were serious, and none of the events were considered related. All participants in the NVX arm with events of cardiomyopathy or cardiac failure had a history of previous cardiac disease, obesity, or other co-morbidities, with the exception of one participant with a non-serious event of stress cardiomyopathy who had no medical history reported.

The proportion of participants with events retrieved using the SMQ Cardiac failure (broad and narrow), was slightly higher in the NVX arm (0.2%) compared to the placebo arm (0.1%). However, terms specific for events of cardiac failure were reported by 8 participants in the NVX arm (0.04%) compared to 2 participants in the placebo arm (0.02%). The onset of the event reported in the placebo arm was 8 days post-Dose 2 of placebo. Of the 8 cases in the NVX arm, 6 occurred in participants with a history of congestive heart failure, 6 had time to onset within 21 days of the most recent NVX-CoV2373 dose, 6 were serious, and none were considered related. All participants had co-morbidities, including obesity.

The proportion of participants with events retrieved using the SMQ Cardiac arrythmia (broad and narrow) was comparable between the NVX-CoV2373 (0.3%) and placebo (0.3%) arms. Events of atrial fibrillation heart rate increased were reported by a slightly higher proportion of participants in the NVX arm compared to the placebo arm, although the differences were small and most events of atrial fibrillation were >2 weeks following vaccination and most events of heart rate increased were the day of or shortly following vaccination, which may reflect reactogenicity.

In the post-crossover period through September 27, 2021, a total of 53/21,714 (0.2%) participants who received NVX-CoV2373 either in the pre-or post-crossover period experienced adverse events in the SOC Cardiac disorders. Of the 61 events, 40 (66%) were serious, including 3 fatal events (1 event each of cardiac arrest and myocardial infarction, and 1 event of

alcoholic cardiomyopathy). The time to onset of the fatal events from the most recent NVX-CoV2373 dose was 8 days for an event of cardiac arrest and >80 days for the remaining events. Three events (myocarditis, pericarditis, and bradycardia) were considered related by the investigator. Although the arm that crossed over to receive placebo is not a true comparator, given the previous exposure to NVX-CoV2373, imbalances during the post-crossover period that may reflect short-term risk interval windows were assessed. A total of 6/6,416 (0.1%) participants who crossed over to receive NVX-CoV2373 experienced events consistent with myocardial infarction compared to 7/15,298 (0.05%) participants who crossed over to receive placebo. Events in the arm that crossed over to NVX-CoV2373 had time to onset of <30 days (n=3), 31-60 days (n=1), and >90 days (n=2), compared to events in the arm that crossed over to receive placebo, which had time to onset of <30 days (n=4), 31-60 days (n=2), and >90 days (n=1), relative to the most recent placebo dose. The time to onset is comparably distributed across the treatment arms, suggesting that there is no increase in events occurring in the risk window immediately following vaccination; however, varying lengths of follow up post-crossover may limit a full assessment of temporal clustering.

A review of cases retrieved using the SMQs Ischemic heart disease, Cardiac failure, Cardiac arrhythmias, and Cardiomyopathy did not reveal additional imbalances between participants who crossed over to receive NVX-CoV2373 or placebo.

Additional data provided at FDA's request in a dataset with a cutoff date of February 17, 2022, was used to assess additionally accrued AEs of cardiac events in the post-crossover period. An imbalance in the proportion of participants was observed for the terms of acute myocardial infarction (n=6/6,146, 0.09% in participants crossed over to NVX-CoV-2373 and n=4/15,298, 0.03% in participants crossed over to placebo) and coronary artery disease (n=5/6,146, 0.08% in participants crossed over to NVX-CoV-2373 and n=1/15,298, 0.01% in participants crossed over to placebo). In aggregate, terms associated with myocardial infarction were reported by 18/6,146 (0.3%) participants who crossed over to receive NVX-CoV2373 compared to 19/15,298 (0.1%) of participants who crossed over to receive placebo. The time to onset was comparably distributed among the treatment arms, as described above.

The February 17, 2022, updated data reflected a cumulative total of 48 participants who received NVX-CoV2373 in the pre- or post-crossover period (n=26,106) and reported events consistent with the medical concept of myocardial infarction (n=37), myocarditis (n=3), pericarditis (n=1), and cardiac arrest (n=7). To assess for potential long-term cardiac events, events consistent with the medical concept of cardiomyopathy and cardiac failure were analyzed. A total of 22 participants reported 27 AEs, none of which were considered related, without temporal clustering noted. With the exception of stress cardiomyopathy, all participants with these events had risk factors for cardiac disease (e.g., obesity, pre-existing heart disease).

In summary, numerical imbalances were noted between the treatment arms with respect to events of cardiac failure and cardiomyopathy, including some events in close temporal proximity to vaccination. Cardiac events, including fatal events of cardiac arrest and myocardial infarction, were reported with close temporal relationship to NVX-CoV2373; however, the proportions of participants with fatal, serious, and ischemic cardiac events were generally balanced across the treatment arms for the blinded pre-crossover period, with comparable times to onset.

As discussed in the Deaths section below, there was little to no information available on many of the cardiac deaths, precluding a full assessment of causality. Although it is possible that some cardiac events, including fatal events, were severe manifestations of undiagnosed myocarditis (see below), there is comparability across treatment arms in aggregate analyses of the type, severity, and temporality of cardiac events. Additionally, attribution of causality in many of the cardiac events is confounded by the presence of pre-existing conditions and risk factors.

Anaphylactic Reaction

In the pre-crossover period through September 27, 2021, the proportion of participants with adverse events retrieved using the algorithmic SMQ Anaphylaxis was higher in the placebo arm (0.02%) compared to the NVX arm (0.01%), and all events were either rash, asthma or cough. The proportion of participants with AEs retrieved using the SMQ Anaphylactic Reaction (broad) was slightly higher in the NVX arm (1.4%) compared to the placebo arm (1.2%). Events representing potential allergic reactions to vaccine included two events of angioedema (one serious and one mild non-serious), both considered related by the investigator, and with onset 2- and 5-days post-Dose 1, respectively. The event of angioedema is described further in Table 23. An additional Grade 3 non-serious event of allergy to vaccine considered related by the investigator with onset 2 days post-Dose 2 of NVX-CoV2373 was reported. No adverse events of anaphylaxis were reported.

FDA considers the event of serious angioedema to be potentially related to vaccine, although confounded by concomitant use of an antibiotic. There is insufficient detail on the remaining case of angioedema and allergy to vaccine to assess causality.

Hypertension

Due to 3 SAEs of hypertension (hypertensive crisis, hypertensive emergency, and hypertensive urgency) reported in the NVX arm, the SMQ Hypertension was used to assess for imbalances in events of hypertension in the treatment arms. In the pre-crossover period through September 27, 2021, the proportion of participants with adverse events retrieved using the SMQ Hypertension (narrow and broad) was comparable in the NVX and placebo arms (0.6% in each). Of the 111 events in the NVX arm, 29 (26%) had onset within 3 days of vaccination. Five events were considered serious (including hypertension [n=2] hypertensive crisis, hypertensive emergency, and hypertensive urgency). The time to onset for serious events in the NVX arm ranged from 11 to 90 days following the most recent dose of NVX. Of the 111 events in the NVX arm, 29 (26%) had onset within 3 days of vaccination. Nine events in the NVX arm (all non-serious) were considered related by the investigator, with time to onset ranging from 1 to 28 days following the most recent dose of NVX. In the placebo arm, 3 events were considered related by the investigator, 1 event was serious, and 10 (17%) had onset within 3 days of vaccination. The SMQ Hypertension (broad) was used to retrieve events with onset through 3 and 7 days, and no imbalances were observed at these time points. The majority of the participants in the NVX-CoV2373 and placebo arms with new onset hypertension were older and/or had obesity as a comorbidity.

In the post-crossover period through September 27, 2021, the proportion of participants reported events in the SMQ Hypertension (narrow and broad) was comparable between participants who crossed over to receive NVX-CoV2373 or placebo (0.2% in each). Events with onset within 3 days of the most recent dose were reported by a higher proportion of participants who crossed over to receive placebo.

No pattern of severity, relatedness, or temporality was identified to suggest a possible association of NVX-CoV2373 with hypertensive events.

Biliary Events

Due to an observed imbalance in biliary events (specifically cholecystitis and cholelithiasis) observed in the pre-crossover period, the SMQ Biliary disorders was used to further analyze these events. Through September 27, 2021, the proportion of participants with events retrieved using this SMQ was higher in the NVX arm (0.08%) compared to the placebo arm (0.04%) in the pre-crossover period. Events of cholecystitis (including acute and chronic) were reported by 10 participants (0.05%) in the NVX arm compared to 1 participant in the placebo arm (0.01%). None of the events were considered related by the investigator. All of the events were serious, with the exception of one non-serious event in the NVX arm. Of the 10 events in the NVX arm, four (40%) had onset within ~2 weeks of the most recent vaccination; the event in the placebo arm occurred 84 days after the last placebo dose. The remaining events in the NVX arm had time to onset ranging from 25 to 117 days. Most participants with these events were female, obese, and/or had a history of cholelithiasis.

Events of cholelithiasis were reported by 7 participants (0.04%) in the NVX arm compared to 2 participants in the placebo arm (0.02%). Two events in the NVX arm were serious, and the remaining events were non-serious; none were considered related by the investigator. In the NVX arm, the time to onset was within 30 days of the most recent vaccination in five events, with onset at 52 and 63 days for the remaining events. The events in the placebo arm occurred at 9 and 30 days after the most recent placebo dose.

In the post-crossover period through September 27, 2021, the proportion of participants with events retrieved using the SMQ Biliary disorders was higher in the NVX arm (0.14%) compared to the placebo arm (0.03%). Events of cholecystitis (including acute and chronic) were reported by 8 participants (0.1%) who crossed over to receive NVX arm compared to 3 participants who crossed over to receive placebo (0.02%). One event of chronic cholecystitis was considered related by the investigator, with onset 25 days post-Dose 2 of NVX-CoV2373. All events in both arms were serious. The time to onset following crossover placebo doses was 4, 47, and 87 days after the most recent dose, and time to onset following crossover NVX-CoV2373 doses was 21 to 130 days, with 2 events within 30 days of vaccination. Events of cholelithiasis were reported by one participant who crossed over to receive NVX-CoV2373 115 days post-crossover Dose 2 and two participants who crossed over to receive placebo at 9 and 25 days after the last dose of placebo. All 11 participants with cholecystitis events had underlying risk factors for cholelithiasis, including overweight/obesity and biliary dyskinesia.

Cumulatively, through the February 17, 2022, data extraction date, a total of 38 of the 26,106 participants (0.1%) who received NVX-CoV2373 in the pre- or post-crossover periods reported events consistent with cholelithiasis and cholecystitis, and 24 of these events were cholecystitis.

Although small imbalances in events of cholelithiasis were seen in the pre-crossover placebo-controlled period of the study, there is no clear biologically plausible mechanism to support a causal association, and the temporal pattern of events was similar in both treatment arms. An imbalance in cholecystitis events was noted in both the pre- and post-crossover period, with some clustering of events in temporal relationship to vaccination in participants with risk factors for gallstones. The available data do not allow for a conclusion of a causal relationship, nor do they allow for a definitive conclusion against the vaccine as a contributing factor. Surveillance

for further evaluation of hepatobiliary events would be conducted with deployment of the vaccine into larger populations.

Neurovascular Events

In the pre-crossover period through September 27, 2021, the proportion of participants with adverse events retrieved using the SMQ Central nervous system disorders (broad) were comparable across the treatment arms. However, an imbalance was observed in the proportion of participants with adverse events consistent with the clinical concept of stroke in the NVX arm (n=11; 0.06%) compared to the placebo arm (n=2; 0.02%). Events in the NVX arm included cerebrovascular accident (CVA; n=7), ischemic stroke (n=1), cerebral infarction (n=1), and transient ischemic attack (n=2) and occurred in individuals between the ages of 49 and 74 years. One event of CVA was reported after a subject withdrew from the study but was recorded; this case is included in this analysis for completeness. One event of CVA 49 days after the most recent NVX-CoV2373 was fatal. The range of time to onset for the remaining events was between 11 and 84 days, including 3 events within 15 days of the most recent dose of NVX-CoV2373, 5 events between 32 and 49 days of the most recent dose of NVX-CoV2373, and 3 events occurring 77 days or more following the most recent dose of NVX-CoV2373. Of the 11 participants, 2 had potential alternative etiologies, including 1 participant with atrial fibrillation and a computed tomography angiography (CTA) with/without contrast of the head that was negative for stroke and one participant who was admitted with stroke-like symptoms but discharged home without intervention with a referral to neurology for a “pinched nerve.” With one exception, all participants had co-morbidities that may have increased the risk of stroke (e.g., hypertension, obesity). Events in the placebo arm included cerebellar infarction and transient ischemic attack and occurred in participants 61 and 58 years of age, respectively, at 9 and 14 days after the most recent dose of placebo.

In the post-crossover period through September 27, 2021, the proportion of participants with adverse events retrieved using the SMQ Central nervous system disorders (broad) was higher in the participants who crossed over to receive placebo. A total of 5 participants who crossed over to receive placebo experienced adverse events consistent with the clinical concept of stroke, including transient ischemic attack (n=3), ischemic stroke, and CVA. These events occurred in participants 35 to 79 years of age, most of whom had co-morbidities that may have increased the risk of stroke (e.g., elderly, obesity). The range of time to onset was between 74 and 155 days following the most recent dose of NVX-CoV2373, with 3 of the 5 events occurring >140 days following vaccination.

Additional safety data provided at FDA’s request with a data extraction date of February 17, 2022, added 1 event of CVA each in the NVX-CoV2373 and placebo arms in the pre-crossover period, with time to onset of 319 and 267 days following the most recent vaccination, respectively. In the post-crossover period, an additional 2 events were reported, including CVA and transient ischemic attack, with time to onset 142 and 299 days after the most recent dose of NVX-CoV2373, respectively. Cumulatively, a total of 19 events were reported following NVX-CoV2373 in the pre- and post-crossover periods (n=26,106), with time to onset <30 days (n=3), 31-60 days (n=5), 61- 90 days (n=4), 90-120 days (n=1), and >121 days (n=6). The outcome of these events was recovered with sequelae (n=6), recovered or recovering (n=11), and fatal (n=2, events with onset 155- and 49-days post-Dose 2 of NVX).

Assessment of the numerical imbalance in the pre-crossover period is confounded by the presence of risk factors in the individual participants, the observation of events in close temporal relationship to vaccination in both treatment arms, and no clear pattern in the time to onset of

events to suggest a specific pathophysiologic mechanism for a causal relationship to NVX-CoV2373. It is notable that several neurovascular events were associated with arterial wall defects, including two strokes associated with arterial dissections, including the carotid and right vertebral artery, one stroke with a possible dissection noted on imaging, and a fatal event of a traumatic rupture of a vertebral artery aneurysm (not included above as a stroke case).

As noted previously, surveillance for further evaluation of thromboembolic and neurovascular events would be conducted with deployment of the vaccine into larger populations.

Guillain-Barre Syndrome/Neuropathy

As discussed in Section 7, 1 participant in Study 302 reported an event consistent with Guillain-Barre syndrome (GBS). No events of GBS were reported in Study 301; however, the SMQs Guillain-Barre syndrome, Peripheral neuropathy, and Demyelination were used to identify potential cases. In the pre-crossover period through September 27, 2021, the proportions of participants reporting events retrieved using the SMQs Guillain Barre syndrome and Peripheral neuropathy were comparable between the NVX-CoV2373 (0.2%) and placebo (0.3%) arms. No imbalances in specific event terms were noted. No events were retrieved using the SMQ Demyelination.

Events consistent with the medical concept of radiculopathy, neuropathy, or neuropathic pain were reported by 27 participants in the NVX arm (0.1%) and 15 participants in the placebo arm (0.2%). There were no imbalances across the treatment arms with regard to each specific event. All of the events had onset within 26 days of the last NVX-CoV2373 or placebo dose; the time to onset was within 7 days of the most recent dose for 9 events (60%) in the placebo arm and 20 events (71%) in the NVX arm.

In the post-crossover period through September 27, 2021, the proportion of participants reporting events retrieved using the Guillain Barre syndrome SMQ was comparable between participants who crossed over to receive placebo (0.3%) or NVX-CoV2373 (0.2%). No imbalances in specific event terms were noted. The proportion of participants reporting events retrieved using Peripheral neuropathy SMQ was numerically higher in participants who crossed over to receive NVX-CoV2373 (0.09%) compared to participants who crossed over to receive placebo (0.05%). Only 1 event was retrieved using the Demyelination SMQ, in a participant who crossed over to receive placebo.

Events consistent with the medical concept of radiculopathy, neuropathy, or neuropathic pain were reported by 6 participants who crossed over to receive placebo (0.04%) and 3 who crossed over to receive NVX-CoV2373 (0.05%). The time to onset of events relative to the last dose of NVX-CoV2373 (either in the pre- or post-crossover period) was >60 days for 6 events and 1, 4, and 22 days for the remaining events. Two events of clinical interest were reported, including immune-mediated neuropathy and neuralgic amyotrophy. The event of immune-mediated neuropathy was reported 68 days post-Dose 2 of NVX-CoV2373 in a 33-year old woman. Neurologic symptoms included tingling in the right arm and leg and weakness in the right arm. This event was considered related to vaccination by the investigator, and the participant was discontinued from vaccination. There is insufficient information to inform a causality assessment and the rationale for the diagnosis of immune-mediated neuropathy is not provided. The event of neuralgic amyotrophy (Parsonage-Turner syndrome) in a 57-year old male participant with a history of right upper extremity Parsonage Turner syndrome (2008-2009) and right frozen shoulder was severe and considered related by the investigator. Four days after the first post-crossover dose of NVX-CoV2373 administered into the right arm, the participant

reported neck and left arm pain which subsequently resolved but then recurred 6 weeks later. A magnetic resonance imaging (MRI) scan of the cervical spine showed progressive multilevel degenerative disc disease, spinal stenosis, and left and right foraminal stenosis. Subsequent workup approximately 3 months after the initial presentation included an electromyogram which suggested branchial neuritis and an MRI of the left brachial plexus which was compatible with mild acute or chronic brachial plexopathy. This event was ongoing at the time of the report. The prior history of Parsonage-Turner syndrome and vaccination into the contralateral arm suggest a plausible alternative etiology.

Additional data provided at FDA's request in a dataset with extraction date of February 17, 2022, did not identify any additional participants diagnosed with GBS.

Embolic and Thrombotic Events

In the context of neurovascular and cardiac events described above, assessment of thrombotic and embolic events was performed using the SMQ Embolic and Thrombotic Events to retrieve cases.

In the pre-crossover period through September 27, 2021, the proportion of participants with adverse events retrieved using the SMQ Embolic and Thrombotic Events (broad) was comparable between the NVX arm (0.16%) and the placebo arm (0.14%). The proportion of participants with each event in the SMQ was comparable with the exception of an imbalance with respect to neurovascular events as described in detail above. Excluding cardiac and neurovascular events, a total of 11 participants in the NVX arm (0.06%) reported thrombotic and embolic events, including pulmonary embolism (n=4), deep vein thrombosis (n=3), thrombosis (n=2), mesenteric artery thrombosis, and peripheral arterial occlusive disease (n=1 each). A total of six participants in the placebo arm (0.06%) reported events, including pulmonary embolism (n=2), deep vein thrombosis, embolism, peripheral arterial occlusive disease, and catheter site thrombosis (n=1 each). None of the events were considered related by the investigator. These events are summarized in Table 22.

Table 22. Non-Cardiac/Non-Neurovascular Embolic and Thrombotic Events Pre-Crossover Through September 27, 2021, Safety Analysis Set, Study 301

Pre-Crossover Treatment	Age/ Sex	Preferred Term	Risk Factors	Serious	Time to Onset (Days)	Comment
Placebo	72/F	Pulmonary embolism	Hypertension, obesity, diabetes mellitus	Yes	16 PD 1	Concomitant COVID-19
Placebo	59/M	Pulmonary embolism and deep vein thrombosis	Coronary artery disease, myocardial infarction, obesity	Yes	30 PD 2	Prolonged inactivity prior to events
Placebo	62/M	Catheter site thrombosis	Hypertension and sacral osteomyelitis	Yes	32 PD 2	Peripherally inserted central catheter clot
Placebo	57/F	Embolism	Breast cancer, obesity	Yes	74 PD 1	Limited information available on site of thrombus
Placebo	75/M	Peripheral arterial occlusive disease	Peripheral arterial disease, diabetes mellitus, hypertension, coronary artery disease	Yes	74 PD 2	Occlusion of prior fem-fem graft
NVX-CoV2373	83/M	Pulmonary embolism and Deep vein thrombosis	Myocardial infarction, chronic bilateral lower extremity DVT with inferior vena cava filter placement, hypertension, Type 2 diabetes mellitus, morbid obesity, chronic obstructive pulmonary disease, Alzheimer's disease, and dyslipidemia	Yes	3 PD 1	Computed tomography angiography of the chest with contrast showed right lower lobar and segmental pulmonary emboli, duplex ultrasound of the bilateral lower extremities showed bilateral DVTs, and echocardiogram revealed an ejection fraction of 35-45% and severely dilated left atrium. Acute on chronic decompensated systolic congestive heart failure exacerbation, acute respiratory failure, and pulmonary embolism were diagnosed. presented with respiratory distress and peripheral edema 2 days post-Dose 1 of NVX-CoV2373. The platelet count was 134 x 10^3/µL.
NVX-CoV2373	54/M	Pulmonary embolism	Primary thrombophilia, recurrent DVT left leg and recurrent pulmonary embolism, morbid obesity, lower extremity stent placement	Yes	5 PD 1	Presented with left leg and hip pain and diagnosed with deep vein thrombosis and pulmonary embolism.

Pre-Crossover Treatment	Age/ Sex	Preferred Term	Risk Factors	Serious	Time to Onset (Days)	Comment
NVX-CoV2373	65/M	Mesenteric artery thrombosis	Admitted with perforated appendicitis and non-occlusive thrombus in superior mesenteric artery noted on CT scan	No	13 PD 1	Unclear whether the clot was pre-existing, related to acute abdominal infection, or spontaneous and coincidental
NVX-CoV2373	59/M	Deep vein thrombosis	Alcohol abuse, deep vein thrombosis, drug abuse, hyperlipidemia, hypertension, obesity, diabetes mellitus	No	15 PD 1	No narrative available
NVX-CoV2373	61/M	Peripheral arterial occlusive disease	Morbid obesity	No	15 PD 2	No narrative available
NVX-CoV2373	58/M	Thrombosis	Hypertension, overweight	No	16 PD 1	No narrative available
NVX-CoV2373	71/F	Pulmonary embolism	Deep vein thrombosis, obesity	Yes	20 PD 1	COVID-19 11 days prior to onset provides plausible alternative etiology
NVX-CoV2373	58/M	Thrombosis	Atrial fibrillation	No	29 PD 2	Blood clot in knee, no narrative available
NVX-CoV2373	60/F	Deep vein thrombosis	Obesity	No	59 PD 2	No narrative available
NVX-CoV2373	42/F	Pulmonary embolism	Cerebral venous sinus thrombosis, obesity	Yes	152 PD 2	Deep vein thrombosis also present

Source: FDA-generated analysis from September 27, 2021, ADAE dataset.
Abbreviations: COVID-19=coronavirus disease-2019; CT=computed tomography; DVT=deep vein thrombosis; F=female; M=male; PD=post-dose.

A total of 7 participants in the NVX arm experienced thrombotic/embolic events within 21 days of the most recent NVX-CoV2373 dose, two of whom had plausible alternative etiologies (appendicitis and COVID-19). Only one participant in the placebo arm had onset of thrombotic/embolic events within 21 days of the most recent dose, with a clear alternative etiology of COVID-19.

In the post-crossover period through September 27, 2021, a total of 9 participants who crossed over to receive placebo (0.06%) reported ten non-cardiac, non-neurovascular events in the SMQ Embolic and Thrombotic Events, including pulmonary embolism (n=5), deep vein thrombosis (n=3), and peripheral arterial disease (n=2), 6 of which had onset within 2 weeks following the most recent crossover placebo dose (onset was 60 days or more following NVX-CoV0373 administered in the pre-crossover period). None of these events was considered related by the investigator. A total of 4 participants who crossed over to receive NVX-CoV0373 (0.06%) reported 4 events in the SMQ Embolic and Thrombotic Events, including pulmonary embolism (n=3) and portal vein thrombosis. Two events of pulmonary embolism (one of which was considered related by the investigator) and the event of portal vein thrombosis all had onset within 9 days of NVX-CoV2373, and the remaining event of pulmonary embolism occurred 110 days after NVX-CoV2373. The events of pulmonary embolism occurred in participants with risk factors (e.g., use of concomitant estrogen in one participant, obesity) at 7 and 9 days after the second crossover dose of NVX-CoV2373. The event of portal vein thrombosis was reported by a 77-year-old male with a history of hyperlipidemia, hypertension, allergies to influenza and pneumococcal vaccine, and transient ischemic attack who presented with ongoing fever and anemia (hemoglobin decreased to 9.5 g/dL from 14.0 g/dL), mildly elevated transaminases and bilirubin 9 days after the second post-crossover dose of NVX-CoV2373. A diagnosis of systemic inflammatory response was made. A right upper quadrant ultrasound showed hepatic steatosis versus fibrosis and hepatic cysts. It was reported that the systemic inflammatory response syndrome was likely secondary to bacterial versus rickettsial infection, although diagnostic testing did not reveal an etiology. Additional diagnoses during this stay included pan-diverticulosis, portal vein thrombosis, melena due to suspected gastrointestinal bleed (resolved), microcytic anemia due to suspected gastrointestinal bleed. There was an improvement in transaminitis over the course of the hospitalization and the participant was discharged home with anticoagulation. Attribution of causality for the event of portal vein thrombosis in this case is confounded by a lack of information on the presence of underlying hepatic disease or assessment of chronic versus acute portal vein thrombosis, as well as no clear alternative infectious etiology for the presenting complaint of fever.

Cumulatively, through the data extraction date of February 17, 2022, a total of 83 of the 26,106 participants (0.3%) who received NVX-CoV2373 in the pre-or post-crossover period reported events captured by the SMQ Embolic and Thrombotic Events (narrow and broad). The most commonly reported events included events consistent with stroke (n=19; 0.1%), pulmonary embolism (n=18, 0.1%), myocardial infarction/acute myocardial infarction (n=24, 0.1%), and deep vein thrombosis (n=11, 0.05%). An imbalance in events of pulmonary embolism was noted for the post-crossover period (0.1% of participants who crossed over to receive NVX compared to 0.05% of participants who crossed over to receive placebo). However, most events in both treatment arms had onset >90 days following the most recent dose, and the proportion of events with onset <2 weeks was comparable.

For non-cardiac, non-neurovascular events (Table 22), the proportion of participants with thrombotic and embolic events was comparable across treatment arms in the pre-crossover period; however, a close temporal relationship to vaccine was more commonly observed

following doses of NVX-CoV2373 compared to placebo. Attribution of causality is confounded by the presence of the pre-existing conditions and risk factors. As such, data at this time are insufficient to conclude a causal relationship between the vaccine and thromboembolic events. As noted previously, surveillance for further evaluation of thromboembolic events, including cardiac and neurovascular events, would be conducted with deployment of the vaccine into larger populations.

6.2.5.5 Medically Attended Adverse Events

In the pre-crossover period through September 27, 2021, the proportions of participants reporting MAAEs and related MAAEs was comparable across the treatment arms (5.8% and 0.5%, respectively, in the NVX arm and 5.7% and 0.3%, respectively, in the placebo arm). In the pre-crossover period, the proportion of participants reporting each MAAE was comparable across the treatment arms, and no specific preferred term was reported by more than 0.3% of participants in the NVX arm. The highest risk difference between treatment groups was for the events of vertigo (0.07% in the NVX arm and 0.01% in the placebo arm) and oropharyngeal pain (0.07% in the NVX arm and 0.01% in the placebo arm). There were no trends in the pre-crossover MAAE data that were not identified in review of the unsolicited safety data.

In the post-crossover period through September 27, 2021, the proportions of participants reporting MAAEs and related MAAEs was comparable across the treatment arms (4.7% and 0.3%, respectively, in the NVX arm and 4.0% and 0.2%, respectively, in the placebo arm). Excluding cases of COVID-19 and COVID-19 pneumonia, the highest risk difference between treatment groups was for the events of depression (0.1% in the participants who crossed over to receive NVX-CoV2373 and 0.06% in the participants who crossed over to receive placebo) and urinary tract infection (0.2% in the participants who crossed over to receive NVX-CoV2373 and 0.1% in the participants who crossed over to receive placebo). There were no trends in the post-crossover MAAE data that were not identified in review of the unsolicited safety data.

Through February 17, 2022, the proportions of participants reporting MAAEs and related MAAEs was comparable across the treatment arms in the pre-crossover period (6.1% and 0.5%, respectively, in the NVX arm and 5.9% and 0.3%, respectively, in the placebo arm) and the post-crossover period (6.2% and 0.4%, respectively, in participants who crossed over to NVX and 5.5% and 0.2%, respectively, in participants who crossed over to placebo). There were no trends in the additional or cumulative pre- and post-crossover MAAE data that were not already identified in review of the overall unsolicited adverse events.

6.2.5.7 Serious Adverse Events (Pre-Crossover)

Deaths

As of September 27, 2021, 11 (<0.1%) participants in the NVX arm and 5 (<0.1%) participants in the placebo arm died in the pre-crossover period. One death in the placebo arm (myocardial infarction) was assessed by the investigator as related to trial vaccine, and no deaths in the NVX arm were assessed by the Sponsor as related to trial vaccine.

Deaths in the NVX arm included cardiac arrest (n=5), myocardial infarction, toxicity to various agents, accidental overdose, cerebrovascular accident (CVA), gunshot wound, and septic shock. Deaths in the placebo arm included cardiac arrest (n=3), myocardial infarction, and COVID-19 pneumonia.

Of the 11 deaths in the NVX arm, 4 had a clear alternative etiology, including toxicity to various agents (cocaine, fentanyl, and heroin intoxication), accidental overdose (alcohol and prescription drugs), gunshot wound to the head, and septic shock (pneumonia and blood cultures positive for *Streptococcus pneumoniae*). Details of the remaining 7 deaths are as follows:

- A 75-year-old female with a history of hypertension experienced a fatal CVA 48 days following the second dose of NVX-CoV2373. Imaging showed middle cerebral artery and intracranial internal carotid artery occlusion with large infarct. Chest X-ray showed bibasilar pneumonia with pulmonary edema. Following thrombectomy, repeat imaging revealed hemorrhagic conversion of ischemic CVA. Despite a right decompressive craniotomy, the events were fatal. Although no clear alternative etiology is identified for this CVA, this participant had several risk factors for CVA, including her age and a history of hypertension. Additionally, the concomitant pneumonia could be a contributing factor to an increased risk of stroke. The temporal distance from the most recent vaccination (>45 days) make a causative association with NVX-CoV2373 unlikely and the Sponsor and investigator's assessment that the CVA is not related is reasonable.
- A total of 5 cardiac arrests were reported (0.03% of participants). The time to onset for each event was between 12 and 58 days following the most recent NVX-CoV2373 dose. Fatal adverse events of cardiac arrest were reported 12 and 21 days after the first NVX-CoV2373 dose in a 44-year-old female and a 66-year-old male, respectively, both of whom were found pulseless and unable to be resuscitated. The 3 remaining fatal events of cardiac arrest occurred 23-, 40-, and 58-days post-Dose 2, respectively, in participants 39-, 50-, and 45-years of age, respectively. No autopsy data were available for any of these participants. Of the 5 participants with fatal cardiac arrest, 4 had co-morbidities as well as histories of substance use, including cocaine, methamphetamine, and alcohol, and 1 death was attributed to a suspected drug overdose. There was no medical history available for the remaining participant. Most participants with fatal cardiac arrests had underlying conditions that are risk factors for cardiac arrest; however, there is limited information available to assess the cause of death as autopsy data were not available. At this time, there is insufficient information to assess for causality to NVX-CoV2373 and in FDA's assessment vaccination cannot be definitively excluded as a contributory factor. While some of the fatal events occurred within several weeks of vaccination, there were 3 similar events of cardiac arrest on Day 6, 8, and 14 post-Dose 1 in the placebo arm (0.03%), which suggests that the cases in the NVX arm may reflect background rates of cardiac arrests in the study population, unrelated to vaccination. Please see Section 6.2.5.4 for additional discussion of cardiac events.
- A 79-year-old female with a history of hypertension, hyperlipidemia, sleep apnea, and obesity (BMI=43.4 kg/m^2) experienced a fatal myocardial infarction 64 days following the second dose of NVX-CoV2373. This participant's age and co-morbidities are significant risk factors for myocardial infarction. In the context of these risk factors and temporal distance from vaccination (>2 months), the Sponsor and investigator's assessment that the event is not related is reasonable.

In summary, there are no deaths that appear to be clearly causally related to vaccine; fatal events were generally balanced across the treatment arms with respect to time to onset and number of cardiac-related events. However, the lack of autopsy information for multiple fatal events of cardiac arrest following NVX-CoV2373 limits assessments of causality. Please see Section 6.2.5.4 for additional discussion of cardiac events.

Serious Adverse Events

In the pre-crossover period through September 27, 2021, SAEs were reported by 199/19,735 participants (1.0%) in the NVX arm and 108/9,847 participants in the placebo arm (1.1%). Related SAEs were reported by five participants in the NVX arm (<0.1%) and three participants in the placebo arm. In individuals 18 to <65 years of age, SAEs were reported by 150/17,255 (0.9%) participants in the NVX arm and 85/8,612 (1.0%) participants in the placebo arm. In individuals ≥65 years of age, SAEs were reported by 50/2,480 (2.0%) participants in the NVX arm and 23/1,235 (1.9%) participants in the placebo arm.

In the pre-crossover period through September 27, 2021, the relative difference in the proportions of participants in each treatment arm with specific serious preferred terms was small (maximum relative difference per hundred= 0.03). SAEs reported by 4 or more participants in the NVX arm included atrial fibrillation and acute kidney injury (n=8 [<0.1%]); cerebrovascular accident (n=7 [<0.1%]); cholecystitis acute, appendicitis (n=6 each [<0.1%]); COVID-19, cardiac arrest, prostate cancer, myocardial infarction (n=5 [<0.1%] each); pneumonia, pulmonary embolism, pneumonia aspiration, and depression (n=4 each [<0.1%]). One event each of myocardial infarction, cerebrovascular accident, and acute kidney injury were recorded with onset dates subsequent to withdrawal of the participant from the study; however, these are included in the case counts for the purposes of completeness.

The most common SAEs occurring at higher rates in the NVX arm than the placebo arm were cerebrovascular accident and cholecystitis acute (0.04% in vaccine group, 7 cases vs. 0 cases in placebo arm); and atrial fibrillation (0.04% in vaccine group, 8 cases vs. 2 cases in placebo arm); and pneumonia aspiration and spontaneous abortion (0.02% in vaccine group, 4 cases vs. 0 cases in placebo arm). The small numbers of cases of spontaneous abortion and pneumonia aspiration do not suggest a causal relationship. The most common SAEs occurring at higher rates in the placebo arm than the NVX arm included COVID-19 pneumonia (1% and 0.1%, respectively), COVID-19 (0.03% and 0.06%, respectively), and suicidal ideation (0.04% and 0.01%, respectively).

A total of 5 participants in the NVX arm (0.03%) and 3 participants in the placebo arm (0.03%) experienced SAEs that were considered related by the investigator. Of the SAEs in the NVX arm, three were considered not related by the Sponsor, including events of headache, Basedow's disease, and thrombocytopenia. These related SAEs are summarized in Table 23.

Table 23. Serious Adverse Events Considered Related by Investigator in the Pre-Crossover Period, Safety Analysis Set, Study 301

Investigational Product	Serious Adverse Event	Onset (Days After Vaccination)[1]	Demographics/Risk Factors	Resolution	Related (Per Novavax)
NVX-CoV2373	Headache	Day 45 (PD2)	53/F History of migraines	Recovered/ Resolved	No
NVX-CoV2373	Angioedema	Day 5 (PD1)	32/F History of penicillin allergy. Urticarial eruption which progressed the following day to diffuse rash with swelling of lower lips, tongue, and periorbital area. Resolved following treatment with epinephrine, dexamethasone, diphenhydramine, and famotidine. Concurrent urinary tract infection, concomitant medication Macrobid	Recovered/ Resolved	Yes
NVX-CoV2373	Basedow's disease	Day 29 (PD2)	39/F Baseline serum, prior to vaccination, positive for elevated thyroid stimulating immunoglobin	Not recovered/ Not resolved	No
NVX-CoV2373	Thrombocytopenia	Day 32 (PD2)	63/M Hypertension, concomitant use of losartan. Laboratory testing positive for Losartan immunoglobin G platelet antibody	Recovering/ Resolving	No
NVX-CoV2373	Nervous system disorder	Day 2 (PD2)	55/M Unilateral distal left lower extremity (LLE) peripheral neuropathy, acute left peroneal nerve palsy, and acute left foot drop. Recent physical assault and alcohol intoxication.	Recovering/ Resolving	Yes
Placebo	Myocarditis	Day 73 (PD2)	31/F High cholesterol, hypertriglyceridemia, hyperlipidemia, obesity	Recovered/ Resolved	No
Placebo	Pneumonia Septic shock Acute kidney injury	Day 4 (PD2)	58/M Type 2 diabetes mellitus, hypercholesterolemia, hypertension, hyperlipidemia, neuropathy, obesity	Recovered/ Resolved	No
Placebo	Myocardial infarction	Day 7 (PD2)	70/M Type 2 diabetes mellitus, hypertension, obesity, high cholesterol, obstructive sleep apnea	Fatal	No

Source: EUA 28237 Amendment 24, Table 42.
Abbreviations: F=female; M=male; PD1=post-Dose 1; PD2=post-Dose 2; PD3=post-Dose 3; PD4=post-Dose 4.
1. Day of onset post last vaccination (most recent vaccination number).

Following review of the narratives, FDA's opinion is that the event of angioedema is considered potentially related to NVX-CoV2373. The event of unilateral localized peroneal nerve injury is unlikely to be related based on plausible alternative etiology (trauma) and an implausible biological mechanism. The event of thrombocytopenia is unlikely to be related based on a plausible alternative etiology (losartan-induced). Due to plausible alternative etiologies, including laboratory data that was not available to the investigator at the time of the initial causality assessment, the vaccine was unlikely to have contributed to the other SAEs assessed by the investigator as related.

The proportions of participants with SAEs occurring within 7 or 28 days of the last dose was comparable between the NVX arm (0.1% and 0.5%, respectively) and the placebo arm (0.1% and 0.5%, respectively). A total of 24 participants reported 34 SAEs within 7 days of NVX-CoV2373, including 23 events with likely alternative etiologies: appendicitis; breast cancer; prostate cancer; intervertebral disc protrusion; non-Hodgkin's lymphoma; intestinal obstruction; exacerbation of chronic kidney disease (acute kidney injury); nephrolithiasis; osteomyelitis; lower limb fracture; depression; alcohol poisoning with hypotension, pneumonia aspiration, and altered state of consciousness; COVID-19 with respiratory failure; snake bite with cellulitis and abscess; acute exacerbation of chronic congestive heart failure with onset of symptoms prior to Dose 2; cholecystitis acute associated with gallstones and histopathology consistent with chronic cholecystitis and cholelithiasis; and palpitations. One event of hypotension was reported with insufficient information to assess the case. Two events were considered related by the Applicant (angioedema and nervous system disorder and are discussed in Table 23). The remaining 8 events in 5 participants did not have a clear alternative etiology and are described further as follows:

- A 56-year-old female participant with a history of obesity, coronary artery disease, hypertension, and hyperlipidemia reported symptoms of chest pain 2 days post-Dose 2 of NVX-CoV2373. She was diagnosed with Non-ST Elevated Myocardial Infarction (NSTEMI). Relevant laboratory test results included platelet count of 274 (units and reference range not provided) and troponin levels of 4.570 and 5.770 (reference range: 0-0.4 ng/mL). A cardiac catheterization was performed and drug-eluting stents to the circumflex and large obtuse marginal artery were placed.
- A 58-year-old male participant with a history of obesity (BMI 41 kg/m^2), high cholesterol, diabetes, and hypertension experienced an anterolateral ST elevation myocardial infarction approximately 45 minutes post-Dose 2 of NVX-CoV2373. Troponin I was normal with a result of less than 0.015 ng/mL (reference range: 0-0.045). The participant underwent a successful balloon angioplasty of the first diagonal branch, with stent placement.
- An 83-year-old male participant with a history of myocardial infarction, chronic bilateral lower extremity deep vein thromboses (DVT) with inferior vena cava filter placement, hypertension, Type 2 diabetes mellitus, morbid obesity, chronic obstructive pulmonary disease, Alzheimer's disease, and dyslipidemia presented with respiratory distress and peripheral edema 2 days post-Dose 1 of NVX-CoV2373. The platelet count was 134 K/mm^3. Computed tomography angiography (CTA) of the chest with contrast showed right lower lobar and segmental pulmonary emboli, duplex ultrasound of the bilateral lower extremities showed bilateral DVTs, and echocardiogram revealed an ejection fraction of 35-45% and severely dilated left atrium. Acute on chronic decompensated systolic congestive heart failure exacerbation, acute respiratory failure, and pulmonary embolism were diagnosed. Anti-coagulation was initiated, and the participant was discharged home. He subsequently experienced recurrent exacerbations of congestive heart failure.

- A 54-year-old male participant with a history of obesity, primary thrombophilia, recurrent deep vein thrombosis (DVT) left leg and recurrent pulmonary embolism from 2012, non-compliance issues and morbid obesity since 2012, left femoral stent placement in 2012, and stents on proximal left lower extremities presented with leg and hip pain 4 days post-Dose 1 of NVX-CoV2373 and was diagnosed with an acute DVT and pulmonary embolism.
- A 44-year-old male participant with a history of obesity, hypertriglyceridemia, proximal right coronary artery (RCA) stenosis with stent placement presented with palpitations (heart rate increased to 140 beats per minute) and chest and left arm pain on the day of the first dose of NVX-CoV2373 (following a caffeinated beverage and exercise). Electrocardiogram (EKG) was consistent with sinus tachycardia with a rate of 130 without sinus ischemic changes, and echocardiogram was normal, and the troponin was abnormal at 25 ng/L (normal: <20). The tachycardia and elevated troponin resolved overnight.

The 5 participants with cardiac events and thromboembolic events within 7 days of NVX-CoV2373 all had multiple co-morbidities with significant risk factors for the reported cardiac and thrombotic and embolic events. Attribution of causality is confounded by the presence of the pre-existing conditions and risk factors, and similar cardiac events were also reported in the placebo arm within 7 days of vaccination, including fatal events. Please see Section 6.2.5.4 for additional discussion of thrombotic and embolic events.

A total of 13 participants reported 17 SAEs within 7 days of placebo, including fatal events of myocardial infarction (considered related by the Investigator) and cardiac arrest. One participant reported events of acute kidney injury, pneumonia, and septic shock. Additional events included appendicitis (n=3), fracture (n=3), road traffic accident, panic attack, COVID-19 pneumonia, and lumbar vertebral fracture.

Please see Section 6.2.5.4 for a discussion of SAEs of particular clinical interest.

6.2.5.8 Serious Adverse Events (Post-Crossover)

Although participants originally randomized to the NVX arm crossed over to receive placebo and comparisons across crossover treatment arms may discern imbalances in adverse events manifesting shortly after vaccination, prior vaccination with NVX-CoV2373 must be considered in assessments of causality for events occurring in the post-crossover period.

Deaths

As of September 27, 2021, a total of 6 (<0.1%) participants who crossed over to receive NVX-CoV2373 and 10 (<0.1%) participants who crossed over to receive placebo died in the post-crossover period. None of the deaths were considered related.

Of the 6 deaths in participants who crossed over to receive NVX, 4 had a clear alternative etiology (motor vehicle accident [n=2], toxicity due to various agents [toxic effects of fentanyl], and septic shock with recent diagnosis of esophageal cancer six weeks after last dose). Details of the remaining 2 deaths are as follows:

- A 35-year-old female with hypertension, obesity, and a history of alcohol and tobacco use experienced a traumatic rupture of a left vertebral artery aneurysm with subarachnoid hemorrhage, brain stem herniation, and subsequent brain death two days post-Dose 2 of NVX-CoV2373. An autopsy was performed (reports not available), and a formal death certificate was provided. The immediate cause of death was cerebral anoxia, as a

consequence of a rupture of a left vertebral artery aneurysm. Traumatic events are a plausible alternative etiology for the aneurysmal rupture, although details on a specific trauma were not provided in the case narrative. FDA's opinion is that this event is unlikely to be related to vaccine.

- A 47-year-old male with obesity and concomitant use of quetiapine and Adderall 7 days post-Dose 2 of NVX-CoV2373 experienced a medical emergency while out on a walk and was transported to an Emergency Room (ER) in cardiac arrest and died. An autopsy was not performed, and the death certificate could not be obtained. The cause of death was reported as cardiac arrest. At this time, there is insufficient information to assess for causal relationship to NVX-CoV2373, although cardiac events were reported in close temporal relationship to study vaccination in both NVX and placebo arms.

Of the 10 deaths in participants who crossed over to receive placebo, 6 had a clear alternative etiology including completed suicide, respiratory failure and chronic obstructive pulmonary disease, end stage chronic obstructive pulmonary disease, toxicity to various agents (alprazolam, oxycodone, and oxymorphone), hepatorenal syndrome (alcoholic liver cirrhosis), and alcoholic cardiomyopathy. The remaining 4 events included ischemic stroke 155 days after the last dose of NVX-CoV2373 and 38 days after the second placebo crossover dose, myocardial infarction 193 days after the last dose of NVX-CoV2373 and 108 days after the second crossover placebo dose, and 2 events of death of unknown cause at 114 and 208 days after the last dose NVX-CoV2373 and 17 and 117 days after the second crossover placebo dose, respectively. The time to onset of all events relative to Dose 2 of NVX-CoV2373 ranged from 83 to 224 days, making a causal relationship to NVX-CoV2373 unlikely.

Serious Adverse Events

As of September 27, 2021, SAEs were reported by 88/6,416 (1.4%) participants who crossed over to receive NVX-CoV2373 and 178/15,298 (1.2%) participants who crossed over to receive placebo. The relative difference in the proportions of participants across treatment arms in the post-crossover period with specific serious preferred terms was small (maximum relative difference per hundred=0.07). The most common SAEs reported by a higher proportion of participants in the arm that crossed over to NVX-CoV2373 compared to the arm that crossed over to placebo included acute myocardial infarction (0.08% after NVX-CoV2373 and 0.01% after placebo), cholecystitis/cholecystitis chronic/cholecystitis acute (0.1% after NVX-CoV2373 and 0.02% after placebo), pneumonia (0.06% after NVX-CoV2373 and 0.02% after placebo), and coronary artery disease (0.05% after NVX-CoV2373 and 0.01% after placebo).

A total of 2 SAEs in the arm that crossed over to NVX-CoV2373 (<0.1%) and three SAEs in the arm that crossed over to placebo (<0.1%) were considered related by the investigator. None were considered related by the Sponsor. SAEs in the arm that crossed over to NVX-CoV2373 and considered related to vaccination by the investigator included a pulmonary embolism 7 days post-Dose 2 of NVX-CoV2373 in a 39-year old woman with obesity, concomitant estradiol use and recent inactivity due to fatigue post-vaccination, and events of biliary dyskinesia and mild chronic cholecystitis 25 days post-Dose 2 of NVX-CoV2373 in a 25-year old male with pathologic changes suggestive of a chronic condition. The participant with pulmonary embolism had risk factors for clotting events, and the pathologic changes suggestive of chronicity make a causal relationship of the events of biliary dyskinesia and cholecystitis unlikely. Please see Section 6.2.5.4 for an aggregate review of cholecystitis and thrombotic/embolic events following vaccination.

SAEs in the arm that crossed over to placebo and considered related to vaccination by the investigator included lymphoma, cerebrovascular accident, and acute pancreatitis. The event of acute pancreatitis occurred 129 days post-Dose 2 of NVX-CoV2373 in the pre-crossover period, which is inconsistent with a causal relationship to an acute event. The participant with lymphoma reported inguinal swelling that was present prior to randomization and enlarged after administration of NVX-CoV2373; subsequent to placebo dosing in the post-crossover period, the mass was biopsied, and the diagnosis of lymphoma was made 119 days post-Dose 2 of NVX-CoV2373 in the pre-crossover period. The pre-existing mass prior to vaccination makes a causal relationship unlikely. The event of cerebrovascular accident was reported by a generally healthy 57-year-old male 73 days post-Dose 2 of NVX-CoV2373 in the pre-crossover period. Magnetic resonance imaging (MRI) showed an acute dissection of the right vertebral artery. This event was temporally distant from the last vaccination (~10 weeks). Please see Section 6.2.5.4 for an aggregate review of neurovascular events following vaccination.

SAEs within 7 days of a post-crossover were reported by 7 participants who crossed over to receive NVX-CoV2373 and by 12 participants who crossed over to receive placebo. SAEs within 7 days of the post-crossover NVX-CoV0373 dose included events with a clear alternative etiology (pneumonia, bacteremia, pyelonephritis, urinary tract infection, intentional self-injury, and rib fracture with pneumothorax). A fatal case of traumatic rupture of left vertebral artery aneurysm is described in the Deaths section above. A 40-year-old female participant with obesity on ethinyl estradiol/norgestimate developed left lung pain 7 days after the second post-crossover dose of NVX-CoV0373 and was diagnosed with pulmonary embolism (platelet count 237k/mm^3); ultrasound was negative for DVT. This event was considered related by the Investigator. Attribution of causality is confounded by the presence of the pre-existing conditions and risk factors. Please see Section 6.2.5.4 for an aggregate review of thrombotic/embolic events following vaccination.

SAEs within 7 days of the post-crossover placebo dose included expected events in the study population, including breast lesions, uterine leiomyoma, acute cholecystitis, infectious (appendicitis, cellulitis, epididymitis), rhabdomyolysis, alcohol withdrawal syndrome, acute respiratory distress, pancreatitis, and renal cell carcinoma.

SAEs of particular clinical interest that occurred in the post-crossover period are included in the discussion in Section 6.2.5.4.

6.2.5.9 Serious Adverse Events Reported From Later Follow-Up

At FDA's request, the Sponsor provided additional safety data through a February 17, 2022, extraction date to conduct a cumulative safety evaluation through a more recent time point; however, this data is subject to further cleaning and may change.

For the pre-crossover period, a total of 12 additional SAEs were reported by 10 participants in the NVX arm between September 27, 2021, and February 17, 2022, none of which were fatal or considered related, and all of which occurred >250 days after the most recent vaccination. These events included drug hypersensitivity (dilaudid), hepatic hemorrhage (due to biopsy), atrioventricular block complete, cardiac failure congestive, heart rate irregular, pancreatic neuroendocrine tumor, splenic infarction, appendicitis perforated, subdural hematoma, respiratory distress, suicidal ideation, and cerebrovascular accident. There was no specific pattern of events to reflect a long-term safety risk due to vaccine. A total of 9 additional SAEs were reported by 6 participants in the placebo arm, including one additional fatal event, all of which occurred >230 days after the most recent placebo dose. These events included breast

cancer, accidental overdose (insulin), gastric ulcer and gastric ulcer hemorrhage in the same participant, death (unknown cause), cerebrovascular accident, and pregnancy complications in one participant, including placenta previa, premature rupture of membranes, and premature delivery.

For the post-crossover period, SAEs were reported by an additional 62 participants who crossed over to receive NVX-CoV-2373 and an additional 127 participants who crossed over to receive placebo. The proportion of participants reporting SAEs was comparable for participants who crossed over to receive NVX-CoV2373 (2.3%) and participants who crossed over to receive placebo (2.0%). A review of SAEs including these additional events did not reveal any imbalances that were not identified in review of the data through September 27, 2021. Of the additional SAEs, 2 were considered related, including an event of COVID-19 in a participant who crossed over to receive placebo and an event of scleroderma in a participant who crossed over to receive NVX-CoV2373 (discussed in Section 6.2.5.4).

An additional 4 deaths were reported in the participants who crossed over to receive NVX-CoV2373 and an additional 13 deaths were reported in participants who crossed over to receive placebo; none of these deaths were considered related. All deaths had a time to onset of 140 days or more following Dose 4 in the crossover period. The causes of death included death (n=5); road traffic accident, multiple organ dysfunction syndrome, and septic shock (n=2 each); cardiac arrest, chronic obstructive pulmonary disease exacerbation, cardiac failure congestive, dyspnea, urosepsis, angiosarcoma, and accidental overdose (n=1 each).

Cumulatively, 26,106 participants received NVX-CoV2373 in either the pre-or post-crossover period. A total of 30 participants (0.1%) reported 41 SAEs within 7 days of NVX-CoV2373 doses. Events reported more than once included pulmonary embolism (n= 3) and hypotension (n= 2). The most commonly reported SAEs at any time following NVX-CoV2373 (at least 0.1% of participants) included COVID-19, COVID-19 pneumonia, pneumonia, atrial fibrillation, pulmonary embolism, acute kidney injury, appendicitis, and cellulitis, each of which was reported by 0.1% of vaccinated participants. In general, the cumulative reported SAEs appear consistent with expected diseases in the study population and those collected through the September 27, 2021, data cutoff.

6.2.5.10 Subgroup Analyses of Safety

Overall, the proportion of participants reporting different categories of AEs (solicited, unsolicited and SAEs) were comparable between subgroups by race and ethnicity. However, when comparing risk differences between the NVX and placebo arms across the race groups, participants who are Asian and Hawaiian Pacific Islander had numerically higher reporting rates of solicited AEs, unsolicited AEs and SAEs, although these did not reach statistical significance. No significant differences in time to resolution or outcomes were observed among racial or ethnic subgroups. A detailed review of types of SAEs in these subgroups did not reveal any pattern in type of events or clear temporal association, and most were likely unrelated to vaccination. Overall AE rates were low, and therefore it is not possible to conclude based on small numbers of events whether a true difference exists. Variability in reporting adverse events may reflect cultural differences across different geographical regions, such as relationships between patients and healthcare providers, access to healthcare providers and tolerance of pain and discomfort. Furthermore, there may be variation among clinical trial investigators across regions in adherence to clinical trial protocols related to AE reporting. However, a potentially higher risk of adverse reactions among Asian and Pacific Island subjects cannot definitively be ruled out.

Solicited local and systemic events were reported at higher rates after the second dose than after the first dose among participants 18-64 years of age and ≥65 years of age. As compared with participants ≥65 years of age, participants 18-64 years of age had higher rates of local and systemic events, with a slightly higher proportion of Grade 3 events in this younger age group. There were fewer subjects with solicited events that lasted more than 7 days in those ≥65 years of age as compared with those 18-64 years of age. Unsolicited events and SAEs rates were higher among those ≥65 years of age; the difference was driven mainly by events in the SOCs of Cardiac disorders and Vascular disorders. The risk differences between vaccine and placebo arms for these SOCs in the older cohort were similar to those in the younger cohort.

There were no notable differences in the distribution and severity of adverse events by sex.

Otherwise, there were no specific safety concerns identified in subgroup analyses by race, sex, and ethnicity, and occurrence of solicited, unsolicited, and serious adverse events in these subgroups were generally consistent with the overall study population.

6.2.5.11 Pregnancy Outcomes

A summary table of pregnancy outcomes was provided by the Sponsor in their briefing document; however, source data was not provided, and FDA is unable to verify this data. According to the Sponsor, as of 15 March 2022, a total of 147 pregnancies were reported across the entire period of the clinical studies in participants who received NVX-CoV2373.

Table 24. Sponsor Summary of Pregnancies During Pre-Crossover Period and Post-Crossover Period Combined Number of Pregnancies With Outcomes in Participants Who Received Active Vaccine in All Clinical Studies

Pregnancy Outcome	Total NVX-CoV2373 N=147	Vaccination Before LMP N=105	Vaccination 0-30 Days After LMP N=22	Vaccination >30 Days After LMP N=9	Vaccination Relative to LMP Unknown N=11
Known pregnancy outcome, n	136	99	19	8	10
Ongoing	56	51	1	3	1
Live birth	41	24	12	3	2
Miscarriage	25	18	4	1	2
Voluntary termination	13	6	2	1	4
Ectopic pregnancy	1	0	0	0	1
Stillbirth	0	0	0	0	0
Unknown, n	11	6	3	1	1

Source: EUA 28237 Sponsor's Briefing Document in Amendment 37, Table 18
Abbreviations: LMP=last menstrual period; N=number of participants in cohort; n=number of participants with indicated outcome
Note: Data current as of 15 March 2022.

For each time period of vaccine exposure relative to the last menstrual period, the rate of miscarriage appears consistent with expected background rates in the general population; however, information on the timing of pregnancy loss and risk factors was not provided by the Sponsor. The available data are insufficient to establish the presence or absence of vaccine-associated risk during pregnancy.

6.2.6 Summary of Study 2019nCoV-301

Vaccine efficacy (VE) against central laboratory-confirmed mild, moderate, or severe COVID-19 over a median follow-up period of 2.5 months after completion of the primary series was 90.4% (95% CI 82.9, 94.6) for the prevention of PCR-confirmed symptomatic COVID-19 illness diagnosed ≥7 days after completion of the second vaccination. Due to limited numbers of

COVID-19 cases in the elderly, effectiveness in the elderly population was further supported by post-hoc analyses showing similar vaccine efficacy for participants 50-64 years of age compared to the subgroup of participants 18-64 years of age and similar neutralizing antibody titers in participants ≥65 years of age compared to those 50-64 years of age.

The available safety database (N=29,582; 19,735 vaccine, 9,847 placebo) meets the expectations in FDA's Guidance on Development and Licensure of Vaccines to Prevent COVID-19 for efficacy. The initial EUA request was based on data from the pre-specified interim analysis (September 27, 2021, data cutoff), which serves as the primary basis of this EUA review and conclusions. With this data, a large majority of subjects had completed 2 months of follow-up after their series of vaccinations both pre- and post-crossover. FDA has independently verified the complete efficacy and safety data with the September 27, 2021, cutoff and analyzed additional data on deaths, PIMMCs, and SAEs through February 17, 2022. The totality of the data package submitted to the EUA meets the Agency's expectations on the minimum duration of follow-up.

Local site reactions and systemic solicited events were more common after NVX-CoV2373 compared to placebo, with increased frequency and severity following the second dose. The most frequently reported local AR was injection site pain/tenderness. After NVX-CoV2373, any Grade 3 local AR was reported by 1.1% of participants post-Dose 1 and 6.6% of participants post-Dose 2. Grade 4 local ARs were only reported following the second dose of NVX-CoV2373 and occurred in <0.1% of participants. The median time to onset for any local AR was 2 days following vaccination and the median duration was 2-3 days. After NVX-CoV2373, Grade 3 and 4 solicited systemic ARs were reported by <1.5% and <0.1% of participants, respectively, post-Dose 1 and by 12% and 0.1% of participants, respectively, post-Dose 2. In both treatment groups and for both Dose 1 and 2, fatigue/malaise, headache, and muscle pain (myalgia) were the most commonly reported solicited systemic ARs. For any solicited systemic AR, the median time to onset was 2 days and the median duration was 2 days (range 1-7) for Doses 1 and 2 in both treatment arms.

Multiple events of myocarditis/pericarditis were reported in temporal relationship to NVX, and FDA considers some of these events potentially related to vaccination. Events of lymphadenopathy were infrequent but reported by a higher proportion of participants in the NVX arm, with the highest rate observed after Dose 2 (0.2%). An event of Guillain Barre syndrome (reported in Study 302) occurred with close temporal relationship to vaccination and with no alternative etiology identified, and was considered related to the vaccine. Review of the data also identified several numerical imbalances in specific adverse events of particular interest, although a conclusion of causal association cannot be made based on available data; these include thromboembolic events, including cardiac and neurovascular events, hypersensitivity, cholecystitis, uveitis, cardiac failure, and cardiomyopathy.

7. Additional Safety Data

Additional safety data (SAEs and AESIs, including PIMMCs) were reviewed from 3 studies: Study 101, 501- and 302; NVX-CoV2373 vaccine manufactured at Emergent BioSolutions was administered as the primary series. For Study 101 (parts 1 and 2), safety data from only those participants who received the 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant vaccine formulation are presented in this section. See Appendix B for study description and population demographic and baseline characteristics.

SAEs, AESIs, and PIMMCs were monitored throughout the studies, starting from Dose 1, and safety data collection is ongoing. FDA reviewed analyses derived from data available through the following dates:

Table 25. Duration of Safety Follow-up, Safety Analysis Set

Study	NVX-CoV2373 N	Placebo N	Total % of Participants Completing at Least 2 Months of Safety Follow-up After Dose 2	Date of Crossover, Unblinding, End of Study[a], Booster[b] or Data Cut-off[c]
302	7569	7570	81.2%	February 23, 2021
501	2211	2197	95.4%	February 23, 2021
101, Part 1	29	23	0%	December 19, 2020
101, Part 2	514	255	97.6%	December 15, 2020

Source: FDA-generated table.
N: number of participants who received at least 1 dose of study product.
a. Study 2019nCoV-101, Part 1.
b. Study 2019nCoV-101, Part 2.
c. The date reflects whichever timepoint came first.

The median duration of follow-up after Dose 2 was 2.7 months (study 302), 3 months (study 501), 6.3 months (study 101, part 2) and 1.2 months (study 101, part 1).

Events of clinical interest in Study 302 included:

- One event of myocarditis was reported by a 19-year-old male in the NVX arm who developed myocarditis 2 days after Dose 2. Details of this event are provided in Table 20.
- One event of Guillain-Barre syndrome was reported by a 65-year-old female NVX recipient who experienced progressive neuropathy starting 9 days following Dose 1. Some of her neuropathy symptoms were consistent with features of Guillain-Barre syndrome. Initially, she experienced hand paresthesias, which gradually progressed to numbness of feet during the month, and eventually required a walker for walking. The participant received the second dose of vaccine 21 days after the first dose of vaccine as scheduled. After approximately 4 months, she developed pain in the shoulder, back, and hip. The subject was treated with tramadol and pregabalin. The study investigator and consulting neurologist also considered the progressive neuropathy to be related to vaccination. FDA agrees with the study investigator's assessment.

There were no new SAEs, AESIs or PIMMCs in studies 101, 302, or 501 that were considered at least possibly related by FDA that were not previously identified in study 301.

8. Foreign Postmarketing Experience

This section describes postmarketing reports of adverse events following administration of Novavax COVID-19 Vaccine in other countries. Data from passive surveillance systems are subject to several limitations, including but not limited to 1) potential reporting bias (underreporting or stimulated reporting), 2) possible missing or inaccurate information in reports, 3) lack of a control group, 4) reported diagnoses are not necessarily medically confirmed diagnoses, and 5) reporting behaviors may vary between countries. Due to these limitations, passive surveillance data alone are generally insufficient for determining causality for a given adverse event after vaccination. Nonetheless, postmarketing reports can serve as a useful tool for detecting unusual or unexpected patterns of adverse events (also known as "safety signals")

that warrant further investigation or corroboration with other data sources (Shimabukuro et al, 2015; UMC, 2021).

The Sponsor submitted their third Monthly Safety Summary Report (MSSR), covering reporting period April 1, 2022, to April 30, 2022, for review during this EUA request. MSSRs contain worldwide interval and cumulative postmarketing safety data for NVX-CoV2373 (including vaccine distributed to foreign markets under the trade names Nuvaxovid and Covovax). Cumulatively, more than 41 million doses of NVX-CoV2373 were distributed globally. Among countries/jurisdictions with available administration data (i.e., Australia, Canada, European Union, New Zealand, and South Korea), 744,235 NVX-CoV2373 doses had been administered cumulatively. The Sponsor's global vaccine safety database for NVX-CoV2373 contained a cumulative total of 923 spontaneous Individual Case Safety Reports (ICSRs), representing a total of 3,859 adverse events (AEs). Of these AEs, 424 were serious and unlisted, 124 were serious and listed, 2,012 were non-serious and unlisted, and 1,299 were non-serious and listed. There was one pregnancy-related ICSR and no fatal ICSRs reported.

The Sponsor identified myocarditis and pericarditis as a new "potential safety signal" in their third MSSR. As of April 30, 2022, a total of 37 individual case safety reports (ICSRs) for myocarditis and pericarditis were received, involving a total of 38 adverse events (AEs). Two of these ICSRs were identified as duplicates and invalidated, leaving a total of 35 valid cumulative ICSRs representing 36 AEs. Of these 35 valid ICSRs, 14 were considered medically confirmed and 21 were non-medically confirmed. The Sponsor performed observed-to-expected (O/E) analyses for both the cumulative AEs (n=38) and AEs from medically confirmed cases only (n=14). The Sponsor used a background rate from ACCESS (vACCine covid-19 monitoring readinESS project), an open access resource of 10 data sources from seven European countries (VAC4EU, 2019; EMA, 2020). O/E analyses for the cumulative AEs revealed significantly elevated O/E rate ratios for both the main analysis (RR 4.95, 95% CI 3.50 - 6.79) as well as sensitivity analyses that assume a reporting sensitivity of 50% (RR 9.90, 95% CI 7.00 – 13.58) and 25% (RR 19.79, 95% CI 14.01 – 27.17), respectively. O/E rate ratios for the medically confirmed cases only were also elevated (RR 1.82, 95% CI 1.00 – 3.06), but statistically significant only for the sensitivity analyses (reporting sensitivity of 50%: RR 3.65, 95% CI 1.99 – 6.18; reporting sensitivity of 25%: RR 7.29, 95% CI 3.98 – 12.23). The majority of ICSRs for myocarditis and pericarditis were submitted from Australia's Therapeutic Goods Administration (TGA). The Sponsor planned to review additional report details from the TGA and adjudicate a subset of reports against a case definition.

FDA reviewer assessment of the limited report details provided in the third MSSR for the 35 valid cases showed that the 36 associated AEs were coded with the following Preferred Terms (PTs): Pericarditis (n=29), Myocarditis (n=4), Myopericarditis (n=2), and Carditis (n=1). The median known age was 34 years (range 23 – 62 years) and there were more males (n=20) than females (n=15). Outcomes were reported as follows: Unknown (n=14), Not Recovered/Not Resolved (n=17), Recovering/Resolving (n=2), Recovered with Sequalae (n=1), and Recovered/Resolved (n=1). In addition, six reports involved recurrent pericarditis. In five of these cases, the prior episode of pericarditis was reported to have occurred following an mRNA COVID-19 vaccine.

The FDA queried the World Health Organization's VigiBase on May 31, 2022 (UMC, 2022a). VigiBase is a global database of reported potential side effects of medicinal products, developed and maintained by Uppsala Monitoring Centre (UMC), with around 150 actively contributing countries (UMC, 2022b). The information presented here does not represent the opinion of the

UMC or the World Health Organization. Reports come from a variety of sources and the probability that the suspected adverse effect is drug-related is not the same in all cases. For additional details on the limitations and conditions of VigiBase, see the UMC Caveat Document (UMC, 2021). This query revealed a total of 1,677 reports for Novavax COVID-19 Vaccine. The following three countries accounted for over 90% of reports: Australia (n=726; 43.3%), Germany (n=709; 42.3%), and Italy (n=122; 7.3%). Two hundred sixty-six (15.9%) reports were serious, and 1,411 (84.1%) reports were not serious. The ten most common adverse events (AEs) in reports (represented by MedDRA Preferred Terms [PTs]) were: 1) Headache (n=440; 26.2%), 2) Fatigue (n=341; 20.3%), 3) Chest pain (n=223; 13.3%), 4) Pyrexia (n=223; 13.3%), 5) Dizziness (n=222; 13.2%), 6) Myalgia (n=222; 13.2%), 7) Nausea (n=193;11.5%), 8) Injection site pain (n=176;10.5%), 9) Paraesthesia (n=174; 10.4%) and 10) Chills (n=149; 8.9%). Among the 1,677 reports for Novavax COVID-19 Vaccine overall, 46 reports contained 48 AEs pertinent to myocarditis/pericarditis: Pericarditis (n=37), Myocarditis (n=6), Myopericarditis (n=4), and Carditis (n=1). Most of these reports (n=41; 89.1%) were from Australia.

9. Pharmacovigilance Activities

The Sponsor submitted a Pharmacovigilance Plan to monitor safety concerns that could be associated with the Novavax COVID-19 Vaccine. The Sponsor identified vaccine-associated enhanced disease including vaccine-associated enhanced respiratory disease, myocarditis and pericarditis, and anaphylaxis as important potential risks. Use in pregnancy and while breast feeding, use in immunocompromised patients, use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders), use in patients with autoimmune or inflammatory disorders, interaction with other vaccines, and long-term safety are areas the Sponsor identified as missing information. Based on cases of myocarditis and pericarditis in both the clinical trials and foreign post-marketing reports, the FDA requested that the Sponsor change “myocarditis and pericarditis” to an important identified risk. At the time of this writing, the Sponsor had not agreed to make this change.

The Sponsor will conduct both passive and active surveillance activities for continued vaccine safety monitoring. Passive surveillance activities will include submitting spontaneous reports of the following events to the Vaccine Adverse Event Reporting System (VAERS) within 15 days:

- Serious adverse events (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome in adults
- Cases of COVID-19 that result in hospitalization or death

The Sponsor will also conduct periodic aggregate review of safety data and submit periodic safety reports in accordance with a reporting interval and due date agreed upon with the Office of Biostatistics and Pharmacovigilance (OBPV). Each periodic safety report is required to contain descriptive information which includes:

- A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest
- A narrative summary and analysis of vaccine administration errors, whether or not associated with an adverse event, that were identified since the last reporting interval
- Newly identified safety concerns in the interval

- Actions taken since the last report because of adverse experiences (e.g., changes made to Vaccination Provider fact sheets, changes made to studies or studies initiated)

The Sponsor studies will include completion of long-term follow-up from ongoing clinical trials as well as the following five planned surveillance studies.

- Pregnancy Exposure Registry: The Sponsor plans to use the COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER)—a multi-country, observational, prospective cohort study of women vaccinated during pregnancy with a COVID-19 vaccine—to evaluate obstetric, neonatal, and infant outcomes among women vaccinated during pregnancy with the Novavax COVID-19 Vaccine. The planned study duration is 48 months for enrollment and follow-up of participants.
- US Active Follow-Up for Safety: This is an active safety surveillance study to evaluate the risk of select AESIs in association with administration of the Novavax COVID-19 Vaccine in adults 18 years of age and older in the real-world setting in the US. The Sponsor plans to use a large US-based insurance claims database and/or electronic health records database. The study design includes two methods: 1) a self-controlled case series design and 2) a retrospective comparative matched cohort study design. The planned study duration is 30 months following receipt of regulatory authorization of the Novavax COVID-19 Vaccine in the US.
- UK Active Follow-Up for Safety: This is an active safety surveillance study to evaluate the risk of select AESIs in association with administration of the Novavax COVID-19 Vaccine in adults 18 years of age and older in the real-world setting in the United Kingdom (UK). The Sponsor plans to use the Clinical Practice Research Datalink and associated linked databases for this study. The study design includes two methods: 1) a self-controlled case series design and 2) a retrospective comparative matched cohort study design. The planned study duration is 30 months following receipt of regulatory authorization of the Novavax COVID-19 Vaccine in the UK.
- US Real World Effectiveness Study: This study is a real-world effectiveness study to assess the effectiveness of the Novavax COVID-19 Vaccine in preventing SARS-CoV-2 infection in adults 18 years of age and older in the US. The Sponsor plans to use a large US-based insurance claims database and/or electronic health records database. The study design is a retrospective comparative cohort study design. The planned study duration is 30 months following FDA concurrence on the final study protocol.
- European Real World Effectiveness Study: This is a real-world effectiveness study to assess the effectiveness of the Novavax COVID-19 Vaccine against hospitalization due to laboratory-confirmed SARS-CoV-2 in adults 18 years of age and older in multiple European countries. The Sponsor plans to use COVIDRIVE, a multi-stakeholder, public-private partnership program, as the data source. The study is a prospective, hospital-based case-control study using a test-negative design. The planned duration of the study is a minimum of one year with an expected study duration of two years.

FDA will provide feedback on these studies after further review of protocols once submitted by the Sponsor.

Reporting to VAERS and Novavax

Providers administering the Novavax COVID-19 Vaccine must report to VAERS (as required by the National Childhood Vaccine Injury Act) and to the extent feasible, report to Novavax, the following information associated with the vaccine of which they become aware:

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome in adults
- Cases of COVID-19 that result in hospitalization or death

Additional VAERS Reporting

An additional source of VAERS reports will be through a program administered by the CDC known as v-safe. V-safe is a smartphone-based opt-in program that uses text messaging and web surveys to help COVID-19 vaccine recipients monitor for and report side effects. The system also will provide telephone follow-up to anyone who reports medically important adverse events. Responses indicating missed work, inability to do normal daily activities, or receipt of care from a doctor or other healthcare professional will trigger the VAERS Call Center to reach out to the participant and collect information for a VAERS report, if appropriate.

10. Benefit/Risk Assessment in the Context of the Proposed Indication and Use Under EUA

10.1 Known and Potential Benefits

The known benefits among vaccine recipients 18 years of age and older relative to placebo are reduction in the risk of mild to severe COVID-19 occurring at least 7 days after the second primary series vaccination. Vaccine efficacy estimates from study 301 are generally consistent across subgroups stratified by demographic variables (including age, race, and ethnicity) and risk for severe COVID-19, with variability in efficacy estimates for some subgroups likely due to small numbers of cases reported in those subgroups. Although only 4 severe cases occurring at least 7 days after the second primary series vaccination were reported in the study, all 4 severe cases were in the placebo arm. This observation is consistent with the consistent observation that preventive vaccines, including other COVID-19 vaccines that have been authorized or approved for use in the US, are generally more effective at preventing severe disease than preventing mild disease.

10.2 Uncertainties in Benefits

Effectiveness against Currently Circulating SARS-CoV-2 Variants

The study enrollment and efficacy follow-up occurred during December 27, 2020, to September 27, 2021, and mainly when the Alpha variant of SARS-CoV-2 was predominant and prior to the emergence of Delta and Omicron variants. Post-authorization experience with other COVID-19 vaccines has demonstrated substantially decreased effectiveness of a primary series against the currently circulating Omicron variant and sublineages, in particular against milder COVID-19, than was demonstrated in pre-authorization clinical trials conducted when the ancestral strain was circulating. Relevant data to assess effectiveness of NVX-CoV2373 against the Omicron variant and sublineages, including observational data from use in other countries where the vaccine has been deployed, are currently unavailable; however, based on the efficacy estimate in the clinical trial of this vaccine, it is more likely than not that the vaccine will provide some meaningful level of protection against COVID-19 due to Omicron, in particular against more severe disease. The extent to which a booster dose, administered at some time after completion of the primary series, would provide additional protection remains a question to be further evaluated.

Duration of Protection

The analyses have a limited length of follow up, therefore, it is not currently possible to assess sustained efficacy over a period longer than 2 months.

Effectiveness in Certain Populations at Higher Risk of Severe COVID-19

Although the proportion of participants at high risk of severe COVID-19 is adequate for the overall evaluation of safety in the available follow-up period, the subsets of certain groups such as immunocompromised individuals (e.g., those with HIV/AIDS) and participants with cardiovascular, chronic renal, and chronic liver disease are too small to evaluate efficacy outcomes. Additionally, few cases of PCR-confirmed COVID-19 were analyzed for participants ≥65 years of age, limiting the robustness of the efficacy estimate for this age subgroup**.**

Effectiveness in Individuals Previously Infected With SARS-CoV-2

There were no COVID-19 cases reported in individuals with prior SARS-CoV-2 infection. However, observational data with other COVID-19 vaccines have demonstrated an added benefit of vaccination to protection conferred by natural immunity (Plumb et al, 2022). Additionally, for individuals previously infected with the Omicron variant of SARS-CoV-2, a vaccine based on the ancestral strain S protein could provide a greater breadth of protection against SARS-CoV-2 variants.

Effectiveness in Pediatric Populations

Data to directly inform vaccine effectiveness in pediatric age groups (17 years of age and younger) were not included or considered as part of this EUA request. If the vaccine is authorized under EUA for use in adults, data from studies in pediatric age groups could be considered in EUA amendments to expand the authorized use to include those age groups.

Future Vaccine Effectiveness as Influenced by Characteristics of the Pandemic

The continued evolution of the pandemic, including changes in the virus infectivity, antigenically significant mutations to the S protein, and changes in practice of nonpharmacologic interventions to mitigate against transmission, will likely influence vaccine effectiveness over

time. Continued evaluation of vaccine effectiveness following issuance of an EUA and/or licensure will be critical.

Effectiveness Against Long-Term Effects of COVID-19 Disease

Available data are not conclusive on the effectiveness of COVID-19 vaccines currently in use against long-term sequelae of COVID-19 among individuals who are infected despite vaccination. Additional evaluation is needed to assess the effect of this vaccine in preventing long-term effects of COVID-19, including data from clinical trials and from the vaccine's use post-authorization.

Effectiveness Against Asymptomatic Infection and Transmission

Available data for COVID-19 vaccines currently in use has demonstrated that effectiveness against asymptomatic infection is lower and less durable than effectiveness against symptomatic COVID-19. Available data also do not indicate high-level or durable effectiveness against transmission of SARS-CoV-2 from vaccinated individuals with breakthrough infections. Data for these outcomes are not currently available for NVX-CoV2373, it is more likely than not that the observations with other COVID-19 vaccines (with similar antigens and routes of administration) will apply to this vaccine as well.

10.3 Known and Potential Risks

In clinical evaluation, local and systemic adverse reactions, usually lasting 1 to 3 days, were reported at higher frequencies among NVX-CoV2373 recipients as compared to placebo recipients. The most common solicited adverse reactions were injection site pain/tenderness, fatigue, headache, and myalgia. Overall, solicited reactions were reported more commonly in younger participants. Hypersensitivity reactions and lymphadenopathy were observed post vaccination. Reporting rates of medically attended adverse events, serious adverse events, and potential immune-mediated medical conditions in the clinical trials were generally low and balanced between NVX-CoV-2373 and placebo arms.

Myocarditis events were identified across the clinical development program, including four events of myocarditis (and one additional event that in FDA's assessment is clinically consistent with myocarditis) within the 20-day window post vaccination. There were no myocarditis cases in the placebo arm within 0-20 days post vaccination. These events raise the concern for a causal association with this vaccine, similar to the association documented with mRNA COVID-19 vaccines. Data from passive surveillance during post-authorization use in other countries also indicate a higher than expected rate of myocarditis and pericarditis (mainly pericarditis) associated with the vaccine. However, interpretation of these passive surveillance data is not straightforward, and further evaluation is needed to inform the risk of myocarditis and pericarditis associated with this vaccine, and their outcomes, as additional data emerge over time.

One case of Guillain-Barre syndrome was observed in the clinical development program, in temporal association post-vaccination and without an identified alternative cause. Guillain-Barre syndrome is known to be associated with other vaccines.

10.4 Uncertainties in Risks

Safety in Certain Subpopulations

There are currently insufficient data to make conclusions about the safety of the vaccine in subpopulations such as children, pregnant and lactating individuals and their infants, and immunocompromised individuals.

Adverse Reactions That are Uncommon or That Require Longer Follow-Up To Be Detected

Following authorization of the vaccine, use in large numbers of individuals may reveal additional, potentially less frequent and/or more serious adverse events not detected in the clinical trial safety population.

Certain adverse events of clinical interest were reported infrequently in the clinical trials but with small numerical imbalances between the NVX-CoV2373 and placebo arms. These include:

- *Biliary events*: an imbalance was observed in the rate of acute cholecystitis, although this observation confounded by underlying risk factors.
- Neurovascular events: While there is a slight numerical imbalance in the pre-crossover period, the total number of events was small, and events in close temporal relationship to vaccination were reported in both treatment arms. There is no clear pattern in the time to onset of events to suggest a specific pathophysiologic mechanism for a causal relationship to NVX-CoV2373.
- Cardiac events: Numerical imbalances were noted between the treatment arms with respect to events of cardiac failure and cardiomyopathy, including some events in close temporal proximity to vaccination. Cardiac events overall, including fatal events of cardiac arrest and myocardial infarction, were reported with close temporal relationship to NVX-CoV2373; however, the proportions of participants with fatal, serious, and specific cardiac events were generally balanced across the treatment arms for the blinded pre-crossover period, with comparable times to onset.
- Uveitis: Although there was no imbalance in cases in the placebo-controlled pre-crossover period, there were 3 events of uveitis/iridocyclitis occurred within 21 days of NVX-CoV2373, including 1 event that recurred upon re-challenge with Dose 2 of NVX-CoV2373.

Active and passive safety surveillance will continue during the post authorization period to further evaluate these events and to detect new safety signals.

10. Topic for Vaccines and Related Biological Products Advisory Committee Discussion

The Vaccines and Related Biological Products Advisory Committee is being convened to discuss and provide recommendations on whether, based on the totality of scientific evidence available, the benefits of the Novavax COVID-19 Vaccine 2-dose primary series outweigh its risks for use in individuals 18 years of age and older.

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13. Appendix A. Other Clinical Studies

13.1 Study 2019nCoV-302

Study 302 is an ongoing Phase 3, randomized, observer-blind, placebo-controlled study to evaluate the efficacy, safety and immunogenicity of NVX-CoV2373 in adults ≥18 years of age in the United Kingdom, and included adults at risk to develop severe COVID-19: obesity (BMI >30 kg/m^2), chronic kidney or lung disease, cardiovascular disease and diabetes mellitus type 2, life circumstances (living or working conditions involving known frequent exposure to SARS-CoV-2).

Of the total of 15,139 adults randomized 1:1 (NVX-CoV2373: saline placebo), 7,569 NVX-CoV2373 and 7,570 placebo recipients were included in the safety analysis set. During the course of study, 34.6% (2,555 NVX-CoV2373, 2,680 placebo) were unblinded to the vaccine assignment because they became eligible and elected to receive an EUA-approved COVID-19 vaccine, and approximately 98% of the unblinded participants continued safety evaluations in the study.

Of the total study population, 27.2% of participants were 65-84 years of age; 48.4% were female; <5% were Asian or Black, 94.3% were White; 0.8% were Hispanic or Latino; 26.3% were obese; 44.7% had a medical history of at least 1 comorbid condition reported, or obesity; and 4.2% of participants had evidence of SARS-CoV-2 infection (by ELISA) at Day 0.

13.2 Study 2019nCoV-501

Study 501 is an ongoing Phase 2, randomized, observer-blind, placebo-controlled study to evaluate the efficacy, immunogenicity, and safety of NVX-CoV2373 in adults 18-84 years of age in South Africa. HIV-positive adults were eligible to enroll in the study if they were receiving highly active antiretroviral therapy, had no opportunistic infections in the 1 year prior to the first study vaccination, and had a HIV-1 viral load <1,000 copies/mL within 45 days of randomization.

Of the total 4,419 adults randomized 1:1 (NVX-CoV2373: saline placebo), 2,211 NVX-CoV2373 and 2,197 placebo recipients, including 244 HIV-positive recipients (122/per study group) were included in the safety analysis set.

The demographic and baseline characteristics of the study population are as follows:

- HIV-negative population (n=4,164): 4.4% were 65-84 years of age; 95% were Black, 41% were female; 1.5% were Hispanic or Latino; 77.8% had no co-morbidities (i.e., hypertension, diabetes, or obesity); 19.3% were obese; and 34.1% had evidence of SARS-CoV-2 infection at baseline (defined as detectable IgG antibody to N-protein specific for SARS-CoV-2 rS at Day 0 and/or (+) PCR through Day 21).

- HIV-positive population (n= 244 NVX-CoV2373): all were between 20-60 years of age (median 38 years); 73% were female, 100% were Black; 4.5% were Hispanic or Latino; the medical history included obesity (32.8% of participants), hypertension (6.1% of participants), or diabetes (1.2% of participants); and 34.0% of participants had evidence of SARS-CoV-2 infection at baseline

13.3 Study 2019nCoV-101

Study 101 was designed as a phase 1/2 study to evaluate the safety and immunogenicity of several vaccine and Matrix-M1 adjuvant combinations. The 5 µg SARS-CoV-2 rS + 50 µg Matrix-M formulation was administered to 29 participants 18-59 years of age (part 1; 2 doses) in Australia, and 514 participants 18-84 years of age (part 2; 1 dose or 2 doses [n=257/per dose cohort]) In Australia and the US.

In part 1, the median age was 27 years (range 18, 52), and 50% of participants were female. Eighteen participants (69%) were White, 6 (23%) were Asian, 2 (8%) were American Indian or Alaskan Native; and 6 (23%) were Hispanic or Latino.

In part 2, the median age was 57 years (range 18, 83), and 50% of participants were female. 86% were White, 8% were Asian, and <3% were Black, African American, American Indian or Alaskan Native; 4% were Hispanic or Latino; 52% were from Australia; the median BMI was 26 (17, 35); and 2% of participants had evidence of SARS-CoV-2 infection at baseline.

14. Appendix B. Potential Immune-Mediated Medical Conditions

Table 26. Potential Immune-Mediated Medical Conditions, Study 301

Category	Diagnoses (as MedDRA Preferred Terms)
Neuroinflammatory disorders	Acute disseminated encephalomyelitis (including site-specific variants: e.g., non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis), cranial nerve disorders including paralyses/paresis (e.g., Bell's palsy), generalized convulsion, Guillain-Barre syndrome (including Miller Fisher syndrome and other variants), immune-mediated peripheral neuropathies and plexopathies (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy), myasthenia gravis, multiple sclerosis, narcolepsy, optic neuritis, transverse myelitis, uveitis.
Musculoskeletal and connective tissue disorders	Antisynthetase syndrome, dermatomyositis, juvenile chronic arthritis (including Still's disease), mixed connective tissue disorder, polymyalgia rheumatic, polymyositis, psoriatic arthropathy, relapsing polychondritis, rheumatoid arthritis, scleroderma (including diffuse systemic form and CREST syndrome), spondyloarthritis (including ankylosing spondylitis, reactive arthritis [Reiter's Syndrome] and undifferentiated spondyloarthritis), systemic lupus erythematosus, systemic sclerosis, Sjogren's syndrome.
Vasculitides:	Large vessels vasculitis (including giant cell arteritis such as Takayasu's arteritis and temporal arteritis), medium sized and/or small vessels vasculitis (including polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome [allergic granulomatous angiitis], Buerger's disease [thromboangiitis obliterans], necrotizing vasculitis and ANCA-positive vasculitis [type unspecified], Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis).
Gastrointestinal disorders	Crohn's disease, celiac disease, ulcerative colitis, ulcerative proctitis.

Category	Diagnoses (as MedDRA Preferred Terms)
Hepatic disorders	Autoimmune hepatitis, autoimmune cholangitis, primary sclerosing cholangitis, primary biliary cirrhosis.
Renal disorders	Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis).
Cardiac disorders	Autoimmune myocarditis/cardiomyopathy.
Skin disorders	Alopecia areata, psoriasis, vitiligo, Raynaud's phenomenon, erythema nodosum, autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis), cutaneous lupus erythematosus, morphoea, lichen planus, Stevens-Johnson syndrome, Sweet's syndrome.
Hematologic disorders	Autoimmune hemolytic anemia, autoimmune thrombocytopenia, antiphospholipid syndrome, thrombocytopenia.
Metabolic disorders	Autoimmune thyroiditis, Grave's or Basedow's disease, new onset Hashimoto thyroiditis, diabetes mellitus type 1, Addison's disease.
Other disorders	Goodpasture syndrome, idiopathic pulmonary fibrosis, pernicious anemia, sarcoidosis.

Source: Adapted from protocol 2019nCoV-301 Table 11. IND 22430.
Abbreviations: ANCA=anti-neutrophil cytoplasmic antibody; CREST=calcinosis, Raynaud's phenomenon; esophageal dysmotility; sclerodactyly, telangiectasia; IgA=immunoglobulin A; MedDRA=Medical Dictionary for Regulatory Activities

Notes	Symptoms	Symptoms Code	Vaccine Type	Vaccine Type Code	Events Reported	Percent
	EMBOLISM	10061169	COVID19 VACCINE	COVID19	96	0.0098
	EMBOLISM	10061169	COVID19-2	COVID19-2	3	0.0003
Total	EMBOLISM	10061169			99	0.0101
	MYOCARDITIS	10028606	COVID19 VACCINE	COVID19	3302	0.3368
	MYOCARDITIS	10028606	COVID19-2	COVID19-2	35	0.0036
Total	MYOCARDITIS	10028606			3337	0.3403
	PERICARDITIS	10034484	COVID19 VACCINE	COVID19	2293	0.2339
	PERICARDITIS	10034484	COVID19-2	COVID19-2	58	0.0059
Total	PERICARDITIS	10034484			2351	0.2398
	THROMBOSIS	10043607	COVID19 VACCINE	COVID19	5310	0.5416
	THROMBOSIS	10043607	COVID19-2	COVID19-2	68	0.0069
Total	THROMBOSIS	10043607			5378	0.5485
	THROMBOSIS WITH THROMBOCYTOPENIA SYNDROME	10086158	COVID19 VACCINE	COVID19	28	0.0029
	THROMBOSIS WITH THROMBOCYTOPENIA SYNDROME	10086158	COVID19-2	COVID19-2	1	0.0001
Total	THROMBOSIS WITH THROMBOCYTOPENIA SYNDROME	10086158			29	0.003
Total					11194	1.1417

Total

Dataset: The Vaccine Adverse Event Reporting System (VAERS)

Query Parameters:

State / Territory: The United States/Territories/Unknown

Symptoms: EMBOLISM, MYOCARDITIS, PERICARDITIS; THROMBOSIS, THROMBOSIS WITH THROMBOCYTOPENIA SYNDROME

Vaccine Manufacturer: JANSSEN; MODERNA; NOVAVAX; PFIZER\BIONTECH

Vaccine Products: COVID19 (COVID19 (JANSSEN)) (1203); COVID19 (COVID19 (MODERNA)) (1201); COVID19 (COVID19 (NOVAVAX)) (1210); COVID19 (COVID19 (PFIZER-BIONTECH)) (1200); COVID19-2 (COVID19-2)

Help: See http://wonder.cdc.gov/wonder/help/vaers.html for more information.

Query Date: Sep 8, 2023 12:26:26 PM

Suggested Citation: Accessed at http://wonder.cdc.gov/vaers.html on Sep 8, 2023 12:26:26 PM

Messages:

1. VAERS data in CDC WONDER are updated every Friday. Hence, results for the same query can change from week to week.
2. These results are for 9,805 total events.

Footnotes:

1. Submitting a report to VAERS does not mean that healthcare personnel or the vaccine caused or contributed to the adverse event (possible side effect).

Caveats:

1. VAERS accepts reports of adverse events and reactions that occur following vaccination. Healthcare providers, vaccine manufacturers, and the public can submit reports to VAERS. While very important in monitoring vaccine safety, VAERS reports alone cannot be used to determine if a vaccine caused or contributed to an adverse event or illness. The reports may contain information that is incomplete, inaccurate, coincidental, or unverifiable. Most reports to VAERS are voluntary, which means they are subject to biases. This creates specific limitations on how the data can be used scientifically. Data from VAERS reports should always be interpreted with these limitations in mind. The strengths of VAERS are that it is national in scope and can quickly provide an early warning of a safety problem with a vaccine. As part of CDC and FDA's multi-system approach to post-licensure vaccine safety monitoring, VAERS is designed to rapidly detect unusual or unexpected patterns of adverse events, also known as "safety signals." If a safety signal is found in VAERS, further studies can be done in safety systems such as the CDC's Vaccine Safety Datalink (VSD) or the Clinical Immunization Safety Assessment (CISA) project. These systems do not have the same limitations as VAERS, and can better assess health risks and possible connections between adverse events and a vaccine.

Key considerations and limitations of VAERS data: Vaccine providers are encouraged to report any clinically significant health problem following vaccination to VAERS, whether or not they believe the vaccine was the cause. Reports may include incomplete, inaccurate, coincidental and unverified information. The number of reports alone cannot be interpreted or used to reach conclusions about the existence, severity, frequency, or rates of problems associated with vaccines. VAERS data are limited to vaccine adverse event reports received between 1990 and the most recent date for which data are available. VAERS data do not represent all known safety information for a vaccine and should be interpreted in the context of other scientific information.

Some items may have more than 1 occurrence in any single event report, such as Symptoms, Vaccine Products, Manufacturers, and Event Categories. If data are grouped by any of these items, then the number in the Events Reported column may exceed the total number of unique events. If percentages are shown, then the associated percentage of total unique event reports will exceed 100% In such cases. For example, the number of Symptoms mentioned is likely to exceed the number of events reported, because many reports include more than 1 Symptom. When more than 1 Symptom occurs in a single report, then the percentage of Symptoms to unique events is more than 100%. More information: http://wonder.cdc.gov/wonder/help/vaers.html#Suppress.

These items in the results table are not fully selected: COVID19 VACCINE. The Query Description lists the actual values selected.

Data contains VAERS reports processed as of 09/01/2023. The VAERS data in WONDER are updated weekly, yet the VAERS system receives continuous updates including revisions and new reports for preceding time periods. Duplicate event reports and/or reports determined to be false are removed from VAERS. More information: http://wonder.cdc.gov/wonder/help/vaers.html#Reporting.

Notes	Symptoms	Symptoms Code	Vaccine Type	Vaccine Type Code	State / Territory	State / Territory Code	Events Reported	Fr	ent
	EMBOLISM	10061169	COVID19 VACCINE	COVID19	South Carolina	45	1	0.009	
Total	EMBOLISM	10061169	COVID19 VACCINE	COVID19			1	0.009	
	EMBOLISM	10061169	COVID19-2	COVID19-2	South Carolina	45	0	0	
Total	EMBOLISM	10061169	COVID19-2	COVID19-2			0	0	
Total	EMBOLISM	10061169					1	0.009	
	MYOCARDITIS	10028606	COVID19 VACCINE	COVID19	South Carolina	45	33	0.2973	
Total	MYOCARDITIS	10028606	COVID19 VACCINE	COVID19			33	0.2973	
	MYOCARDITIS	10028606	COVID19-2	COVID19-2	South Carolina	45	0	0	
Total	MYOCARDITIS	10028606	COVID19-2	COVID19-2			0	0	
Total	MYOCARDITIS	10028606					33	0.2973	
	PERICARDITIS	10034484	COVID19 VACCINE	COVID19	South Carolina	45	31	0.2793	
Total	PERICARDITIS	10034484	COVID19 VACCINE	COVID19			31	0.2793	
	PERICARDITIS	10034484	COVID19-2	COVID19-2	South Carolina	45	0	0	
Total	PERICARDITIS	10034484	COVID19-2	COVID19-2			0	0	
Total	PERICARDITIS	10034484					31	0.2793	
	THROMBOSIS	10043607	COVID19 VACCINE	COVID19	South Carolina	45	60	0.5405	
Total	THROMBOSIS	10043607	COVID19 VACCINE	COVID19			60	0.5405	
	THROMBOSIS	10043607	COVID19-2	COVID19-2	South Carolina	45	0	0	
Total	THROMBOSIS	10043607	COVID19-2	COVID19-2			0	0	
Total	THROMBOSIS	10043607					60	0.5405	
	THROMBOSIS WITH THROMBOCYTOPENIA SYNDROME	10086158	COVID19 VACCINE	COVID19	South Carolina	45	0	0	
Total	THROMBOSIS WITH THROMBOCYTOPENIA SYNDROME	10086158	COVID19 VACCINE	COVID19			0	0	
	THROMBOSIS WITH THROMBOCYTOPENIA SYNDROME	10086158	COVID19-2	COVID19-2	South Carolina	45	0	0	
Total	THROMBOSIS WITH THROMBOCYTOPENIA SYNDROME	10086158	COVID19-2	COVID19-2			0	0	
Total	THROMBOSIS WITH THROMBOCYTOPENIA SYNDROME	10086158					0	0	
Total							128	1.1261	

Dataset: The Vaccine Adverse Event Reporting System (VAERS)
Query Parameters:
State / Territory: South Carolina
Symptoms: EMBOLISM; MYOCARDITIS; PERICARDITIS; THROMBOSIS; THROMBOSIS WITH THROMBOCYTOPENIA SYNDROME
Vaccine Manufacturer: JANSSEN; MODERNA; NOVAVAX; PFIZER\BIONTECH
Vaccine Products: COVID19 VACCINE (COVID19); COVID19-2 (COVID19-2)

Help: See http://wonder.cdc.gov/wonder/help/vaers.html for more information.

Query Date: Sep 11, 2023 11:19:50 AM

Suggested Citation: Accessed at http://wonder.cdc.gov/vaers.html on Sep 11, 2023 11:19:58 AM

Messages:
1. VAERS data in CDC WONDER are updated every Friday. Hence, results for the same query can change from week to week.
2. These results are for 111 total events.

Footnotes:
1. Submitting a report to VAERS does not mean that healthcare personnel or the vaccine caused or contributed to the adverse event (possible side effect).

Caveats:
VAERS accepts reports of adverse events and reactions that occur following vaccination. Healthcare providers, vaccine manufacturers, and the public can submit reports to VAERS. While very important in monitoring vaccine safety, VAERS reports alone cannot be used to determine if a vaccine caused or contributed to an adverse event or illness. The reports may contain information that is incomplete, inaccurate, coincidental, or unverifiable. Most reports to VAERS are voluntary, which means they are subject to biases. This creates specific limitations on how the data can be used scientifically. Data from VAERS reports should always be interpreted with these limitations in mind. The strengths of VAERS are that it is national in scope and can quickly provide an early warning of a safety problem with a vaccine. As part of CDC and FDA's multi-system approach to post-licensure vaccine safety monitoring, VAERS is designed to rapidly detect unusual or unexpected patterns of adverse events, also known as "safety signals." If a safety signal is found in VAERS, further studies can be done in safety systems such as the CDC's Vaccine Safety Datalink (VSD) or the Clinical Immunization Safety Assessment (CISA) project. These systems do not have the same limitations as VAERS, and can better assess health risks and possible connections between adverse events and a vaccine.

Key considerations and limitations of VAERS data: Vaccine providers are encouraged to report any clinically significant health problem following vaccination to VAERS, whether or not they believe the vaccine was the cause. Reports may include incomplete, inaccurate, coincidental and unverified information. The number of reports alone cannot be interpreted or used to reach conclusions about the existence, severity, frequency, or rates of problems associated with vaccines. VAERS data are limited to vaccine adverse event reports received between 1990 and the most recent date for which data are available. VAERS data do not represent all known safety information for a vaccine and should be interpreted in the context of other scientific information

Some items may have more than 1 occurrence in any single event report, such as Symptoms, Vaccine Products, Manufacturers, and Event Categories. If data are grouped by any of these items, then the number in the Events Reported column may exceed the total number of unique events. If percentages are shown, then the associated percentage of total unique event reports will exceed 100% in such cases. For example, the number of Symptoms mentioned is likely to exceed the number of events reported, because many reports include more than 1 Symptom. When more than 1 Symptom occurs in a single report, then the percentage of Symptoms to unique events is more than 100%. More information: http://wonder.cdc.gov/wonder/help/vaers.html#Suppress

Data contains VAERS reports processed as of 09/01/2023. The VAERS data in WONDER are updated weekly, yet the VAERS system receives continuous updates including revisions and new reports for preceding time periods. Duplicate event reports and/or reports determined to be false are removed from VAERS. More information: http://wonder.cdc.gov/wonder/help/vaers.html#Reporting

U.S. FOOD & DRUG ADMINISTRATION

May 25, 2023

Pfizer, Inc.
Attention: Karen Baker
Director, Global Regulatory Affairs
235 East 42nd Street
New York, NY 10017-5755

RE: Emergency Use Authorization 105

Dear Ms. Baker:

This letter is in response to Pfizer, Inc.'s (Pfizer) request that the Food and Drug Administration (FDA or Agency) issue an Emergency Use Authorization (EUA) for the emergency use of PAXLOVID (nirmatrelvir co-packaged with ritonavir) for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in certain adults and pediatric patients pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §360bbb-3).

On February 4, 2020, as amended on March 15, 2023, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency, or a significant potential for a public health emergency, that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19).[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[2]

On December 22, 2021, the FDA issued an EUA for emergency use of PAXLOVID for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and

[1] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*. February 4, 2020; U.S. Department of Health and Human Services, *Amended Determination of a Public Health Emergency or Significant Potential for a Public Health Emergency Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3(b)*. March 15, 2023. 88 FR 16644 (March 20, 2023) ("Amended Determination").

[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020). *See* Amended Determination ("The declarations issued pursuant to section 564(b)(1) of the FD&C Act that circumstances exist justifying the authorization of emergency use of certain in vitro diagnostics, personal respiratory protective devices, other medical devices and drugs and biological products, as set forth in those declarations, and that are based on the February 4, 2020 determination, remain in effect until those declarations are terminated in accordance with section 564 of the FD&C Act.").

older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. At that time, PAXLOVID was not FDA-approved for any indication.

PAXLOVID is comprised of nirmatrelvir, a SARS-CoV-2 main protease inhibitor (M^{pro}: also referred to as $3CL^{pro}$ or nsp5 protease), co-packaged with ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor. Ritonavir, which has no activity against SARS-CoV-2 on its own, is included to inhibit the CYP3A-mediated metabolism of nirmatrelvir and consequently increase nirmatrelvir plasma concentrations to levels anticipated to inhibit SARS-CoV-2 replication.

FDA subsequently reissued the Letter of Authorization (LOA) on March 17, 2022[3], April 14, 2022[4], July 6, 2022[5], August 5, 2022[6], October 27, 2022[7], and February 1, 2023.[8]

On May 25, 2023, FDA approved NDA 217188 for PAXLOVID, which is indicated for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.

On May 25, 2023, having concluded that revising this EUA is appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA is reissuing the February 1, 2023 letter in its entirety, to incorporate revisions to the authorized use for PAXLOVID under this EUA, to revise condition L on the monitoring and analysis of SARS-CoV-2 variants, and to remove certain post-authorization requirements from this LOA that are adequately addressed as post-market requirements or post-market commitments associated with the approval of NDA 217188.

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[3] In its March 17, 2022 revision, FDA revised the LOA to add a new condition of authorization regarding registration and listing. Condition H in the LOA was also revised to require Pfizer to recall distributed product, upon request by FDA, in the event a significant quality problem is identified that impacts already distributed PAXLOVID.

[4] In its April 14, 2022 revision, FDA revised the LOA to authorize an additional dose pack presentation of PAXLOVID with appropriate dosing for patients within the scope of this authorization with moderate renal impairment. Corresponding revisions were also incorporated into the "How Supplied" section of the Fact Sheet for Healthcare Providers.

[5] In its July 6, 2022 revision, FDA authorized state-licensed pharmacists to prescribe PAXLOVID subject to certain conditions detailed in Section II (Scope of Authorization) of this LOA. Corresponding revisions were also incorporated into the Fact Sheet for Healthcare Providers. Updates were also incorporated to certain post-authorization requirements detailed in Condition O of this letter.

[6] In its August 5, 2022 revision, FDA revised the LOA to add new post-authorization requirements in Condition O of this letter for Pfizer to conduct a clinical trial in patients with "COVID-19 rebound" and a clinical trial evaluating different durations of treatment in immunocompromised patients with mild-to-moderate COVID-19. The Fact Sheet for Patients, Parents, and Caregivers was also revised to include additional clarifying information on how to take PAXLOVID, which included pictures of packaging and tablets for both dosing presentations.

[7] In its October 27, 2022 revision, FDA incorporated clarifying revisions to Condition X of this letter. Condition W was also revised to require that all printed matter, advertising and promotional materials relating to the use of PAXLOVID under this authorization be submitted to FDA for consideration at least 14 calendar days prior to initial dissemination or first use.

[8] In its February 1, 2023 revision, FDA revised the scope of authorization to no longer require positive results of direct SARS-CoV-2 viral testing. As revised, the scope of authorization required, in addition to other requirements, that adults and pediatric patients (12 years of age and older weighing at least 40 kg) have a current diagnosis of mild-to-moderate COVID-19. Corresponding changes were also made to the authorized Fact Sheets. Condition O in this letter was also revised based on the completion of a post-authorization requirement. The Fact Sheet for Healthcare Providers was also revised to reflect the current indication for Veklury, an approved alternative to Paxlovid, and to include new information on drug-drug interactions.

Corresponding revisions, when appropriate, were incorporated into the authorized Fact Sheets. The authorized Fact Sheet for Healthcare Providers was also revised to include a boxed warning on the identification of and assessment for drug-drug interactions with PAXLOVID. Relevant information on drug-drug interactions was also incorporated in the Fact Sheet for Patients, Parents and Caregivers.

Based on the totality of scientific evidence available to FDA, including data from the clinical trial EPIC-HR (NCT04960202), a Phase 2/3 randomized, double blind, placebo-controlled clinical trial, it is reasonable to believe that PAXLOVID may be effective for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (Section II), and when used under the conditions described in this authorization, the known and potential benefits of PAXLOVID outweigh the known and potential risks of such product.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of PAXLOVID for the treatment of mild-to-moderate COVID-19 in certain adults and pediatric patients (12 years of age and older weighing at least 40 kg), as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of PAXLOVID for the treatment of COVID-19, when administered as described in the Scope of Authorization (Section II), meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

1. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that PAXLOVID may be effective for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (Section II), and that, when used under the conditions described in this authorization, the known and potential benefits of PAXLOVID outweigh the known and potential risks of such product; and

3. There is no adequate, approved, and available alternative to the emergency use of PAXLOVID for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death.[9,10]

[9] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.
[10] Veklury (remdesivir) is an FDA-approved alternative to PAXLOVID when used for the treatment of mild-to-

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Distribution of the authorized PAXLOVID will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Pfizer will supply PAXLOVID to authorized distributor(s)[11], who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed;

- PAXLOVID may only be used by healthcare providers for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death;

  Limitations on Authorized Use

  - PAXLOVID is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.[12]
  - PAXLOVID is not authorized for use as pre-exposure or as post-exposure prophylaxis for prevention of COVID-19.
  - PAXLOVID is not authorized for use for longer than 5 consecutive days.

- PAXLOVID may be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs.[13]

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moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death. Veklury is administered via intravenous infusion for a total treatment duration of 3 days. Although Veklury is an FDA-approved alternative to PAXLOVID as described above, FDA does not consider Veklury to be an adequate alternative to PAXLOVID for this authorized use because it may not be feasible or practical for certain patients (e.g., it requires an intravenous infusion daily for 3 days). Additionally, although different presentations of PAXLOVID are now FDA-approved for the treatment of mild-to-moderate COVID-19 in certain adults, there are not sufficient quantities of the approved PAXLOVID available for distribution to this population in its entirety at the time of reissuance of the EUA, and PAXLOVID is not FDA-approved for individuals younger than 18 years of age. Apart from the previous sentence, all reference to the term "PAXLOVID" in this LOA refer to product that is labeled in accordance with this EUA. See "Product Description" in this LOA for more information.

[11] "Authorized Distributor(s)" are identified by Pfizer as an entity or entities allowed to distribute authorized PAXLOVID.

[12] Patients requiring hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID may complete the full 5-day treatment course per the healthcare provider's discretion.

[13] The term "State" includes any State or Territory of the United States, the District of Columbia, and the Commonwealth of Puerto Rico. See Section 201(a)(1) of the Act.

- PAXLOVID may also be prescribed for an individual patient by a state-licensed pharmacist under the following conditions:

    - Sufficient information is available, such as through access to health records less than 12 months old or consultation with a health care provider in an established provider-patient relationship with the individual patient, to assess renal and hepatic function; and
    - Sufficient information is available, such as through access to health records, patient reporting of medical history, or consultation with a health care provider in an established provider-patient relationship with the individual patient, to obtain a comprehensive list of medications (prescribed and non-prescribed) that the patient is taking to assess for potential drug interaction.

- The use of PAXLOVID covered by this authorization must be in accordance with the authorized Fact Sheets.

Product Description

PAXLOVID consists of 150 mg tablets of nirmatrelvir that are co-packaged with 100 mg tablet ritonavir.

PAXLOVID is authorized to be distributed in the following presentations, which are distinguishable by the specific amount of active ingredient per treatment course:

- *300 mg nirmatrelvir;100 mg ritonavir*: Each carton contains 30 tablets divided in 5 daily-dose blister cards. Each blister card contains 4 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each). Nirmatrelvir tablets and ritonavir tablets are supplied in separate blister cavities within the same child-resistant blister card. Each carton and individual blister card include the following statement: "For use under Emergency Use Authorization."
- *150 mg nirmatrelvir; 100 mg ritonavir*[14]: Each carton contains 20 tablets divided in 5 daily-dose blister cards. Each blister card contains 2 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each). Nirmatrelvir tablets and ritonavir tablets are supplied in separate blister cavities within the same child-resistant blister card. Each carton and individual blister card include the following statement: "For use under Emergency Use Authorization."

The authorized storage and handling information for PAXLOVID is included in the authorized Fact Sheet for Healthcare Providers.

PAXLOVID is authorized for emergency use with the following product-specific information required to be made available to healthcare providers and to patients, parents, and caregivers,

[14] The 150 mg nirmatrelvir;100 mg ritonavir presentation is designed to provide appropriate dosing for patients within the scope of this authorization with moderate renal impairment. See section 2.2 of the Fact Sheet for Healthcare Providers for more information.

respectively, through Pfizer's website www.COVID19oralRX.com (referred to as the "authorized labeling"):

- Fact Sheet for Healthcare Providers: Emergency Use Authorization (EUA) for PAXLOVID
- Fact Sheet for Patients, Parents and Caregivers: Emergency Use Authorization (EUA) of PAXLOVID for Coronavirus Disease 2019 (COVID-19)

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of PAXLOVID, when used for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg), and used in accordance with this Scope of Authorization (Section II), outweigh the known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that PAXLOVID may be effective for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that PAXLOVID (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of PAXLOVID under this EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), PAXLOVID is authorized for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

Pfizer and Authorized Distributors[15]

A. Pfizer and authorized distributor(s) will ensure that PAXLOVID is distributed and the authorized labeling (i.e., Fact Sheets) will be made available to healthcare facilities and/or healthcare providers as described in Section II of this Letter of Authorization.

[15] Supra at Note 11.

B. Pfizer and authorized distributor(s) will ensure that appropriate storage is maintained until the product is delivered to healthcare facilities and/or healthcare providers.

C. Pfizer and authorized distributor(s) will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., U.S. government agencies, state and local government authorities, authorized distributors, healthcare facilities, healthcare providers) involved in distributing or receiving PAXLOVID. Pfizer will provide to all relevant stakeholders a copy of this Letter of Authorization and communicate any subsequent amendments that might be made to this Letter of Authorization and its authorized accompanying materials (i.e., Fact Sheets).

D. Pfizer may request changes to this authorization, including to the authorized Fact Sheets for PAXLOVID. Any request for changes to this EUA must be submitted to the Office of Infectious Diseases/Office of New Drugs/Center for Drug Evaluation and Research. Such changes require appropriate authorization prior to implementation.[16]

E. Pfizer may develop and disseminate instructional and educational materials (e.g., materials providing information on product administration and/or patient monitoring) that are consistent with the authorized emergency use of PAXLOVID as described in this Letter of Authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs. Any instructional and educational materials that are inconsistent with the authorized labeling for PAXLOVID are prohibited. If the Agency notifies Pfizer that any instructional and educational materials are inconsistent with the authorized labeling, Pfizer must cease distribution of such instructional and educational materials. Furthermore, as part of its notification, the Agency may also require Pfizer to issue corrective communication(s).

F. Pfizer will report to FDA all serious adverse events and medication errors potentially related to PAXLOVID use that are reported to Pfizer using either of the following options.

   Option 1: Submit reports through the Safety Reporting Portal (SRP) as described on the FDA SRP web page.

   Option 2: Submit reports directly through the Electronic Submissions Gateway (ESG) as described on the FAERS electronic submissions web page.

[16] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study; (8) new strengths of the authorized product, new product sources (e.g., of active pharmaceutical ingredient) or of product components. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), (7), or (8), review and concurrence is required from the Counter-Terrorism and Emergency Coordination Staff/Office of the Center Director/CDER and the Office of Counterterrorism and Emerging Threats/Office of the Chief Scientist.

Submitted reports under both options must state: "PAXLOVID use for COVID-19 under Emergency Use Authorization (EUA)." For reports submitted under Option 1, include this language at the beginning of the question "Describe Event" for further analysis. For reports submitted under Option 2, include this language at the beginning of the "Case Narrative" field.

G. All manufacturing, packaging, and testing sites for both drug substance and drug product will comply with current good manufacturing practice requirements of Section 501(a)(2)(B) of the Act.

H. Pfizer will submit information to the Agency within three working days of receipt of any information concerning significant quality problems with distributed drug product of PAXLOVID that includes the following:

- Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or
- Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the product to meet the established specifications.

If a significant quality problem affects unreleased product and may also impact product(s) previously released and distributed, then information must be submitted for all potentially impacted lots.

Pfizer will include in its notification to the Agency whether the batch, or batches, in question will be recalled. If FDA requests that these, or any other batches, at any time, be recalled, Pfizer must recall them.

If not included in its initial notification, Pfizer must submit information confirming that Pfizer has identified the root cause of the significant quality problems, taken corrective action, and provide a justification confirming that the corrective action is appropriate and effective. Pfizer must submit this information as soon as possible but no later than 45 calendar days from the initial notification.

I. Pfizer will manufacture PAXLOVID to meet all quality standards and per the manufacturing process and control strategy as detailed in Pfizer's EUA request. Pfizer will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product, without notification to and concurrence by the Agency as described under Condition D.

J. Pfizer will list each presentation of PAXLOVID with a unique product NDC under the marketing category of Emergency Use Authorization. Further, the listing will include each establishment where manufacturing is performed for the drug and the type of operation performed at each such establishment.

K. Through a process of inventory control, Pfizer and authorized distributor(s) will maintain records regarding distribution of PAXLOVID (i.e., lot numbers, quantity, receiving site, receipt date).

L. Pfizer must provide the following information to the Agency:

1. Pfizer will conduct a study to monitor genomic database(s) for the emergence of SARS-CoV-2 variants with amino acid polymorphisms in M^{pro} or M^{pro} cleavage sites. Pfizer will conduct these surveillance activities on at least a monthly basis and submit reports to FDA on these surveillance activities on a quarterly basis. In these reports, Pfizer will provide monthly counts of M^{pro} and M^{pro} cleavage site polymorphisms (minimum 0.1% frequency) globally, in the U.S., and in individual countries (any countries with a minimum of 1,000 sequences in at least one month).
2. Pfizer will also provide ad-hoc reports (between quarterly reports) whenever a novel M^{pro} or M^{pro} cleavage site polymorphism is detected at a monthly frequency $\geq$1% either globally, in the U.S., or in an individual country with a minimum of 1,000 sequences. Pfizer will conduct phenotypic analysis for any M^{pro} or M^{pro} cleavage site polymorphisms that are detected at a frequency $\geq$1% either globally or in the U.S. for any single month.

M. Pfizer shall provide samples as requested of the authorized nirmatrelvir to HHS for evaluation of activity against emerging global viral variants of SARS-CoV-2, including specific amino acid substitution(s) of interest (e.g., variants that are highly prevalent or that harbor substitutions in the target protein(s) or target cleavage sites) within 5 business days of any request made by HHS. Analyses performed with the supplied quantity of authorized nirmatrelvir may include, but are not limited to, cell culture potency assays, biochemical assays, and in vivo efficacy assays.

N. Pfizer and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

Healthcare Facilities to Whom PAXLOVID Is Distributed and Healthcare Providers Administering PAXLOVID

O. Healthcare facilities and healthcare providers will ensure that they are aware of the Letter of Authorization, and the terms herein, and that the authorized Fact Sheets are made available to healthcare providers and to patients, parents, and caregivers, respectively, through appropriate means, prior to administration of PAXLOVID.

P. Healthcare facilities and healthcare providers receiving PAXLOVID will track all serious adverse events and medication errors that are considered to be potentially related to PAXLOVID use and must report these to FDA in accordance with the Fact Sheet for Healthcare Providers. Complete and submit a MedWatch form (www.fda.gov/medwatch/report.htm), or complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178) (these forms can be found via link above). Call 1-

800-FDA-1088 for questions. Submitted reports must state, "PAXLOVID use for COVID-19 under Emergency Use Authorization" at the beginning of the question "Describe Event" for further analysis. A copy of the completed FDA Form 3500 must also be provided to Pfizer per the instructions in the authorized labeling.

Q. Healthcare facilities and healthcare providers will ensure that appropriate storage is maintained until the product is administered consistent with the terms of this letter and the authorized labeling.

R. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensing and administration of PAXLOVID for the use authorized in this letter (i.e., lot numbers, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered).

S. Healthcare facilities will ensure that any records associated with this EUA are maintained until notified by Pfizer and/or FDA. Such records will be made available to Pfizer, HHS, and FDA for inspection upon request.

T. Healthcare facilities and providers will report therapeutics information and utilization data as directed by HHS.

Conditions Related to Printed Matter, Advertising, and Promotion

U. All descriptive printed matter, advertising, and promotional materials relating to the use of PAXLOVID under this authorization shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in Section 502(a) and (n) of the Act, as applicable, and FDA implementing regulations. References to "approved labeling", "permitted labeling", or similar terms in these requirements shall be understood to refer to the authorized labeling for the use of PAXLOVID under this authorization. In addition, such materials shall:

- Be tailored to the intended audience.
- Not take the form of reminder advertisements, as that term is described in 21 CFR 202.1(e)(2)(i), 21 CFR 200.200 and 21 CFR 201.100(f).
- Present the same risk information relating to the major side effects and contraindications concurrently in the audio and visual parts of the presentation for advertising and promotional materials in audio-visual format.
- Be accompanied by the authorized labeling, if the promotional materials are not subject to Section 502(n) of the Act.
- Be submitted to FDA accompanied by Form FDA-2253 for consideration at least 14 calendar days prior to initial dissemination or first use.

V. Pfizer may disseminate descriptive printed matter, advertising, and promotional materials relating to the emergency use of PAXLOVID that provide accurate descriptions of safety results and efficacy results on a clinical endpoint(s) from the clinical trial(s) summarized

in the authorized labeling. Such materials must include any limitations of the clinical trial data as described in the authorized labeling. Pfizer may not imply that PAXLOVID is FDA-approved for its authorized use in the pediatric patient population as detailed in the Scope of Authorization (Section II) by making statements such as "PAXLOVID is safe and effective for the treatment of COVID-19 in pediatric patients."

W. All descriptive printed matter, advertising, and promotional material, relating to the use of PAXLOVID under this authorization clearly and conspicuously shall state that:

- PAXLOVID has not been approved, but has been authorized for emergency use by FDA under an EUA, for the treatment of mild-to-moderate COVID-19 in pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death; and
- The emergency use of PAXLOVID is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

If the Agency notifies Pfizer that any descriptive printed matter, advertising, or promotional materials do not meet the terms set forth in Conditions U through W of this EUA, Pfizer must cease distribution of such descriptive printed matter, advertising, or promotional materials in accordance with the Agency's notification. Furthermore, as part of its notification, the Agency may also require Pfizer to issue corrective communication(s).

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

_____

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR PAXLOVID™

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use PAXLOVID™ under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for PAXLOVID.

PAXLOVID (nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use
Original EUA Authorized Date: 12/2021
Revised EUA Authorized Date: 05/2023

WARNING: SIGNIFICANT DRUG INTERACTIONS WITH PAXLOVID
See full prescribing information for complete boxed warning.

- **PAXLOVID includes ritonavir, a strong CYP3A inhibitor, which may lead to greater exposure of certain concomitant medications, resulting in potentially severe, life-threatening, or fatal events.** ***(4, 5.1, 7)***
- **Prior to prescribing PAXLOVID: 1) Review all medications taken by the patient to assess potential drug-drug interactions with a strong CYP3A inhibitor like PAXLOVID and 2) Determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring.** ***(7)***
- **Consider the benefit of PAXLOVID treatment in reducing hospitalization and death, and whether the risk of potential drug-drug interactions for an individual patient can be appropriately managed.** ***(5.1, 7, 14)***

----------RECENT MAJOR CHANGES----------

Boxed Warning: added	05/2023
Limitations of Authorized Use (1): updated	05/2023
Contraindications (4): add rifapentine	05/2023
Warnings and Precautions (5.1, 5.2): updated	05/2023
Adverse Reactions (6.1, 6.2): updated	05/2023
Drug Interactions (7.1, 7.3): updated	05/2023
Use in Specific Populations (8.1, 8.2, 8.5, 8.6): updated	05/2023
Clinical Pharmacology (12.1, 12.2, 12.3, 12.4): updated	05/2023
Nonclinical Toxicology (13.1, 13.2): updated	05/2023
Clinical Studies (14.1, 14.2, 14.3): updated	05/2023
Emergency Use Authorization (1): removal of requirement of SARS-CoV-2 viral testing	02/2023
Warnings and Precautions (5.2, 17): revision to hypersensitivity reactions to PAXLOVID including anaphylaxis	09/2022
Adverse Reactions (6.2): addition of new adverse reactions	09/2022
Microbiology (12.4): addition of Omicron sub-variants, *in vivo*, and resistance data	09/2022
Drug Interactions (7.3): addition of new drug interactions	08/2022
Emergency Use Authorization (1): addition of pharmacist prescribing guidance	07/2022
Contraindications (4): addition of new contraindicated drugs	06/2022
Microbiology (12.4): addition of viral RNA rebound	06/2022

----------EUA FOR PAXLOVID ----------

The U.S. Food and Drug Administration has issued an EUA for the emergency use of PAXLOVID which includes nirmatrelvir, a SARS-CoV-2 main protease (M^{pro}: also referred to as 3CLpro or nsp5 protease) inhibitor, and ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor, for the treatment of adults and pediatric patients (12 years of age and older weighing at least 40 kg) with mild-to-moderate coronavirus disease 2019 (COVID-19) and who are at high risk for progression to severe COVID-19, including hospitalization or death.

LIMITATIONS OF AUTHORIZED USE

- PAXLOVID is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.
- PAXLOVID is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
- PAXLOVID is not authorized for use longer than 5 consecutive days.

PAXLOVID may be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs.

PAXLOVID may also be prescribed for an individual patient by a state-licensed pharmacist under the following conditions:

- Sufficient information is available, such as through access to health records less than 12 months old or consultation with a health care provider in an established provider-patient relationship with the individual patient, to assess renal and hepatic function; and
- Sufficient information is available, such as through access to health records, patient reporting of medical history, or consultation with a health care provider in an established provider-patient relationship with the individual patient, to obtain a comprehensive list of medications (prescribed and non-prescribed) that the patient is taking to assess for potential drug interaction.

The state-licensed pharmacist should refer an individual patient for clinical evaluation (e.g., telehealth, in-person visit) with a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs, if any of the following apply:

- Sufficient information is not available to assess renal and hepatic function.
- Sufficient information is not available to assess for a potential drug interaction.
- Modification of other medications is needed due to a potential drug interaction.
- PAXLOVID is not an appropriate therapeutic option based on the authorized Fact Sheet for Healthcare Providers or due to potential drug interactions for which recommended monitoring would not be feasible.

PAXLOVID is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of PAXLOVID under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

See Full Fact Sheet for Healthcare Providers for the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19.

----------DOSAGE AND ADMINISTRATION ----------

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. (2.1)
Nirmatrelvir must be co-administered with ritonavir. (2.1)

- Initiate PAXLOVID treatment as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset. (2.1)
- Administer orally with or without food. (2.1)
- Dosage: 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together twice daily for 5 days. (2.1, 2.2)
- **Dose reduction for moderate renal impairment (eGFR ≥30 to <60 mL/min)**: 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet), with both tablets taken together twice daily for 5 days. (2.3)
- PAXLOVID is not recommended in patients with severe renal impairment (eGFR <30 mL/min). (2.3, 8.6)
- PAXLOVID is not recommend in patients with severe hepatic impairment (Child-Pugh Class C). (2.4, 8.7)

----------DOSAGE FORMS AND STRENGTHS ----------

- Tablets: nirmatrelvir 150 mg (3)
- Tablets: ritonavir 100 mg (3)

----------CONTRAINDICATIONS----------

- History of clinically significant hypersensitivity reactions to the active ingredients (nirmatrelvir or ritonavir) or any other components. (4)

- Co-administration with drugs highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions. (4, 7.3)
- Co-administration with potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. (4)

---------- WARNINGS AND PRECAUTIONS----------

- The concomitant use of PAXLOVID and certain other drugs may result in potentially significant drug interactions. Consult the full prescribing information prior to and during treatment for potential drug interactions. (5.1, 7)
- Hypersensitivity Reactions: Anaphylaxis, serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome), and other hypersensitivity reactions have been reported with PAXLOVID. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue PAXLOVID and initiate appropriate medications and/or supportive care. (5.2)
- Hepatotoxicity: Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir. (5.3)
- HIV-1 Drug Resistance: PAXLOVID use may lead to a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection. (5.4)

---------- ADVERSE REACTIONS ----------

Adverse events (incidence ≥1% and greater incidence than in the placebo group) were dysgeusia and diarrhea. (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to PAXLOVID (1) by submitting FDA Form 3500 online, (2) by downloading this form and then submitting by mail or fax, or (3) contacting the FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to Pfizer Inc. at fax number: 1-866-635-8337. (6.4)

----------DRUG INTERACTIONS----------

Co-administration of PAXLOVID can alter the plasma concentrations of other drugs and other drugs may alter the plasma concentrations of PAXLOVID. Consider the potential for drug interactions prior to and during PAXLOVID therapy and review concomitant medications during PAXLOVID therapy. (4, 5.1, 7, 12.3)

See FACT SHEET FOR PATIENTS, PARENTS, AND CAREGIVERS.

TABLE OF CONTENTS*

* Sections or subsections omitted from the EUA are not listed.

FULL FACT SHEET FOR HEALTHCARE PROVIDERS

WARNING: SIGNIFICANT DRUG INTERACTIONS WITH PAXLOVID

- **PAXLOVID includes ritonavir, a strong CYP3A inhibitor, which may lead to greater exposure of certain concomitant medications, resulting in potentially severe, life-threatening, or fatal events *[see Contraindications (4), Warnings and Precautions (5.1), and Drug Interactions (7)]*.**
- **Prior to prescribing PAXLOVID: 1) Review all medications taken by the patient to assess potential drug-drug interactions with a strong CYP3A inhibitor like PAXLOVID and 2) Determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring *[see Drug Interactions (7)]*.**
- **Consider the benefit of PAXLOVID treatment in reducing hospitalization and death, and whether the risk of potential drug-drug interactions for an individual patient can be appropriately managed *[see Warnings and Precautions (5.1), Drug Interactions (7), and Clinical Studies (14)]*.**

1 EMERGENCY USE AUTHORIZATION

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of PAXLOVID for the treatment of adults and pediatric patients (12 years of age and older weighing at least 40 kg) with mild-to-moderate coronavirus disease 2019 (COVID-19) and who are at high risk[1] for progression to severe COVID-19, including hospitalization or death.

LIMITATIONS OF AUTHORIZED USE

- PAXLOVID is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19 [see Dosage and Administration (2.1)].[2]
- PAXLOVID is not authorized for use as pre-exposure or post-exposure prophylaxis for prevention of COVID-19 *[see Clinical Studies (14.3)]*.
- PAXLOVID is not authorized for use for longer than 5 consecutive days.

PAXLOVID may be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs.

PAXLOVID may also be prescribed for an individual patient by a state-licensed pharmacist under the following conditions:

- Sufficient information is available, such as through access to health records less than 12 months old or consultation with a health care provider in an established provider-patient relationship with the individual patient, to assess renal and hepatic function; and
- Sufficient information is available, such as through access to health records, patient reporting of medical history, or consultation with a health care provider in an established provider-patient

[1] Determining whether a patient is at high risk for progression to severe COVID-19, including hospitalization or death, is based on the provider's assessment of the individual patient being considered for treatment of COVID-19 and that patient's medical history. For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html.

[2] Patients requiring hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID may complete the full 5-day treatment course per the healthcare provider's discretion.

relationship with the individual patient, to obtain a comprehensive list of medications (prescribed and non-prescribed) that the patient is taking to assess for potential drug interaction.

The state-licensed pharmacist should refer an individual patient for clinical evaluation (e.g., telehealth, in-person visit) with a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs, if any of the following apply:

- Sufficient information is not available to assess renal and hepatic function.
- Sufficient information is not available to assess for a potential drug interaction.
- Modification of other medications is needed due to a potential drug interaction.
- PAXLOVID is not an appropriate therapeutic option based on the authorized Fact Sheet for Healthcare Providers or due to potential drug interactions for which recommended monitoring would not be feasible.

PAXLOVID is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of PAXLOVID under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Justification for Emergency Use of Drugs During the COVID-19 Pandemic

There is currently an outbreak of COVID-19 caused by SARS-CoV-2, a novel coronavirus. The Secretary of Health and Human Services (HHS) has:

- Determined that there is a public health emergency, or significant potential for a public health emergency.[3]
- Declared that circumstances exist justifying the authorization of emergency use of drugs and biological products for the prevention or treatment of COVID-19.[4]

An EUA is a U.S. Food and Drug Administration authorization for the emergency use of an unapproved product or unapproved use of an approved product (i.e., drug, biological product, or device) in the United States under certain circumstances including, but not limited to, when the Secretary of HHS declares that there is a public health emergency that affects the national security or the health and security of United States citizens living abroad, and that involves biological agent(s) or a disease or condition that may be attributable to such agent(s). Criteria for issuing an EUA include:

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[3] *See* U.S. Department of Health and Human Services, Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3. February 4, 2020; https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency. *See also* U.S. Department of Health and Human Services, Amended Determination of a Public Health Emergency or Significant Potential for a Public Health Emergency Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3(b). March 15, 2023 ("Amended Determination"); https://www.federalregister.gov/documents/2023/03/20/2023-05609/covid-19-emergency-use-authorization-declaration.

[4] *See* U.S. Department of Health and Human Services, Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3, 85 FR 18250 (April 1, 2020); https://www.federalregister.gov/documents/2020/04/01/2020-06905/emergency-use-authorization-declaration. *See also* Amended Determination ("The declarations issued pursuant to section 564(b)(1) of the FD&C Act that circumstances exist justifying the authorization of emergency use of certain in vitro diagnostics, personal respiratory protective devices, other medical devices and drugs and biological products, as set forth in those declarations, and that are based on the February 4, 2020 determination, remain in effect until those declarations are terminated in accordance with section 564 of the FD&C Act.").

- The biological agent(s) can cause a serious or life-threatening disease or condition;
- Based on the totality of the available scientific evidence (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that
    - the product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition; and
    - the known and potential benefits of the product—when used to diagnose, prevent, or treat such disease or condition—outweigh the known and potential risks of the product, taking into consideration the material threat posed by the biological agent(s);
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the serious or life-threatening disease or condition.

Information Regarding Approved Alternatives for the EUA Authorized Use[5]

PAXLOVID is FDA-approved for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. Although different presentations of PAXLOVID are now FDA-approved for the treatment of mild-to-moderate COVID-19 in certain adults, there are not currently sufficient supplies of the approved PAXLOVID available for distribution to this patient population in its entirety; therefore, this EUA continues to authorize the emergency use of PAXLOVID[6] for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death, at this time. Apart from this paragraph, all references to the term "PAXLOVID" in this Fact Sheet refer to product that is labelled in accordance with this EUA.

Veklury (remdesivir) is an FDA-approved alternative to PAXLOVID when used for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death. Veklury is administered via intravenous infusion for a total treatment duration of 3 days. Although Veklury is an FDA-approved alternative to PAXLOVID as described above, FDA does not consider Veklury to be an adequate alternative to PAXLOVID for this authorized use because it may not be feasible or practical for certain patients (e.g., it requires an intravenous infusion daily for 3 days).

Other therapeutics are currently authorized for the same use as PAXLOVID. For additional information on all products authorized for treatment or prevention of COVID-19, please see https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

For information on clinical studies that are testing the use of PAXLOVID in COVID-19, please see www.clinicaltrials.gov.

[5] This section only describes the uses for which an FDA-approved drug is considered to be an alternative to PAXLOVID. For additional information, including the full indications for the FDA-approved drugs referenced within this section, please refer to the relevant Prescribing Information at: Drugs@FDA: FDA-Approved Drugs. As stated in the Letter of Authorization, the emergency use of PAXLOVID must be consistent with the terms and conditions of its authorization.
[6] See the Letter of Authorization and section 16 (HOW SUPPLIED/STORAGE AND HANDLING) in this Fact Sheet for the specific presentations of PAXLOVID authorized under this EUA.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Information for Emergency Use of PAXLOVID

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. There are two different dose packs available:

- PAXLOVID (nirmatrelvir; ritonavir) co-packaged for oral use 300 mg;100 mg *[see Dosage and Administration (2.2)]*.
- PAXLOVID (nirmatrelvir; ritonavir) co-packaged for oral use 150 mg;100 mg for patients with moderate renal impairment *[see Dosage and Administration (2.3)]*.

Nirmatrelvir must be co-administered with ritonavir. Failure to correctly co-administer nirmatrelvir with ritonavir may result in plasma levels of nirmatrelvir that are insufficient to achieve the desired therapeutic effect.

Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID [see Dosage and Administration (2.2, 2.3)]. Completion of the full 5-day treatment course and continued isolation in accordance with public health recommendations are important to maximize viral clearance and minimize transmission of SARS-CoV-2.

The 5-day treatment course of PAXLOVID should be initiated as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset even if baseline COVID-19 symptoms are mild. Should a patient require hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID, the patient should complete the full 5-day treatment course per the healthcare provider's discretion.

If the patient misses a dose of PAXLOVID within 8 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 8 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose.

PAXLOVID (both nirmatrelvir and ritonavir tablets) can be taken with or without food *[see Clinical Pharmacology (12.3)]*. The tablets should be swallowed whole and not chewed, broken, or crushed.

2.2 Recommended Dosage

The recommended dosage for PAXLOVID is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) with all 3 tablets taken together orally twice daily for 5 days.

2.3 Dosage in Patients with Renal Impairment

No dosage adjustment is recommended in patients with mild renal impairment (eGFR ≥60 to <90 mL/min).

In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), the dosage of PAXLOVID is 150 mg nirmatrelvir (one 150 mg tablet) and 100 mg ritonavir (one 100 mg tablet) with both tablets taken together twice daily for 5 days *[see How Supplied/Storage and Handling (16)]. Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID.* Providers should counsel patients about renal dosing instructions *[see Patient Counseling Information (17)]*.

PAXLOVID is not recommended in patients with severe renal impairment (eGFR <30 mL/min) until more data are available; the appropriate dosage for patients with severe renal impairment has not been determined *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

2.4 Use in Patients with Hepatic Impairment

No dosage adjustment is needed in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in subjects with severe (Child-Pugh Class C) hepatic impairment; therefore, PAXLOVID is not recommended for use in patients with severe hepatic impairment *[see Use in Specific Populations (8.7)]*.

3 DOSAGE FORMS AND STRENGTHS

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets.

- Nirmatrelvir is supplied as oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Each tablet contains 150 mg of nirmatrelvir.

- Ritonavir is supplied as white or white to off-white film-coated tablets uniquely identified by the color, shape, and debossing *[see How Supplied/Storage and Handling (16)]*. Each tablet contains 100 mg of ritonavir.

4 CONTRAINDICATIONS

PAXLOVID is contraindicated in patients with a history of clinically significant hypersensitivity reactions [e.g., toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome] to its active ingredients (nirmatrelvir or ritonavir) or any other components of the product.

PAXLOVID is contraindicated with drugs that are primarily metabolized by CYP3A and for which elevated concentrations are associated with serious and/or life-threatening reactions and drugs that are strong CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. There are certain other drugs for which concomitant use with PAXLOVID should be avoided and/or dose adjustment, interruption, or therapeutic monitoring is recommended. Drugs listed in this section are a guide and not considered a comprehensive list of all drugs that may be contraindicated with PAXLOVID. The healthcare provider should consult other appropriate resources such as the prescribing information for the interacting drug for comprehensive information on dosing or monitoring with concomitant use of a strong CYP3A inhibitor like PAXLOVID *[see Drug Interactions (7.3)]*:

- Drugs that are primarily metabolized by CYP3A for which elevated concentrations are associated with serious and/or life-threatening reactions *[see Drug Interactions (7.3)]*:

  - Alpha 1-adrenoreceptor antagonist: alfuzosin
  - Antianginal: ranolazine
  - Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
  - Anti-gout: colchicine (in patients with renal and/or hepatic impairment *[see Table 1, Drug Interactions (7.3)]*)
  - Antipsychotics: lurasidone, pimozide

- Benign prostatic hyperplasia agents: silodosin
- Cardiovascular agents: eplerenone, ivabradine
- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
- HMG-CoA reductase inhibitors: lovastatin, simvastatin (these drugs can be temporarily discontinued to allow PAXLOVID use *[see Table 1, Drug Interactions (7.3)]*)
- Immunosuppressants: voclosporin
- Microsomal triglyceride transfer protein inhibitor: lomitapide
- Migraine medications: eletriptan, ubrogepant
- Mineralocorticoid receptor antagonists: finerenone
- Opioid antagonists: naloxegol
- PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)
- Sedative/hypnotics: triazolam, oral midazolam
- Serotonin receptor 1A agonist/serotonin receptor 2A antagonist: flibanserin
- Vasopressin receptor antagonists: tolvaptan

➢ Drugs that are strong CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. PAXLOVID cannot be started immediately after discontinuation of any of the following medications due to the delayed offset of the recently discontinued CYP3A inducer *[see Drug Interactions (7.3)]*:

- Anticancer drugs: apalutamide
- Anticonvulsant: carbamazepine, phenobarbital, primidone, phenytoin
- Antimycobacterials: rifampin, rifapentine
- Cystic fibrosis transmembrane conductance regulator potentiators: lumacaftor/ivacaftor
- Herbal products: St. John's Wort (*hypericum perforatum*)

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Adverse Reactions Due to Drug Interactions

Initiation of PAXLOVID, which contains ritonavir, a strong CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving PAXLOVID, may increase plasma concentrations of medications metabolized by CYP3A. Medications that induce CYP3A may decrease concentrations of PAXLOVID. These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications.
- Loss of therapeutic effect of PAXLOVID and possible development of viral resistance.

Severe, life-threatening, and/or fatal adverse reactions due to drug interactions have been reported in patients treated with PAXLOVID. The most commonly reported concomitant medications resulting in serious adverse reactions were calcineurin inhibitors (e.g., tacrolimus, cyclosporine), followed by calcium channel blockers.

Prior to prescribing PAXLOVID, review all medications taken by the patient to assess potential drug-drug interactions and determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring (e.g., calcineurin inhibitors) *[see Contraindications (4) and Drug Interactions (7)]*. See Table 1 for clinically significant drug interactions, including contraindicated

drugs. Drugs listed in Table 1 are a guide and not considered a comprehensive list of all possible drugs that may interact with PAXLOVID.

Consider the benefit of PAXLOVID treatment in reducing hospitalization and death, and whether the risk of potential drug-drug interactions for an individual patient can be appropriately managed *[see Drug Interactions (7) and Clinical Studies (14)]*.

5.2 Hypersensitivity Reactions

Anaphylaxis, serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome), and other hypersensitivity reactions have been reported with PAXLOVID *[see Adverse Reactions (6.2)]*. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue PAXLOVID and initiate appropriate medications and/or supportive care.

5.3 Hepatotoxicity

Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering PAXLOVID to patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis.

5.4 Risk of HIV-1 Resistance Development

Because nirmatrelvir is co-administered with ritonavir, there may be a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection *[see Contraindications (4), and Drug Interactions (7)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity reactions *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of PAXLOVID is based on two Phase 2/3 randomized, placebo-controlled trials in symptomatic adult subjects 18 years of age and older with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Subjects in both studies received PAXLOVID (nirmatrelvir/ritonavir 300 mg/100 mg) or placebo every 12 hours for 5 days for the treatment of mild-to-moderate COVID-19 within 5 days of symptom onset *[see Clinical Studies (14)]*:

- Trial C4671005 (EPIC-HR) enrolled subjects who were at high risk for progression to severe disease.
- Trial C4671002 (EPIC-SR) enrolled subjects who were at standard risk for progression to severe disease (previously unvaccinated subjects at standard risk or fully vaccinated subjects with at least 1 risk factor for progression to severe disease).

Adverse reactions were those reported while subjects were on study medication and through 28 days after the last dose of study treatment.

In Trial C4671005 (EPIC-HR), 1,038 subjects received PAXLOVID and 1,053 subjects received placebo. The most common adverse reactions (≥1% incidence in the PAXLOVID group and occurring at a greater frequency than in the placebo group) were dysgeusia (5% and <1%, respectively) and diarrhea (3% and 2%, respectively).

Among vaccinated or unvaccinated subjects at standard risk or fully vaccinated subjects with at least 1 risk factor for progression to severe disease in Trial C4671002 (EPIC-SR), 540 subjects received PAXLOVID and 528 subjects received placebo. The adverse reactions observed were consistent with those observed in EPIC-HR.

6.2 Post-Authorization Experience

The following adverse reactions have been identified during post-authorization use of PAXLOVID.

Immune System Disorders: Anaphylaxis, hypersensitivity reactions *[see Warnings and Precautions (5.2)]*
Skin and Subcutaneous Tissue Disorders: Toxic epidermal necrolysis, Stevens-Johnson syndrome *[see Warnings and Precautions (5.2)]*
Nervous System Disorders: Headache
Vascular Disorders: Hypertension
Gastrointestinal Disorders: Abdominal pain, nausea, vomiting
General Disorders and Administration Site Conditions: Malaise

6.4 Required Reporting for Serious Adverse Events and Medication Errors

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events* and medication errors potentially related to PAXLOVID within 7 calendar days from the healthcare provider's awareness of the event, using FDA Form 3500 (for information on how to access this form, see below). The FDA requires that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race).
- A statement " PAXLOVID use for COVID-19 under Emergency Use Authorization (EUA)" under the "**Describe Event, Problem, or Product Use/Medication Error**" heading.
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes).
- Patient's pre-existing medical conditions and use of concomitant products.
- Information about the product (e.g., dosage, route of administration, NDC #).

Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online: https://www.fda.gov/medwatch/report.htm
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax to 1-800-FDA-0178, or
- Call 1-800-FDA-1088 to request a reporting form

In addition, please provide a copy of all FDA MedWatch forms to:

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of PAXLOVID.

*Serious adverse events are defined as:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- Other important medical event, which may require a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

6.5 Other Reporting Requirements

Healthcare facilities and providers will report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

7 DRUG INTERACTIONS

7.1 Potential for PAXLOVID to Affect Other Drugs

PAXLOVID (nirmatrelvir co-packaged with ritonavir) is a strong inhibitor of CYP3A, and an inhibitor of CYP2D6, P-gp and OATP1B1. Co-administration of PAXLOVID with drugs that are primarily metabolized by CYP3A and CYP2D6 or are transported by P-gp or OATP1B1 may result in increased plasma concentrations of such drugs and increase the risk of adverse events. Co-administration of PAXLOVID with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated *[see Contraindications (4) and Drug Interactions (7.3) Table 1]*. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring as shown in Table 1.

7.2 Potential for Other Drugs to Affect PAXLOVID

Nirmatrelvir and ritonavir are CYP3A substrates; therefore, drugs that induce CYP3A may decrease nirmatrelvir and ritonavir plasma concentrations and reduce PAXLOVID therapeutic effect *[see Contraindications (4) and Drug Interactions (7.3) Table 1]*.

7.3 Established and Other Potentially Significant Drug Interactions

Table 1 provides a listing of clinically significant drug interactions, including contraindicated drugs *[see Contraindications (4) and Warnings and Precautions (5.1)]*. Drugs listed in Table 1 are a guide and not considered a comprehensive list of all possible drugs that may interact with PAXLOVID. The healthcare provider should consult other appropriate resources such as the prescribing information for the interacting drug for comprehensive information on dosing or monitoring with concomitant use of a strong CYP3A inhibitor such as ritonavir.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Alpha 1-adrenoreceptor antagonist	alfuzosin	↑ alfuzosin	Co-administration contraindicated due to potential hypotension *[see Contraindications (4)]*.
Alpha 1-adrenoreceptor antagonist	tamsulosin	↑ tamsulosin	Avoid concomitant use with PAXLOVID.
Antianginal	ranolazine	↑ ranolazine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions *[see Contraindications (4)]*.
Antiarrhythmics	amiodarone, dronedarone, flecainide, propafenone, quinidine	↑ antiarrhythmic	Co-administration contraindicated due to potential for cardiac arrhythmias *[see Contraindications (4)]*.
Antiarrhythmics	lidocaine (systemic), disopyramide	↑ antiarrhythmic	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics if available.
Anticancer drugs	apalutamide	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Anticancer drugs	abemaciclib, ceritinib, dasatinib, encorafenib, ibrutinib, ivosidenib, neratinib, nilotinib, venetoclax, vinblastine, vincristine	↑ anticancer drugs	Avoid co-administration of encorafenib or ivosidenib due to potential risk of serious adverse events such as QT interval prolongation. Avoid use of neratinib, venetoclax or ibrutinib. Co-administration of vincristine and vinblastine may lead to significant hematologic or gastrointestinal side effects. For further information, refer to individual product label for anticancer drug.
Anticoagulants	warfarin	↑↓ warfarin	Closely monitor international normalized ratio (INR) if co-administration with warfarin is necessary.
	rivaroxaban	↑ rivaroxaban	Increased bleeding risk with rivaroxaban. Avoid concomitant use.
	dabigatran[a]	↑ dabigatran	Increased bleeding risk with dabigatran. Depending on dabigatran indication and renal function, reduce dose of dabigatran or avoid concomitant use. Refer to the dabigatran product label for further information.
	apixaban	↑ apixaban	Combined P-gp and strong CYP3A inhibitors increase blood levels of apixaban and increase the risk of bleeding. Dosing recommendations for co-administration of apixaban with PAXLOVID depend on the apixaban dose. Refer to the apixaban product label for more information.
Anticonvulsants	carbamazepine[a], phenobarbital, primidone, phenytoin	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.
Anticonvulsants	clonazepam	↑ anticonvulsant	A dose decrease may be needed for clonazepam when co-administered with PAXLOVID and clinical monitoring is recommended.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Antidepressants	bupropion	↓ bupropion and active metabolite hydroxy-bupropion	Monitor for an adequate clinical response to bupropion.
	trazodone	↑ trazodone	Adverse reactions of nausea, dizziness, hypotension, and syncope have been observed following co-administration of trazodone and ritonavir. A lower dose of trazodone should be considered. Refer to trazadone product label for further information.
Antifungals	voriconazole	↓ voriconazole	Avoid concomitant use of voriconazole.
	ketoconazole, isavuconazonium sulfate, itraconazole[a]	↑ ketoconazole ↑ isavuconazonium sulfate ↑ itraconazole	Refer to ketoconazole, isavuconazonium sulfate, and itraconazole product labels for further information.
		↑ nirmatrelvir/ritonavir	A nirmatrelvir/ritonavir dose reduction is not needed.
Anti-gout	colchicine	↑ colchicine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment *[see Contraindications (4)]*.
Anti-HIV protease inhibitors	atazanavir, darunavir, tipranavir	↑ protease inhibitor	For further information, refer to the respective protease inhibitors' prescribing information. Patients on ritonavir- or cobicistat-containing HIV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or protease inhibitor adverse events.
Anti-HIV	efavirenz, maraviroc, nevirapine, zidovudine, bictegravir/ emtricitabine/ tenofovir	↑ efavirenz ↑ maraviroc ↑ nevirapine ↓ zidovudine ↑ bictegravir ↔ emtricitabine ↑ tenofovir	For further information, refer to the respective anti-HIV drugs prescribing information.
Anti-infective	clarithromycin, erythromycin	↑ clarithromycin ↑ erythromycin	Refer to the respective prescribing information for anti-infective dose adjustment.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Antimycobacterial	rifampin, rifapentine	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance. Alternate antimycobacterial drugs such as rifabutin should be considered *[see Contraindications (4)]*.
Antimycobacterial	bedaquiline	↑ bedaquiline	Refer to the bedaquiline product label for further information.
	rifabutin	↑ rifabutin	Refer to rifabutin product label for further information on rifabutin dose reduction.
Antipsychotics	lurasidone, pimozide	↑ lurasidone ↑ pimozide	Co-administration contraindicated due to serious and/or life-threatening reactions such as cardiac arrhythmias *[see Contraindications (4)]*.
Antipsychotics	quetiapine	↑ quetiapine	If co-administration is necessary, reduce quetiapine dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations.
	clozapine	↑ clozapine	If co-administration is necessary, consider reducing the clozapine dose and monitor for adverse reactions.
Benign prostatic hyperplasia agents	silodosin	↑ silodosin	Co-administration contraindicated due to potential for postural hypotension *[see Contraindications (4)]*.
Calcium channel blockers	amlodipine, diltiazem, felodipine, nicardipine, nifedipine, verapamil	↑ calcium channel blocker	Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with PAXLOVID. If co-administered, refer to individual product label for calcium channel blocker for further information.
Cardiac glycosides	digoxin	↑ digoxin	Caution should be exercised when co-administering PAXLOVID with digoxin, with appropriate monitoring of serum digoxin levels. Refer to the digoxin product label for further information.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Cardiovascular agents	eplerenone	↑ eplerenone	Co-administration with eplerenone is contraindicated due to potential for hyperkalemia *[see Contraindications (4)]*.
	ivabradine	↑ ivabradine	Co-administration with ivabradine is contraindicated due to potential for bradycardia or conduction disturbances *[see Contraindications (4)]*.
Cardiovascular agents	aliskiren, ticagrelor, vorapaxar	↑ aliskiren ↑ ticagrelor ↑ vorapaxar	Avoid concomitant use with PAXLOVID.
	clopidogrel	↓ clopidogrel active metabolite	
	cilostazol	↑ cilostazol	Dosage adjustment of cilostazol is recommended. Refer to the cilostazol product label for more information.
Corticosteroids primarily metabolized by CYP3A	betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone, mometasone, triamcinolone	↑ corticosteroid	Co-administration with corticosteroids (all routes of administration) of which exposures are significantly increased by strong CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression. However, the risk of Cushing's syndrome and adrenal suppression associated with short-term use of a strong CYP3A inhibitor is low. Alternative corticosteroids including beclomethasone, prednisone, and prednisolone should be considered.
Cystic fibrosis transmembrane conductance regulator potentiators	lumacaftor/ivacaftor	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.
Cystic fibrosis transmembrane conductance regulator potentiators	ivacaftor	↑ ivacaftor	Reduce dosage when co-administered with PAXLOVID. Refer to individual product labels for more information.
	elexacaftor/tezacaftor/ivacaftor	↑elexacaftor/tezacaftor/ivacaftor	
	tezacaftor/ivacaftor	↑ tezacaftor/ivacaftor	
Dipeptidyl peptidase 4 (DPP4) inhibitors	saxagliptin	↑ saxagliptin	Dosage adjustment of saxagliptin is recommended. Refer to the saxagliptin product label for more information.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Endothelin receptor antagonists	bosentan	↑ bosentan ↓ nirmatrelvir/ritonavir	Discontinue use of bosentan at least 36 hours prior to initiation of PAXLOVID. Refer to the bosentan product label for further information.
Ergot derivatives	dihydroergotamine, ergotamine, methylergonovine	↑ dihydroergotamine ↑ ergotamine ↑ methylergonovine	Co-administration contraindicated due to potential for acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system *[see Contraindications (4)]*.
Hepatitis C direct acting antivirals	elbasvir/grazoprevir glecaprevir/ pibrentasvir ombitasvir/paritaprevir /ritonavir and dasabuvir sofosbuvir/velpatasvir/ voxilaprevir	↑ antiviral	Increased grazoprevir concentrations can result in alanine transaminase (ALT) elevations. Avoid concomitant use of glecaprevir/pibrentasvir with PAXLOVID. Refer to the ombitasvir/paritaprevir/ritonavir and dasabuvir label for further information. Refer to the sofosbuvir/velpatasvir/voxilaprevir product label for further information. Patients on ritonavir-containing HCV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or HCV drug adverse events with concomitant use.
Herbal products	St. John's Wort (*hypericum perforatum*)	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
HMG-CoA reductase inhibitors	lovastatin, simvastatin	↑ lovastatin ↑ simvastatin	Co-administration contraindicated due to potential for myopathy including rhabdomyolysis *[see Contraindications (4)]*. If treatment with PAXLOVID is considered medically necessary, discontinue use of lovastatin and simvastatin at least 12 hours prior to initiation of PAXLOVID, during the 5 days of PAXLOVID treatment and for 5 days after completing PAXLOVID.
HMG-CoA reductase inhibitors	atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Consider temporary discontinuation of atorvastatin and rosuvastatin during treatment with PAXLOVID. Atorvastatin and rosuvastatin do not need to be withheld prior to or after completing PAXLOVID.
Hormonal contraceptive	ethinyl estradiol	↓ ethinyl estradiol	An additional, non-hormonal method of contraception should be considered during the 5 days of PAXLOVID treatment and until one menstrual cycle after stopping PAXLOVID.
Immunosuppressants	voclosporin	↑ voclosporin	Co-administration contraindicated due to potential for acute and/or chronic nephrotoxicity *[see Contraindications (4)]*.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Immunosuppressants	calcineurin inhibitors: cyclosporine, tacrolimus	↑ cyclosporine ↑ tacrolimus	Avoid concomitant use of calcineurin inhibitors with PAXLOVID when close monitoring of immunosuppressant concentrations is not feasible. If co-administered, dose adjustment of the immunosuppressant and close and regular monitoring for immunosuppressant concentrations and adverse reactions are recommended during and after treatment with PAXLOVID. Obtain expert consultation to appropriately manage the complexity of this co-administration *[see Warnings and Precautions (5.1)]*.
	mTOR inhibitors: everolimus, sirolimus	↑ everolimus ↑ sirolimus	Avoid concomitant use of everolimus and sirolimus and PAXLOVID. Refer to the individual immunosuppressant product label and latest guidelines for further information.
Janus kinase (JAK) inhibitors	tofacitinib, upadacitinib	↑ tofacitinib	Dosage adjustment of tofacitinib is recommended. Refer to the tofacitinib product label for more information.
		↑ upadacitinib	Dosing recommendations for co-administration of upadacitinib with PAXLOVID depends on the upadacitinib indication. Refer to the upadacitinib product label for more information.
Long-acting beta-adrenoceptor agonist	salmeterol	↑ salmeterol	Avoid concomitant use with PAXLOVID. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Microsomal triglyceride transfer protein (MTTP) inhibitor	lomitapide	↑ lomitapide	Co-administration contraindicated due to potential for hepatotoxicity and gastrointestinal adverse reactions *[see Contraindications (4)]*.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Migraine medications	eletriptan	↑ eletriptan	Co-administration of eletriptan within at least 72 hours of PAXLOVID is contraindicated due to potential for serious adverse reactions including cardiovascular and cerebrovascular events *[see Contraindications (4)]*.
	ubrogepant	↑ ubrogepant	Co-administration of ubrogepant with PAXLOVID is contraindicated due to potential for serious adverse reactions *[see Contraindications (4)]*.
Migraine medications	rimegepant	↑ rimegepant	Avoid concomitant use with PAXLOVID.
Mineralocorticoid receptor antagonists	finerenone	↑ finerenone	Co-administration contraindicated due to potential for serious adverse reactions including hyperkalemia, hypotension, and hyponatremia *[see Contraindications (4)]*.
Muscarinic receptor antagonists	darifenacin	↑ darifenacin	The darifenacin daily dose should not exceed 7.5 mg when co-administered with PAXLOVID. Refer to the darifenacin product label for more information.
Narcotic analgesics	fentanyl, hydrocodone, oxycodone, meperidine	↑ fentanyl ↑ hydrocodone ↑ oxycodone ↑ meperidine	Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl, hydrocodone, oxycodone, or meperidine is concomitantly administered with PAXLOVID. If concomitant use with PAXLOVID is necessary, consider a dosage reduction of the narcotic analgesic and monitor patients closely at frequent intervals. Refer to the individual product label for more information.
	methadone	↓ methadone	Monitor methadone-maintained patients closely for evidence of withdrawal effects and adjust the methadone dose accordingly.
Neuropsychiatric agents	suvorexant	↑ suvorexant	Avoid concomitant use of suvorexant with PAXLOVID.
	aripiprazole, brexpiprazole, cariprazine, iloperidone, lumateperone, pimavanserin	↑ aripiprazole ↑ brexpiprazole ↑ cariprazine ↑ iloperidone ↑ lumateperone ↑ pimavanserin	Dosage adjustment of aripiprazole, brexpiprazole, cariprazine, iloperidone, lumateperone, and pimavanserin is recommended. Refer to individual product label for more information.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Opioid antagonists	naloxegol	↑ naloxegol	Co-administration contraindicated due to the potential for opioid withdrawal symptoms *[see Contraindications (4)]*.
Pulmonary hypertension agents (PDE5 inhibitors)	sildenafil (Revatio®)	↑ sildenafil	Co-administration of sildenafil with PAXLOVID is contraindicated for use in pulmonary hypertension due to the potential for sildenafil associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope *[see Contraindications (4)]*.
Pulmonary hypertension agents (PDE5 inhibitors)	tadalafil (Adcirca®)	↑ tadalafil	Avoid concomitant use of tadalafil with PAXLOVID for pulmonary hypertension.
Pulmonary hypertension agents (sGC stimulators)	riociguat	↑ riociguat	Dosage adjustment is recommended for riociguat when used for pulmonary hypertension. Refer to the riociguat product label for more information.
Erectile dysfunction agents (PDE5 inhibitors)	avanafil	↑ avanafil	Do not use PAXLOVID with avanafil because a safe and effective avanafil dosage regimen has not been established.
	sildenafil, tadalafil, vardenafil	↑ sildenafil ↑ tadalafil ↑ vardenafil	Dosage adjustment is recommended for use of sildenafil, tadalafil or vardenafil with PAXLOVID when used for erectile dysfunction. Refer to individual product label for more information.
Sedative/hypnotics	triazolam, oral midazolam[a]	↑ triazolam ↑ midazolam	Co-administration contraindicated due to potential for extreme sedation and respiratory depression *[see Contraindications (4)]*.
Sedative/hypnotics	buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem	↑ sedative/hypnotic	A dose decrease may be needed for these drugs when co-administered with PAXLOVID and monitoring for adverse events.
	midazolam (administered parenterally)	↑ midazolam	Co-administration of midazolam (parenteral) should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered,

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
			especially if more than a single dose of midazolam is administered. Refer to the midazolam product label for further information.
Serotonin receptor 1A agonist/ serotonin receptor 2A antagonist	flibanserin	↑ flibanserin	Co-administration contraindicated due to potential for hypotension, syncope, and CNS depression *[see Contraindications (4)]*.
Vasopressin receptor antagonists	tolvaptan	↑ tolvaptan	Co-administration contraindicated due to potential for dehydration, hypovolemia and hyperkalemia *[see Contraindications (4)]*.

a. See Pharmacokinetics, Drug Interaction Studies Conducted with Nirmatrelvir and Ritonavir (12.3).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data on the use of nirmatrelvir during pregnancy are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Published observational studies on ritonavir use in pregnant women have not identified an increase in the risk of major birth defects. Published studies with ritonavir are insufficient to identify a drug-associated risk of miscarriage *(see Data)*. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy *(see Clinical Considerations)*.

In an embryo-fetal development study with nirmatrelvir, reduced fetal body weights following oral administration of nirmatrelvir to pregnant rabbits were observed at systemic exposures (AUC) approximately 11 times higher than clinical exposure at the authorized human dose of PAXLOVID. No other adverse developmental outcomes were observed in animal reproduction studies with nirmatrelvir at systemic exposures (AUC) greater than or equal to 3 times higher than clinical exposure at the authorized human dose of PAXLOVID *(see Data)*.

In embryo-fetal developmental studies with ritonavir, no evidence of adverse developmental outcomes was observed following oral administration of ritonavir to pregnant rats and rabbits at systemic exposures (AUC) 5 (rat) or 8 (rabbits) times higher than clinical exposure at the authorized human dose of PAXLOVID *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the authorized population is unknown. All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryo-fetal Risk
COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

Data

Human Data

Ritonavir
Based on prospective reports to the antiretroviral pregnancy registry of live births following exposure to ritonavir-containing regimens (including over 3,500 live births exposed in the first-trimester and over 3,500 live births exposed in the second and third trimesters), there was no difference in the rate of overall birth defects for ritonavir compared with the background birth defect rate of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The prevalence of birth defects in live births was 2.4% [95% confidence interval (CI): 1.9%-2.9%] following first-trimester exposure to ritonavir-containing regimens and 2.9% (95% CI: 2.4%-3.5%) following second and third trimester exposure to ritonavir-containing regimens. While placental transfer of ritonavir and fetal ritonavir concentrations are generally low, detectable levels have been observed in cord blood samples and neonate hair.

Animal Data

Nirmatrelvir
Embryo-fetal developmental (EFD) toxicity studies were conducted in pregnant rats and rabbits administered oral nirmatrelvir doses of up to 1,000 mg/kg/day during organogenesis [on Gestation Days (GD) 6 through 17 in rats and GD 7 through 19 in rabbits]. No biologically significant developmental effects were observed in the rat EFD study. At the highest dose of 1,000 mg/kg/day, the systemic nirmatrelvir exposure (AUC_{24}) in rats was approximately 9 times higher than clinical exposures at the authorized human dose of PAXLOVID. In the rabbit EFD study, lower fetal body weights (9% decrease) were observed at 1,000 mg/kg/day in the absence of significant maternal toxicity findings. At 1,000 mg/kg/day, the systemic exposure (AUC_{24}) in rabbits was approximately 11 times higher than clinical exposures at the authorized human dose of PAXLOVID. No other significant developmental toxicities (malformations and embryo-fetal lethality) were observed up to the highest dose tested, 1,000 mg/kg/day. No developmental effects were observed in rabbits at 300 mg/kg/day resulting in systemic exposure (AUC_{24}) approximately 3 times higher than clinical exposures at the authorized human dose of PAXLOVID. A pre- and postnatal developmental (PPND) study in pregnant rats administered oral nirmatrelvir doses of up to 1,000 mg/kg/day from GD 6 through Lactation Day (LD) 20 showed no adverse findings. Although no difference in body weight was noted at birth when comparing offspring born to nirmatrelvir treated versus control animals, a decrease in the body weight of offspring was observed on Postnatal Day (PND) 17 (8% decrease) and PND 21 (up to 7% decrease) in the absence of maternal toxicity. No significant differences in offspring body weight were observed from PND 28 to PND 56. The maternal systemic exposure (AUC_{24}) at 1,000 mg/kg/day was approximately 9 times higher than clinical exposures at the authorized human dose of PAXLOVID. No body weight changes in the offspring were noted at 300 mg/kg/day, where maternal systemic exposure (AUC_{24}) was approximately 6 times higher than clinical exposures at the authorized human dose of PAXLOVID.

Ritonavir
Ritonavir was administered orally to pregnant rats (at 0, 15, 35, and 75 mg/kg/day) and rabbits (at 0, 25, 50, and 110 mg/kg/day) during organogenesis (on GD 6 through 17 in rats and GD 6 through 19 in rabbits). No evidence of teratogenicity due to ritonavir was observed in rats and rabbits at systemic exposures (AUC) 5 (rats) or 8 (rabbits) times higher than exposure at the authorized human dose of PAXLOVID. Increased incidences of early resorptions, ossification delays, and developmental variations, as well as decreased fetal body weights were observed in rats in the presence of maternal toxicity, at systemic exposures (AUC) approximately 10 times higher than exposure at the authorized human dose of PAXLOVID. In rabbits, resorptions, decreased litter size, and decreased fetal weights were observed at maternally toxic doses, at systemic exposures greater than 8 times higher than exposure at the authorized human dose of PAXLOVID. In a PPND study in rats, administration of 0, 15, 35, and 60 mg/kg/day ritonavir from GD 6 through PND 20 resulted in no developmental toxicity, at ritonavir systemic exposures greater than 10 times the exposure at the authorized human dose of PAXLOVID.

8.2 Lactation

Risk Summary

There are no available data on the presence of nirmatrelvir in human or animal milk, the effects on the breastfed infant, or the effects on milk production. A transient decrease in body weight was observed in the nursing offspring of rats administered nirmatrelvir *(see Data)*. Limited published data reports that ritonavir is present in human milk. There is no information on the effects of ritonavir on the breastfed infant or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PAXLOVID and any potential adverse effects on the breastfed infant from PAXLOVID or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

Data
In the PPND study, transiently lower body weight (up to 8%) was observed in the offspring of pregnant rats administered nirmatrelvir at maternal systemic exposure (AUC_{24}) approximately 9 times higher than clinical exposures at the authorized human dose of PAXLOVID. No body weight changes in the offspring were noted at maternal systemic exposure (AUC_{24}) approximately 6 times higher than clinical exposures at the authorized human dose of PAXLOVID.

8.3 Females and Males of Reproductive Potential

Contraception

Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Advise patients using combined hormonal contraceptives to use an effective alternative contraceptive method or an additional barrier method of contraception *[see Drug Interactions (7.3)]*.

8.4 Pediatric Use

PAXLOVID is not authorized for use in pediatric patients younger than 12 years of age or weighing less than 40 kg. The safety and effectiveness of PAXLOVID have not been established in pediatric patients. The authorized adult dosing regimen is expected to result in comparable serum exposures of nirmatrelvir and ritonavir in patients 12 years of age and older and weighing at least 40 kg as

observed in adults, and adults with similar body weight were included in the trial EPIC-HR *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

8.5 Geriatric Use

Clinical studies of PAXLOVID include subjects 65 years of age and older and their data contributes to the overall assessment of safety and efficacy *[see Adverse Reactions (6.1) and Clinical Studies (14.1)]*. Of the total number of subjects in the integrated dataset consisting of EPIC-HR and EPIC-SR who were randomized to and received PAXLOVID (N=1,578), 165 (10%) were 65 years of age and older and 39 (2%) were 75 years of age and older. No overall differences in safety were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in safety between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

Renal impairment increases nirmatrelvir exposure, which may increase the risk of PAXLOVID adverse reactions. No dosage adjustment is recommended in patients with mild renal impairment (eGFR ≥60 to <90 mL/min). Reduce the PAXLOVID dosage in patients with moderate renal impairment (eGFR ≥30 to <60 mL/min). PAXLOVID is not recommended for use in patients with severe renal impairment (eGFR <30 mL/min) or patients with end stage renal disease (eGFR <15 mL/min) receiving dialysis until more data are available. The appropriate dosage for patients with severe renal impairment has not been determined *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]. Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID.* Providers should counsel patients about renal dosing instructions *[see Patient Counseling Information (17)]*.

8.7 Hepatic Impairment

No dosage adjustment of PAXLOVID is recommended for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in subjects with severe (Child-Pugh Class C) hepatic impairment, therefore, PAXLOVID is not recommended for use in patients with severe (Child-Pugh Class C) hepatic impairment *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Treatment of overdose with PAXLOVID should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with PAXLOVID.

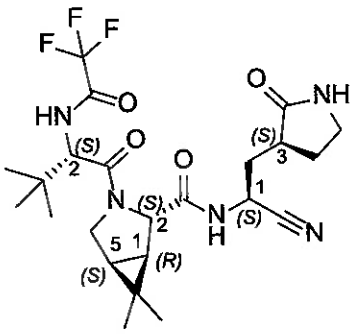
11 DESCRIPTION

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. Nirmatrelvir is a SARS-CoV-2 main protease (M^{pro}) inhibitor, and ritonavir is an HIV-1 protease inhibitor and CYP3A inhibitor.

Nirmatrelvir

The chemical name of active ingredient of nirmatrelvir is (1*R*,2*S*,5*S*)-*N*-((1*S*)-1-Cyano-2-((3*S*)-2-oxopyrrolidin-3-yl)ethyl)-3-((2*S*)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3-

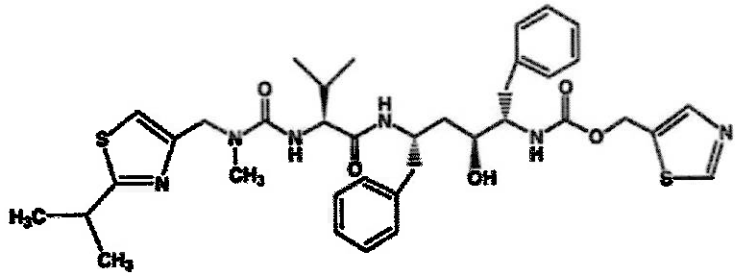
azabicyclo[3.1.0]hexane-2-carboxamide]. It has a molecular formula of $C_{23}H_{32}F_3N_5O_4$ and a molecular weight of 499.54. Nirmatrelvir has the following structural formula:



Nirmatrelvir is available as immediate-release, film-coated tablets. Each tablet contains 150 mg nirmatrelvir with the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, and sodium stearyl fumarate. The following are the ingredients in the film coating: hydroxy propyl methylcellulose, iron oxide red, polyethylene glycol, and titanium dioxide.

Ritonavir

Ritonavir is chemically designated as 10-Hydroxy-2-methyl-5-(1-methylethyl)-1- [2-(1 methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12- tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]. Its molecular formula is $C_{37}H_{48}N_6O_5S_2$, and its molecular weight is 720.95. Ritonavir has the following structural formula:



Ritonavir is available as film-coated tablets. Each tablet contains 100 mg ritonavir with the following inactive ingredients: anhydrous dibasic calcium phosphate, colloidal silicon dioxide, copovidone, sodium stearyl fumarate, and sorbitan monolaurate. The film coating may include the following ingredients: colloidal anhydrous silica, colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, polyethylene glycol, polysorbate 80, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nirmatrelvir is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antiviral drug *[see Microbiology (12.4)]*.

Ritonavir is an HIV-1 protease inhibitor but is not active against SARS-CoV-2 M^{pro}. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At 3 times the steady state peak plasma concentration (C_{max}) at the recommended dose, nirmatrelvir does not prolong the QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

The pharmacokinetics of nirmatrelvir/ritonavir were similar in healthy subjects and in subjects with mild-to-moderate COVID-19.

Nirmatrelvir AUC increased in a less than dose proportional manner over a single dose range from 250 mg to 750 mg (0.83 to 2.5 times the authorized recommended dose) and multiple dose range from 75 mg to 500 mg (0.25 to 1.67 times the authorized recommended dose), when administered in combination with 100 mg ritonavir. Nirmatrelvir steady state was achieved on Day 2 following administration of the authorized recommended dosage and the mean accumulation ratio was approximately 2-fold.

The pharmacokinetic properties of nirmatrelvir/ritonavir are displayed in Table 2.

Table 2: Pharmacokinetic Properties of Nirmatrelvir and Ritonavir in Healthy Subjects

	Nirmatrelvir (When Given With Ritonavir)	Ritonavir
Absorption		
T_{max} (hr), median	3.00[a]	3.98[a]
Food effect	Test/reference (fed/fasted) ratios of adjusted geometric means (90% CI) AUC_{inf} and C_{max} for nirmatrelvir were 119.67 (108.75, 131.68) and 161.01 (139.05, 186.44), respectively.[b]	
Distribution		
% bound to human plasma proteins	69%	98-99%
Blood-to-plasma ratio	0.60	0.14[d]
V_z/F (L), mean	104.7[c]	112.4[c]
Elimination		
Major route of elimination	Renal elimination[d]	Hepatic metabolism
Half-life ($T_{1/2}$) (hr), mean	6.05[a]	6.15[a]
Oral clearance (CL/F) (L/hr), mean	8.99[c]	13.92[c]
Metabolism		
Metabolic pathways	Nirmatrelvir is a CYP3A substrate but when dosed with ritonavir, metabolic clearance is minimal.	Major CYP3A, Minor CYP2D6
Excretion		
% drug-related material in feces	35.3%[e]	86.4%[f]
% of dose excreted as total (unchanged drug) in feces	27.5%[e]	33.8%[f]
% drug-related material in urine	49.6%[e]	11.3%[f]
% of dose excreted as total (unchanged drug) in urine	55.0%[e]	3.5%[f]

Abbreviations: CL/F=apparent clearance; hr=hour; L/hr=liters per hour; $T_{½}$=terminal elimination half-life; T_{max}=the time to reach C_{max}; V_z/F=apparent volume of distribution.

a. Represents data after a single dose of 300 mg nirmatrelvir (2 x 150 mg tablet formulation) administered together with 100 mg ritonavir tablet in healthy subjects.
b. Following a single oral dose of nirmatrelvir 300 mg boosted ritonavir 100 mg at -12 hours, 0 hours and 12 hours, administered under fed (high fat and high calorie meal) or fasted conditions.
c. 300 mg nirmatrelvir (oral suspension formulation) co-administered with 100 mg ritonavir (tablet formulation) twice daily for 3 days.
d. Red blood cell to plasma ratio.
e. Determined by ^{19}F-NMR analysis following 300 mg nirmatrelvir oral suspension administered at 0 hr enhanced with 100 mg ritonavir at -12 hours, 0 hours, 12 hours, and 24 hours.
f. Determined by ^{14}C analysis following 600 mg ^{14}C-ritonavir oral solution (6 times the authorized ritonavir dose).

The predicted Day 5 nirmatrelvir exposure parameters in adult subjects with mild-to-moderate COVID-19 who were treated with PAXLOVID in EPIC-HR are presented in Table 3.

Table 3: Predicted Day 5 Nirmatrelvir Exposure Parameters Following Administration of Nirmatrelvir/Ritonavir 300 mg/100 mg Twice Daily in Subjects with Mild-to-Moderate COVID-19

Pharmacokinetic Parameter (units)[a]	Nirmatrelvir[b]
C_{max} (µg/mL)	3.43 (2.59, 4.52)
AUC_{tau} (µg*hr/mL)[c]	30.4 (22.9, 39.8)
C_{min} (µg/mL)	1.57 (1.16, 2.10)

Abbreviations: C_{max}=predicted maximal concentration; C_{min}=predicted minimal concentration (C_{trough}).

a. Data presented as geometric mean (10th and 90th percentile).
b. Based on 1,016 subjects with their post hoc PK parameters.
c. AUC_{tau}=predicted area under the plasma concentration-time profile from time 0 to 12 hours for twice-daily dosing.

Effect of Food
No clinically significant differences in the pharmacokinetics of nirmatrelvir were observed following administration of a high fat meal (800-1000 calories; 50% fat) to healthy subjects.

Specific Populations

There were no clinically significant differences in the pharmacokinetics of nirmatrelvir based on age (18 to 86 years), sex, or race/ethnicity.

Pediatric Patients
The pharmacokinetics of nirmatrelvir/ritonavir in patients less than 18 years of age have not been established.

Patients with Renal Impairment
The pharmacokinetics of nirmatrelvir in patients with renal impairment following administration of a single oral dose of nirmatrelvir 100 mg (0.33 times the authorized recommended dose) co-administered with ritonavir 100 mg are presented in Table 4. Compared to healthy controls with no renal impairment, the C_{max} and AUC of nirmatrelvir in patients with mild renal impairment was 30% and 24% higher, in patients with moderate renal impairment was 38% and 87% higher, and in patients with severe renal impairment was 48% and 204% higher, respectively.

Table 4: Impact of Renal Impairment on Nirmatrelvir/Ritonavir Pharmacokinetics

	Normal Renal Function (n=8)	Mild Renal Impairment (n=8)	Moderate Renal Impairment (n=8)	Severe Renal Impairment (n=8)
C_{max} (µg/mL)	1.60 (31)	2.08 (29)	2.21 (17)	2.37 (38)
AUC_{inf} (µg*hr/mL)	14.46 (20)	17.91 (30)	27.11 (27)	44.04 (33)
T_{max} (hr)	2.0 (1.0 - 4.0)	2.0 (1.0 – 3.0)	2.50 (1.0 – 6.0)	3.0 (1.0 - 6.1)
$T_{1/2}$ (hr)	7.73 ± 1.82	6.60 ± 1.53	9.95 ± 3.42	13.37 ± 3.32

Abbreviations: AUC_{inf}=area under the plasma concentration-time profile from time zero extrapolated to infinite time; C_{max}=the observed maximum concentration; CV=coefficient of variation; SD=standard deviation; $T_{½}$=terminal elimination half-life; T_{max}=the time to reach C_{max}.
Values are presented as geometric mean (geometric % CV) except median (range) for T_{max} and arithmetic mean ± SD for $T_{1/2}$.

Patients with Hepatic Impairment
The pharmacokinetics of nirmatrelvir were similar in patients with moderate (Child-Pugh Class B) hepatic impairment compared to healthy subjects following administration of a single oral dose of nirmatrelvir 100 mg (0.33 times the authorized recommended dose) co-administered with ritonavir 100 mg. The impact of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of nirmatrelvir or ritonavir has not been studied.

Clinical Drug Interaction Studies

Table 5 describes the effect of other drugs on the C_{max} and AUC of nirmatrelvir.

Table 5: The Effect of Other Drugs on the Pharmacokinetic Parameters of Nirmatrelvir

Co-administered Drug	Dose (Schedule)		N	Percent Ratio (in combination with co-administered drug/alone) of Nirmatrelvir Pharmacokinetic Parameters (90% CI); No Effect=100	
	Co-administered Drug	Nirmatrelvir/ Ritonavir		C_{max}	AUC[a]
Carbamazepine[b]	300 mg twice daily (16 doses)	300 mg/100 mg once daily (2 doses)	10	56.82 (47.04, 68.62)	44.50 (33.77, 58.65)
Itraconazole	200 mg once daily (8 doses)	300 mg/100 mg twice daily (5 doses)	11	118.57 (112.50, 124.97)	138.82 (129.25, 149.11)

Abbreviations: AUC=area under the plasma concentration-time curve; AUC_{inf}=area under the plasma concentration-time profile from time zero extrapolated to infinite time; AUC_{tau}=area under the plasma concentration-time profile from time zero to time tau (τ), the dosing interval. CI=confidence interval; C_{max}=observed maximum plasma concentrations.

a. For carbamazepine, AUC=AUC_{inf}; for itraconazole, AUC=AUC_{tau}.

b. Carbamazepine titrated up to 300 mg twice daily on Day 8 through Day 15 (e.g., 100 mg twice daily on Day 1 through Day 3 and 200 mg twice daily on Day 4 through Day 7).

Table 6 describes the effect of nirmatrelvir/ritonavir on the C_{max} and AUC of other drugs.

Table 6: Effect of Nirmatrelvir/Ritonavir on Pharmacokinetics of Other Drugs

Co-administered Drug	Dose (Schedule)		N	Percent Ratio of Test/Reference of Geometric Means (90% CI); No Effect=100	
	Co-administered Drug	Nirmatrelvir/ Ritonavir		C_{max}	AUC[a]
Midazolam[b]	2 mg (1 dose)	300 mg/100 mg twice daily (9 doses)	10	368.33 (318.91, 425.41)	1430.02 (1204.54, 1697.71)
Dabigatran[b]	75 mg (1 dose)	300 mg/100 mg twice daily (4 doses)[b]	24	233.06 (172.14, 315.54)	194.47 (155.29, 243.55)

Abbreviations: AUC=area under the plasma concentration-time curve; CI=confidence interval; C_{max}=observed maximum plasma concentrations; P-gp=p-glycoprotein.

a. AUC=AUC_{inf} for both midazolam and dabigatran.

b. For midazolam, Test=nirmatrelvir/ritonavir plus midazolam, Reference=Midazolam. Midazolam is an index substrate for CYP3A. For dabigatran, Test=nirmatrelvir/ritonavir plus dabigatran, Reference=Dabigatran. Dabigatran is an index substrate for P-gp.

In Vitro Studies
Cytochrome P450 (CYP) Enzymes:

- Nirmatrelvir is a reversible and time-dependent inhibitor of CYP3A, but not an inhibitor CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Nirmatrelvir is an inducer of CYP2B6, 2C8, 2C9, and 3A4, but there is minimal risk for pharmacokinetic interactions arising from induction of these CYP enzymes at the proposed therapeutic dose.
- Ritonavir is a substrate of CYP2D6 and CYP3A. Ritonavir is an inducer of CYP1A2, CYP2C9, CYP2C19, CYP2B6, and CYP3A.

Transporter Systems: Nirmatrelvir is an inhibitor of P-gp and OATP1B1. Nirmatrelvir is a substrate for P-gp, but not BCRP, MATE1, MATE2K, NTCP, OAT1, OAT2, OAT3, OCT1, OCT2, PEPT1, OATP1B1, OATP1B3, OATP2B1, or OATP4C1.

12.4 Microbiology

Mechanism of Action

Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (M^{pro}), also referred to as 3C-like protease ($3CL^{pro}$) or nonstructural protein 5 (nsp5) protease. Inhibition of SARS-CoV-2 M^{pro} renders it incapable of processing the viral polyproteins pp1a and pp1ab, preventing viral replication. Nirmatrelvir inhibited the activity of recombinant SARS-CoV-2 M^{pro} in a biochemical assay with a K_i value of 3.1 nM and an IC_{50} value of 19.2 nM. Nirmatrelvir was found to bind directly to the SARS-CoV-2 M^{pro} active site by X-ray crystallography.

Antiviral Activity

Cell Culture Antiviral Activity
Nirmatrelvir exhibited antiviral activity against SARS-CoV-2 (USA-WA1/2020 isolate) infection of differentiated normal human bronchial epithelial (dNHBE) cells with EC_{50} and EC_{90} values of 62 nM (31 ng/mL) and 181 nM (90 ng/mL), respectively, after 3 days of drug exposure.

The antiviral activity of nirmatrelvir against the Omicron sub-variants BA.2, BA.2.12.1, BA.4, BA.4.6, BA.5, BF.7, BQ.1, BQ.1.11, and XBB.1.5 was assessed in Vero E6-TMPRSS2 cells in the presence of a P-gp inhibitor. Nirmatrelvir had a median EC_{50} value of 83 nM (range: 39-146 nM) against the Omicron sub-variants, reflecting EC_{50} value fold-changes ≤1.5 relative to the USA-WA1/2020 isolate.

In addition, the antiviral activity of nirmatrelvir against the SARS-CoV-2 Alpha, Beta, Gamma, Delta, Lambda, Mu, and Omicron BA.1 variants was assessed in Vero E6 P-gp knockout cells. Nirmatrelvir had a median EC_{50} value of 25 nM (range: 16-141 nM). The Beta variant was the least susceptible variant tested, with an EC_{50} value fold-change of 3.7 relative to USA-WA1/2020. The other variants had EC_{50} value fold-changes ≤1.1 relative to USA-WA1/2020.

Clinical Antiviral Activity
In clinical trial EPIC-HR, which enrolled subjects who were primarily infected with the SARS-CoV-2 Delta variant, PAXLOVID treatment was associated with a 0.83 $\log_{10}$ copies/mL greater median decline in viral RNA shedding levels in nasopharyngeal samples through Day 5 (mITT1 analysis set, all treated subjects with onset of symptoms ≤5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment); similar results were observed in the mITT2 analysis set (all treated subjects with onset of symptoms ≤5 days). In the EPIC-SR trial, which included subjects who were infected with SARS-CoV-2 Delta (79%) or Omicron (19%) variants,

PAXLOVID treatment was associated with a 1.05 $\log_{10}$ copies/mL greater median decline in viral RNA shedding levels in nasopharyngeal samples through Day 5, with similar declines observed in subjects infected with Delta or Omicron variants. The degree of reduction in viral RNA levels relative to placebo following 5 days of PAXLOVID treatment was similar between unvaccinated high-risk subjects in EPIC-HR and vaccinated high-risk subjects in EPIC-SR.

Antiviral Resistance

In Cell Culture and Biochemical Assays
SARS-CoV-2 M^{pro} residues potentially associated with nirmatrelvir resistance have been identified using a variety of methods, including SARS-CoV-2 resistance selection, testing of recombinant SARS-CoV-2 viruses with M^{pro} substitutions, and biochemical assays with recombinant SARS-CoV-2 M^{pro} containing amino acid substitutions. Table 7 indicates M^{pro} substitutions and combinations of M^{pro} substitutions that have been observed in nirmatrelvir-selected SARS-CoV-2 in cell culture. Individual M^{pro} substitutions are listed regardless of whether they occurred alone or in combination with other M^{pro} substitutions. Note that the M^{pro} S301P and T304I substitutions overlap the P6 and P3 positions of the nsp5/nsp6 cleavage site located at the C-terminus of M^{pro}. Substitutions at other M^{pro} cleavage sites have not been associated with nirmatrelvir resistance in cell culture. The clinical significance of these substitutions is unknown.

Table 7: SARS-CoV-2 M^{pro} Amino Acid Substitutions Selected by Nirmatrelvir in Cell Culture

Single Substitutions (EC_{50} value fold-change)	T21I (1.1-4.6), L50F (1.5-4.2), P108S (ND), T135I (ND), F140L (4.1), S144A (2.2-5.3), C160F (ND), E166A (3.3), E166V (25-288), L167F (ND), T169I (ND), H172Y (ND), A173V (0.9-1.7), V186A (ND), R188G (ND), A191V (ND), A193P (ND), P252L (5.9), S301P (ND), and T304I (1.4-5.5).
≥2 Substitutions (EC_{50} value fold-change)	T21I+S144A (9.4), T21I+E166V (83), T21I+A173V (3.1), T21I+T304I (3.0-7.9), L50F+E166V (34-175), L50F+T304I (5.9), T135I+T304I (3.8), F140L+A173V (10.1), H172Y+P252L (ND), A173V+T304I (20.2), T21I+L50F+A193P+S301P (28.8), T21I+S144A+T304I (27.8), T21I+C160F+A173V+V186A+T304I (28.5), T21I+A173V+T304I (15), and L50F+F140L+L167F+T304I (54.7).

Abbreviation: ND=no data.

In a biochemical assay using recombinant SARS-CoV-2 M^{pro} containing amino acid substitutions, the following SARS-CoV-2 M^{pro} substitutions led to ≥3-fold reduced nirmatrelvir activity (fold-change based on K_i values): Y54A (25), F140A (21), F140L (7.6), F140S (260), G143S (3.6), S144A (46), S144E (480), S144T (170), H164N (6.7), E166A (35), E166G (6.2), E166V (7,700), H172Y (250), A173S (4.1), A173V (16), R188G (38), Q192L (29), Q192P (7.8), and V297A (3.0). In addition, the following combinations of M^{pro} substitutions led to ≥3-fold reduced nirmatrelvir activity: T21I+S144A (20), T21I+E166V (11,000), T21I+A173V (15), L50F+E166V (4,500), T135I+T304I (5.1), F140L+A173V (95), H172Y+P252L (180), A173V+T304I (28), T21I+S144A+T304I (51), T21I+A173V+T304I (55), L50F+E166A+L167F (210), T21I+L50F+A193P+S301P (7.3), L50F+F140L+L167F+T304I (190), and T21I+C160F+A173V+V186A+T304I (28). The following substitutions and substitution combinations emerged in cell culture but conferred <3-fold reduced nirmatrelvir activity in biochemical assays: T21I (1.6), L50F (0.2), P108S (2.9), T135I (2.2), C160F (0.6), L167F (0.9), T169I (1.4), V186A (0.8), A191V (0.8), A193P (0.9), P252L (0.9), S301P (0.2), T304I (1.0), T21I+T304I (1.8), and L50F+T304I (1.3). The clinical significance of these substitutions is unknown.

In Clinical Trials

Treatment-emergent substitutions were evaluated among subjects in clinical trials EPIC-HR/SR with sequence data available at both baseline and a post-baseline visit (n=907 PAXLOVID-treated subjects, n=946 placebo-treated subjects). SARS-CoV-2 M^{pro} amino acid changes were classified as PAXLOVID treatment-emergent substitutions if they occurred at the same amino acid position in 3 or more PAXLOVID-treated subjects and were ≥2.5-fold more common in PAXLOVID-treated subjects than placebo-treated subjects. The following PAXLOVID treatment-emergent M^{pro} substitutions were observed: T98I/R/del(n=4), E166V (n=3), and W207L/R/del (n=4). Within the M^{pro} cleavage sites, the following PAXLOVID treatment-emergent substitutions were observed: A5328S/V(n=7) and S6799A/P/Y (n=4). These cleavage site substitutions were not associated with the co-occurrence of any specific M^{pro} substitutions.

None of the treatment-emergent substitutions listed above in M^{pro} or M^{pro} cleavage sites occurred in PAXLOVID-treated subjects who experienced hospitalization. Thus, the clinical significance of these substitutions is unknown.

Viral RNA Rebound (With and Without COVID-19 Symptoms) and Treatment-Emergent Substitutions

EPIC-HR and EPIC-SR were not designed to evaluate COVID-19 rebound; exploratory analyses were conducted to assess the relationship between PAXLOVID use and rebound in viral RNA shedding levels or self-reported COVID-19 symptoms.

Post-treatment increases in SARS-CoV-2 RNA shedding levels in nasopharyngeal samples were observed on Day 10 and/or Day 14 in a subset of PAXLOVID and placebo recipients in EPIC-HR and EPIC-SR, irrespective of COVID-19 symptoms. The frequency of detection of post-treatment viral RNA rebound varied according to analysis parameters, but was generally similar among PAXLOVID and placebo recipients. A similar or smaller percentage of placebo recipients compared to PAXLOVID recipients had nasopharyngeal viral RNA results <lower limit of quantitation (LLOQ) at all study timepoints in both the treatment and post-treatment periods.

In EPIC-HR, of 59 PAXLOVID-treated subjects identified with post-treatment viral RNA rebound and with available viral sequence data, treatment-emergent substitutions in M^{pro} potentially reducing nirmatrelvir activity were detected in 2 (3%) subjects, including E166V in 1 subject and T304I in 1 subject. Both subjects had viral RNA shedding levels <LLOQ by Day 14.

Post-treatment viral RNA rebound was not associated with the primary clinical outcome of COVID-19-related hospitalization or death from any cause through Day 28 following the single 5-day course of PAXLOVID treatment. The clinical relevance of post-treatment increases in viral RNA following PAXLOVID or placebo treatment is unknown.

The frequency of symptom rebound through Day 28, irrespective of viral RNA results, was similar among PAXLOVID and placebo recipients. The frequency of combined viral RNA rebound plus symptom rebound could not be fully assessed as most episodes of symptom rebound occurred after Day 14 (the last day SARS-CoV-2 RNA levels were routinely assessed).

Cross-Resistance

Cross-resistance is not expected between nirmatrelvir and remdesivir or any other anti-SARS-CoV-2 agents with different mechanisms of action (i.e., agents that are not M^{pro} inhibitors).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Nirmatrelvir

Carcinogenicity studies have not been conducted with nirmatrelvir.

Nirmatrelvir was negative for mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the *in vitro* micronucleus assay using human lymphoblastoid TK6 cells, and the *in vivo* rat micronucleus assays.

In a fertility and early embryonic development study, nirmatrelvir was administered orally to male and female rats at doses of 60, 200, or 1,000 mg/kg/day once daily beginning 14 days prior to mating, throughout the mating phase, and continued through GD 6 for females and for a total of 32 doses for males. There were no effects on fertility, reproductive performance, or early embryonic development at doses up to 1,000 mg/kg/day, resulting in systemic exposure (AUC_{24}) approximately 5 times higher than exposure at the authorized human dose of PAXLOVID.

Ritonavir

Carcinogenicity studies in mice and rats have been conducted on ritonavir. In male mice, at levels of 50, 100, or 200 mg/kg/day, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 25 times higher than the exposure in humans at the authorized human dose of PAXLOVID. No carcinogenic effects were observed in females at up to the highest dose tested, resulting in systemic exposure (AUC_{24}) approximately 25 times higher than the exposure in humans at the authorized human dose of PAXLOVID. In rats dosed at levels of 7, 15, or 30 mg/kg/day, there were no carcinogenic effects. In this study, the exposure at the high dose was approximately 5 times higher than the exposure in humans at the authorized human dose of PAXLOVID.

Ritonavir was found to be negative for mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Ritonavir produced no effects on fertility in rats at drug exposures approximately 18 (male) and 27 (female) times higher than the exposure in humans at the authorized human dose of PAXLOVID.

14 CLINICAL STUDIES

14.1 Efficacy in Subjects at High Risk of Progression to Severe COVID-19 (EPIC-HR)

EPIC-HR (NCT04960202) was a Phase 2/3, randomized, double-blind, placebo-controlled trial in non-hospitalized symptomatic adult subjects with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Eligible subjects were 18 years of age and older with at least 1 of the following risk factors for progression to severe disease: diabetes, overweight (BMI >25), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, sickle cell disease,

neurodevelopmental disorders, active cancer, medically-related technological dependence, or were 60 years of age and older regardless of comorbidities. Subjects with COVID-19 symptom onset of ≤5 days were included in the study. Subjects were randomized (1:1) to receive PAXLOVID (nirmatrelvir/ritonavir 300 mg/100 mg) or placebo orally every 12 hours for 5 days. The trial excluded individuals with a history of prior COVID-19 infection or vaccination and excluded individuals taking any medications with clinically significant drug interactions with PAXLOVID. The primary efficacy endpoint was the proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28. The analysis was conducted in the modified intent-to-treat (mITT) analysis set [all treated subjects with onset of symptoms ≤3 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic monoclonal antibody (mAb) treatment], the mITT1 analysis set (all treated subjects with onset of symptoms ≤5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment), and the mITT2 analysis set (all treated subjects with onset of symptoms ≤5 days).

A total of 2,113 subjects were randomized to receive either PAXLOVID or placebo. At baseline, mean age was 45 years; 51% were male; 71% were White, 15% were Asian, 9% were American Indian or Alaska Native, 4% were Black or African American, and 1% was missing or unknown; 41% were Hispanic or Latino; 67% of subjects had onset of symptoms ≤3 days before initiation of study treatment; 49% of subjects were serological negative at baseline; the mean (SD) baseline viral RNA in nasopharyngeal samples was 4.71 $\log_{10}$ copies/mL (2.89); 27% of subjects had a baseline viral RNA of ≥10^7 ($\log_{10}$ copies/mL); 6% of subjects either received or were expected to receive COVID-19 therapeutic monoclonal antibody treatment at the time of randomization and were excluded from the mITT and mITT1 analyses.

The baseline demographic and disease characteristics were balanced between the PAXLOVID and placebo groups.

The proportions of subjects who discontinued treatment due to an adverse event were 2.0% in the PAXLOVID group and 4.2% in the placebo group.

Table 8 provides results of the primary endpoint in mITT1 analysis population. For the primary endpoint, the relative risk reduction in the mITT1 analysis population for PAXLOVID compared to placebo was 86% (95% CI: 72%, 93%).

Table 8: COVID-19 Related Hospitalization or Death from Any Cause Through Day 28 in Non-Hospitalized Adults with COVID-19 (mITT1 Analysis Set): EPIC-HR

	PAXLOVID (N=977)	Placebo (N=989)
COVID-19 Related Hospitalization or Death from Any Cause Through Day 28		
n (%)	9 (0.9%)	64 (6.5%)
Reduction Relative to Placebo[a] (95% CI), %	-5.6 (-7.3, -4.0)	
COVID-19 Related Hospitalization Through Day 28, %	9 (0.9%)	63 (6.4%)
All-cause Mortality Through Day 28[b], %	0	12 (1.2%)

Abbreviations: CI=confidence interval; COVID-19=coronavirus disease 2019; mAb=monoclonal antibody; mITT1=modified intent-to-treat 1 (all treated subjects with onset of symptoms ≤5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment).

The determination of primary efficacy was based on a planned interim analysis of 754 subjects in mITT population. The estimated risk reduction was -6.5% with a 95% CI of (-9.3%, -3.7%) and 2-sided p-value <0.0001.

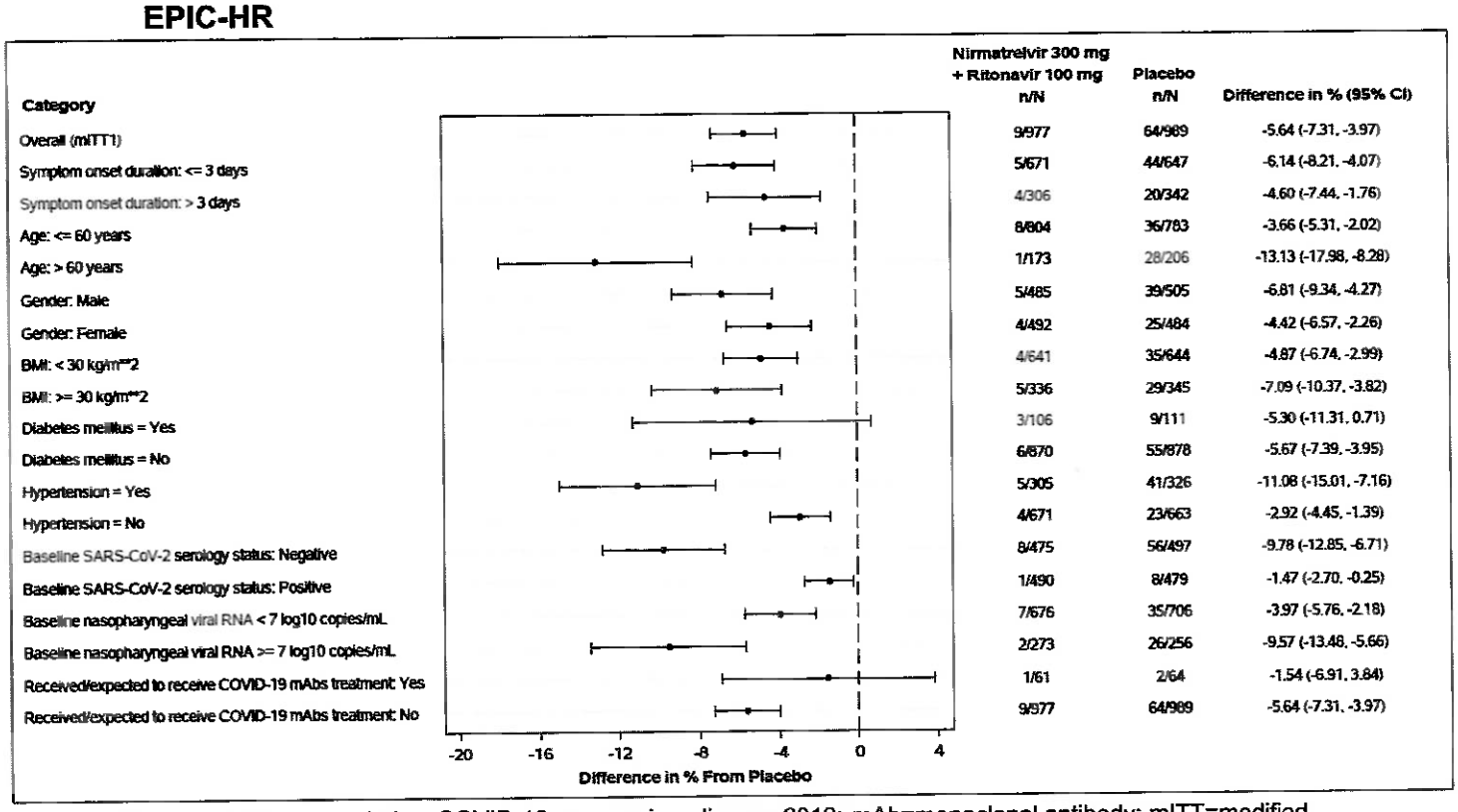
a. The estimated cumulative proportion of subjects hospitalized or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.

b. For the secondary endpoint of all-cause mortality through Week 24, there were 0 and 15 (1%) events in the PAXLOVID arm and placebo arm, respectively.

Consistent results were observed in the mITT and mITT2 analysis populations.

Similar trends have been observed across subgroups of subjects *(see Figure 1)*.

Figure 1: Subgroup Analysis of Adults with COVID-19 Dosed within 5 Days of Symptom Onset with COVID-19 Related Hospitalization or Death from Any Cause Through Day 28: EPIC-HR



Abbreviations: BMI=body mass index; COVID-19=coronavirus disease 2019; mAb=monoclonal antibody; mITT=modified intent-to-treat; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.
N=number of subjects in the category of the analysis set.
All categories are based on mITT1 population except for COVID-19 mAb treatment which is based on mITT2 population.
Seropositivity was defined if results were positive in either Elecsys anti-SARS-CoV-2 S or Elecsys anti-SARS-CoV-2 (N) assay.
The difference of the proportions in the 2 treatment groups and its 95% confidence interval based on normal approximation of the data are presented.

Among subjects who were SARS-CoV-2 seropositive at baseline, 1/490 (0.2%) PAXLOVID recipients versus 8/479 (1.7%) placebo recipients met the primary endpoint of COVID-19 related hospitalization or death from any cause through Day 28 [reduction relative to placebo -1.47% (-2.70%, -0.25%)].

14.2 Trial in Unvaccinated Subjects Without a Risk Factor for Progression to Severe COVID-19 or Subjects Fully Vaccinated Against COVID-19 With at Least One Factor for Progression to Severe COVID-19 (EPIC-SR)

PAXLOVID is not authorized for the treatment of COVID-19 in patients without a risk factor for progression to severe COVID-19.

EPIC-SR (NCT05011513) was a Phase 2/3, randomized, double-blind, placebo-controlled trial in non-hospitalized symptomatic adult subjects with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Eligible subjects were 18 years of age or older with COVID-19 symptom onset of ≤5 days who were at standard risk for progression to severe disease. The trial included previously unvaccinated subjects with no risk factors for progression to severe disease or subjects fully vaccinated against COVID-19 (i.e., completed a primary vaccination series) with at least 1 of the risk factors for progression to severe disease as defined in EPIC-HR. Through the December 19, 2021, data cutoff, a total of 1,075 subjects were randomized (1:1) to receive PAXLOVID or placebo orally every 12 hours for 5 days; of these, 59% were fully vaccinated high-risk subjects.

The primary endpoint in this trial, the difference in time to sustained alleviation of all targeted COVID-19 signs and symptoms through Day 28 among PAXLOVID versus placebo recipients, was not met.

In an exploratory analysis of the subgroup of fully vaccinated subjects with at least 1 risk factor for progression to severe disease, a non-statistically significant numerical reduction relative to placebo for the secondary endpoint of COVID-19 related hospitalization or death from any cause through Day 28 was observed.

14.3 Post-Exposure Prophylaxis Trial

PAXLOVID is not authorized for the post-exposure prophylaxis of COVID-19.

In a double-blind, double-dummy, placebo-controlled trial, the efficacy of PAXLOVID when administered for 5 or 10 days as post-exposure prophylaxis of COVID-19 was evaluated. Eligible subjects were asymptomatic adults 18 years of age and older who were SARS-CoV-2 negative at baseline and who lived in the same household with symptomatic individuals with a recent diagnosis of SARS-CoV-2. A total of 2,736 subjects were randomized (1:1:1) to receive PAXLOVID orally every 12 hours for 5 days, PAXLOVID orally every 12 hours for 10 days, or placebo.

The primary endpoint for this trial was not met. The primary endpoint was the risk reduction between the 5-day and 10-day PAXLOVID regimens versus placebo in the proportion of subjects who developed RT-PCR or RAT-confirmed symptomatic SARS-CoV-2 infection through Day 14 who had a negative SARS-CoV-2 RT-PCR result at baseline. The proportion of subjects who had events through Day 14 was 2.6% for the 5-day PAXLOVID regimen, 2.4% for the 10-day PAXLOVID regimen, and 3.9% for placebo. There was not a statistically significant risk reduction versus placebo for either the 5-day or 10-day PAXLOVID regimen.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. It is supplied in two different Dose Packs.

Nirmatrelvir tablets and ritonavir tablets are supplied in separate blister cavities within the same child-resistant blister card.

Dose Pack	Content	NDC	Description
300 mg nirmatrelvir; 100 mg ritonavir	**Each Carton Contains:** 30 tablets divided in 5 daily-dose blister cards	0069-1085-30	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White film-coated ovaloid tablets debossed with the "a" logo and the code NK.
		Or	

		0069-0345-30	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White to off-white, capsule-shaped, film-coated tablets debossed with "H" on one side and "R9" on the other side.
	Each Blister Card[a] Contains: 4 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each)	0069-1085-06	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White film-coated ovaloid tablets debossed with the "a" logo and the code NK.
		Or	
		0069-0345-06	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White to off-white, capsule-shaped, film-coated tablets debossed with "H" on one side and "R9" on the other side.
150 mg nirmatrelvir; 100 mg ritonavir	**Each Carton Contains:** 20 tablets divided in 5 daily-dose blister cards	0069-1101-20	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White film-coated ovaloid tablets debossed with the "a" logo and the code NK.
	Each Blister Card[a] Contains: 2 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each)	0069-1101-04	Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side. Ritonavir tablets: White film-coated ovaloid tablets debossed with the "a" logo and the code NK.

a. Indicates which tablets need to be taken in the morning and evening.

Storage and Handling

Store at USP controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

17 PATIENT COUNSELING INFORMATION

As a healthcare practitioner, you must communicate to the patient and/or caregiver information consistent with the "FACT SHEET FOR PATIENTS, PARENTS, AND CAREGIVERS" and provide them with a copy of this Fact Sheet prior to administration of PAXLOVID.

Drug Interactions

Inform patients that PAXLOVID may interact with certain drugs and is contraindicated for use with certain drugs; therefore, advise patients to report to their healthcare provider the use of any prescription, non-prescription medication, or herbal products *[see Boxed Warning, Contraindications (4), Warnings and Precautions (5.1), and Drug Interactions (7)].*

Hypersensitivity Reactions

Inform patients that anaphylaxis, serious skin reactions, and other hypersensitivity reactions have been reported, even following a single dose of PAXLOVID. Advise them to immediately discontinue the drug and to inform their healthcare provider at the first sign of a skin rash, hives or other skin reactions, difficulty in swallowing or breathing, any swelling suggesting angioedema (for example, swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction *[see Warnings and Precautions (5.2)].*

Dosage Modification in Patients with Moderate Renal Impairment

To ensure appropriate dosing in patients with moderate renal impairment, instruct such patients that they will be taking one 150 mg nirmatrelvir tablet with one 100 mg ritonavir tablet together twice daily for 5 days *[see Dosage and Administration (2.3)].*

In the event that the PAXLOVID 150 mg;100 mg dose pack is unavailable: pharmacist should refer to the provided instructions entitled "IMPORTANT PAXLOVID™ EUA DISPENSING INFORMATION FOR PATIENTS WITH MODERATE RENAL IMPAIRMENT" for dispensing of PAXLOVID to patients with moderate renal impairment *[see Dosage and Administration (2.3)]* and patients should be informed that their daily blister card has been altered to ensure they receive the correct dose.

Administration Instructions

Inform patients to take PAXLOVID with or without food as instructed. Advise patients to swallow all tablets for PAXLOVID whole and not to chew, break, or crush the tablets. Alert the patient of the importance of completing the full 5-day treatment course and to continuing isolation in accordance with public health recommendations to maximize viral clearance and minimize transmission of SARS-CoV-2. If the patient misses a dose of PAXLOVID within 8 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 8 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose *[see Dosage and Administration (2.1)].*

18 MANUFACTURER INFORMATION

For general questions, visit the website or call the telephone number provided below.

Website	Telephone number
www.COVID19oralRx.com	1-877-219-7225 (1-877-C19-PACK)

For Medical Information about PAXLOVID, please visit www.pfizermedinfo.com or call 1-800-438-1985.

Pfizer

Distributed by
Pfizer Labs
Division of Pfizer Inc.
New York, NY 10001

LAB-1492-12.4b
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U.S. FOOD & DRUG ADMINISTRATION

Questions related to Paxlovid's approval or EUA

Q: Is Paxlovid FDA-approved to treat or prevent COVID-19?

A. On May 25, 2023, FDA approved a New Drug Application (NDA) for Paxlovid for the treatment of mild-to-moderate coronavirus disease (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. FDA has determined Paxlovid is safe and effective when used in accordance with the FDA-approved labeling.

Paxlovid is not FDA-approved for use as pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

Q. Now that Paxlovid is an approved drug, is the EUA continuing, and what does the EUA authorize?

A. Yes. The EUA authorizes the emergency use of Paxlovid for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death.

The EUA continues to authorize Paxlovid for emergency use to treat certain eligible pediatric patients, a patient population that is not covered under the approved NDA for Paxlovid at this time. Paxlovid also remains authorized under EUA to ensure continued access for all eligible patients to the U.S. government's supply of Paxlovid, including adult patients who are the subject of the approved NDA, pending commercial launch of the approved product.

Paxlovid is not authorized:

- for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.
- for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
- for use longer than five consecutive days.

The use of Paxlovid under the EUA must be consistent with the terms and conditions of the authorization.

Q. Does the authorized Paxlovid provide the same clinical benefit as the approved Paxlovid, once the approved Paxlovid is available?

A. Yes. The authorized Paxlovid contains the same tablets (nirmatrelvir tablets and ritonavir tablets) as the Paxlovid that is now FDA-approved. Since Paxlovid was initially authorized for emergency use, Pfizer has also been required, as a condition under the EUA, to comply with the same good manufacturing practices that apply to approved products. Based on these considerations, it is FDA's expectation that patients being treated with Paxlovid for COVID-19 will receive the same clinical benefit as long as the product is used in accordance with the labeling, regardless of whether the authorized or approved Paxlovid is dispensed.

Paxlovid is FDA-approved for the treatment of mild-to-moderate COVID-19 in certain adults. Paxlovid is authorized for emergency use, but not FDA-approved, for the treatment of mild-to-moderate COVID-19 in certain pediatric patients.

Q. Why does the EUA authorize Paxlovid for its approved patient population, specifically for the treatment of mild-to-moderate COVID-19 in high-risk adults?

A. Although different presentations of PAXLOVID are now FDA-approved for the treatment of mild-to-moderate COVID-19 in certain adults, there are not sufficient quantities of the approved PAXLOVID available for distribution to this population in its entirety at the time of reissuance of this EUA. To ensure continued access to the U.S. government's supply for Paxlovid and fully meet the public health need before commercial launch of the approved product, the EUA continues to include the patient population now approved under the NDA for Paxlovid.

The use of Paxlovid under the EUA must be consistent with the terms and conditions of the authorization.

Q. May health care providers prescribe Paxlovid for uses not authorized under EUA?

A. At this time, the U.S. government continues to oversee the distribution of Paxlovid, which consists solely of Paxlovid that is labeled and packaged in accordance with the EUA. The Letter of Authorization for the EUA provides for the use of Paxlovid only when consistent with the terms and conditions of the authorization. Paxlovid is currently authorized for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death. Although Paxlovid has been approved for use in eligible adult patients who are also included in the EUA population, the approved product has not yet commercially launched.

In certain circumstances, Paxlovid labeled and packaged in accordance with the EUA may also be accessed through an Expanded Access Investigational New Drug Application, also referred to as "compassionate use", for uses not within the scope of the EUA for Paxlovid, as appropriate. Expanded access may be considered when **all** of the following apply:

- Patient has a serious or immediately life-threatening disease or condition.
- There is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition.
- Patient enrollment in a clinical trial is not possible.
- Potential patient benefit justifies the potential risks of treatment.
- Providing the investigational medical product will not interfere with investigational trials that could support a medical product's development or marketing approval for the treatment indication.

Health care providers seeking to obtain Paxlovid under expanded access should first contact Pfizer through its website.

Once Pfizer has provided the requisite authorization, health care providers should contact FDA using the information detailed below to complete the process:

- During normal business hours (8:00 a.m. – 4:30 p.m. ET, weekdays):
  - By phone – (301) 796-3400 or (855) 543-3784

- By email – DDI.EIND@fda.hhs.gov
- Outside of normal business hours (After 4:30 p.m. ET weekdays and all day on weekends/federal holidays)
  - By phone – (301) 796-9900
  - By email – CDER-EIND@fda.hhs.gov

General information on expanded access for providers and patients, respectively, can be found on FDA's website.

Q. Paxlovid is approved and authorized only for certain patients at "high risk". What does "high risk" mean?

A. Determining whether a patient is at high risk for progression to severe COVID-19, including hospitalization or death, is based on the provider's assessment of the individual patient being considered for treatment with COVID-19 and that patient's medical history.

Resources providing information on conditions that place a patient with mild-to-moderate COVID-19 at high risk for disease progression, including hospitalization or death, can be found at the Centers for Disease Control and Prevention site: Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals and at NIH's COVID-19 Treatment Guidelines: Clinical Spectrum of SARS-CoV-2 Infection.

Q. Why is pediatric use not approved for Paxlovid and only authorized under the EUA?

A. The clinical development of Paxlovid for pediatric use is ongoing.

Q. How can Paxlovid be obtained for use under the EUA?

A. For questions on how to obtain Paxlovid, please contact COVID19therapeutics@hhs.gov. Information about Paxlovid's distribution can be found here.

Efficacy and Safety Considerations

Q. Are there data showing the benefit of Paxlovid for treatment of mild-to-moderate COVID-19 for certain patients?

A. Yes. The primary data supporting the approval as well as the EUA for Paxlovid are from EPIC-HR, a randomized, double-blind, placebo-controlled clinical trial studying Paxlovid for the treatment of non-hospitalized symptomatic adults with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Patients were adults 18 years of age and older with a prespecified risk factor for progression to severe disease or were 60 years and older regardless of prespecified chronic medical conditions. All patients had not received a COVID-19 vaccine and had not been previously infected with COVID-19. The main outcome measured in the trial was the proportion of people who were hospitalized due to COVID-19 or died due to any cause during 28 days of follow-up. Paxlovid significantly reduced the proportion of people with COVID-19 related hospitalization or death from any cause through 28 days of follow-up by 86% compared to placebo among patients treated within five days of symptom onset and who did not receive COVID-19 therapeutic monoclonal antibody treatment.

In this analysis, 977 patients received Paxlovid, and 989 patients received placebo, and among these patients, 0.9% who received Paxlovid were hospitalized due to COVID-19 or died from any cause during 28 days of follow-up compared to 6.5% of the patients who received placebo. Of the people who received Paxlovid, no patients died through 24 weeks after receipt compared to 15 people who received placebo.

Details on the clinical trial results can be found in Section 14 of the authorized Fact Sheet for Health Care Providers and approved Prescribing Information.

Q. Are there data supporting the benefit of Paxlovid for high-risk patients with mild-moderate COVID-19 regardless of prior/acquired immunity?

A. Benefit of Paxlovid was observed in patients with prior immunity to the virus that causes COVID-19. Among patients in EPIC-HR who were antibody positive at trial enrollment, the risk of COVID-19-related hospitalization or death from any cause during 28 days of follow-up was 0.2% among those treated with Paxlovid compared with 1.7% of those receiving placebo. EPIC-SR was another clinical trial that enrolled vaccinated patients with at least one risk factor for progression to severe COVID-19. Among these vaccinated patients, there was a reduction in the risk of COVID-19 related hospitalization or death from any cause with use of PAXLOVID versus placebo, although not statistically significant.

Q. Does Paxlovid retain activity against currently circulating Omicron variants?

A. Yes. Based on virology data, Paxlovid retains activity against currently circulating Omicron variants.

Q. Does Paxlovid cause COVID-19 rebound?

A. EPIC-HR, described above, and EPIC-SR, another trial that enrolled vaccinated patients with at least one risk factor for progression to severe COVID-19 or unvaccinated patients with no risk factors for progression to severe COVID-19, were both randomized placebo-controlled trials. These trials provide useful data to assess COVID-19 rebound. Data from these two trials showed that rebound in SARS-CoV-2 (RNA or virus) shedding or self-reported COVID-19 symptoms occurred in a subset of patients and happened at similar rates in both the patients receiving Paxlovid and placebo. Based on the data currently available to FDA, there is not a clear association between Paxlovid treatment and COVID-19 rebound.

Q. Are there potential side effects of Paxlovid?

A. Yes. Paxlovid consists of nirmatrelvir and ritonavir, and ritonavir interacts with many other medicines, which may lead to serious or life-threatening adverse reactions. Patients should tell their health care providers all of the medicines they are taking, including over-the-counter medications and herbal supplements, when deciding whether to take Paxlovid.

Because of the importance of reducing the risk of significant drug-drug interactions with Paxlovid, the approved Prescribing Information and authorized Fact Sheet for Health Care Providers for the Paxlovid EUA include a boxed warning with instructions for providers to review all medications taken by the patient to assess for potential drug-drug interactions and determine if other medicines that a patient may be taking require a dose adjustment, interruption and/or additional monitoring.

The most common side effects of taking Paxlovid include impaired sense of taste (for example, a metallic taste in the mouth) and diarrhea.

Liver problems have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering Paxlovid to patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis. Patients should talk with their health care provider if they have a history of liver problems.

Paxlovid is not recommended for patients with severe kidney problems, and a different dose is needed for patients with moderate kidney problems. Patients should talk with their health care provider if they have a history of kidney problems.

See Warnings and Precautions in the FDA-approved Prescribing Information and the Fact Sheet for Health Care Providers for additional information on risks associated with Paxlovid.

Q. Why was a boxed warning included in the Paxlovid prescribing information?

A. Paxlovid includes ritonavir, a strong CYP3A inhibitor, which may lead to greater exposure of certain other medications the patient may be taking, resulting in potentially severe, life-threatening, or fatal events due to drug-drug interactions. Such interactions can be avoided by appropriate handling of the patient's other medications when starting treatment with Paxlovid or, in some situations when adjustments of the patient's other medication may not be feasible, choosing an alternative COVID-19 treatment for the individual patient. Since the authorization of Paxlovid under EUA, FDA has reviewed new data related to the risk of drug-drug interactions. These data were discussed by FDA during the recent Antimicrobial Drugs Advisory Committee on March 16, 2023.

- FDA identified more than 250 cases of serious adverse events assessed as possibly or probably related to Paxlovid drug-drug interactions. Many of these cases reported hospitalization, and a fatal outcome was reported in a few cases.
- FDA determined that greater than 50% of Paxlovid-eligible Medicare and VA patients were taking medications that were identified as having a drug-drug interaction with Paxlovid. FDA noted that most of these potential drug-drug interactions could be prevented or managed with dose modification, interruption, and/or additional monitoring.
- FDA determined that most Paxlovid prescriptions were written by a broad range of health care providers, who may not be familiar with managing potential drug-drug interactions associated with ritonavir, which is more commonly prescribed by infectious disease physicians and other specialists who may have more experience managing ritonavir drug-drug interactions.

Drug-drug interactions are not unique to Paxlovid and are almost always manageable risks. Prior to prescribing Paxlovid, health care providers must: 1) review all medications taken by the patient to assess potential drug-drug interactions with a strong CYP3A inhibitor like Paxlovid and 2) determine if medications require a dose adjustment, interruption, and/or additional monitoring if taken at the same time as Paxlovid.

There are resources for health care providers to identify and manage potential drug-drug interactions with Paxlovid. These include: the approved prescribing information, the Fact Sheet for Health Care Providers and the Prescriber Patient Eligibility Screening Checklist available on the FDA EUA webpage. Other resources include: the NIH COVID-19 Treatment Guidelines, the IDSA COVID-19 Treatment Guidelines and the University of Liverpool COVID-19 Drug Interactions online checker.

U.S. FOOD & DRUG ADMINISTRATION

Provider Considerations When Prescribing Paxlovid

Q. Who may prescribe Paxlovid?

A. Paxlovid may be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs.

Paxlovid may also be prescribed for an individual patient by a state-licensed pharmacist under certain conditions that are listed in the EUA. For more information on this topic, please refer to the section titled Questions for Pharmacist Prescribers below.

Q. When should Paxlovid be administered to a patient?

A. Patients should talk to their health care provider to determine whether, based on their individual circumstances, they are eligible to receive Paxlovid. Paxlovid treatment should be initiated as soon as possible after diagnosis of COVID-19, even if symptoms are mild, and within five days after symptoms start.

More information about administration is available in the in the FDA-approved Prescribing Information and the Fact Sheet for Health Care Providers.

Q: Is a positive result from a direct SARS-CoV-2 viral test required prior to prescribing Paxlovid to a patient who is at high risk for severe COVID-19?

A: No. FDA recognizes that, in rare instances, individuals with a recent known exposure (e.g., a household contact) who develop signs and symptoms consistent with COVID-19 may be diagnosed by their health care provider as having COVID-19 even if they have a negative direct SARS-CoV-2 viral test result. In such instances, their health care provider may determine that treatment with Paxlovid for COVID-19 is appropriate if the patient reports mild-to-moderate symptoms of COVID-19 and is at high-risk for progression to severe COVID-19, including hospitalization or death, and the terms and conditions of the authorization are met, as detailed in the Letter of Authorization for Paxlovid and the authorized Fact Sheet for Healthcare Providers.

The agency continues to recommend that providers use direct SARS-CoV-2 viral testing to help diagnose COVID-19.

Q. I am traveling soon. May I receive Paxlovid under the EUA prior to travel in case I become sick with COVID-19?

A. Individuals being considered for Paxlovid treatment must meet the eligibility requirements under the EUA at the time of prescription. Providers must determine that patients have signs and symptoms consistent with mild-to-moderate COVID-19, assess risk for disease progression, assess renal and hepatic function, and review all medications taken by the patient to assess for potential drug-drug interactions and determine if other medicines that a patient may be taking require a dose adjustment, interruption and/or additional monitoring.

Q. What if I have questions about the expiration date on the Paxlovid carton or container?

A. FDA has authorized an extension to the expiration date (shelf-life) for certain lots of Paxlovid. To find the extended expiration date, enter the lot number found on the side of the carton or bottom of the blister pack at this website or talk with the pharmacist or provider.

Information on the authorized shelf-life extensions for Paxlovid may also be found on FDA's website.

Questions for pharmacist prescribers

Q. Are pharmacists permitted to prescribe Paxlovid?

A. The EUA authorizes state-licensed pharmacists to prescribe Paxlovid for an individual patient, subject to the terms and conditions of the EUA (e.g., eligible patient populations), under the following conditions:

- Sufficient information is available, such as through access to health records less than 12 months old or consultation with a health care provider in an established provider-patient relationship with the individual patient, to assess renal and hepatic function; and
- Sufficient information is available, such as through access to health records, patient reporting of medical history, or consultation with a health care provider in an established provider-patient relationship with the individual patient, to obtain a comprehensive list of medications (prescribed and non-prescribed) that the patient is taking to assess for potential drug interaction.

The state-licensed pharmacist should refer an individual patient for clinical evaluation (e.g., telehealth, in-person visit) with a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs, if any of the following apply:

- Sufficient information is not available to assess renal and hepatic function.
- Sufficient information is not available to assess for a potential drug interaction.
- Modification of other medications is needed due to a potential drug interaction.
- Paxlovid is not an appropriate therapeutic option based on the authorized Fact Sheet for Healthcare Providers or due to potential drug interactions for which recommended monitoring would not be feasible.

Q. What do state-licensed pharmacist prescribers need to do to determine whether a patient may be eligible to receive Paxlovid?

A. State-licensed pharmacist prescribers have the same requirements as all other prescribers to assess an adult or pediatric patient (12 years of age and older weighing at least 40 kg), who is being considered for treatment with Paxlovid, to determine that they have a diagnosis of mild-to-moderate COVID-19 and are at high risk for progression to severe COVID-19, including hospitalization or death.

A review of reported symptoms should be completed to determine that patients have signs and symptoms consistent with mild-to-moderate COVID-19, and not severe COVID-19. Patients reporting

shortness of breath or difficulty breathing should be immediately referred for further medical assessment to determine whether their illness has progressed to the severe stage, which may require hospitalization. Paxlovid is not authorized or approved for the treatment of severe COVID-19.

Definitions for mild and moderate illness are provided in NIH's COVID-19 Treatment Guidelines: Clinical Spectrum of SARS-CoV-2 Infection.

State-licensed pharmacist prescribers may determine whether an individual patient is at high risk for severe COVID-19 by obtaining a medical history from the patient or by accessing the patient's medical records. Resources about conditions that place a patient with mild-to-moderate COVID-19 at increased risk for disease progression or death can be found at the Centers for Disease Control and Prevention site: Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals and at NIH's COVID-19 Treatment Guidelines: Clinical Spectrum of SARS-CoV-2 Infection.

Q. How do state-licensed pharmacist prescribers assess for potential drug interactions?

A. All prescribers are expected to utilize available health records or patient history to obtain a complete list of all medications (prescribed and non-prescribed) that the patient is taking. State-licensed pharmacists may also consult with a health care provider in an established provider-patient relationship with the individual patient to obtain a comprehensive list of medications the patient is taking. Resources to identify potential drug interactions include the approved Prescribing Information, the Fact Sheet for Health Care Providers and the Prescriber Patient Eligibility Screening Checklist available on the FDA EUA webpage. Other resources include: the NIH COVID-19 Treatment Guidelines, the IDSA COVID-19 Treatment Guidelines and the University of Liverpool COVID-19 Drug Interactions.

Should an adjustment to another medication be needed due to a potential drug interaction, the state-licensed pharmacist should refer the individual patient for clinical evaluation with a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs.

Q. How do state-licensed pharmacist prescribers assess renal and hepatic function?

A. State-licensed pharmacist prescribers must have access to sufficient information from health records to assess renal and hepatic function. Health records include access to an electronic health record system containing this information in progress notes or laboratory records, reviewing a printed health record such as a laboratory report provided by the patient, or reviewing information in electronic health records the patient may have access to through a phone app or other means. Health records within the past 12 months are generally acceptable, provided there is no patient self-report or other information suggestive of kidney or liver disease. State-licensed pharmacists may also consult with a health care provider in an established provider-patient relationship with the individual patient to obtain this information. If sufficient information is not available to assess renal and hepatic function, the state-licensed pharmacist should refer the individual patient to a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs.

Physicians, advanced practice registered nurses, and physician assistants may rely on patient history and access to the patient's health records to make an assessment regarding the likelihood of renal

impairment. These providers may consider ordering a serum creatinine or calculating the estimated glomerular filtration rate (eGFR) for certain patients after assessment on a case-by-case basis.

Q. Will state-licensed pharmacists be able to prescribe both the standard and renal doses of Paxlovid?

A. Yes, the EUA authorizes state-licensed pharmacists to prescribe both the standard and renal doses of Paxlovid, subject to the terms and conditions on pharmacist prescribing as detailed in the EUA, provided the pharmacist has adequate information to assess renal function and the patient is otherwise eligible to receive Paxlovid.

General EUA-related questions

Q. What is an emergency use authorization (EUA)?

A. Under section 564 of the Federal Food, Drug & Cosmetic Act, after a declaration by the HHS Secretary based on one of four types of determinations, FDA may authorize an unapproved product or unapproved uses of an approved product for emergency use. In issuing an EUA, FDA must determine, among other things, that based on the totality of scientific evidence available to the agency, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by a chemical, biological, radiological, or nuclear agent; that the known and potential benefits of the product, when used to treat, diagnose or prevent such disease or condition, outweigh the known and potential risks of the product; and that there are no adequate, approved, and available alternatives. Emergency use authorization is NOT the same as FDA approval or licensure.

Q. Are there reporting requirements for health care facilities and providers as part of the EUA?

A. Yes. As part of the EUA, FDA requires health care providers who prescribe Paxlovid to report all medication errors and serious adverse events considered to be potentially related to Paxlovid through FDA's MedWatch Adverse Event Reporting program. Providers can complete and submit the report online; or download and complete the form, then submit it via fax at 1-800-FDA-0178. This requirement is outlined in the EUA's Fact Sheet for Health Care Providers. FDA MedWatch forms should also be provided to Pfizer.

Health care facilities and providers must report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

Q. Do patient outcomes need to be reported under the EUA?

A. No, reporting of patient outcomes is not required under the EUA. However, reporting of all medication errors and serious adverse events considered to be potentially related to Paxlovid occurring during treatment is required.

Q. FDA has issued a number of EUAs including for therapeutics. If state laws impose different or additional requirements on the medical product covered by an EUA, are those state laws preempted?

A. As stated in FDA's Emergency Use Authorization of Medical Products and Related Authorities Guidance, "FDA believes that the terms and conditions of an EUA issued under section 564 preempt state or local law, both legislative requirements and common-law duties, that impose different or additional requirements on the medical product for which the EUA was issued in the context of the emergency declared under section 564." The guidance explains the basis for FDA's views on this subject.

Q. Can health care providers share the patient/caregiver Fact Sheet electronically?

A. Under the authorization, Pfizer must make available the authorized Fact Sheets on its website at: www.COVID19oralRX.com. Health care facilities and health care providers must ensure that fact sheets are made available to patients, parents, and caregivers through "appropriate means" and electronic delivery of the Fact Sheet is an appropriate means.

U.S. FOOD & DRUG ADMINISTRATION

February 1, 2023

Merck Sharp & Dohme LLC
Attention: Sushma Kumar, PhD, PMP
Senior Director, Global Regulatory Affairs and Clinical Safety
1 Merck Drive
PO Box 100
Whitehouse Station, NJ 08889-0100

RE: Emergency Use Authorization 108

Dear Dr. Kumar:

This letter is in response to Merck Sharp & Dohme Corp.'s (Merck) request that the Food and Drug Administration (FDA or Agency) issue an Emergency Use Authorization (EUA) for the emergency use of LAGEVRIO (molnupiravir)[1] for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in certain adults who are at high risk for progression to severe COVID-19, including hospitalization or death, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §360bbb-3).

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19).[2] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[3]

On December 23, 2021 the Food and Drug Administration (FDA) issued an EUA for emergency use of LAGEVRIO as treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing, who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.

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[1] The December 23, 2021, and February 11, 2022 Letters of Authorization (LOA) referred to the authorized drug as "molnupiravir,"; however, Merck subsequently requested, and FDA concurred, that the Fact Sheets be revised to add references to molnupiravir's trade name, "LAGEVRIO." "LAGEVRIO" is used in this March 23, 2022 reissued letter.

[2] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3.* February 4, 2020.

[3] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).

LAGEVRIO capsules contain molnupiravir; a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis. LAGEVRIO is not FDA-approved for any uses, including use as treatment for COVID-19.

FDA subsequently reissued the LOA on February 11, 2022[4], March 23, 2022[5], and August 5, 2022[6], and October 27, 2022.[7]

On February 1, 2023, again having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the October 27, 2022 letter in its entirety, to revise the scope of authorization to no longer require positive results of direct SARS-CoV-2 viral testing. As revised, the scope of authorization now requires, in addition to other requirements, that adults have a current diagnosis of mild-to-moderate COVID-19. Corresponding changes have also been made to the authorized Fact Sheets. Conditions P and U in this letter and the Fact Sheets have been revised to include updated information on the collection of pregnancy exposure and outcomes data through a pregnancy registry. The Fact Sheets have also been revised to include information on administering LAGEVRIO via nasogastric and orogastric tubes. The Fact Sheet for Healthcare Providers was also revised to reflect the current indication for Veklury, an approved alternative to Paxlovid, and to include additional carcinogenicity and virology information.

Based on the review of the data from the MOVe-OUT clinical trial (NCT04575597), a Phase III randomized, double-blind, placebo-controlled clinical trial studying LAGEVRIO for the treatment of non-hospitalized patients with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, it is reasonable to believe that LAGEVRIO may be effective for the treatment of adults with a current diagnosis of mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate, as described in the Scope of Authorization (Section II), and when used under the conditions described in this authorization, the known and potential benefits of LAGEVRIO outweigh the known and potential risks of such product.

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[4] In its February 11, 2022 revision, FDA revised the scope of this LOA to account for the FDA approval of Veklury (remdesivir) for the treatment of COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, who are not hospitalized and have mild-to-moderate COVID-19, and who are at high risk for progression to severe COVID-19, including hospitalization or death. The letter of authorization was also revised to include a new condition regarding registration and listing. The authorized Fact Sheets were also revised to reflect the revision to the scope of authorization for LAGEVRIO as described above and include information on post-authorization reports of hypersensitivity reactions and rashes.

[5] In its March 23, 2022 revision, FDA revised this LOA to add references to molnupiravir's trade name, "LAGEVRIO". Corresponding revisions were also made to the authorized Fact Sheets. The Fact Sheet for Healthcare Providers was also revised to include updated antiviral activity and resistance information.

[6] In its August 5, 2022 revision, FDA revised this LOA to update certain post-authorization requirements as detailed in Condition O of this letter. The Fact Sheet for Healthcare Providers was also revised to include additional virology information and to identify Veklury (remdesivir) as an approved alternative to Lagevrio.

[7] In its October 27, 2022 revision, FDA incorporated clarifying revisions to Condition BB of this letter. Condition AA was also revised to require that all printed matter, advertising and promotional materials relating to the use of LAGEVRIO under this authorization be submitted to FDA for consideration at least 14 calendar days prior to initial dissemination or first use.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of LAGEVRIO for the treatment of adults with a current diagnosis of mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of LAGEVRIO for treatment of mild-to-moderate COVID-19, when administered as described in the Scope of Authorization (Section II), meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

1. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that LAGEVRIO may be effective for the treatment of adults with a current diagnosis of mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (section II), and that, when used under the conditions described in this authorization, the known and potential benefits of LAGEVRIO outweigh the known and potential risks of such product; and

3. There is no adequate, approved, and available alternative[8] to the emergency use of LAGEVRIO for the treatment of adults with a current diagnosis of mild-to-moderate COVID-19 as further described in the Scope of Authorization (section II).[9]

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Distribution of the authorized LAGEVRIO will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Merck will supply LAGEVRIO to authorized distributor(s)[10], who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed;

- LAGEVRIO may only be used for the treatment of adults with a current diagnosis of mild-to-moderate COVID-19:

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[8] Although Veklury (remdesivir) is an approved alternative to treat COVID-19 in adults within the scope of this authorization, FDA does not consider it to be an adequate alternative for certain patients for whom it may not be feasible or practical (e.g., it requires a 3-day treatment duration).

[9] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

[10] "Authorized Distributor(s)" are identified by Merck as an entity or entities allowed to distribute authorized molnupiravir.

- Who are at high risk[11] for progression to severe COVID, including hospitalization or death, and for
- Whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

Limitations on Authorized Use

- LAGEVRIO is not authorized for use in patients who are less than 18 years of age.
- LAGEVRIO is not authorized for initiation of treatment in patients requiring hospitalization due to COVID-19.[12] Benefit of treatment with LAGEVRIO has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19.
- LAGEVRIO is not authorized for use for longer than 5 consecutive days.
- LAGEVRIO is not authorized for use as pre-exposure or as post-exposure prophylaxis for prevention of COVID-19.

- LAGEVRIO may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state[13] law to prescribe drugs in the therapeutic class to which LAGEVRIO belongs (i.e., anti-infectives).

- The use of LAGEVRIO covered by this authorization must be in accordance with the authorized Fact Sheets.

Product Description

The authorized LAGEVRIO is supplied as a bottle (NDC-0006-5055-06, NDC-0006-5055-07, NDC-0006-5055-09) containing a sufficient quantity of LAGEVRIO 200 mg capsules to complete a full treatment course (i.e., 40 capsules). LAGEVRIO is manufactured as a Swedish Orange, opaque capsule containing the Merck corporate logo and "82" printed in white ink.

The authorized storage and handling information is included in the authorized Fact Sheet for Healthcare Providers.

LAGEVRIO is authorized for emergency use with the following product-specific information required to be made available to healthcare providers and to patients and caregivers, respectively, through Merck's website www.molnupiravir.com (referred to as the "authorized labeling"):

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[11] For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html.

[12] Patients requiring hospitalization after starting treatment with molnupiravir may complete the full 5-day treatment course per the healthcare provider's discretion.

[13] The term "State" includes any State or Territory of the United States, the District of Columbia, and the Commonwealth of Puerto Rico. See section 201(a)(1) of the Act.

- Fact Sheet for Healthcare Providers: Emergency Use Authorization (EUA) for LAGEVRIO
- Fact Sheet for Patients and Caregivers: Emergency Use Authorization (EUA) of LAGEVRIO for Coronavirus Disease 2019 (COVID-19)

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of LAGEVRIO, when used for the treatment of adults with a current diagnosis of mild-to-moderate COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh the known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that LAGEVRIO may be effective for the treatment of adults with a current diagnosis of mild-to-moderate COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that LAGEVRIO (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of LAGEVRIO product under this EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), LAGEVRIO is authorized for the treatment of adults with a current diagnosis of mild-to-moderate COVID-19 as described in this Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

Merck and Authorized Distributors[14]

A. Merck and authorized distributor(s) will ensure that LAGEVRIO is distributed and the authorized labeling (i.e., Fact Sheets) will be made available to healthcare facilities and/or healthcare providers as described in Section II of this Letter of Authorization.

B. Merck and authorized distributor(s) will ensure that appropriate storage is maintained until the product is delivered to healthcare facilities and/or healthcare providers.

C. Merck and authorized distributor(s) will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., U.S. government agencies, state and local

[14] Supra at Note 10.

government authorities, authorized distributors, healthcare facilities, healthcare providers) involved in distributing or receiving LAGEVRIO. Merck will provide to all relevant stakeholders a copy of this Letter of Authorization and communicate any subsequent amendments that might be made to this Letter of Authorization and its authorized accompanying materials (i.e., Fact Sheets).

D. Merck may request changes to this authorization, including to the authorized Fact Sheets for LAGEVRIO. Any request for changes to this EUA must be submitted to the Office of Infectious Diseases/Office of New Drugs/Center for Drug Evaluation and Research. Such changes require appropriate authorization prior to implementation.[15]

E. Merck may develop and disseminate instructional and educational materials (e.g., materials providing information on product administration and/or patient monitoring) that are consistent with the authorized emergency use of LAGEVRIO as described in this Letter of Authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs. Any instructional and educational materials that are inconsistent with the authorized labeling for LAGEVRIO are prohibited. If the Agency notifies Merck that any instructional and educational materials are inconsistent with the authorized labeling, Merck must cease distribution of such instructional and educational materials. Furthermore, as part of its notification, the Agency may also require Merck to issue corrective communication(s).

F. Merck will report to FDA all serious adverse events and medication errors potentially related to LAGEVRIO use that are reported to Merck using either of the following options.

Option 1: Submit reports through the Safety Reporting Portal (SRP) as described on the FDA SRP web page.

Option 2: Submit reports directly through the Electronic Submissions Gateway (ESG) as described on the FAERS electronic submissions web page.

Submitted reports under both options must state: "LAGEVRIO use for COVID-19 under Emergency Use Authorization (EUA)." For reports submitted under Option 1, include this language at the beginning of the question "Describe Event" for further analysis. For reports submitted under Option 2, include this language at the beginning of the "Case Narrative" field.

[15] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study; (8) new strengths of the authorized product, new product sources (e.g., of active pharmaceutical ingredient) or of product components. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), (7), or (8), review and concurrence is required from the Counter-Terrorism and Emergency Coordination Staff/Office of the Center Director/CDER and the Office of Counterterrorism and Emerging Threats/Office of the Chief Scientist.

G. All manufacturing, packaging, and testing sites for both drug substance and drug product used for EUA supply will comply with current good manufacturing practice requirements of Section 501(a)(2)(B) of the Act.

H. Merck will submit information to the Agency within three working days of receipt of any information concerning significant quality problems with distributed drug product of LAGEVRIO that includes the following:

- Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or
- Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the product to meet the established specifications.

If a significant quality problem affects unreleased product and may also impact product(s) previously released and distributed, then information must be submitted for all potentially impacted lots.

Merck will include in its notification to the Agency whether the batch, or batches, in question will be recalled. If FDA requests that these, or any other batches, at any time, be recalled, Merck must recall them.

If not included in its initial notification, Merck must submit information confirming that Merck has identified the root cause of the significant quality problems, taken corrective action, and provide a justification confirming that the corrective action is appropriate and effective. Merck must submit this information as soon as possible but no later than 45 calendar days from the initial notification.

I. Merck will manufacture LAGEVRIO to meet all quality standards and per the manufacturing process and control strategy as detailed in Merck's EUA request. Merck will also test the active pharmaceutical ingredient (API) starting material for additional quality attributes agreed upon by Merck and the Agency. Merck will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product, without notification to and concurrence by the Agency as described under condition D.

J. Merck will list LAGEVRIO with a unique product NDC under the marketing category of Emergency Use Authorization. Further, the listing will include each establishment where manufacturing is performed for the drug and the type of operation performed at each such establishment.

K. Through a process of inventory control, Merck and authorized distributor(s) will maintain records regarding distribution of LAGEVRIO (i.e., lot numbers, quantity, receiving site, receipt date).

L. Merck will establish a process for monitoring genomic database(s) for the emergence of global viral variants of SARS-CoV-2. Merck will provide reports to the Agency on a monthly basis summarizing any findings as a result of its monitoring activities and, as needed, any follow-up assessments planned or conducted.

M. FDA may require Merck to assess the activity of the authorized LAGEVRIO against any global SARS-CoV-2 variant(s) of interest (e.g., variants that are prevalent or becoming prevalent that harbor substitutions in the target protein or in protein(s) that interact with the target protein). Merck will perform the required assessment in a manner and timeframe agreed upon by Merck and the Agency. Merck will submit to FDA a preliminary summary report immediately upon completion of its assessment followed by a detailed study report within 30 calendar days of study completion. Merck will submit any relevant proposal(s) to revise the authorized labeling based on the results of its assessment, as may be necessary or appropriate based on the foregoing assessment.

N. Merck shall provide samples as requested of LAGEVRIO to the U.S. Department of Health and Human Services (HHS) for evaluation of activity against emerging global viral variants of SARS-CoV-2, including specific amino acid substitution(s) of interest (e.g., variants that are highly prevalent or that harbor substitutions in the target protein) within 5 business days of any request made by HHS. Analyses performed with the supplied quantity of LAGEVRIO may include, but are not limited to, cell culture potency assays, biochemical assays, and in vivo efficacy assays.

O. Merck must provide the following information to the Agency:

1. Merck will conduct a thorough investigation into the differences in efficacy observed in the first and second half of Part 2 of trial MK-4482-002. This assessment should involve the synthesis of data, including, but not limited to, additional baseline serology testing, a detailed comparison of baseline characteristics (including demographic, clinical disease, and virologic characteristics), and an exploration of potential differences in standard of care by region and over time. Merck will submit a final report, including available serology results, to the Agency no later than September 30, 2022.
2. Merck will conduct a pharmacokinetic (PK) study in wild type Fisher 344 rats to establish if NHC or NHC-TP is detected in testes. The study should include plasma exposure levels that meet/exceed the human exposure for NHC. Merck will submit the results of the PK study no later than March 31, 2022.

    - If the results of the PK study demonstrate NHC or NHC-TP distribution to testes, Merck will also conduct a male germ cell mutation assay in the Big Blue rat model. Merck must submit a protocol for the Big Blue rat assay no later than 30 days after the PK results are submitted to FDA, or by April 30, 2022. Results from the Big Blue rat assay will be submitted no later than July 31, 2023.

P. Merck must participate in a pregnancy registry to collect information through telephone and online reporting of pregnancies and collect outcomes for individuals who are exposed to LAGEVRIO during pregnancy. Merck must submit to the Agency reports detailing any available exposure information and outcome(s) data on a monthly basis unless otherwise notified by FDA.

Q. Merck and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

Healthcare Facilities to Whom LAGEVRIO Is Distributed and Healthcare Providers Administering LAGEVRIO

R. Healthcare facilities and healthcare providers will ensure that they are aware of the Letter of Authorization, and the terms herein. Healthcare providers must provide and document that a copy of the authorized Fact Sheet for Patients and Caregivers has been provided, either through electronic means or hardcopy, to the patient or caregiver prior to prescribing LAGEVRIO.

S. Healthcare providers must inform patients or caregivers of the information detailed in the section *Mandatory Requirements for Administration of LAGEVRIO Under Emergency Use Authorization* in the Fact Sheet for Healthcare Providers.

T. LAGEVRIO may only be prescribed to a pregnant individual after the prescribing healthcare provider has completed the mandatory requirements on patient assessment, patient counseling, and documentation as described in the Fact Sheet for Healthcare Providers. See *Mandatory Requirements for Administration of LAGEVRIO Under Emergency Use Authorization* in the Fact Sheet for Healthcare Providers.

U. Healthcare providers must inform and document that pregnant individuals who are prescribed LAGEVRIO have been made aware of the pregnancy registry at https://covid-pr.pregistry.com or 1-800-616-3791.

V. Healthcare facilities and healthcare providers receiving LAGEVRIO will track all serious adverse events and medication errors that are considered to be potentially related to LAGEVRIO use and must report these to FDA in accordance with the Fact Sheet for Healthcare Providers. Complete and submit a MedWatch form (www.fda.gov/medwatch/report.htm), or complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178) (these forms can be found via link above). Call 1-800-FDA-1088 for questions. Submitted reports must state, "LAGEVRIO use for COVID-19 under Emergency Use Authorization" at the beginning of the question "Describe Event" for further analysis.

W. Healthcare facilities and healthcare providers will ensure that appropriate storage is maintained until the product is administered consistent with the terms of this letter and the authorized labeling.

X. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensing and administration of LAGEVRIO for the use authorized in this letter (i.e., lot numbers, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered).

Y. Healthcare facilities will ensure that any records associated with this EUA are maintained until notified by Merck and/or FDA. Such records will be made available to Merck, HHS, and FDA for inspection upon request.

Z. Healthcare facilities and providers will report therapeutics information and utilization data as directed by HHS.

Conditions Related to Printed Matter, Advertising, and Promotion

AA. All descriptive printed matter, advertising, and promotional materials relating to the use of LAGEVRIO under this authorization shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in Section 502(a) and (n) of the Act, as applicable, and FDA implementing regulations. References to "approved labeling", "permitted labeling" or similar terms in these requirements shall be understood to refer to the authorized labeling for the use of LAGEVRIO under this authorization. In addition, such materials shall:

- Be tailored to the intended audience.
- Not take the form of reminder advertisements, as that term is described in 21 CFR 202.1(e)(2)(i), 21 CFR 200.200 and 21 CFR 201.100(f).
- Present the same risk information relating to the major side effects and contraindications concurrently in the audio and visual parts of the presentation for advertising and promotional materials in audio-visual format.
- Be accompanied by the authorized labeling, if the promotional materials are not subject to Section 502(n) of the Act.
- Be submitted to FDA accompanied by Form FDA-2253 for consideration at least 14 calendar days prior to initial dissemination or first use.

BB. Merck may disseminate descriptive printed matter, advertising, and promotional materials relating to the emergency use of LAGEVRIO that provide accurate descriptions of safety results and efficacy results on a clinical endpoint(s) from the clinical trial(s) summarized in the authorized labeling. Such materials must include any limitations of the clinical trial data as described in the authorized labeling. Merck may not imply that LAGEVRIO is FDA-approved for its authorized use by making statements such as "LAGEVRIO is safe and effective for the treatment of COVID-19."

CC. All descriptive printed matter, advertising, and promotional material, relating to the use of LAGEVRIO under this authorization clearly and conspicuously shall state that:

- LAGEVRIO has not been approved, but has been authorized for emergency use by FDA under an EUA, for the treatment of adults with a current diagnosis of mild-to-moderate COVID-19, who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate; and

- The emergency use of LAGEVRIO is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

If the Agency notifies Merck that any descriptive printed matter, advertising or promotional materials do not meet the terms set forth in conditions AA through CC of this EUA, Merck must cease distribution of such descriptive printed matter, advertising, or promotional materials in accordance with the Agency's notification. Furthermore, as part of its notification, the Agency may also require Merck to issue corrective communication(s).

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

--/S/--

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR LAGEVRIO™ (molnupiravir) CAPSULES

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use LAGEVRIO under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for LAGEVRIO.

LAGEVRIO™ (molnupiravir) capsules, for oral use
Original EUA Authorized Date: 12/23/2021
Revised EUA Authorized Date: 07/2023

MANDATORY REQUIREMENTS FOR ADMINISTRATION OF LAGEVRIO UNDER EMERGENCY USE AUTHORIZATION

Refer to FULL FACTSHEET for details.

----------RECENT MAJOR CHANGES----------

Adverse Reactions (Section 6.2): update to post-authorization experience section	07/2023
Mandatory Requirements Box, Use in Specific Populations (Section 8.1): Updates to pregnancy registry information	02/2023
Emergency Use Authorization (Section 1): Removal of requirement of SARS-CoV-2 viral testing	02/2023
Dosage and Administration (Section 2.3): Addition of preparation and administration instructions via nasogastric and orogastric tube.	02/2023
Microbiology (Section 12.4): Addition of Omicron subvariants	02/2023
Nonclinical Toxicology (Section 13.1): Updated carcinogenicity data	02/2023
Microbiology (Section 12.4): addition of viral RNA rebound	08/2022
Mandatory Requirements Box: Revised requirements pertaining to other therapeutics	02/2022
Emergency Use Authorization (Section 1): Updates on available alternatives to LAGEVRIO	02/2022
Warnings and Precautions (Sections 5.2 and 17): addition of hypersensitivity including anaphylaxis	02/2022
Adverse Reactions (Section 6.2): addition of post-authorization experience section	02/2022

----------EUA FOR LAGEVRIO----------

The U.S. Food and Drug Administration (FDA) has issued an EUA for the emergency use of the unapproved LAGEVRIO, a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis for the treatment of adults with a current diagnosis of mild-to-moderate coronavirus disease 2019 (COVID-19):

- who are at high risk for progression to severe COVID-19, including hospitalization or death, and for
- whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

LAGEVRIO is not FDA-approved for any use including for use for the treatment of COVID-19. Prior to initiating treatment with LAGEVRIO, carefully consider the known and potential risks and benefits. (1)

LIMITATIONS OF AUTHORIZED USE (1)

- LAGEVRIO is not authorized
  - for use in patients less than 18 years of age (5.3)
  - for initiation of treatment in patients requiring hospitalization due to COVID-19. Benefit of treatment with LAGEVRIO has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19. (2.1)
  - for use for longer than 5 consecutive days.
  - for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

LAGEVRIO may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which LAGEVRIO belongs (i.e., anti-infectives).

LAGEVRIO is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of LAGEVRIO under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

See the box in the beginning of the Full Fact Sheet for details on mandatory requirements for administration of LAGEVRIO under emergency use authorization.

See Full Fact Sheet for Healthcare Providers for the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19.

----------DOSAGE AND ADMINISTRATION----------

- 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food. (2.1, 2.3)
- Take LAGEVRIO as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset. (2.1)
- Completion of the full 5-day treatment course and continued isolation in accordance with public health recommendations are important to maximize viral clearance and minimize transmission of SARS-CoV-2. (2.1)
- LAGEVRIO is not authorized for use for longer than 5 consecutive days because the safety and efficacy have not been established. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 200 mg (3)

----------CONTRAINDICATIONS----------

No contraindications have been identified based on the limited available data on the emergency use of LAGEVRIO authorized under this EUA. (4)

----------WARNINGS AND PRECAUTIONS----------

- Embryo-Fetal Toxicity: LAGEVRIO is not recommended for use during pregnancy. (5.1, 8.1, 8.3)
- Hypersensitivity reactions, including anaphylaxis have been reported with LAGEVRIO. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue LAGEVRIO. (5.2)
- Bone and Cartilage Toxicity: LAGEVRIO is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth. (5.3, 8.4, 13.2)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥ 1%) are diarrhea, nausea, and dizziness. (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to LAGEVRIO (1) by submitting FDA Form 3500 online, (2) by downloading this form and then submitting by mail or fax, or (3) contacting the FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to Merck Sharp & Dohme LLC, Rahway, NJ USA at 1-800-672-6372 or Fax 215-616-5677 (6.4)

----------DRUG INTERACTIONS----------

No drug interactions have been identified based on the limited available data on the emergency use of LAGEVRIO authorized under this EUA. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: The use of LAGEVRIO is not recommended during pregnancy. Advise individuals of childbearing potential to use effective contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of LAGEVRIO. (8.1, 8.3)
- Lactation: Breastfeeding is not recommended during treatment and for 4 days after the last dose of LAGEVRIO. A lactating individual

may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for 4 days after the last dose of LAGEVRIO. (8.2)

See FACT SHEET FOR PATIENTS AND CAREGIVERS.

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* Sections or subsections omitted from the EUA are not listed

FULL FACT SHEET FOR HEALTHCARE PROVIDERS

MANDATORY REQUIREMENTS FOR ADMINISTRATION OF LAGEVRIO UNDER EMERGENCY USE AUTHORIZATION

In order to mitigate the risks of using this unapproved product under the EUA and to optimize the potential benefit of LAGEVRIO, the following steps are required. Use of LAGEVRIO under this EUA is limited to the following (all requirements must be met):

1. Treatment of adults with a current diagnosis of mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate *[see Limitations of Authorized Use (1)]*.

2. As the prescribing healthcare provider, review the information contained within the "Fact Sheet for Patients and Caregivers" with your patient or caregiver prior to the patient receiving LAGEVRIO. Healthcare providers must provide the patient/caregiver with an electronic or hard copy of the "Fact Sheet for Patients and Caregivers" prior to the patient receiving LAGEVRIO and must document that the patient/caregiver has been given an electronic or hard copy of the "Fact Sheet for Patients and Caregivers".

3. The prescribing healthcare providers must inform the patient/caregiver that:
    i. LAGEVRIO is an unapproved drug that is authorized for use under this Emergency Use Authorization.
    ii. Other therapeutics are currently approved or authorized for the same use as LAGEVRIO *[see Emergency Use Authorization (1) - Information Regarding Available Alternatives for the EUA Authorized Use]*.
    iii. There are benefits and risks of taking LAGEVRIO as outlined in the "Fact Sheet for Patients and Caregivers."
    iv. There is a pregnancy registry.
    v. Females of childbearing potential should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of LAGEVRIO.
    vi. Males of reproductive potential who are sexually active with females of childbearing potential should use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose.

4. The prescribing healthcare provider must assess whether a female of childbearing potential is pregnant or not, if clinically indicated *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.3)]*.

5. Based on findings from animal reproduction studies, LAGEVRIO may cause fetal harm when administered to pregnant individuals. If LAGEVRIO is used during pregnancy, prescribing healthcare providers must communicate to the patient the known and potential benefits and the potential risks of LAGEVRIO use during pregnancy, as outlined in the "Fact Sheet for Patients and Caregivers" *[see Warnings and Precautions (5.1, 5.3), Use in Specific Populations (8.1, 8.3) and Nonclinical Toxicology (13.1)]*.

6. If the decision is made to use LAGEVRIO during pregnancy, the prescriber must document that the known and potential benefits and the potential risks of LAGEVRIO use during pregnancy, as outlined in the "Fact Sheet for Patients and Caregivers," were discussed with the patient.

7. The prescribing healthcare provider must document that a pregnant individual was made aware of the pregnancy registry at https://covid-pr.pregistry.com or 1-800-616-3791.

8. The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all medication errors and serious adverse events potentially related to LAGEVRIO within 7 calendar days from the healthcare provider's awareness of the event *[see Adverse Reactions (6.4)]*.

For information on clinical studies of LAGEVRIO and other therapies for the treatment of COVID-19, see www.clinicaltrials.gov .

1 EMERGENCY USE AUTHORIZATION

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product LAGEVRIO™ for treatment of adults with a current diagnosis of mild-to-moderate coronavirus disease 2019 (COVID-19):

- who are at high risk for progression to severe COVID-19, including hospitalization or death. Refer to CDC website[1] for additional details, and for
- whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

LIMITATIONS OF AUTHORIZED USE

- LAGEVRIO is not authorized for use in patients who are less than 18 years of age *[see Warnings and Precautions (5.3)]*.
- LAGEVRIO is not authorized for initiation of treatment in patients hospitalized due to COVID-19[2]. Benefit of treatment with LAGEVRIO has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19 *[see Dosing and Administration (2.1)]*.
- LAGEVRIO is not authorized for use for longer than 5 consecutive days.
- LAGEVRIO is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

LAGEVRIO may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which LAGEVRIO belongs (i.e., anti-infectives).

LAGEVRIO is not approved for any use, including for use for the treatment of COVID-19.

Prior to initiating treatment with LAGEVRIO, carefully consider the known and potential risks and benefits *[see Warnings and Precautions (5.1, 5.3), Use in Specific Populations (8.1, 8.3) and Nonclinical Toxicology (13.1)]*.

LAGEVRIO is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of LAGEVRIO under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Justification for Emergency Use of Drugs During the COVID-19 Pandemic

There is currently an outbreak of Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2, a novel coronavirus. The Secretary of HHS has declared that:

- A public health emergency related to COVID-19 has existed since January 27, 2020.

[1] https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html . Healthcare providers should consider the benefit-risk for an individual patient.

[2] Should a patient require hospitalization after starting treatment with LAGEVRIO, the patient may complete the full 5 day treatment course per the healthcare provider's discretion.

- Circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic (March 27, 2020 declaration).

An EUA is a FDA authorization for the emergency use of an unapproved product or unapproved use of an approved product (i.e., drug, biological product, or device) in the United States under certain circumstances including, but not limited to, when the Secretary of HHS declares that there is a public health emergency that affects the national security or the health and security of United States citizens living abroad, and that involves biological agent(s) or a disease or condition that may be attributable to such agent(s). Criteria for issuing an EUA include:

- The biological agent(s) can cause a serious or life-threatening disease or condition;
- Based on the totality of the available scientific evidence (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that
  - the product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition; and
  - the known and potential benefits of the product - when used to diagnose, prevent, or treat such disease or condition - outweigh the known and potential risks of the product, taking into consideration the material threat posed by the biological agent(s);
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the serious or life-threatening disease or condition.

APPROVED AVAILABLE ALTERNATIVES

Veklury (remdesivir) is FDA-approved for the treatment of COVID-19 in adults and pediatric patients (at least 28 days old and weighing at least 3 kg) who are not hospitalized and have mild-to-moderate COVID-19, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Veklury is administered via intravenous infusion for a total treatment duration of 3 days.

Although Veklury is an approved alternative treatment of mild-to-moderate COVID-19 in adults and who are at high risk for progression to severe COVID-19, including hospitalization or death, FDA does not consider Veklury to be an adequate alternative to LAGEVRIO for this authorized use because it may not be feasible or clinically appropriate for certain patients.

Other therapeutics are currently authorized for the same use as LAGEVRIO. For additional information on all products authorized for treatment or prevention of COVID-19, please see https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization .

For information on clinical studies of LAGEVRIO and other therapies for the treatment of COVID-19, see www.clinicaltrials.gov.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Emergency Use of LAGEVRIO in Adult Patients

The dosage in adult patients is 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food *[see Clinical Pharmacology (12.3)]*. Take LAGEVRIO as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset *[see Emergency Use Authorization (1) and Clinical Studies (14)]*.

Completion of the full 5-day treatment course and continued isolation in accordance with public health recommendations are important to maximize viral clearance and minimize transmission of SARS-CoV-2 *[see Patient Counseling Information (17)]*.

LAGEVRIO is not authorized for use for longer than 5 consecutive days because the safety and efficacy have not been established.

If the patient misses a dose of LAGEVRIO within 10 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 10 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose.

Should a patient require hospitalization after starting treatment with LAGEVRIO, the patient may complete the full 5 day treatment course per the healthcare provider's discretion.

2.2 Dosage Adjustments in Specific Populations
No dosage adjustment is recommended based on renal or hepatic impairment or in geriatric patients *[see Use in Specific Populations (8.5, 8.6, 8.7)]*.

2.3 Administration via Nasogastric (NG) or Orogastric (OG) Tube (12F or Larger)

1. Open four (4) capsules and transfer contents into a clean container with a lid.
2. Add 40 mL of water to the container.
3. Put the lid on the container and shake to mix the capsule contents and water thoroughly for 3 minutes.
   - **NOTE**: Capsule contents may not dissolve completely.
   - The prepared mixture may have visible undissolved particulates and are acceptable for administration.
4. Flush NG/OG tube with 5 mL of water prior to administration.
5. Using a catheter tip syringe, draw up the entire contents from the container and administer immediately through the NG/OG tube (12F or larger). Do not keep the mixture for future use.
6. If any portion of the capsule contents are left in the container, add 10 mL of water to the container, mix, and using the same syringe draw up the entire contents of the container and administer through the NG/OG (12F or larger). Repeat as needed until no capsule contents are left in the container or syringe.
7. Flush the NG/OG tube with 5 mL of water twice (10 mL total) after administration of the mixture.

3 DOSAGE FORMS AND STRENGTHS
Capsules: 200 mg, Swedish Orange opaque size 0 capsules. The capsules have the corporate logo and "82" printed in white ink.

4 CONTRAINDICATIONS
No contraindications have been identified based on the limited available data on the emergency use of LAGEVRIO authorized under this EUA.

5 WARNINGS AND PRECAUTIONS
There are limited clinical data available for LAGEVRIO. Serious and unexpected adverse events may occur that have not been previously reported with LAGEVRIO use.

5.1 Embryo-Fetal Toxicity
Based on findings from animal reproduction studies, LAGEVRIO may cause fetal harm when administered to pregnant individuals. There are no available human data on the use of LAGEVRIO in pregnant individuals to evaluate the risk of major birth defects, miscarriage or adverse maternal or fetal outcomes; therefore, LAGEVRIO is not recommended for use during pregnancy. When considering LAGEVRIO for a pregnant individual, the prescribing healthcare provider must communicate the known and potential benefits and the potential risks of using LAGEVRIO during pregnancy to the pregnant individual. LAGEVRIO is authorized to be prescribed to a pregnant individual only after the healthcare provider has determined that the benefits would outweigh the risks for that individual patient. If the decision is made to use LAGEVRIO during pregnancy, the prescribing healthcare provider must document that the known

and potential benefits and the potential risks of using LAGEVRIO during pregnancy were communicated to the pregnant individual.

Advise individuals of childbearing potential of the potential risk to a fetus and to use an effective method of contraception correctly and consistently, as applicable, during treatment with LAGEVRIO and for 4 days after the final dose *[see Use in Specific Populations (8.1, 8.3 and Nonclinical Toxicology (13.1)]*.

Prior to initiating treatment with LAGEVRIO, assess whether an individual of childbearing potential is pregnant or not, if clinically indicated. Pregnancy status does not need to be confirmed in patients who have undergone permanent sterilization, are currently using an intrauterine system or contraceptive implant, or in whom pregnancy is not possible. In all other patients, assess whether the patient is pregnant based on the first day of last menstrual period in individuals who have regular menstrual cycles, is using a reliable method of contraception correctly and consistently or have had a negative pregnancy test. A pregnancy test is recommended if the individual has irregular menstrual cycles, is unsure of the first day of last menstrual period or is not using effective contraception correctly and consistently *[see Box]*.

5.2 Hypersensitivity Including Anaphylaxis
Hypersensitivity reactions, including anaphylaxis, have been reported with LAGEVRIO. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue LAGEVRIO and initiate appropriate medications and/or supportive care.

5.3 Bone and Cartilage Toxicity
LAGEVRIO is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth. Bone and cartilage toxicity was observed in rats after repeated dosing *[see Nonclinical Toxicity (13.2)]*. The safety and efficacy of LAGEVRIO have not been established in pediatric patients *[see Use in Specific Populations (8.4)]*.

6 ADVERSE REACTIONS
6.1 Adverse Reactions from Clinical Studies
The following adverse reactions have been observed in the clinical study of LAGEVRIO that supported the EUA. The adverse reaction rates observed in these clinical trials cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Additional adverse events associated with LAGEVRIO may become apparent with more widespread use.

Overall, more than 900 subjects have been exposed to LAGEVRIO 800 mg twice daily in clinical trials. The safety assessment of LAGEVRIO is primarily based on an analysis from subjects followed through Day 29 in the Phase 3 study in non-hospitalized subjects with COVID-19 (MOVe-OUT) *[see Clinical Studies (14)]*.

The safety of LAGEVRIO was evaluated based on an analysis of a Phase 3 double-blind trial (MOVe-OUT) in which 1,411 non-hospitalized subjects with COVID-19 were randomized and treated with LAGEVRIO (N=710) or placebo (N=701) for up to 5 days. Adverse events were those reported while subjects were on study intervention or within 14 days of study intervention completion/discontinuation.

Discontinuation of study intervention due to an adverse event occurred in 1% of subjects receiving LAGEVRIO and 3% of subjects receiving placebo. Serious adverse events occurred in 7% of subjects receiving LAGEVRIO and 10% receiving placebo; most serious adverse events were COVID-19 related. Adverse events leading to death occurred in 2 (<1%) subjects receiving LAGEVRIO and 12 (2%) of subjects receiving placebo.

The most common adverse reactions in the LAGEVRIO treatment group in MOVe-OUT are presented in Table 1, all of which were Grade 1 (mild) or Grade 2 (moderate).

Table 1: Adverse Reactions Occurring in Greater Than or Equal to 1% of Subjects Receiving LAGEVRIO in MOVe-OUT*

	LAGEVRIO N=710	Placebo N=701
Diarrhea	2%	2%
Nausea	1%	1%
Dizziness	1%	1%
*Frequencies of adverse reactions are based on all adverse events attributed to study intervention by the investigator.		

Laboratory Abnormalities
Selected Grade 3 and 4 laboratory abnormalities in chemistry (alanine aminotransferase, aspartate aminotransferase, creatinine, and lipase) and hematology (hemoglobin, platelets, and leukocytes) parameters all occurred at a rate of less than or equal to 2% and occurred at a similar rate across arms in MOVe-OUT.

6.2 Post-Authorization Experience
The following adverse reactions have been identified during post-authorization use of LAGEVRIO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders
vomiting

Immune System Disorders
hypersensitivity, anaphylaxis, angioedema *[see Warnings and Precautions (5.2)]*

Skin and Subcutaneous Tissue Disorders
erythema, pruritus, rash, urticaria

6.4 Required Reporting for Serious Adverse Events and Medication Errors
The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events* and medication errors potentially related to LAGEVRIO within 7 calendar days from the healthcare provider's awareness of the event, using FDA Form 3500 (for information on how to access this form, see below). The FDA requires that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race)
- A statement "*LAGEVRIO* use for COVID-19 under Emergency Use Authorization (EUA)" under the **"Describe Event, Problem, or Product Use/Medication Error"** heading
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes).
- Patient's preexisting medical conditions and use of concomitant products
- Information about the product (e.g., dosage, route of administration, NDC #).

Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
    - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
    - Fax to 1-800-FDA-0178, or
- Call 1-800-FDA-1088 to request a reporting form

In addition, please provide a copy of all FDA MedWatch forms to:
Merck Sharp & Dohme LLC, Rahway, NJ USA
Fax: 215-616-5677
E-mail: dpoc.usa@msd.com

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of LAGEVRIO.

*Serious adverse events are defined as:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- Other important medical event, which may require a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

6.5 Other Reporting Requirements
Healthcare facilities and providers will report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

7 DRUG INTERACTIONS
No drug interactions have been identified based on the limited available data on the emergency use of LAGEVRIO authorized under this EUA. No clinical drug-drug interaction trials of LAGEVRIO with concomitant medications, including other treatments for mild-to-moderate COVID-19, have been conducted *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Registry
There is a pregnancy registry that monitors pregnancy outcomes in individuals exposed to LAGEVRIO during pregnancy. The prescribing healthcare provider must document that a pregnant individual was made aware of the pregnancy registry at https://covid-pr.pregistry.com or 1-800-616-3791. Pregnant individuals exposed to LAGEVRIO or their healthcare providers can also report the exposure by contacting Merck Sharp & Dohme LLC, Rahway, NJ USA at 1-877-888-4231.

Risk Summary
Based on animal data, LAGEVRIO may cause fetal harm when administered to pregnant individuals. There are no available human data on the use of LAGEVRIO in pregnant individuals to evaluate the risk of major birth defects, miscarriage or adverse maternal or fetal outcomes; therefore, LAGEVRIO is not recommended during pregnancy *[see Box and Warnings and Precautions (5.1)]*. In an animal reproduction study, oral administration of molnupiravir to pregnant rats during the period of organogenesis resulted in embryofetal lethality and teratogenicity at 8 times the human NHC (N4-hydroxycytidine) exposures at the recommended

human dose (RHD) and reduced fetal growth at ≥ 3 times the human NHC exposure at the RHD. Oral administration of molnupiravir to pregnant rabbits during the period of organogenesis resulted in reduced fetal body weights at 18 times the human NHC exposure at the RHD (see *Data*). When considering LAGEVRIO for a pregnant individual, the prescribing healthcare provider must communicate the known and potential benefits and the potential risks of using LAGEVRIO during pregnancy to the pregnant individual. LAGEVRIO may only be prescribed to a pregnant individual after the prescribing healthcare provider has determined that the benefits would outweigh the risks for that individual patient. If the decision is made to use LAGEVRIO during pregnancy, the prescribing healthcare provider must document that the known and potential benefits and potential risks of using LAGEVRIO during pregnancy were communicated to the pregnant individual *[see Box]*. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy *(see Clinical Considerations)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

Data

Animal Data

In an embryofetal development (EFD) study in rats, molnupiravir was administered orally to pregnant rats at 0, 100, 250, or 500 mg/kg/day from gestation days (GDs) 6 to 17. Molnupiravir was also administered orally to pregnant rats at up to 1,000 mg/kg/day from GDs 6 to 17 in a preliminary EFD study. Developmental toxicities included post-implantation losses, malformations of the eye, kidney, and axial skeleton, and rib variations at 1,000 mg/kg/day (8 times the human NHC exposure at the RHD) and decreased fetal body weights and delayed ossification at ≥500 mg/kg/day (3 times the human NHC exposure at the RHD). There were no developmental toxicities at ≤250 mg/kg/day (less than the human NHC exposure at the RHD). Maternal toxicities included decreased food consumption and body weight losses, resulting in the early sacrifice of two of sixteen animals at 1,000 mg/kg/day, and decreased body weight gain at 500 mg/kg/day.

In an EFD study in rabbits, molnupiravir was administered orally to pregnant rabbits at 0, 125, 400, or 750 mg/kg/day from GDs 7 to 19. Developmental toxicity was limited to reduced fetal body weights at 750 mg/kg/day (18 times the human NHC exposures at the RHD). There was no developmental toxicity at ≤400 mg/kg/day (7 times the human NHC exposures at the RHD). Maternal toxicities included reduced food consumption and body weight gains, and abnormal fecal output at 750 mg/kg/day.

In a pre- and post-natal developmental study, molnupiravir was administered orally to female rats at doses up to 500 mg/kg/day (similar to the human NHC exposure at the RHD) from GD6 through lactation day 20. No effects were observed in offspring.

8.2 Lactation

Risk Summary

There are no data on the presence of molnupiravir or its metabolites in human milk. NHC was detected in the plasma of nursing pups from lactating rats administered molnupiravir *(see Data)*. It is unknown whether molnupiravir has an effect on the breastfed infant or effects on milk production.

Based on the potential for adverse reactions in the infant from LAGEVRIO, breastfeeding is not recommended during treatment with LAGEVRIO and for 4 days after the final dose. A lactating individual may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for 4 days after the last dose of LAGEVRIO *[see Warnings and Precautions (5.1, 5.3)]*.

Data
When molnupiravir was administered to lactating rats at ≥250 mg/kg/day in the pre- and post-natal development study, NHC was detected in plasma of nursing pups.

8.3 Females and Males of Reproductive Potential
Based on animal studies, LAGEVRIO may cause fetal harm when administered to a pregnant individual.

Pregnancy Testing
Prior to initiating treatment with LAGEVRIO, assess whether an individual of childbearing potential is pregnant or not, if clinically indicated *[see Warnings and Precautions (5.1)]*.

Contraception
Females
Advise individuals of childbearing potential to use a reliable method of contraception correctly and consistently, as applicable for the duration of treatment and for 4 days after the last dose of LAGEVRIO *[see Warnings and Precautions (5.1)]*.

Males
While the risk is regarded as low, nonclinical studies to fully assess the potential for LAGEVRIO to affect offspring of treated males have not been completed. Advise sexually active individuals with partners of childbearing potential to use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose of LAGEVRIO. The risk beyond three months after the last dose of LAGEVRIO is unknown. Studies to understand the risk beyond three months are ongoing.

Molnupiravir was equivocal (neither clearly positive nor negative) in one *in vivo* mutagenicity assay of reticulocytes and RBCs which are used to reflect prior effects on hematopoietic stem cells in bone marrow. Molnupiravir was not mutagenic when assessed in a second *in vivo* assay of liver (somatic cells) and bone marrow (somatic cells and stem cells) from transgenic rats administered molnupiravir for 28 days. In contrast to somatic cells, germ cells (eggs and sperm) pass genetic information from generation to generation. A planned study of male testicular germ cells from transgenic rats will assess the potential for molnupiravir to affect offspring of treated males *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use
LAGEVRIO is not authorized for use in patients less than 18 years of age.
Bone and cartilage toxicity were observed in a 3-month, repeat-dose toxicology study in rats. The safety and efficacy of LAGEVRIO have not been established in pediatric patients *[see Warnings and Precautions (5.3) and Nonclinical Toxicology (13.2)]*.

8.5 Geriatric Use
In MOVe-OUT, there was no difference in safety and tolerability between patients ≥65 years of age and younger patients who were treated with LAGEVRIO. No dosage adjustment is recommended based on age. The PK of NHC was similar in geriatric patients compared to younger patients *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment
No dosage adjustment in patients with any degree of renal impairment is recommended. Renal clearance is not a meaningful route of elimination for NHC. Mild or moderate renal impairment did

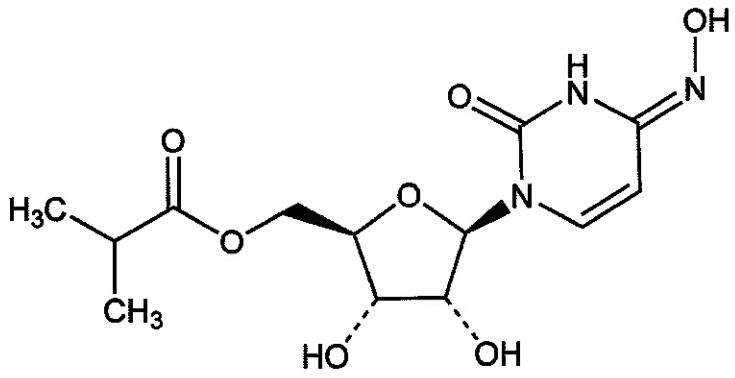
not have a meaningful impact on the PK of NHC. While the PK of NHC has not been evaluated in patients with eGFR less than 30 mL/min/1.73m^2 or on dialysis, severe renal impairment, and end-stage renal disease (ESRD) are not expected to have a significant effect on NHC exposure *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment
No dosage adjustment in patients with hepatic impairment is recommended. Preclinical data indicate that hepatic elimination is not expected to be a major route of NHC elimination therefore, hepatic impairment is unlikely to affect NHC exposure *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE
There is no human experience of overdosage with LAGEVRIO. Treatment of overdose with LAGEVRIO should consist of general supportive measures including the monitoring of the clinical status of the patient. Hemodialysis is not expected to result in effective elimination of NHC.

11 DESCRIPTION
LAGEVRIO capsules contain molnupiravir, a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis and is the 5′-isobutyrate ester of the ribonucleoside analog N4-hydroxycytidine (NHC).

The chemical name for molnupiravir is {(2R,3S,4R,5R)-3,4-Dihydroxy-5-[(4Z)-4-(hydroxyimino)-2-oxo-3,4-dihydropyrimidin-1(2H)-yl]oxolan-2-yl}methyl 2-methylpropanoate. It has an empirical formula of $C_{13}H_{19}N_3O_7$ and its molecular weight is 329.31 g/mol. Its structural formula is:



Molnupiravir is a white to off-white powder that is soluble in water.

Each LAGEVRIO capsule, for oral use, contains 200 mg of molnupiravir and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate and microcrystalline cellulose and purified water. The capsule shell is made of hypromellose, red iron oxide and titanium dioxide. The capsule is printed with white ink made of butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac, strong ammonia solution and titanium dioxide.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Molnupiravir is a prodrug with antiviral activity against SARS-CoV-2. It is metabolized to the cytidine nucleoside analogue, NHC which distributes into cells where NHC is phosphorylated to form the pharmacologically active ribonucleoside triphosphate (NHC-TP). NHC-TP incorporation (as NHC-monophosphate [NHC-MP]) into SARS-CoV-2 RNA by the viral RNA polymerase (nsp12) results in an accumulation of errors in the viral genome leading to inhibition of replication. The mechanism of action (known as viral error catastrophe or viral lethal mutagenesis) is supported by biochemical and cell culture data, studies of SARS-CoV-2

infection in animal models, and analyses of SARS-CoV-2 genome sequences in human subjects treated with LAGEVRIO.

12.2 Pharmacodynamics

The relationship between NHC and intracellular NHC-TP with antiviral efficacy has not been evaluated clinically.

12.3 Pharmacokinetics

Molnupiravir is a 5′-isobutyrate prodrug of NHC that is hydrolyzed during or after absorption. NHC, the primary circulating analyte, is taken up by cells and anabolized to NHC-TP. NHC is eliminated by metabolism to uridine and/or cytidine through the same pathways involved in endogenous pyrimidine metabolism. NHC pharmacokinetics are shown in Table 2.

Plasma NHC concentrations in patients (N=5) following administration of molnupiravir via nasogastric or orogastric tube fell within the range of NHC concentrations following oral molnupiravir capsule administration under the same dosing regimen.

Table 2: Pharmacokinetics of NHC After Multiple Oral Administration of 800 mg LAGEVRIO Every 12 Hours

	NHC Geometric Mean (%CV)
Pharmacokinetics in Patients	
$AUC_{0\text{-}12hr}$ (ng*hr/mL)*	8260 (41.0)
C_{max} (ng/mL)*	2330 (36.9)
C_{12hr} (ng/mL)*	31.1 (124)
Pharmacokinetics in Healthy Subjects	
$AUC_{0\text{-}12hr}$ (ng*hr/mL)	8330 (17.9)
C_{max} (ng/mL)	2970 (16.8)
C_{12hr} (ng/mL)	16.7 (42.8)
AUC Accumulation Ratio	1.09 (11.8)
Absorption	
T_{max} (hr)†	1.50 [1.00 – 2.02]
Effect of Food	35% reduction in C_{max}, no effect on AUC
Distribution	
Plasma Protein Binding (*in vitro*)	0%
Apparent Volume of Distribution (L)*	142
Elimination	
Effective $t_{1/2}$ (hr)	3.3
Apparent Clearance (L/hr)*	76.9
Fraction of dose excreted in urine over the time interval of 0-12 hours	3% (81.6%)

Values were obtained from a Phase 1 study of healthy subjects, unless otherwise indicated.
*Values were obtained from population PK analysis.
†Median [min - max]

Specific Populations

Population PK analysis results indicated that age, sex, race, ethnicity, or disease severity do not meaningfully influence the PK of NHC.

Pediatric Patients

LAGEVRIO has not been studied in pediatric patients.

Patients with Renal Impairment

Renal clearance is not a meaningful route of elimination for NHC. In a population PK analysis, mild or moderate renal impairment did not have a meaningful impact on the PK of NHC. The PK

of molnupiravir and NHC has not been evaluated in patients with eGFR less than 30 mL/min/1.73m^2 or on dialysis.

Patients with Hepatic Impairment
The PK of molnupiravir and NHC has not been evaluated in patients with moderate and severe hepatic impairment. Preclinical data indicate that hepatic elimination is not expected to be a major route of NHC elimination; therefore, hepatic impairment is unlikely to affect NHC exposure.

Drug Interaction Studies
In vitro study results indicated that molnupiravir and NHC are not substrates of CYP enzymes or human P-gp and BCRP transporters. *In vitro* study results also indicated that molnupiravir and NHC are not inhibitors of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 or inhibitors of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2K, MRP2, MDR1 and BCRP or inducers of CYP1A2, 2B6, and 3A4. The interaction between molnupiravir with concomitant medications, including other treatments for mild-to-moderate COVID-19, has not been evaluated.

12.4 Microbiology
Antiviral Activity
NHC, the nucleoside analogue metabolite of molnupiravir, was active in cell culture assays against SARS-CoV-2 (USA-WA1/2020 isolate) with 50% effective concentrations (EC_{50} values) ranging between 0.67 to 2.7 µM in A-549 cells and 0.32 to 2.0 µM in Vero E6 cells. NHC had similar antiviral activity against SARS-CoV-2 variants Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), Lambda (C.37), Mu (B.1.621) and Omicron (B.1.1.529/BA.1, BA.1.1, BA.2, BA.4 and BA.5), with mean EC_{50} values of 0.55-3.0 µM. NHC had non-antagonistic antiviral activity with remdesivir against SARS-CoV-2 in cell culture.

Resistance
No amino acid substitutions in SARS-CoV-2 associated with resistance to NHC have been identified in Phase 2 clinical trials evaluating LAGEVRIO for the treatment of COVID-19. Studies to evaluate selection of resistance to NHC with SARS-CoV-2 in cell culture have not been completed. Resistance selection studies have been conducted with other coronaviruses (MHV and MERS-CoV) and showed a low likelihood of resistance development to NHC. Following 30 passages in cell culture, only a 2-fold decrease in susceptibility was observed and no NHC resistance-associated amino acid substitutions were identified.

In clinical trials, encoded amino acid changes (substitutions, deletions or insertions) were more likely to be detected in viral sequences in subjects treated with LAGEVRIO compared to placebo. In a small number of subjects amino acid changes in the spike protein occurred at positions targeted by monoclonal antibodies and vaccines. The clinical and public health significance of these changes are unknown.

Cross-Resistance
NHC retained activity in cell culture against virus with polymerase (nsp 12) substitutions (e.g., F480L, V557L and E802D) associated with decreased remdesivir susceptibility, indicating a lack of cross-resistance.

Activity against SARS-CoV-2 in animal models
The antiviral activity of molnupiravir has been demonstrated in mouse, hamster, and ferret models of SARS-CoV-2 infection when dosing was administered prior to or within 1-2 days after viral challenge. In SARS-CoV-2 infected ferrets, molnupiravir significantly reduced SARS-CoV-2 viral titers in the upper respiratory tract and completely inhibited viral spread to untreated contact animals. In SARS-CoV-2 infected Syrian hamsters, molnupiravir reduced viral RNA and infectious virus titers in the lungs of animals. Histopathological analysis of lung tissue harvested after infection showed significantly reduced SARS-CoV-2 viral antigen levels and a lower abundance of pulmonary lesions in molnupiravir-treated animals compared with controls.

In Vitro Cytotoxicity
NHC, the nucleoside analogue metabolite of molnupiravir, had variable cytotoxicity against different mammalian cell types with CC_{50} values ranging from 7.5 µM (human lymphoid CEM cell line) to >100 µM, in 3-day exposure assays. Molnupiravir inhibited the proliferation of human bone marrow progenitor cells with CC_{50} values of 24.9 µM and 7.7 µM for erythroid and myeloid progenitor proliferation, respectively, in 14-day colony formation assays.

Viral RNA Rebound
Post-treatment increases in SARS-CoV-2 RNA shedding levels (i.e., viral RNA rebound) in nasopharyngeal samples were observed on Day 10, Day 15, and/or Day 29 in a subset of LAGEVRIO and placebo recipients in the Phase 3 MOVe-OUT trial. Approximately 1% of both LAGEVRIO and placebo recipients had evidence of recurrent COVID-19 symptoms coinciding with a rebound in viral RNA levels in nasopharyngeal samples.

Post-treatment viral RNA rebound was not associated with the primary clinical outcome of hospitalization or death through Day 29 following the single 5-day course of LAGEVRIO treatment. Post-treatment viral RNA rebound also was not associated with the detection of cell culture infectious virus in nasopharyngeal swab samples.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Molnupiravir was not carcinogenic in a 6-month oral carcinogenicity study in RasH2 transgenic (Tg.RasH2) mice at any dose tested (30, 100 or 300 mg/kg/day).

Mutagenesis
Molnupiravir and NHC were positive in the *in vitro* bacterial reverse mutation assay (Ames assay) with and without metabolic activation. Molnupiravir was studied in two *in vivo* rodent mutagenicity models. The *in vivo* Pig-a mutagenicity assay gave equivocal results. Molnupiravir was negative in the *in vivo* Big Blue® (cII Locus) transgenic rodent mutagenicity assay. Molnupiravir was negative for induction of chromosomal damage in *in vitro* micronucleus (with and without metabolic activation) and *in vivo* rat micronucleus assays. To assess effects on germ cells, a transgenic rodent male germ cell mutagenicity assay is planned.

Based on the totality of the available genotoxicity data and the duration of treatment (5 days), molnupiravir is low risk for genotoxicity.

Impairment of Fertility
There were no effects on fertility, mating performance or early embryonic development when molnupiravir was administered to female or male rats at NHC exposures approximately 2 and 6 times, respectively, the human NHC exposure at the RHD.

13.2 Animal Toxicology and/or Pharmacology

Bone and cartilage toxicity changes resulting in impaired transformation of growth cartilage into new bone were observed in the femur and tibia of rats in a 3-month toxicity study at ≥ 500 mg/kg/day (5 times the human NHC exposure at the RHD). There was no bone or cartilage toxicity in a 1-month toxicity study in rats up to 500 mg/kg/day (4 and 8 times the human NHC exposure at the RHD in females and males, respectively), in dogs dosed for 14 days up to 50 mg/kg/day (similar to the human NHC exposure at the RHD), or in a 1-month toxicity study in mice up to 2,000 mg/kg/day (19 times the human NHC exposure at the RHD).

Growth cartilage is not present in mature skeletons, therefore the bone and cartilage findings are not relevant for adult humans but may be relevant for pediatric patients *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.4)]*.

Reversible, dose-related bone marrow toxicity affecting all hematopoietic cell lines was observed in dogs at ≥17 mg/kg/day (less than the human NHC exposure at the RHD). Mild decreases in peripheral blood cell and platelet counts were seen after 7 days of molnupiravir treatment progressing to more severe hematological changes after 14 days of treatment. Neither bone marrow nor hematological toxicity was observed in a 1-month toxicity study in mice up to 2,000 mg/kg/day (19 times the human NHC exposure at the RHD) and a 3-month toxicity study in rats up to 1,000 mg/kg/day (9 and 15 times the human NHC exposure at the RHD in females and males, respectively).

14 CLINICAL STUDIES

Clinical data supporting this EUA are based on data from 1,433 randomized subjects in the Phase 3 MOVe-OUT trial (NCT04575597). MOVe-OUT is a randomized, placebo-controlled, double-blind clinical trial studying LAGEVRIO for the treatment of non-hospitalized patients with mild-to-moderate COVID-19 who are at risk for progressing to severe COVID-19 and/or hospitalization. Eligible subjects were 18 years of age and older and had one or more pre-defined risk factors for disease progression: over 60 years of age, diabetes, obesity (BMI ≥30), chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease, or active cancer. The study included symptomatic subjects not vaccinated against SARS-CoV-2 and who had laboratory confirmed SARS-CoV-2 infection and symptom onset within 5 days of randomization. Subjects were randomized 1:1 to receive 800 mg of LAGEVRIO or placebo orally twice daily for 5 days.

At baseline, in all randomized subjects, the median age was 43 years (range:18 to 90); 17% of subjects were over 60 years of age and 3% were 75 years of age or older; 49% of subjects were male; 57% were White, 5% Black or African American, 3% Asian, 50% Hispanic or Latino. The majority of subjects were enrolled from sites in Latin America (46%) and Europe (33%); 12% were enrolled in Africa, 6% were enrolled in North America and 3% were enrolled in Asia. Forty-eight percent of subjects received LAGEVRIO or placebo within 3 days of COVID-19 symptom onset. The most common risk factors were obesity (74%), over 60 years of age (17%), and diabetes (16%). Among 792 subjects (55% of total randomized population) with available baseline SARS-CoV-2 variant/clade identification results, 58% were infected with Delta (B.1.617.2 and AY lineages), 20% were infected with Mu (B.1.621), 11% were infected with Gamma (P.1), and the remainder were infected with other variants/clades. Overall, baseline demographic and disease characteristics were well balanced between the treatment arms.

Table 3 provides the results of the primary endpoint (the percentage of subjects who were hospitalized or died through Day 29 due to any cause). The efficacy results are based on unvaccinated adults who were 18 years of age and older and had one or more pre-defined risk factors for disease progression: over 60 years of age, diabetes, obesity (BMI ≥30), chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease, or active cancer. Please refer to Figure 1 for results by certain subgroups. These subgroup analyses are considered exploratory. Data are not available in certain subgroups of subjects who are at high risk for progression to severe COVID-19 as defined by CDC.

Table 3. Efficacy Results in Non-Hospitalized Adults with COVID-19*

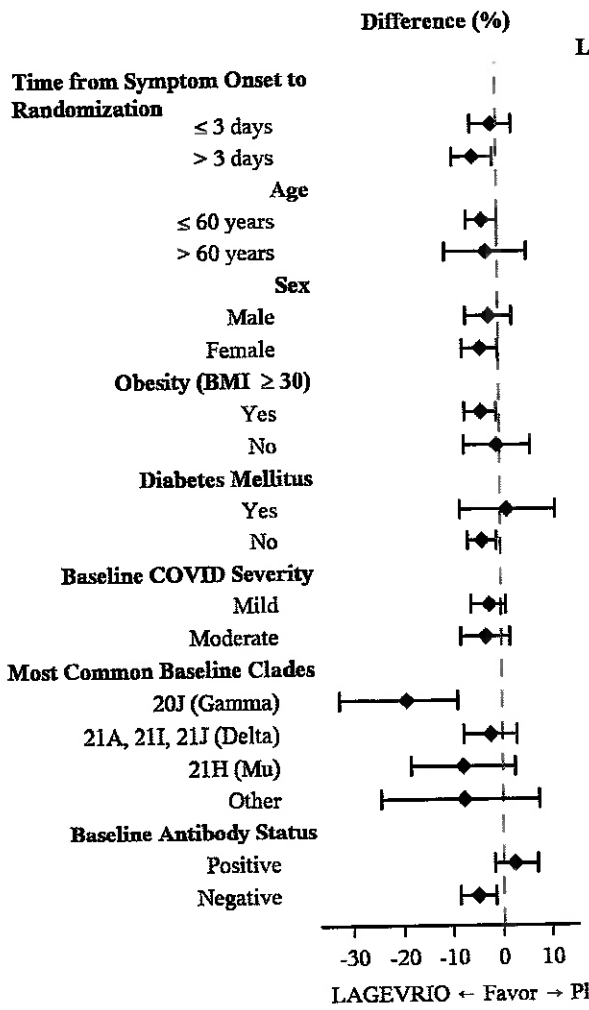
LAGEVRIO (N=709) n (%)	Placebo (N=699) n (%)	Adjusted Risk Difference % (95% CI)
All-cause hospitalization ≥24 hours for acute care or death through Day 29		
48 (6.8%)	68 (9.7%)	-3.0% (-5.9%, -0.1%)
All-cause mortality through Day 29		
1 (0.1%)	9 (1.3%)	

*The determination of primary efficacy was based on a planned interim analysis of 762 subjects. At the interim analysis, 7.3% of patients who received LAGEVRIO were either hospitalized or died through Day 29 (28/385), compared with 14.1% of placebo-treated patients (53/377). The adjusted risk difference was -6.8% with a 95% CI of (-11.3%, -2.4%) and 2-sided p-value = 0.0024.

Adjusted relative risk reduction of LAGEVRIO compared to placebo for all randomized subjects was 30% (95% CI: 1%, 51%).

Analyses are adjusted by the stratification factor of time of COVID-19 symptom onset (≤3 days vs. >3 [4-5] days).

Figure 1. Subgroup Efficacy Results in Non-Hospitalized Adults with COVID-19 - All-Randomized Subjects



	# Events/Subjects LAGEVRIO	# Events/Subjects Placebo	Risk Difference % (95% CI)
Time from Symptom Onset to Randomization			
≤ 3 days	25/339	28/335	-1.0 (-5.2, 3.2)
> 3 days	23/370	40/364	-4.8 (-9.0, -0.7)
Age			
≤ 60 years	36/591	52/572	-3.0 (-6.1, 0.0)
> 60 years	12/118	16/127	-2.4 (-10.6, 5.8)
Sex			
Male	32/330	41/355	-1.9 (-6.5, 2.8)
Female	16/379	27/344	-3.6 (-7.4, -0.2)
Obesity (BMI ≥ 30)			
Yes	29/535	46/507	-3.7 (-6.9, -0.5)
No	19/174	22/192	-0.5 (-7.1, 6.2)
Diabetes Mellitus			
Yes	17/107	17/117	1.4 (-8.2, 11.1)
No	31/602	51/582	-3.6 (-6.6, -0.7)
Baseline COVID Severity			
Mild	19/395	27/376	-2.4 (-5.9, 1.0)
Moderate	29/311	40/321	-3.1 (-8.1, 1.8)
Most Common Baseline Clades			
20J (Gamma)	0/37	9/47	-19.1 (-32.6, -8.9)
21A, 21I, 21J (Delta)	18/237	22/221	-2.4 (-7.8, 2.9)
21H (Mu)	6/75	13/82	-7.9 (-18.5, 2.6)
Other	5/47	7/38	-7.8 (-24.4, 7.4)
Baseline Antibody Status			
Positive	5/136	2/146	2.3 (-1.7, 7.1)
Negative	39/541	64/520	-5.1 (-8.8, -1.6)

The corresponding confidence interval is based on Miettinen & Nurminen method.
The modified intent-to-treat population is the efficacy analysis population.
Baseline serum samples were evaluated with the Roche Elecsys anti-N assay to test for the presence of antibodies (IgM, IgG and IgA) against the SARS-CoV-2 nucleocapsid protein.
The findings of these subgroup analyses are considered exploratory.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

LAGEVRIO capsules are supplied as follows:

Contents	Description	How Supplied	NDC

200 mg molnupiravir	Swedish Orange opaque capsules with corporate logo and "82" printed in white ink	40 count bottles	NDC-0006-5055-06 NDC-0006-5055-07 NDC-0006-5055-09

Storage and Handling
Store LAGEVRIO capsules at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION
As a prescribing healthcare practitioner, you must communicate to the patient and/or caregiver information consistent with the "FACT SHEET FOR PATIENTS AND CAREGIVERS" and document that information was provided. A copy of this Fact Sheet should be provided to the patient and/or caregiver prior to receiving LAGEVRIO *[see Box]*.

Hypersensitivity Reactions
Inform patients that hypersensitivity reactions have been reported, even following a single dose of LAGEVRIO, and to discontinue the drug and to inform their healthcare provider at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema (for example, swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction *[see Warnings and Precautions (5.2)]*.

Risk of Fetal Toxicity
Advise patients that LAGEVRIO is not recommended for use in pregnancy because it may cause fetal harm. Advise individuals of childbearing potential to inform their healthcare provider of a known or suspected pregnancy *[see Box, Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*.

Advise individuals of childbearing potential to use effective contraception correctly and consistently while taking LAGEVRIO and for 4 days after the last dose.

While the risk is regarded as low, nonclinical studies to fully assess the potential for LAGEVRIO to affect offspring of treated males have not been completed. Advise sexually active individuals with partners of childbearing potential to use a reliable method of contraception consistently and correctly while taking LAGEVRIO and for at least 3 months after the last dose of LAGEVRIO. The risk beyond 3 months after the last dose of LAGEVRIO is unknown. Studies to understand the risk beyond three months are ongoing *[see Use in Specific Populations (8.3)]*.

Risk of Bone and Cartilage Toxicity
LAGEVRIO is not authorized for use in patients less than 18 year of age as it may affect bone growth and cartilage formation *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.4)]*.

Pregnancy Registry
There is a pregnancy registry that monitors pregnancy outcomes in individuals exposed to LAGEVRIO during pregnancy. Encourage participation and advise patients about how they may enroll in the pregnancy registry at https://covid-pr.pregistry.com or 1-800-616-3791 *[see Use in Specific Populations (8.1)]*.

Lactation
Breastfeeding is not recommended while taking LAGEVRIO and for 4 days after the last dose of LAGEVRIO. Advise lactating individuals to consider interrupting breastfeeding and to consider

pumping and discarding breast milk during treatment and for 4 days after the last dose of LAGEVRIO *[see Use in Specific Populations (8.2)]*.

Administration Instructions
Inform patients to take LAGEVRIO with or without food. Advise patients to swallow LAGEVRIO capsules whole, and to not open, break, or crush the capsules. Instruct patients that if they miss a dose of LAGEVRIO and it is within 10 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 10 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. Advise the patient to not double the dose to make up for a missed dose *[see Dosage and Administration (2.2)]*.

LAGEVRIO capsule contents can be mixed with water and given via NG/OG tube. Inform patients to follow the instructions as described in the fact sheet for patients and caregivers *[see Dosage and Administration (2.3)]*.

Alert the patient of the importance of completing the full 5-day treatment course and to continuing isolation in accordance with public health recommendations to maximize viral clearance and minimize transmission of SARS-CoV-2 *[see Dosage and Administration (2.1)]*.

18 MANUFACTURER INFORMATION
For additional information visit: www.molnupiravir.com

If you have questions, please contact
1-800-672-6372

Manuf. for: Merck Sharp & Dohme LLC
Rahway, NJ 07065, USA

For patent information: www.msd.com/research/patent

usfshcp-mk4482-c-2307r008

U.S. FOOD & DRUG ADMINISTRATION

Frequently Asked Questions on the Emergency Use Authorization for Lagevrio (molnupiravir) for Treatment of COVID-19

Q: What is an emergency use authorization (EUA)?
A: Under section 564 of the Federal Food, Drug & Cosmetic Act, after a declaration by the HHS Secretary based on one of four types of determinations, FDA may authorize an unapproved product or unapproved uses of an approved product for emergency use. In issuing an EUA, FDA must determine, among other things, that based on the totality of scientific evidence available to the agency, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by a chemical, biological, radiological, or nuclear agent; that the known and potential benefits of the product, when used to treat, diagnose or prevent such disease or condition, outweigh the known and potential risks for the product; and that there are no adequate, approved, and available alternatives. Emergency use authorization is NOT the same as FDA approval or licensure.

Q: What does this EUA authorize? What are the limitations of authorized use?
A: FDA has issued an EUA for the emergency use of the unapproved product Lagevrio (molnupiravir) for the treatment of adults with a current diagnosis of mild-to-moderate coronavirus disease 2019 (COVID-19), who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate. Lagevrio is not FDA-approved for any use including for the treatment of COVID-19. Prior to initiating treatment with Lagevrio, carefully consider the known and potential risks and benefits.

Lagevrio is not authorized:

- for use in patients less than 18 years of age.
- for initiation of treatment in patients requiring hospitalization due to COVID-19. Benefit of treatment with Lagevrio has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19.
- for use for longer than five consecutive days.
- for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

Q: How is high risk defined under the EUA?
A: Information about conditions that place a patient with mild-to-moderate COVID-19 at increased risk for disease progression or death can be found at the Centers for Disease Control and Prevention's People with Certain Medical Conditions website. Health care providers should consider the benefit-risk for an individual patient.

Q: Does the EUA require a positive result from a direct SARS-CoV-2 viral test prior to prescribing Lagevrio to a patient who is at high risk for severe COVID-19?"
A: No. Although the Agency continues to recommend that authorized prescribers use direct SARS-CoV-2 viral testing to help diagnose COVID-19, the Agency removed the requirement for positive test results effective February 1, 2023. FDA recognizes that, in rare instances, individuals with a recent known exposure (e.g., a household contact with a positive direct SARS-CoV-2 viral test) who develop signs and symptoms consistent with COVID-19 may be diagnosed by an authorized prescriber as having COVID-19 even if they have a negative direct SARS-CoV-2 viral test result. In such instances, the authorized prescriber may determine that treatment with Lagevrio for COVID-19 is appropriate if the patient

reports mild-to-moderate symptoms of COVID-19 and is at high-risk for progression to severe COVID-19, including hospitalization or death, and the terms and conditions of the authorization are met, as detailed in the Fact Sheet for Healthcare Providers.

Q: What does direct SARS-CoV-2 viral testing mean?
A: Direct SARS-CoV-2 viral tests diagnose current COVID-19 infection. Direct SARS-CoV-2 viral tests include two types of diagnostic tests for COVID-19:

- Molecular tests, such as reverse transcription polymerase chain reaction (RT-PCR) tests, that detect the virus's genetic material.
- Antigen tests that detect specific proteins from the virus.

Antibody tests should not be used to diagnose COVID-19 and are not direct SARS-CoV-2 viral tests. Antibody tests look for antibodies that the immune system makes in response to the SARS-CoV-2 virus.

Q: Are there any warnings or precautions that should be taken when administering Lagevrio?
A: Yes, health care providers and patients must be aware of the following warnings and precautions:

- Pregnancy
  Lagevrio may cause fetal harm when administered to pregnant individuals. Therefore, **Lagevrio is not recommended for use during pregnancy.** Prior to initiating treatment with Lagevrio, health care providers should assess whether an individual of childbearing potential is pregnant or not, if clinically indicated. Lagevrio is authorized to be prescribed to a pregnant individual only after the health care provider has determined that the benefits would outweigh the risks for that individual patient and the known and potential benefits and potential risks of using Lagevrio during pregnancy are communicated to the pregnant individual.

- Lactation
  Breastfeeding is not recommended during treatment with Lagevrio and for four days after the final dose. A lactating individual may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for 4 days after the last dose of Lagevrio.

- Females of Reproductive Potential
  Females of childbearing potential are advised to use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for four days after the last dose of Lagevrio.

- Males of Reproductive Potential
  While the risk is regarded as low, studies to fully assess the potential for Lagevrio to affect offspring of treated males have not been completed. Sexually active individuals with partners of childbearing potential are advised to use a reliable method of contraception correctly and consistently during treatment and for at least three months after the last dose of Lagevrio. The risk beyond three months after the last dose of Lagevrio is unknown. Studies to understand the risk beyond three months are ongoing.

- Hypersensitivity Including Anaphylaxis

Hypersensitivity reactions, including anaphylaxis, have been reported with Lagevrio. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue Lagevrio and initiate appropriate medications and/or supportive care.

Q: Are there potential side effects of Lagevrio?
A: Possible side effects of Lagevrio include diarrhea, nausea, and dizziness. Lagevrio is not recommended for use during pregnancy because findings from animal reproduction studies showed that Lagevrio may cause fetal harm when administered to pregnant individuals.

Hypersensitivity, anaphylaxis, angioedema, erythema, rash, and urticaria adverse reactions have been identified during post-authorization use of Lagevrio.

Q: Why is Lagevrio only authorized in adults?
A: Lagevrio is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth.

Q: Is Lagevrio approved by the FDA to prevent or treat COVID-19?
A: No. Lagevrio is not FDA-approved to prevent or treat any diseases or conditions, including COVID-19. Lagevrio is an investigational drug.

Q: How can Lagevrio be obtained for use under the EUA?
A: For questions on how to obtain Lagevrio, please contact COVID19therapeutics@hhs.gov.

Q. Who may prescribe Lagevrio under the EUA?
A. Under the authorization, Lagevrio may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which Lagevrio belongs (i.e., anti-infectives).

Q: When should Lagevrio be administered to a patient?
A: Patients should talk to their healthcare provider to determine whether, based on their individual circumstances and whether alternative COVID-19 treatment options approved or authorized by FDA are accessible or clinically appropriate, they are eligible to receive Lagevrio. Patients should take Lagevrio as soon as possible after a diagnosis of COVID-19 has been made, and within five days of symptom onset.

More information about administration is available in the Fact Sheet for Health Care Providers.

Q: Does the EUA permit the use of Lagevrio as authorized in patients hospitalized *for reasons other* than COVID-19?
A: If a patient is hospitalized *for reasons other* than COVID-19, such as for an elective orthopedic procedure, and the patient has a current diagnosis of mild-to-moderate COVID-19, then treatment with Lagevrio is authorized if the patient is also at high risk for progression to severe COVID-19, including hospitalization or death, and the terms and conditions of the authorization are met as detailed in the Fact Sheet for Health Care Providers.

Lagevrio is also authorized for patients who require hospitalization after starting treatment with Lagevrio. These patients may complete the full five-day treatment course per the health care provider's discretion.

Q: Are there data showing treatment with Lagevrio may benefit adults with mild-to-moderate COVID-19 who are at high risk for progressing to severe COVID-19 and/or hospitalization?
A: Yes. The most important scientific evidence supporting the authorization of Lagevrio is from MOVe-OUT, a randomized, placebo-controlled, double-blind clinical trial studying Lagevrio for the treatment of non-hospitalized patients with mild-to-moderate COVID-19 who are at risk for progressing to severe COVID-19 and/or hospitalization. Eligible subjects were 18 years of age and older and had one or more pre-defined risk factors for disease progression: over 60 years of age, diabetes, obesity (BMI ≥30), chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease, or active cancer. The study included symptomatic subjects not vaccinated against SARS CoV-2 and who had laboratory confirmed SARS-CoV-2 infection and symptom onset within five days of randomization.

The main outcome measured in the trial was the percentage of people who were hospitalized or died due to any cause during 29 days of follow-up. Of the 709 people who received Lagevrio, 6.8% were hospitalized or died within this time period compared to 9.7% of the 699 people who received a placebo. This represented an adjusted relative risk reduction of Lagevrio compared to placebo of approximately 30% for all those randomized. Of the people who received Lagevrio, one died within this time period compared to nine people who received a placebo. The safety and effectiveness of Lagevrio for the treatment of COVID-10 continue to be evaluated.

Q: Are there requirements for health care facilities and prescribing health care providers as part of the EUA?
A: Yes.

- As part of the EUA, FDA requires health care providers who prescribe Lagevrio to report all medication errors and serious adverse events considered to be potentially related to Lagevrio through FDA's MedWatch Adverse Event Reporting program. Providers can complete and submit the report online; or download and complete the form, then submit it via fax at 1-800-FDA-0178. This requirement is outlined in the EUA's Fact Sheet for Health Care Providers. FDA MedWatch forms should also be provided to Merck Sharp & Dohme Corp.
- Health care facilities and providers must report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.
- Healthcare providers must provide an electronic or hard copy of the "Fact Sheet for Patients, and Caregivers" prior to the patient receiving Lagevrio and must document that the patient has been given an electronic or hard copy of the "Fact Sheet for Patients and Caregivers".
- Healthcare providers must inform the patient or caregiver that:
    - Lagevrio is an unapproved drug that is authorized for use under this Emergency Use Authorization.
    - Other therapeutics are currently approved or authorized for the same use as Lagevrio [see Emergency Use Authorization (1) - Information Regarding Available Alternatives for the EUA Authorized Use].
    - There are benefits and risks of taking Lagevrio as outlined in the "Fact Sheet for Patients and Caregivers."
    - There is a pregnancy registry for patients exposed to Lagevrio.

  - Females of childbearing potential should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for four days after the last dose of Lagevrio.
  - Males of reproductive potential who are sexually active with females of childbearing potential should use a reliable method of contraception correctly and consistently during treatment and for at least three months after the last dose.
- The prescribing health care provider must assess whether an individual of childbearing potential is pregnant or not, if clinically indicated.
- Based on findings from animal reproduction studies, Lagevrio may cause fetal harm when administered to pregnant individuals. If Lagevrio is used during pregnancy, prescribing healthcare providers must communicate to the patient the known and potential benefits and the potential risks of Lagevrio use during pregnancy, as outlined in the "Fact Sheet for Patients and Caregivers".
- If the decision is made to use Lagevrio during pregnancy, the prescriber must document that the known and potential benefits and the potential risks of Lagevrio use during pregnancy, as outlined in the "Fact Sheet for Patients and Caregivers," were discussed with the patient.
- There is a pregnancy registry that monitors pregnancy outcomes in individuals exposed to Lagevrio during pregnancy. The prescribing healthcare provider must document that a pregnant individual was made aware of the pregnancy registry at https://covid-pr.pregistry.com or 1-800-616-3791. Pregnant individuals exposed to Lagevrio or their healthcare providers can also report the exposure by contacting Merck Sharp & Dohme LLC, Rahway, NJ USA at 1-877-888-4231.

Q: Do patient outcomes need to be reported under the EUA?
A: No, reporting of patient outcomes is not required under the EUA. However, reporting of all medication errors and serious adverse events considered to be potentially related to Lagevrio occurring during treatment is required.

Q: FDA has issued a number of EUAs, including for therapeutics. If state laws impose different or additional requirements on the medical product covered by an EUA, are those state laws preempted?
A: As stated in FDA's Emergency Use Authorization of Medical Products and Related Authorities; Guidance for Industry and Other Stakeholders, "FDA believes that the terms and conditions of an EUA issued under section 564 preempt state or local law, both legislative requirements and common-law duties, that impose different or additional requirements on the medical product for which the EUA was issued in the context of the emergency declared under section 564." The guidance explains the basis for FDA's views on this subject.

Q: Can health care providers share the patient/caregiver fact sheet electronically?
A: Yes. The letter of authorization for Lagevrio authorizes healthcare providers to share the patient/caregiver fact sheet electronically.

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IMPORTANT PRESCRIBING INFORMATION

Subject: **Inconsistencies between VEKLURY® (remdesivir) Prescribing Information and VEKLURY for injection (supplied as lyophilized powder in vial) container label and carton labeling may lead to medication errors in pediatric patients.**

Dear Healthcare Provider:

Gilead Sciences, Inc., would like to alert providers that the **preparation and storage information on the container label and carton labeling of VEKLURY® (remdesivir) for injection (supplied as lyophilized powder in vial) may be inconsistent** with the US Prescribing Information that was revised on 25 April 2022 to include pediatric patients 28 days and older and weighing 3 kg to less than 40 kg.

To prevent medication errors, **healthcare providers should refer to the Dosage and Administration (Sections 2.6 and 2.7) of the most currently approved US Prescribing Information to prepare doses for pediatric patients** 28 days and older and weighing 3 kg to less than 40 kg. The current US Prescribing Information is available at www.gilead.com/science-and-medicine/medicines.

VEKLURY is available in two injectable dosage forms, a solution and lyophilized powder. **Only the VEKLURY for injection dosage form (supplied as lyophilized powder in vial) is approved for pediatric patients 28 days and older and weighing 3 kg to less than 40 kg.**

Reporting Adverse Events and Medication Errors

Healthcare providers are encouraged to report all adverse events and all medication errors when using VEKLURY to Gilead Sciences at Safety_fc@gilead.com and to FDA online at www.fda.gov/medwatch or by calling 1-800-FDA-1088.

Healthcare providers should direct questions on VEKLURY packaging or use to Gilead Sciences at 1-866-633-4474 or www.askgileadmedical.com.

For additional information about VEKLURY, including the full Prescribing Information, please visit www.vekluryhcp.com. Please also see Important Safety Information at the end of this letter.

Information and reports of suspicious, counterfeit, or unregistered remdesivir can be submitted to Gilead anticounterfeiting@gilead.com and/or www.fraud.org/fakerx.

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U.S. Indication and Important Safety Information for VEKLURY® (remdesivir)

Indication

VEKLURY is indicated for the treatment of COVID-19 in adults and pediatric patients (≥28 days old and weighing ≥3 kg) with positive results of SARS-CoV-2 viral testing, who are:

- Hospitalized, or
- Not hospitalized, have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

Important Safety Information

Contraindication

- VEKLURY is contraindicated in patients with a history of clinically significant hypersensitivity reactions to VEKLURY or any of its components.

Warnings and precautions

- **Hypersensitivity, including infusion-related and anaphylactic reactions:** Hypersensitivity, including infusion-related and anaphylactic reactions, has been observed during and following administration of VEKLURY; most occurred within 1 hour. Monitor patients during infusion and observe for at least 1 hour after infusion is complete for signs and symptoms of hypersensitivity as clinically appropriate. Symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, and shivering. Slower infusion rates (maximum infusion time of up to 120 minutes) can potentially prevent these reactions. If a severe infusion-related hypersensitivity reaction occurs, immediately discontinue VEKLURY and initiate appropriate treatment (see Contraindications).
- **Increased risk of transaminase elevations:** Transaminase elevations have been observed in healthy volunteers and in patients with COVID-19 who received VEKLURY; these elevations have also been reported as a clinical feature of COVID-19. Perform hepatic laboratory testing in all patients (see Dosage and Administration). Consider discontinuing VEKLURY if ALT levels increase to >10x ULN. Discontinue VEKLURY if ALT elevation is accompanied by signs or symptoms of liver inflammation.
- **Risk of reduced antiviral activity when coadministered with chloroquine or hydroxychloroquine:** Coadministration of VEKLURY with chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on data from cell culture experiments, demonstrating potential antagonism, which may lead to a decrease in the antiviral activity of VEKLURY.

Adverse reactions

- The most common adverse reaction (≥5% all grades) was nausea.
- The most common lab abnormalities (≥5% all grades) were increases in ALT and AST.

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Drug interactions

- Drug interaction trials of VEKLURY and other concomitant medications have not been conducted in humans.

Dosage and administration

- **Dosage:**
  - For adults and pediatric patients weighing ≥40 kg: 200 mg on Day 1, followed by once-daily maintenance doses of 100 mg from Day 2, administered only via intravenous infusion.
  - For pediatric patients ≥28 days old and weighing ≥3 kg to <40 kg: 5 mg/kg on Day 1, followed by once-daily maintenance doses of 2.5 mg/kg from Day 2, administered only via intravenous infusion.
  - There are two different formulations of VEKLURY: VEKLURY for injection (supplied as 100 mg lyophilized powder in vial) and VEKLURY injection (supplied as 100 mg/20 mL [5 mg/mL] solution in vial). The only approved dosage form for pediatric patients weighing 3 kg to <40 kg is the lyophilized powder formulation; See full Prescribing Information.
- **Treatment duration:**
  - For patients who are hospitalized and require invasive mechanical ventilation and/or ECMO, the recommended total treatment duration is 10 days. VEKLURY should be initiated as soon as possible after diagnosis of symptomatic COVID-19.
  - For patients who are hospitalized and do not require invasive mechanical ventilation and/or ECMO, the recommended treatment duration is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days, for a total treatment duration of up to 10 days.
  - For patients who are not hospitalized, diagnosed with mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death, the recommended total treatment duration is 3 days. VEKLURY should be initiated as soon as possible after diagnosis of symptomatic COVID-19 and within 7 days of symptom onset.
- **Testing prior to and during treatment:** Perform eGFR, hepatic laboratory, and prothrombin time testing prior to initiating VEKLURY and during use as clinically appropriate.
- **Renal impairment:** VEKLURY is not recommended in individuals with eGFR <30 mL/min.
- **Dose preparation and administration:**
  - There are two different formulations of VEKLURY: VEKLURY for injection (supplied as 100 mg lyophilized powder in vial), the only approved dosage form of VEKLURY for pediatric patients weighing 3 kg to <40 kg; and VEKLURY injection (supplied as 100 mg/20 mL [5 mg/mL] solution in vial). See full Prescribing Information.
  - Administration should be under conditions where management of severe hypersensitivity reactions, such as anaphylaxis, is possible.

Pregnancy and lactation

- **Pregnancy:** A pregnancy registry has been established. There are insufficient

human data on the use of VEKLURY during pregnancy. COVID-19 is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

- **Lactation:** It is not known whether VEKLURY can pass into breast milk. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

Please see full Prescribing Information for VEKLURY, available at www.gilead.com.

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FDA announces Evusheld is not currently authorized for emergency use in the U.S.

FDA announces Evusheld is not currently authorized for emergency use in the U.S.

Update [1/26/2023] The U.S. Food and Drug Administration today revised the Emergency Use Authorization (/media/154704/download?attachment) (EUA) for Evusheld (tixagevimab co-packaged with cilgavimab) to limit its use to when the combined frequency of non-susceptible SARS-CoV-2 variants nationally is less than or equal to 90%. Based on this revision, **Evusheld is not currently authorized for use in the U.S. until further notice by the Agency.**

Data show Evusheld is unlikely to be active against certain SARS-CoV-2 variants. According to the most recent CDC Nowcast data (https://covid.cdc.gov/covid-data-tracker/), these variants are projected to be responsible for more than 90% of current infections in the U.S. This means that Evusheld is not expected to provide protection against developing COVID-19 if exposed to those variants.

Today's action to limit the use of Evusheld prevents exposing patients to possible side effects of Evusheld such as allergic reactions, which can be potentially serious, at a time when fewer than 10% of circulating variants in the U.S. causing infection are susceptible to the product.

Monoclonal antibodies are laboratory-made proteins that mimic the immune system's ability to fight off harmful pathogens such as viruses, like SARS-CoV-2. And like other viruses, SARS-CoV-2 can mutate over time, resulting in certain products not working against certain variants. This is the case with Evusheld and prompted the changes to the authorization that FDA is making today.

Should a patient become infected with SARS-CoV-2 and develop symptoms of COVID-19, they should seek medical attention, including starting treatment for COVID-19 as appropriate. There are several treatments (/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs) – Paxlovid, Veklury (remdesivir) and Lagevrio (molnupiravir) – that are expected to work against currently circulating variants, and that are authorized or approved to treat certain patients with mild-to-moderate COVID-19 who are at high risk for progression to severe disease, including hospitalization or death. Healthcare providers should assess whether treatments are right for their patients.

The U.S. Government recommends that facilities and providers with Evusheld retain all product in the event that SARS-CoV-2 variants which are neutralized by Evusheld become more prevalent in the U.S. in the future. Retained product must be appropriately held in accordance with storage conditions detailed in the authorized Fact Sheet for Health Care Providers (/media/154701/download?attachment) and the Letter of Authorization (/media/154704/download?attachment).

FDA will continue to work with ASPR, the CDC, and the National Institutes of Health on surveillance of variants that may impact the use of the therapies authorized for emergency use. We will provide further updates and consider additional action as new information becomes available. Any updates will be made available on FDA's website (/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs).

FDA releases important information about risk of COVID-19 due to certain variants not neutralized by Evusheld

Update [1/6/2023] FDA is closely monitoring the emergence of the XBB.1.5 subvariant, a SARS-CoV-2 Omicron variant that is currently estimated (https://covid.cdc.gov/covid-data-tracker/#variant-proportions) to account for 28% of circulating variants in the U.S. Because of its similarity to variants that are not neutralized by Evusheld (e.g., XBB), FDA does not anticipate that Evusheld will neutralize XBB.1.5. This means that Evusheld may not provide protection against developing COVID-19 for individuals who have received Evusheld and are later exposed to XBB.1.5. However, we are awaiting additional data to verify that Evusheld is not active against XBB.1.5. We will provide further updates as new information becomes available.

Health care providers should inform individuals of the increased risk, compared to other variants, for COVID-19 due to SARS-CoV-2 variants not neutralized by Evusheld.

If signs and symptoms of COVID-19 occur, advise individuals to test for COVID-19 and seek medical attention, including starting treatment for COVID-19 as appropriate.

Update [10/3/2022] FDA added important information to the authorized Fact Sheets for Evusheld (tixagevimab co-packaged with cilgavimab) to inform health care providers and individuals receiving Evusheld of the increased risk for developing COVID-19 when exposed to variants of SARS-CoV-2 that are not neutralized by Evusheld. Detailed neutralization data can be found in the revised authorized **Fact Sheet for Healthcare Providers.** (https://www.fda.gov/media/154701/download) Health care professionals should inform

patients of this risk and advise patients who develop signs or symptoms of COVID-19 to test for SARS-CoV-2 infection and promptly seek medical attention, including starting treatment for COVID-19, as appropriate if they test positive.

Evusheld is currently the only option for pre-exposure prophylaxis (PrEP) of COVID-19 and is authorized under **Emergency Use Authorization (https://www.fda.gov/media/154704/download)** (EUA) for use in immunocompromised individuals who may not mount an adequate response to COVID-19 vaccination, and for individuals for whom COVID-19 vaccination is not recommended due to a history of a severe adverse reaction. It is authorized to be administered every six months. Use of Evusheld is not a substitute for COVID-19 vaccination, and individuals for whom COVID-19 vaccination is recommended should get vaccinated. Individuals who received Evusheld but who develop COVID-19 remain eligible for use of any of the available treatments for COVID-19 if the criteria for use are met.

FDA continues to recommend Evusheld as an appropriate option for PrEP to prevent COVID-19, in combination with other preventative measures like getting vaccinated and boosted as recommended, as Evusheld still offers protection against many of the currently circulating variants and may offer protection against future variants.

What Patients Should Know:

- Talk with your health care provider about appropriate treatment options in case you develop COVID-19. There are several approved and authorized treatments for COVID-19 that are expected to retain activity against currently circulating SARS-CoV-2 variants.
- If you develop COVID-19 symptoms, tell your health care provider and test right away. It's not possible to know which variant of SARS-CoV-2 you may have contracted. Timely treatment can reduce your risk of developing severe disease, including decreasing your risk of hospitalization or death.
- If recommended by your health care provider, get vaccinated or boosted with a bivalent booster dose to help your body increase your protection against SARS-CoV-2 infection. Follow CDC's guidelines (https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html) on additional prevention strategies to protect yourself from getting sick.

What Health Care Providers Should Know:

- Prescribers should monitor CDC regional variant frequency data (https://covid.cdc.gov/covid-data-tracker/#variant-proportions) and refer to the table of variants detailed in the Fact Sheet for Health Care Providers (https://www.fda.gov/media/154701/download) for the latest data on the neutralization

activity of Evusheld against SARS-CoV-2 variants in your area. Prescribers should discuss the risk of developing COVID-19 infection with patients receiving Evusheld.

- There are several treatments (https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs) – Paxlovid, Veklury (remdesivir), bebtelovimab, and Lagevrio (molnupiravir) – that are expected to retain activity against currently circulating variants, and that are authorized or approved to treat certain patients with mild-to-moderate COVID-19 who are at high risk for progression to severe disease, including hospitalization or death. Health care providers should assess whether these treatments are right for their patient in the event the patient develops mild-to-moderate COVID-19.
- FDA has also updated the list of medical conditions or treatments that may result in moderate to severe immune compromise. The conditions listed in the Fact Sheet for Health Care Providers (https://www.fda.gov/media/154701/download) are not intended to be an all-inclusive list. Patients with other conditions not listed may also have moderate to severe immune compromise and therefore be eligible for Evusheld therapy, assuming the remaining terms and conditions of the authorization are met.

FDA authorizes revisions to Evusheld dosing

Update [6/29/2022] There are different variants (and subvariants) of SARS-CoV-2, and FDA continues to evaluate how well Evusheld (tixagevimab co-packaged with cilgavimab) neutralizes them. Currently, the Omicron BA.2, BA.2.12.1, BA.4, and BA.5 subvariants are circulating in the United States. Nonclinical data and pharmacokinetic modeling suggest that activity against these subvariants may be retained for six months at drug concentrations achieved following an Evusheld dose of 300 mg of tixagevimab and 300 mg cilgavimab.

Therefore, on June 29, 2022, FDA revised the Evusheld Fact Sheet for Healthcare Providers (https://www.fda.gov/media/154701/download) to recommend repeat dosing every six months with a dose of 300 mg of tixagevimab and 300 mg cilgavimab if patients need ongoing protection. The previous Fact Sheet for Healthcare Providers did not provide a specific recommendation on the dosing interval.

We continue to monitor the neutralizing activity of Evusheld against emerging SARS-CoV-2 variants and will provide additional updates as needed.

For further details please refer to the Frequently Asked Questions for Evusheld. (https://www.fda.gov/media/154703/download)

[2/24/2022] The U.S. Food and Drug Administration has revised the emergency use authorization for Evusheld (tixagevimab co-packaged with cilgavimab) (https://www.fda.gov/media/154704/download) to change the initial dose for the authorized use as pre-exposure prophylaxis (prevention) of COVID-19 in certain adults and pediatric patients.
Based on the most recent information and data available, Evusheld may be less active against certain Omicron subvariants. The dosing regimen was revised because available data indicate that a higher dose of Evusheld may be more likely to prevent infection by the COVID-19 Omicron subvariants BA.1 and BA.1.1 than the originally authorized Evusheld dose.

Previously, the authorized Evusheld dosage was 150 mg of tixagevimab and 150 mg of cilgavimab administered as two separate consecutive intramuscular injections, with repeat doses every six months while SARS-CoV-2 remains in circulation. With this EUA revision, FDA has increased the initial authorized dose to 300 mg of tixagevimab and 300 mg of cilgavimab. Patients who have already received the previously authorized dose (150 mg of tixagevimab and 150 mg of cilgavimab) should receive an additional dose of 150 mg of tixagevimab and 150 mg of cilgavimab as soon as possible to raise their monoclonal antibody levels to those expected for patients receiving the higher dose.

Evusheld is authorized for the emergency use as pre-exposure prophylaxis (PrEP) for prevention of COVID-19 in certain adults and pediatric patients (12 years of age and older weighing at least 40 kg). Health care providers should only administer it to individuals who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to someone infected with SARS-CoV-2. Evusheld is only authorized for those:

- who have moderate-to-severe immune compromise due to a medical condition or who have received immunosuppressive medications or treatments and may not mount an adequate immune response to COVID-19 vaccination or
- for whom vaccination with any available approved or authorized COVID-19 vaccine is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s).

The duration of protection provided by Evusheld against symptomatic SARS-CoV-2 infection may not be as long as was shown in the clinical trial supporting the initial authorization because the clinical trial data came from a time period before the emergence of the BA.1 and BA.1.1 subvariants. However, it is not known whether BA.1 and BA1.1 will still be circulating in the coming months or whether another Omicron subvariant, BA.2, for which Evusheld is expected to have greater neutralizing activity, will become dominant. Because it is unclear which SARS-CoV-2 variant or Omicron subvariant will become dominant in the United States over the next few months, the recommended timing for repeat dosing cannot be provided at this time. We will

continue to monitor the situation closely and will provide updates with redosing recommendations in the near future when more data are available to determine the appropriate timing of redosing (e.g., 3 months or 6 months after the prior dose).

What should patients know:

- Patients who previously received an initial lower dose of Evusheld (150 mg of tixagevimab and 150 mg of cilgavimab) should contact their health care provider and return for an additional 150 mg of tixagevimab and 150 mg of cilgavimab dose as soon as possible. Any subsequent repeat dosing will be timed from the date of this additional Evusheld dose.
- Patients who have not received any doses of Evusheld should talk to their health care provider to determine whether, based on their individual circumstances, they are eligible to receive it. If they are eligible, they should receive the 300 mg of tixagevimab and 300 mg of cilgavimab dose.
- Patients with any additional questions should contact their health care provider.

What health care professionals should know:

- Health care professionals should contact patients who received the previously authorized Evusheld dose to return for an additional 150 mg tixagevimab and 150 mg cilgavimab dose as soon as possible.
- The volume of each injection for the new, higher dose will be larger, 3 mL instead of 1.5 mL. This means that the injections should be limited to large muscles on the body that can accommodate this volume (e.g., the gluteal muscles).
- Health care professionals should review the updated Fact Sheets and Dear Health Provider Letter for Evusheld.
- As part of the EUA, FDA requires health care providers who prescribe Evusheld to report all medication errors and serious adverse events considered to be potentially related to Evusheld through FDA's MedWatch Adverse Event Reporting program (https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program). Providers can complete and submit the report online (https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home); or download and complete the form, then submit it via fax at 1-800-FDA-0178.

U.S. FOOD & DRUG ADMINISTRATION

Frequently Asked Questions on the Emergency Use Authorization for Evusheld (tixagevimab co-packaged with cilgavimab) for Pre-exposure Prophylaxis (PrEP) of COVID-19

Q. What is an Emergency Use Authorization (EUA)?
A. Under section 564 of the Federal Food, Drug & Cosmetic Act, after a declaration by the HHS Secretary based on one of four types of determinations, FDA may authorize an unapproved product or unapproved uses of an approved product for emergency use. In issuing an EUA, FDA must determine, among other things, that based on the totality of scientific evidence available to the Agency, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by a chemical, biological, radiological, or nuclear agent; that the known and potential benefits, when used to treat, diagnose or prevent such disease or condition, outweigh the known and potential risks for the product; and that there are no adequate, approved, and available alternatives. Emergency use authorization is NOT the same as FDA approval or licensure.

Q. What does this EUA authorize? What are the limitations of authorized use?
A. The EUA authorizes AstraZeneca's Evusheld (tixagevimab co-packaged with cilgavimab) for emergency use as pre-exposure prophylaxis for prevention of COVID-19 in adults and pediatric individuals (12 years of age and older weighing at least 40 kg):

- Who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 **and**
  - Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments **and** may not mount an adequate immune response to COVID-19 vaccination **or**
  - For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s). *[see Warnings and Precautions (5.2)]*.

Limitations of Authorized Use

- Evusheld is not authorized for use in individuals:
  - For treatment of COVID-19, or
  - For post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2.
- Pre-exposure prophylaxis with Evusheld is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended. Individuals for whom COVID-19 vaccination is recommended, including individuals with moderate to severe immune compromise who may derive benefit from COVID-19 vaccination, should receive COVID-19 vaccination.
- In individuals who have received a COVID-19 vaccine, Evusheld should be administered at least two weeks after vaccination.

For any other limitations or conditions on use, please see the letter of authorized use.

Q. What is the initial dose of Evusheld?
A. The authorized Evusheld initial dose is 300 mg of tixagevimab and 300 mg of cilgavimab administered as two separate consecutive intramuscular (IM) injections.

Q. Is repeat dosing of Evusheld needed after the initial dose for ongoing protection?
A. Yes. If ongoing protection is needed, a repeat dose of 300 mg of tixagevimab and 300 mg of cilgavimab should be administered every 6 months.

Q. If an individual already received the original, lower Evusheld dose, what should they do?
A. Individuals who have already received the previously authorized initial dose (150 mg of tixagevimab and 150 mg of cilgavimab) should receive an additional Evusheld dose as soon as possible, with the dose based on the following criteria:

- If the patient received their initial dose less than or equal to 3 months ago, the patient should receive a dose of 150 mg of tixagevimab and 150 mg of cilgavimab.
- If the patient received their initial dose longer than 3 months ago, the patient should receive a dose of 300 mg of tixagevimab and 300 mg of cilgavimab.

Subsequent repeat dosing of Evusheld (300 mg of tixagevimab and 300 mg of cilgavimab) should be timed from the date of the most recent Evusheld dose.

Q. Are tixagevimab and cilgavimab monoclonal antibodies? What is a monoclonal antibody?
A. Yes, tixagevimab and cilgavimab are monoclonal antibodies. Monoclonal antibodies are laboratory-produced molecules engineered to serve as substitute antibodies that can restore, enhance or mimic the immune system's attack on pathogens. Evusheld is designed to block viral attachment and entry into human cells, thus neutralizing the virus.

Q. How is Evusheld affected by the SARS-CoV-2 variants in the U.S.?
A. While Evusheld offers protection against many circulating variants, there are some new variants of SARS-CoV-2 that are not neutralized by Evusheld. This means that Evusheld may provide no protection against developing COVID-19 if individuals receiving Evusheld are exposed to those variants. Health care providers should inform their patients who receive Evusheld of the risk for COVID-19 due to SARS-CoV-2 variants not neutralized by Evusheld. If signs or symptoms of COVID-19 occur, individuals should test for COVID-19 and promptly seek medical attention, including starting treatment for COVID-19 as appropriate.

The frequency of the different SARS-CoV-2 variants is being monitored by the FDA, Centers for Disease Control and Prevention (CDC), and other stakeholders. Health care providers should review the Antiviral Resistance information in Section 12.4 of the authorized Fact Sheets for Evusheld for details regarding specific variants and resistance.

Q. Is Evusheld still an appropriate option for eligible patients?
A. Yes. FDA continues to recommend Evusheld as an appropriate option for PrEP to prevent COVID-19, in combination with other preventative measures like getting vaccinated and boosted as recommended,

as Evusheld still offers protection against many of the currently circulating variants and may offer protection against future variants.

Q. What are some medical conditions or treatments that may lead to an inadequate immune response to the COVID-19 vaccination?

A. Medical conditions or treatments that may result in moderate to severe immunocompromise and an inadequate immune response to COVID-19 vaccination include but are not limited to:

- Active treatment for solid tumor and hematologic malignancies
- Hematologic malignancies associated with poor responses to COVID-19 vaccines regardless of current treatment status (e.g., chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, acute leukemia)
- Receipt of solid-organ transplant or an islet transplant and taking immunosuppressive therapy
- Receipt of chimeric antigen receptor (CAR)-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)
- Moderate or severe primary immunodeficiency (e.g., common variable immunodeficiency disease, severe combined immunodeficiency, DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Advanced or untreated HIV infection (people with HIV and CD4 cell counts <200/mm^3, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV)
- Active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, and biologic agents that are immunosuppressive or immunomodulatory (e.g., B-cell depleting agents)

Q. Are people who have received Evusheld eligible to receive COVID-19 treatments if they develop COVID-19?

A. There are several treatments – for example, Paxlovid, Veklury (remdesivir), and Lagevrio (molnupiravir) – that are expected to retain activity against currently circulating variants, and that are authorized or approved to treat certain patients with mild-to-moderate COVID-19 who are at high risk for progression to severe disease, including hospitalization or death. Health care providers should assess whether these treatments are right for their patients in the event the patient develops mild-to-moderate COVID-19.

FDA is closely monitoring the variants circulating in the United States that may impact the use of the available COVID-19 therapeutics, including Evusheld. The Agency will provide further updates as new information becomes available.

Q. Can people who have had a severe allergic reaction to a COVID-19 vaccine receive Evusheld?

A. Yes. People who have had a severe allergic reaction to a COVID-19 vaccine can receive Evusheld under the EUA. Evusheld contains polysorbate 80, which is in the Janssen COVID-19 Vaccine and is structurally similar to polyethylene glycol (PEG), an ingredient in the Pfizer-BioNTech and Moderna COVID-19 vaccines. Clinicians should consider consulting an allergist-immunologist prior to administering Evusheld to individuals with a history of a severe allergic reaction (e.g., anaphylaxis) to a COVID-19 vaccine.

For all individuals, Evusheld should be administered under the supervision of a health care provider with appropriate medical support to manage severe allergic reactions. In addition, everyone who receives Evusheld should be observed after injection for at least one hour to monitor for hypersensitivity reactions. Signs and symptoms of severe allergic reactions may include the following: dyspnea, chills, fatigue/asthenia, tachycardia, chest pain or discomfort, nausea/vomiting, angioedema, dizziness, urticaria, wheezing, pruritus, flushing, hyperhidrosis, myalgia, vaso-vagal reaction (e.g., pre-syncope, syncope), or throat irritation.

Q. Is Evusheld approved by the FDA to prevent or treat COVID-19?
A. No. Evusheld is not FDA-approved to prevent or treat any diseases or conditions, including COVID-19. Evusheld is an investigational drug.

Q. How can Evusheld be obtained for use under the EUA?
A. For questions on how to obtain Evusheld, please contact COVID19therapeutics@hhs.gov.

Q. Who may prescribe Evusheld under the EUA?
A. Evusheld may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which Evusheld belongs (i.e., anti-infectives).

Q. When should Evusheld be administered to a patient?
A. Patients should talk to their health care provider to determine whether, based on their individual circumstances, they are eligible to receive Evusheld, and when it should be administered.

More information about administration is available in the Fact Sheet for Health Care Providers.

Q. Are there potential side effects of Evusheld?
A. Possible side effects of Evusheld include the following:

Allergic reactions can happen during and after injection of Evusheld. Reactions to Evusheld may include difficulty breathing or swallowing; shortness of breath; wheezing; swelling of the face, lips, tongue or throat; rash including hives; or itching. Everyone who receives Evusheld should be observed after injection for at least one hour to monitor for hypersensitivity reactions, and Evusheld should only be administered under the supervision of a health care provider with appropriate medical support to manage severe allergic reactions. Clinicians should consider consulting an allergist-immunologist prior to administering Evusheld to individuals with a history of a severe allergic reaction to a COVID-19 vaccine.

The side effects of getting any medicine by intramuscular injection may include pain, bruising of the skin, soreness, swelling, and possible bleeding or infection at the injection site.

Serious cardiac adverse events (such as myocardial infarction and heart failure) were infrequent in the clinical trial evaluating Evusheld for pre-exposure prophylaxis for prevention. However, more trial participants had serious cardiac adverse events after receiving Evusheld compared to placebo. These participants all had risk factors for cardiac disease or a history of cardiovascular disease before participating in the clinical trial. It is not clear if Evusheld caused these cardiac adverse events.

These are not all the possible side effects of Evusheld. Not a lot of people have been given Evusheld. Serious and unexpected side effects may happen. Evusheld is still being studied so it is possible that all of the risks are not known at this time.

Q. Are there reporting requirements for health care facilities and providers as part of the EUA?
A. Yes. As part of the EUA, FDA requires health care providers who prescribe Evusheld to report all serious adverse events and medication errors considered to be potentially related to Evusheld through FDA's MedWatch Adverse Event Reporting program. Providers can complete and submit the report online; or download and complete the form, then submit it via fax at 1-800-FDA-0178. This requirement is outlined in the EUA's health care provider Fact Sheet. FDA MedWatch forms should also be provided to AstraZeneca.

Health care facilities and providers must report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

Q. Do patient outcomes need to be reported under the EUA?
A. No, reporting of patient outcomes is not required under the EUA. However, reporting of all medication errors and serious adverse events considered to be potentially related to Evusheld occurring during treatment is required.

Q. FDA has issued a number of EUAs including for therapeutics. If state laws impose different or additional requirements on the medical product covered by an EUA, are those state laws preempted?
A. As stated in FDA's Emergency Use Authorization of Medical Products and Related Authorities Guidance, "FDA believes that the terms and conditions of an EUA issued under section 564 preempt state or local law, both legislative requirements and common-law duties, that impose different or additional requirements on the medical product for which the EUA was issued in the context of the emergency declared under section 564." The guidance explains the basis for FDA's views on this subject.

Q. Can health care providers share the patient/caregiver Fact Sheet electronically?
A. The letter of authorization for Evusheld, requires that Fact Sheets be made available to health care providers and to patients/caregivers "through appropriate means." Electronic delivery of the patient/caregiver Fact Sheet is an appropriate means. For example, when the patient requests the Fact Sheet electronically, it can be delivered as a PDF prior to medication administration. Health care providers should confirm receipt of the Fact Sheet with the patient.

Q. Can I receive a COVID-19 vaccine if I was treated with a monoclonal antibody for COVID-19?
A. Patients and health care providers should refer to recommendations of the Advisory Committee on Immunization Practices regarding vaccination.

Q. Can I receive Evusheld if I recently received a COVID-19 vaccine?
A. Evusheld may reduce your body's immune response to a COVID-19 vaccine. If you receive a COVID-19 vaccine, you should wait to receive Evusheld until at least two weeks after your COVID-19 vaccination.

Q. What were the data that supported the initial authorization of Evusheld?
A. The most important scientific evidence supporting the authorization of Evusheld is from PROVENT, a randomized, double-blind, placebo-controlled clinical trial in adults who had not received a COVID-19 vaccine and did not have a history of SARS-CoV-2 infection or test positive for SARS-CoV-2 infection at

the start of the trial. All trial participants were either ≥60 years of age, had a pre-specified co-morbidity (obesity, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, immunocompromised state, or previous history of severe or serious adverse event after receiving any approved vaccine), or were at increased risk of SARS-CoV-2 infection due to their living situation or occupation.

The main outcome measured in the trial was whether the trial participant had a case of documented COVID-19 after receiving Evusheld (the 150 mg of tixagevimab and 150 mg of cilgavimab dose) or placebo and before day 183 of the trial. In this trial, 3,441 people received Evusheld and 1,731 received a placebo. In the primary analysis, Evusheld recipients saw a 77% reduced risk of developing COVID-19 compared to those who received a placebo, a statistically significant difference. In additional analyses, the reduction in risk of developing COVID-19 was maintained for Evusheld recipients through six months.

Details on the clinical trial results can be found in Section 14 of the authorized Fact Sheet for Health Care Providers.

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR EVUSHELD™ (tixagevimab co-packaged with cilgavimab)

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use EVUSHELD™ under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for EVUSHELD.

EVUSHELD (tixagevimab) injection; (cilgavimab) injection, co-packaged for intramuscular use
Original EUA Authorized Date: 12/2021
Revised EUA Authorized Date: 01/2023

----------RECENT MAJOR CHANGES----------

Limitations of Authorized Use: updated based on variant susceptibility	01/2023
Microbiology (12.4): updated neutralizing data	01/2023
Microbiology (12.4): updated neutralizing data	12/2022
Microbiology (12.4): updated neutralizing data	11/2022
Emergency Use Authorization (1): updated examples	10/2022
Warnings and Precautions (5.3, 17): addition of a new warning	10/2022
Microbiology (12.4): updated neutralizing data	10/2022
Dosage and Administration (2.1, 17): modification of initial dosage and repeat dosing	06/2022
Microbiology (12.4): updated neutralizing data	06/2022
Warnings and Precautions (5.2): addition of new warning	05/2022
Dosage and Administration (2.3)	05/2022
Adverse Reactions (6.1, 12.3): addition of TACKLE data	02/2022

----------EUA FOR EVUSHELD----------

The U.S. Food and Drug Administration has issued an EUA for the emergency use of the unapproved product EVUSHELD (tixagevimab co-packaged with cilgavimab), SARS-CoV-2 spike protein-directed attachment inhibitor, for the pre-exposure prophylaxis of coronavirus disease 2019 (COVID-19) in adults and pediatric individuals (12 years of age and older weighing at least 40 kg):

- Who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 **and**
  - Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments **and** may not mount an adequate immune response to COVID-19 vaccination **or**
  - For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s).

EVUSHELD may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which EVUSHELD belongs (i.e., anti-infectives).

EVUSHELD has been authorized by FDA for the emergency use described above. EVUSHELD is not FDA-approved for any use, including use for pre-exposure prophylaxis of COVID-19. (1)

EVUSHELD is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of EVUSHELD under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

LIMITATIONS OF AUTHORIZED USE

- EVUSHELD is not authorized for use in individuals:
  - For treatment of COVID-19, or
  - For post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2.
- EVUSHELD is authorized for use only when the combined frequency of non-susceptible variants nationally is less than or equal to 90%, based on available information including variant susceptibility to EVUSHELD and national variant frequencies.
- Pre-exposure prophylaxis with EVUSHELD is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended. Individuals for whom COVID-19 vaccination is recommended, including individuals with moderate to severe immune compromise who may derive benefit from COVID-19 vaccination, should receive COVID-19 vaccination.
- In individuals who have received a COVID-19 vaccine, EVUSHELD should be administered at least two weeks after vaccination.

See Full Fact Sheet for Healthcare Providers for examples of medical conditions or treatments that may result in moderate to severe immune compromise and an inadequate immune response to COVID-19 vaccination, the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19. (1)

----------DOSAGE AND ADMINISTRATION----------

The dosage of EVUSHELD for emergency use is:

- Initial dose: 300 mg of tixagevimab and 300 mg of cilgavimab administered as two separate consecutive intramuscular injections. (2.1)
- Dosing for Individuals Who Initially Received 150 mg of Tixagevimab and 150 mg Cilgavimab
  For individuals who initially received 150 mg tixagevimab and 150 mg cilgavimab:
  - Initial dose ≤3 months prior: 150 mg tixagevimab and 150 mg cilgavimab.
  - Initial dose >3 months prior: 300 mg tixagevimab and 300 mg cilgavimab. (2.1)
- Repeat dose: 300 mg of tixagevimab and 300 mg of cilgavimab every 6 months. Repeat dosing should be timed from the date of the most recent EVUSHELD dose. (2.1)

See Full Fact Sheet for Healthcare Providers for detail on preparation and administration. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Injection:

- tixagevimab 150 mg/1.5 mL (100 mg/mL) in a single-dose vial. (3)
- cilgavimab 150 mg/1.5 mL (100 mg/mL) in a single-dose vial. (3)

----------CONTRAINDICATIONS----------

EVUSHELD is contraindicated in individuals with previous severe hypersensitivity reactions, including anaphylaxis, to EVUSHELD. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity Including Anaphylaxis: Serious hypersensitivity reactions, including anaphylaxis, have been observed with EVUSHELD. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy. Clinically monitor individuals after injections and observe for at least 1 hour. (5.1)
- Risk of Cross-Hypersensitivity with COVID-19 Vaccines: EVUSHELD contains polysorbate 80, which is in some COVID-19 vaccines and is structurally similar to polyethylene glycol (PEG), an ingredient in other COVID-19 vaccines. For individuals with a history of severe hypersensitivity reaction to a COVID-19 vaccine, consider consultation with an allergist-immunologist prior to EVUSHELD administration. (5.2)
- Risk for COVID-19 Due to SARS-CoV-2 Viral Variants Not Neutralized by EVUSHELD: Certain SARS-CoV-2 viral variants may not be neutralized by monoclonal antibodies such as tixagevimab and cilgavimab, the components of EVUSHELD. EVUSHELD may not be effective at preventing COVID-19 caused by these SARS-CoV-2 viral variants. Inform individuals of the increased risk, compared to other variants, for COVID-19 due to SARS-CoV-2 viral variants not neutralized by EVUSHELD. If signs and symptoms of COVID-19 occur, advise individuals to test for COVID-19 and seek medical attention, including starting treatment for COVID-19 as appropriate. (5.3)

- Clinically Significant Bleeding Disorders: As with any other intramuscular injection, EVUSHELD should be given with caution to individuals with thrombocytopenia or any coagulation disorder. (5.4)
- Cardiovascular Events: A higher proportion of subjects who received EVUSHELD versus placebo reported myocardial infarction and cardiac failure serious adverse events. All of the subjects with events had cardiac risk factors and/or a prior history of cardiovascular disease, and there was no clear temporal pattern. A causal relationship between EVUSHELD and these events has not been established. Consider the risks and benefits prior to initiating EVUSHELD in individuals at high risk for cardiovascular events, and advise individuals to seek immediate medical attention if they experience any signs or symptoms suggestive of a cardiovascular event. (5.5)

----------ADVERSE REACTIONS----------

Most common adverse events (all grades, incidence ≥3%) are headache, fatigue, and cough. (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to EVUSHELD (1) by submitting FDA Form 3500 online, (2) by downloading this form and then submitting by mail or fax, or (3) contacting the FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to *AstraZeneca* by Fax at 1-866-742-7984 or call 1-800-236-9933. (6.4)

See PATIENT AND PARENTS/CAREGIVER FACT SHEET.

Revised: 01/2023

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* Sections or subsections omitted from the EUA are not listed

FULL FACT SHEET FOR HEALTHCARE PROVIDERS

1 EMERGENCY USE AUTHORIZATION

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of the unapproved product EVUSHELD (tixagevimab co-packaged with cilgavimab) for the pre-exposure prophylaxis of coronavirus disease 2019 (COVID-19) in adults and pediatric individuals (12 years of age and older weighing at least 40 kg):

- Who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 **and**
  - Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments **and** may not mount an adequate immune response to COVID-19 vaccination **or**
  - For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s) *[see Warnings and Precautions (5.2)]*.

EVUSHELD may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which EVUSHELD belongs (i.e., anti-infectives).

EVUSHELD has been authorized by FDA for the emergency use described above. EVUSHELD is not FDA-approved for any use, including use for pre-exposure prophylaxis of COVID-19.

EVUSHELD is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of EVUSHELD under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Medical conditions or treatments that may result in moderate to severe immune compromise and an inadequate immune response to COVID-19 vaccination **include but are not limited to**:

- Active treatment for solid tumor and hematologic malignancies
- Hematologic malignancies associated with poor responses to COVID-19 vaccines regardless of current treatment status (e.g., chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, acute leukemia)
- Receipt of solid-organ transplant or an islet transplant and taking immunosuppressive therapy
- Receipt of chimeric antigen receptor (CAR)-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)
- Moderate or severe primary immunodeficiency (e.g., common variable immunodeficiency disease, severe combined immunodeficiency, DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Advanced or untreated HIV infection (people with HIV and CD4 cell counts <200/mm^3, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV)
- Active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely

immunosuppressive, and biologic agents that are immunosuppressive or immunomodulatory (e.g., B-cell depleting agents)

LIMITATIONS OF AUTHORIZED USE

- EVUSHELD is not authorized for use in individuals:
  - For treatment of COVID-19, or
  - For post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2.
- EVUSHELD is authorized for use only when the combined frequency of non-susceptible variants nationally is less than or equal to 90%, based on available information including variant susceptibility to EVUSHELD and national variant frequencies[1].
- Pre-exposure prophylaxis with EVUSHELD is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended. Individuals for whom COVID-19 vaccination is recommended, including individuals with moderate to severe immune compromise who may derive benefit from COVID-19 vaccination, should receive COVID-19 vaccination.
- In individuals who have received a COVID-19 vaccine, EVUSHELD should be administered at least two weeks after vaccination.

Justification for Emergency Use of Drugs During the COVID-19 Pandemic

There is currently an outbreak of COVID-19 caused by SARS-CoV-2, a novel coronavirus. The Secretary of HHS has declared that:

- A public health emergency related to COVID-19 has existed since January 27, 2020.
- Circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic (March 27, 2020 declaration).

An EUA is a FDA authorization for the emergency use of an unapproved product or unapproved use of an approved product (i.e., drug, biological product, or device) in the United States under certain circumstances including, but not limited to, when the Secretary of HHS declares that there is a public health emergency that affects the national security or the health and security of United States citizens living abroad, and that involves biological agent(s) or a disease or condition that may be attributable to such agent(s). Criteria for issuing an EUA include:

- The biological agent(s) can cause a serious or life-threatening disease or condition;
- Based on the totality of the available scientific evidence (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that
  - The product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition; and
  - The known and potential benefits of the product - when used to diagnose, prevent, or treat such disease or condition - outweigh the known and potential risks of the product, taking into consideration the material threat posed by the biological agent(s);
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the serious or life-threatening disease or condition.

[1] FDA will monitor conditions to determine whether use is consistent with the scope of authorization, referring to available information, including information on variant susceptibility (e.g., Section 12.4 of the authorized Fact Sheet for Healthcare Providers) and CDC variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions.

Information Regarding Available Alternatives for the EUA Authorized Use
There are no adequate, approved and available alternatives to EVUSHELD for the pre-exposure prophylaxis of COVID-19 in individuals who may not mount an adequate immune response to COVID-19 vaccination or for whom COVID-19 vaccination is not recommended due to a history of severe adverse reaction to a COVID-19 vaccine or its components.

For information on clinical studies of EVUSHELD and other therapies for the prophylaxis of COVID-19, see www.clinicaltrials.gov.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Emergency Use of EVUSHELD

Initial Dosing
The initial dosage of EVUSHELD in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) is **300 mg of tixagevimab and 300 mg of cilgavimab** administered as two separate consecutive intramuscular (IM) injections *[see Clinical Pharmacology (12.3)]*. Refer to Table 1 below.

Dosing for Individuals Who Initially Received 150 mg of Tixagevimab and 150 mg of Cilgavimab
Individuals who have already received the previously authorized initial dose (150 mg of tixagevimab and 150 mg of cilgavimab) **should receive an additional EVUSHELD dose as soon as possible, with the dose based on the following criteria:**

- If the patient received their initial dose ≤ 3 months ago, the patient should receive a dose of 150 mg of tixagevimab and 150 mg of cilgavimab, refer to Table 2 below.
- If the patient received their initial dose > 3 months ago, the patient should receive a dose of 300 mg of tixagevimab and 300 mg of cilgavimab, refer to Table 1 below.

Repeat Dosing
The repeat dosage of EVUSHELD in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) is **300 mg of tixagevimab and 300 mg of cilgavimab** administered every 6 months, refer to Table 1 below. Repeat dosing should be timed from the date of the most recent EVUSHELD dose.

The recommendations for dosing are based on the totality of the scientific evidence including clinical pharmacology data, antiviral activity data, and clinical trial data *[see Clinical Pharmacology (12.3), Microbiology (12.4), and Clinical Studies (14)]*. EVUSHELD has only been studied for the prophylaxis of COVID-19 at the EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) dose. There are no data available in a prophylaxis setting for the EVUSHELD (300 mg of tixagevimab and 300 mg of cilgavimab) dose. The clinical safety of the EVUSHELD (300 mg of tixagevimab and 300 mg of cilgavimab) dose is supported by safety data from a treatment study in subjects with mild to moderate COVID-19 *[see Adverse Reactions (6.1)]*. There are limited safety and no efficacy data available with repeat dosing.

To access the most recent EVUSHELD Fact Sheets, please visit http://www.evusheld.com or scan the QR code:

2.2 Dosage Adjustment in Specific Populations

No dosage adjustment is recommended in pregnant or lactating individuals, in geriatrics, and in individuals with renal impairment *[see Use in Specific Populations (8)]*.

2.3 Dose Preparation and Administration

Each EVUSHELD carton contains two vials; one of each antibody. Each vial contains an overfill to allow the withdrawal of 150 mg (1.5 mL).

Table 1 Dosage of 300 mg of Tixagevimab and 300 mg of Cilgavimab

EVUSHELD* (tixagevimab co-packaged with cilgavimab)	Antibody dose	Number of vials needed	Volume to withdraw from vial(s)
	tixagevimab 300 mg	2 vials	3 mL
	cilgavimab 300 mg	2 vials	3 mL

* 300 mg of tixagevimab and 300 mg of cilgavimab are to be administered as separate, consecutive intramuscular injections

Table 2 Dosage of 150 mg of Tixagevimab and 150 mg of Cilgavimab

EVUSHELD* (tixagevimab co-packaged with cilgavimab)	Antibody dose	Number of vials needed	Volume to withdraw from vial
	tixagevimab 150 mg	1 vial	1.5 mL
	cilgavimab 150 mg	1 vial	1.5 mL

* 150 mg of tixagevimab and 150 mg of cilgavimab are to be administered as separate, consecutive intramuscular injections

Preparation

- Tixagevimab and cilgavimab must be prepared by a qualified healthcare provider.
- Tixagevimab and cilgavimab are each supplied in individual single-dose vials. Do not shake the vials.
- Visually inspect the vials for particulate matter and discoloration. Tixagevimab and cilgavimab are clear to opalescent, colorless to slightly yellow solutions. Discard the vials if the solution is cloudy, discolored or visible particles are observed.
- Administer EVUSHELD as TWO separate, consecutive intramuscular (IM) injections, 1 injection of tixagevimab and 1 injection of cilgavimab.

- Withdraw the appropriate amount of tixagevimab solution and the appropriate amount of cilgavimab solution into TWO separate syringes (see Table 1 and Table 2). Discard unused portion in vials.
- This product is preservative-free and therefore, the prepared syringes should be administered immediately. If immediate administration is not possible, and the prepared tixagevimab and cilgavimab syringes need to be stored, the total time from vial puncture to administration must not exceed 4 hours:
    - in a refrigerator at 2°C to 8°C (36°F to 46°F), or
    - at room temperature up to 25°C (77°F).

Administration

- Tixagevimab and cilgavimab should be administered by a qualified healthcare provider with appropriate medical support to manage severe hypersensitivity reactions.
- Administer the two components of EVUSHELD consecutively.
- Administer the IM injections at different injection sites, preferably one in each of the gluteal muscles, one after the other.
    - For the 300 mg tixagevimab and 300 mg cilgavimab dose, ensure that the administration sites are appropriate for the volume (3 mL per injection).
- Clinically monitor individuals after injections and observe for at least 1 hour *[see Warnings and Precautions (5.1, 5.2)]*.

3 DOSAGE FORMS AND STRENGTHS

EVUSHELD is available as an individual single-dose vial of tixagevimab as a clear to opalescent, colorless to slightly yellow solution co-packaged with an individual single-dose vial of cilgavimab as a clear to opalescent, colorless to slightly yellow solution as:

- Injection: 150 mg/1.5 mL (100 mg/mL) of tixagevimab
- Injection: 150 mg/1.5 mL (100 mg/mL) of cilgavimab

4 CONTRAINDICATIONS

EVUSHELD is contraindicated in individuals with previous severe hypersensitivity reactions, including anaphylaxis, to EVUSHELD *[see Warnings and Precautions (5.1, 5.2)]*.

5 WARNINGS AND PRECAUTIONS

There are limited clinical data available for EVUSHELD. Serious and unexpected adverse events may occur that have not been previously reported with EVUSHELD use.

5.1 Hypersensitivity Including Anaphylaxis

Serious hypersensitivity reactions, including anaphylaxis, have been observed with EVUSHELD *[see Adverse Reactions (6.1)]*. Signs and symptoms of hypersensitivity reactions may include: dyspnea, chills, fatigue/asthenia, tachycardia, chest pain or discomfort, nausea/vomiting, angioedema, dizziness, urticaria, wheezing, pruritus, flushing, hyperhidrosis, myalgia, vaso-vagal reactions (e.g., pre-syncope, syncope), or throat irritation.

Administration of EVUSHELD should be done under the supervision of a healthcare provider with appropriate medical support to manage severe hypersensitivity reactions. If signs and symptoms of a

clinically significant hypersensitivity reaction or anaphylaxis occur while taking EVUSHELD, immediately discontinue administration and initiate appropriate medications and/or supportive care. Clinically monitor individuals after injections and observe for at least 1 hour.

5.2 Risk of Cross-Hypersensitivity with COVID-19 Vaccines

EVUSHELD contains polysorbate 80, which is in some COVID-19 vaccines and is structurally similar to polyethylene glycol (PEG), an ingredient in other COVID-19 vaccines *[see Description (11)]*. For individuals with a history of a severe hypersensitivity reaction to a COVID-19 vaccine, consider consultation with an allergist-immunologist prior to EVUSHELD administration.

Administration of EVUSHELD should be done under the supervision of a healthcare provider with appropriate medical support to manage severe hypersensitivity reactions. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur while taking EVUSHELD, immediately discontinue administration and initiate appropriate medications and/or supportive care. Clinically monitor individuals after injections and observe for at least 1 hour.

5.3 Risk for COVID-19 Due to SARS-CoV-2 Viral Variants Not Neutralized by EVUSHELD

Certain SARS-CoV-2 viral variants may not be neutralized by monoclonal antibodies such as tixagevimab and cilgavimab, the components of EVUSHELD. EVUSHELD may not be effective at preventing COVID-19 caused by these SARS-CoV-2 viral variants. The *in-vitro* neutralization activity of EVUSHELD against SARS-CoV-2 viral variants is shown in Table 6 *[see Microbiology (12.4)]*.

Inform individuals of the increased risk, compared to other variants, for COVID-19 due to SARS-CoV-2 viral variants not neutralized by EVUSHELD. If signs or symptoms of COVID-19 occur, advise individuals to test for COVID-19 and seek medical attention, including starting treatment for COVID-19 as appropriate. Symptoms of COVID-19 may include: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, or diarrhea[2].

5.4 Clinically Significant Bleeding Disorders

As with any other intramuscular injection, EVUSHELD should be given with caution to individuals with thrombocytopenia or any coagulation disorder.

5.5 Cardiovascular Events

In PROVENT there was a higher rate of cardiovascular serious adverse events (SAEs), including myocardial infarction (one fatal SAE) and cardiac failure, in subjects who received EVUSHELD compared to placebo *[see Adverse Reactions (6.1)]*. All subjects who experienced cardiac SAEs had cardiac risk factors and/or a prior history of cardiovascular disease, and there was no clear temporal pattern. A causal relationship between EVUSHELD and these events has not been established. There was no signal for cardiac toxicity or thrombotic events identified in the nonclinical studies.

[2] For additional information on the symptoms of COVID-19, please see https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.

Consider the risks and benefits prior to initiating EVUSHELD in individuals at high risk for cardiovascular events, and advise individuals to seek immediate medical attention if they experience any signs or symptoms suggestive of a cardiovascular event.

6 ADVERSE REACTIONS

6.1 Adverse Reactions from Clinical Studies

The following adverse events have been observed in the clinical studies of EVUSHELD that supported the EUA. The adverse event rates observed in these clinical studies cannot be directly compared to rates in the clinical studies of other products and may not reflect the rates observed in clinical practice. Additional adverse events associated with EVUSHELD may become apparent with more widespread use.

Approximately 4,220 subjects have been exposed to EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) in two ongoing Phase III trials, PROVENT and STORM CHASER, for the prophylaxis of COVID-19. The primary safety analysis was based on data through to event driven efficacy data cut-offs, such that individual subjects had variable follow-up times *[see Clinical Studies (14)]*, with a median (range) of follow-up of 83 days (3-166 days) for PROVENT and 49 days (5-115 days) for STORM CHASER. An additional data cut-off was conducted to provide updated analyses with a median (range) of follow-up of 6.5 months (3-282 days) for PROVENT and approximately 6 months (5-249 days) for STORM CHASER. The median and range of follow-up times were similar between EVUSHELD and placebo recipients in each trial.

Four hundred and fifty two (452) non-hospitalized subjects (with the exception of those hospitalized for isolation purposes) with mild to moderate COVID-19 have been exposed to EVUSHELD (300 mg of tixagevimab and 300 mg of cilgavimab) in one ongoing Phase III clinical trial, TACKLE. The median (range) duration of follow-up was 84 days (1-183 days). EVUSHELD is not authorized for treatment of COVID-19 *[see Limitations of Authorized Use (1)]*.

In all studies, adults received EVUSHELD administered as two separate, consecutive IM injections of tixagevimab and cilgavimab or placebo *[see Clinical Studies (14)]*.

PROVENT (EVUSHELD [150 mg of tixagevimab and 150 mg of cilgavimab])
PROVENT enrolled adults ≥18 years of age who were either ≥60 years of age, had pre-specified co-morbidities *[see Clinical Studies (14)]*, or were at increased risk of SARS-CoV-2 infection due to their living situation or occupation. Subjects could not have previously received a COVID-19 vaccine or have known prior or current SARS-CoV-2 infection. Subjects received a single dose of EVUSHELD (N= 3,461) or placebo (N= 1,736).

Adverse events were reported in 1,221 (35%) subjects receiving EVUSHELD and 593 (34%) receiving placebo. SAEs were reported in 50 (1%) subjects receiving EVUSHELD and 23 (1%) receiving placebo. There was 1 adverse event reported as anaphylaxis among subjects who received EVUSHELD. The event began within minutes of EVUSHELD administration and was treated with epinephrine. The event resolved.

Of the reported adverse events (N= 4,507), the majority were mild (73%) or moderate (24%) in severity. All adverse events, occurring in at least 1% of subjects, were reported at similar incidence rates among subjects receiving EVUSHELD compared to those receiving placebo (difference <1%).

The most common treatment-emergent adverse events, occurring in at least 3% of subjects receiving EVUSHELD or placebo are shown in Table 3.

Table 3 Adverse Events (All Grades) Regardless of Causality Occurring in at Least 3% of Subjects Receiving EVUSHELD or Placebo in Primary Safety Analysis

	EVUSHELD N= 3,461	Placebo N= 1,736
Headache	6%	5%
Fatigue	4%	3%
Cough	3%	3%

At the additional data cut-off (median follow-up 6.5 months), the overall adverse event profile for subjects who received EVUSHELD remained similar to events displayed in Table 3.

Cardiac Serious Adverse Events
Through the additional data cut-off in PROVENT, a higher proportion of subjects who received EVUSHELD versus placebo in PROVENT reported myocardial infarction SAEs, one of which resulted in death, and cardiac failure SAEs (see Table 4 below). All subjects who experienced cardiac SAEs had cardiac risk factors and/or a prior history of cardiovascular disease at baseline. There was no clear temporal pattern, with events reported from several hours after EVUSHELD receipt through the end of the follow-up period.

Table 4 Cardiac SAEs Regardless of Causality in PROVENT with Onset Prior to Day 183 Using the Median 6-Month Data Cut-off Date

	EVUSHELD N= 3,461	Placebo N= 1,736
Subjects with any cardiac SAE*	22 (0.6%)	3 (0.2%)
SAEs related to coronary artery disease or myocardial ischemia†	10 (0.3%)	2 (0.1%)
Myocardial infarctions‡	8 (0.2%)	1 (0.1%)
SAEs related to cardiac failure§	6 (0.2%)	1 (0.1%)
SAEs related to an arrhythmia¶	4 (0.1%)	1 (0.1%)
Other (cardiomegaly, cardiomyopathy, and cardio-respiratory arrest)	3 (0.1%)	0

* One EVUSHELD recipient and one placebo recipient had two cardiac SAEs each.
† Includes the preferred terms angina pectoris, coronary artery disease, arteriosclerosis, troponin increased, acute myocardial infarction, and myocardial infarction.
‡ Includes the preferred terms acute myocardial infarction, myocardial infarction, and troponin increased (with a discharge diagnosis of myocardial infarction).
§ Includes the preferred terms cardiac failure congestive, acute left ventricular failure, cardiac failure, and cardiac failure acute.
¶ Includes the preferred terms atrial fibrillation, arrhythmia, paroxysmal atrioventricular block, and heart rate irregular.

STORM CHASER (EVUSHELD [150 mg tixagevimab and 150 mg cilgavimab])
STORM CHASER enrolled adults ≥18 years of age following potential exposure (within 8 days) to an identified individual with a laboratory-confirmed SARS-CoV-2 infection (symptomatic or asymptomatic). Subjects could not have previously received a COVID-19 vaccine, have symptoms consistent with COVID-19, or have a known prior SARS-CoV-2 infection. Subjects received a single dose of EVUSHELD (N= 749) or placebo (N= 372).

Adverse events were reported in 162 (22%) subjects receiving EVUSHELD and 111 (30%) receiving placebo. SAEs were reported in 5 (<1%) subjects receiving EVUSHELD and 3 (<1%) receiving placebo. Of the reported adverse events (N= 777), the majority were mild (75%) or moderate (23%) in severity.

At the additional data cut-off (median follow-up approximately 6 months), the overall adverse event profile for subjects who received EVUSHELD remained similar to earlier results. EVUSHELD is not authorized for post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2 *[see Emergency Use Authorization (1)]*.

Cardiac Serious Adverse Events
In STORM CHASER (N= 1,121) no cardiac SAEs were reported (median follow-up approximately 6 months). Compared to PROVENT, the subjects in STORM CHASER were younger (median age 48 versus 57 years) and had fewer baseline cardiac risk factors (24% versus 36% with hypertension, 11% versus 14% with diabetes, and 3% versus 8% with cardiovascular disease in STORM CHASER versus PROVENT, respectively).

TACKLE (EVUSHELD [300 mg tixagevimab and 300 mg cilgavimab])
TACKLE enrolled adults ≥18 years of age with mild to moderate COVID-19 who were within ≤7 days of symptom onset. Approximately 90% of study subjects had risk factors that put them at high risk for progression to severe COVID-19. Subjects received a single dose of EVUSHELD (N= 452) or placebo (N= 451).

Adverse events were reported in 132 (29%) subjects receiving EVUSHELD and 163 (36%) receiving placebo. Serious adverse events were reported in 33 (7%) subjects receiving EVUSHELD and 54 (12%) receiving placebo. Of the reported adverse events (N= 520), the majority were mild (56%) or moderate (27%) in severity. There were no reports of anaphylaxis or serious hypersensitivity reactions.

Adverse events of insomnia (1% vs. <1%) and dizziness (1% vs. none) were reported at a higher rate with EVUSHELD compared to placebo. No other treatment-emergent adverse events, occurring in at least 1% of subjects, were reported at higher incidence rates (difference ≥1%) among subjects receiving EVUSHELD compared to those receiving placebo.

Cardiac Serious Adverse Events
In TACKLE (N= 903) four subjects reported cardiac SAEs. Acute myocardial infarction was reported for two subjects who received EVUSHELD (one of whom also experienced cardiac failure leading to death) and sudden cardiac death was reported for one subject who received EVUSHELD. One subject who received placebo reported arrhythmia. All subjects who experienced cardiac SAEs had cardiac risk factors and/or a prior history of cardiovascular disease at baseline.

6.4 Required Reporting for Serious Adverse Events and Medication Errors

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events* and medication errors potentially related to EVUSHELD within 7 calendar days from the healthcare provider's awareness of the event, using FDA Form 3500 (for information on how to access this form, see below). The FDA requires that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race)
- A statement "EVUSHELD use for COVID-19 under Emergency Use Authorization (EUA)" under the "**Describe Event, Problem, or Product Use/Medication Error**" heading
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes)
- Patient's preexisting medical conditions and use of concomitant products
- Information about the product (e.g., dosage, route of administration, NDC #)

Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax to 1-800-FDA-0178, or
- Call 1-800-FDA-1088 to request a reporting form

In addition, please provide a copy of all FDA MedWatch forms to AstraZeneca:

- Fax 1-866-742-7984

and to report adverse events please:

- Visit https://contactazmedical.astrazeneca.com, or
- Call AstraZeneca at 1-800-236-9933.

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of EVUSHELD.

*Serious adverse events are defined as:

- Death
- A life-threatening adverse event;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- Other important medical event, which may require a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly;
- Inpatient hospitalization or prolongation of existing hospitalization.

6.5 Other Reporting Requirements

Healthcare facilities and providers will report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

7 DRUG INTERACTIONS

Drug-drug interaction studies have not been performed.

Tixagevimab and cilgavimab are not renally excreted or metabolized by cytochrome P450 (CYP) enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. EVUSHELD should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

Nonclinical reproductive toxicity studies have not been conducted with tixagevimab and cilgavimab. In a tissue cross-reactivity study assessing off-target binding of tixagevimab and cilgavimab to human fetal tissues no binding of clinical concern was observed. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, tixagevimab and cilgavimab have the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of tixagevimab and cilgavimab provides any treatment benefit or risk to the developing fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2 Lactation

Risk Summary
There are no available data on the presence of tixagevimab or cilgavimab in human milk or animal milk, the effects on the breastfed infant, or the effects of the drug on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EVUSHELD and any potential adverse effects on the breastfed infant from EVUSHELD.

8.4 Pediatric Use

EVUSHELD is not authorized for use in pediatric individuals under 12 years of age or weighing less than 40 kg. The safety and effectiveness of EVUSHELD have not been established in pediatric individuals. The dosing regimen is expected to result in comparable serum exposures of tixagevimab and cilgavimab in individuals 12 years of age and older and weighing at least 40 kg as observed in adults, since adults with similar body weight have been included in the trials PROVENT, STORM CHASER and TACKLE *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

8.5 Geriatric Use

Of the 2,555 subjects in the pooled pharmacokinetics (PK) analysis (Phase I and Phase III studies), 21% (N= 533) were 65 years of age or older and 3% (N= 81) were 75 years of age or older. There is no clinically meaningful difference in the PK of tixagevimab and cilgavimab in geriatric subjects (≥65 years) compared to younger subjects.

8.6 Renal Impairment

Tixagevimab and cilgavimab are not eliminated intact in the urine, renal impairment is not expected to affect the exposure of tixagevimab and cilgavimab. Similarly, dialysis is not expected to impact the PK of tixagevimab and cilgavimab.

8.7 Hepatic Impairment

The effect of hepatic impairment on the PK of tixagevimab and cilgavimab is unknown.

8.8 Other Specific Populations

Based on a population PK analysis, the PK profile of tixagevimab and cilgavimab was not affected by sex, age, race, or ethnicity. Population PK model-based simulations suggest that body weight had no clinically relevant effect on the PK of tixagevimab and cilgavimab in healthy adults over the range of 36 kg to 177 kg.

10 OVERDOSAGE

Treatment of overdose with EVUSHELD should consist of general supportive measures including the monitoring of the clinical status of the individual. There is no specific treatment for overdose with EVUSHELD.

11 DESCRIPTION

Tixagevimab, a SARS-CoV-2 spike protein-directed attachment inhibitor, is a human immunoglobulin G1 (IgG1κ) monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. The molecular weight is approximately 149 kDa.

Tixagevimab injection is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow solution supplied in a single-dose vial for intramuscular use. The vial stoppers are not made with natural rubber latex. Each 1.5 mL contains 150 mg tixagevimab, L- histidine (2.4 mg), L- histidine hydrochloride monohydrate (3.0 mg), polysorbate 80 (0.6 mg), sucrose (123.2 mg), and Water for Injection, USP. The pH is 6.0.

Cilgavimab, a SARS-CoV-2 spike protein-directed attachment inhibitor, is a human IgG1κ monoclonal antibody produced in CHO cells by recombinant DNA technology. The molecular weight is approximately 152 kDa.

Cilgavimab injection is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow solution supplied in a single-dose vial for intramuscular use. The vial stoppers are not made with natural rubber latex. Each 1.5 mL contains 150 mg cilgavimab, L- histidine (2.4 mg), L- histidine

hydrochloride monohydrate (3.0 mg), polysorbate 80 (0.6 mg), sucrose (123.2 mg), and Water for Injection, USP. The pH is 6.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tixagevimab and cilgavimab are two recombinant human IgG1κ monoclonal antibodies with amino acid substitutions to extend antibody half-life (YTE), reduce antibody effector function, and minimize the potential risk of antibody-dependent enhancement of disease (TM). Tixagevimab and cilgavimab can simultaneously bind to non-overlapping regions of the receptor binding domain (RBD) of SARS-CoV-2 spike protein. Tixagevimab, cilgavimab, and their combination bind to spike protein with equilibrium dissociation constants of K_D = 2.76 pM, 13.0 pM and 13.7 pM, respectively, blocking its interaction with human ACE2, the SARS-CoV-2 receptor, which is required for virus attachment. Tixagevimab, cilgavimab, and their combination blocked RBD binding to human ACE2 with IC_{50} values of 0.32 nM (48 ng/mL), 0.53 nM (80 ng/mL), and 0.43 nM (65 ng/mL), respectively.

12.3 Pharmacokinetics

A summary of PK parameters and properties of tixagevimab and cilgavimab following administration of a single EVUSHELD (300 mg of tixagevimab and 300 mg of cilgavimab) intramuscular dose is provided in Table 5.

Table 5 Summary of PK Parameters and Properties of Tixagevimab and Cilgavimab Following a Single EVUSHELD (300 mg Tixagevimab and 300 mg Cilgavimab) Intramuscular Dose

PK Parameters	Tixagevimab	Cilgavimab
C_{max} (µg/mL)*	21.9 (61.7)	20.3 (63.6)
T_{max} (day)†	14.9 (1.1 – 86)	15.0 (1.1 – 85)
C_2 (µg/mL)‡	9.5 (77)	9.1 (80)
C_{84} (µg/mL)§	15 (48)	14 (51)
$AUC_{0\text{-}84}$ (day•µg/mL)*	1408 (54)	1307 (58)
Absorption		
Bioavailability#¶	68.5	65.8
Distribution		
Apparent Volume of Distribution (L)#	7.7 (1.97)	8.7 (2.73)
Elimination		
Half-life (days)#¶	87.9 (13.9)	82.9 (12.3)
Apparent Clearance (L/day)#	0.062 (0.019)	0.074 (0.028)
Metabolism	Catabolic pathways; Same manner as endogenous IgG	
Excretion	Not likely to undergo renal excretion	

* Geomean (geometric %CV)
† Median (range)
‡ Observed geomean (geometric %CV) concentration 2 day after dosing
§ Observed geomean (geometric %CV) concentration 84 days after dosing
# Arithmetic mean (SD)
¶ Based on a single EVUSHELD (150 mg tixagevimab and 150 mg cilgavimab)

In the PROVENT repeat dose sub-study, following a second IM dose of EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) administered 10 to 14 months after the initial IM dose of EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) (N= 53), the geometric mean serum concentration was 26.4 µg/mL on post-administration Day 29. This serum concentration was similar to the geometric mean drug concentration on post-administration Day 29 (23.3 µg/mL) following the initial IM EVUSHELD dose (150 mg of tixagevimab and 150 mg of cilgavimab) in the PROVENT parent study.

The primary analysis in the clinical efficacy study PROVENT was conducted prior to the emergence of the Omicron variant; the dominant variants in circulation at that time were Alpha, Beta, Gamma, and Delta. Pharmacokinetic and pharmacodynamic modeling using cell-based EC_{50} values of EVUSHELD against the currently circulating variants in the U.S. suggest in vivo activity against these variants may be retained at drug concentrations achieved following a single EVUSHELD initial dose of 300 mg tixagevimab and 300 mg cilgavimab for 6 months *[see Dosage and Administration (2.1)]*.

Specific Populations

The PK profile of tixagevimab and cilgavimab were not affected by sex, age, race or ethnicity. Body weight had no clinically relevant effect on the PK of tixagevimab and cilgavimab in adults over the range of 36 kg to 177 kg.

Pediatric Population

The PK of tixagevimab and cilgavimab in pediatric individuals have not been evaluated.

The dosing regimen is expected to result in comparable plasma exposures of tixagevimab and cilgavimab in pediatric individuals ages 12 years of age or older who weigh at least 40 kg as observed in adult individuals *[see Use in Specific Populations (8.4)]*.

Renal impairment

Tixagevimab and cilgavimab are not eliminated intact in the urine.

Renal impairment is not expected to impact the PK of tixagevimab and cilgavimab, since monoclonal antibodies with molecular weight >69 kDa are known not to undergo renal elimination. Similarly, dialysis is not expected to impact the PK of tixagevimab and cilgavimab.

There is no difference in the clearance of tixagevimab and cilgavimab in individuals with mild or moderate renal impairment compared to individuals with normal renal function. There were insufficient subjects with severe renal impairment to draw conclusions *[see Use in Specific Populations (8.6)]*.

Hepatic impairment

No specific studies have been conducted to examine the effects of hepatic impairment on the PK of tixagevimab and cilgavimab. The impact of hepatic impairment on the PK of tixagevimab and cilgavimab is unknown *[see Use in Specific Populations (8.7)]*.

Drug Interaction Studies

Drug-drug interaction studies have not been performed. Based on key elimination pathways, tixagevimab and cilgavimab interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely *[see Drug Interactions (7)]*.

12.4 Microbiology

Antiviral Activity
In a neutralization assay on Vero E6 cells, tixagevimab, cilgavimab, and their combination neutralized SARS-CoV-2 (USA-WA1/2020 isolate) with EC_{50} values of 60.7 pM (9 ng/mL), 211.5 pM (32 ng/mL), and 65.9 pM (10 ng/mL), respectively.

Tixagevimab, cilgavimab, and their combination showed reduced or no antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), or antibody-dependent natural killer cell activation (ADNKA) in cell culture studies. Tixagevimab, cilgavimab, and their combination did not mediate antibody-dependent complement deposition (ADCD) activity with guinea pig complement proteins.

Antibody Dependent Enhancement (ADE) of Infection
The potential of tixagevimab and cilgavimab to mediate antibody-dependent viral entry was assessed in FcγRII-expressing Raji cells co-incubated with recombinant virus-like particles (VLPs) pseudotyped with SARS-CoV-2 spike protein, with antibody concentrations at a range of 6.6 nM (1 µg/mL) to 824 pM (125 ng/mL). Tixagevimab, cilgavimab, and their combination did not mediate entry of VLPs into these cells under the tested conditions.

The potential for ADE was also evaluated in a non-human primate model of SARS-CoV-2 using EVUSHELD. Intravascular administration prior to virus inoculation resulted in a dose-dependent improvement in all measured outcomes (total viral RNA in the lungs or nasal mucosae, infectious virus levels in the lungs based on $TCID_{50}$ measurements, or lung injury and pathology based on histology measurements). No evidence of enhancement of viral replication or disease was observed at any dose evaluated, including sub-neutralizing doses down to 0.04 mg/kg.

Antiviral Resistance
There is a potential risk of treatment failure due to the development of viral variants that are resistant to tixagevimab and cilgavimab. Prescribing healthcare providers should consider the prevalence of SARS-CoV-2 variants in their area, where data are available, when considering prophylactic treatment options.

Escape variants were identified following serial passage in cell culture of SARS-CoV-2 or replication competent recombinant vesicular stomatitis virus (VSV) expressing SARS-CoV-2 spike protein in the presence of tixagevimab or cilgavimab individually or in combination. Tixagevimab selected a variant expressing F486S in the spike protein with a >800-fold reduction in susceptibility to tixagevimab. Cilgavimab selected variants that expressed spike protein amino acid substitutions R346G, R346I, K444E, K444N, K444Q, K444R, K444T or N450D were each associated with a >200-fold reduction in susceptibility to cilgavimab. No escape variants to the tixagevimab and cilgavimab combination were selected.

In neutralization assays using recombinant VLPs pseudotyped with SARS-CoV-2 spike and harboring individual spike amino acid substitutions identified in circulating SARS-CoV-2, variants with reduced susceptibility to cilgavimab alone included those with R346I (>200-fold), K444E (>200-fold), K444Q (>200-fold), K444R (>200-fold), V445A (21- to 51-fold), G446V (4.2-fold), N450K (9.1-fold), or L452R (5.8-fold) substitutions. Variants with reduced susceptibility to tixagevimab alone included those with Q414R (4.6-fold), L455F (2.5- to 4.7-fold), G476S (3.3-fold), E484D (7.1-fold), E484K (6.2- to 12-fold), E484Q (3.0-fold), F486S (>600-fold), F486V (121- to 149-fold), Q493K (2.4- to 3.2-fold), Q493R

(7.9-fold), E990A (6.1-fold), or T1009I (8.2-fold) substitutions. Variants harboring an E484K (2.4- to 5.4-fold), Q493R (3.4-fold), E990A (5.7-fold), or T1009I (4.5-fold) substitution exhibited low level reduced susceptibility to tixagevimab and cilgavimab in combination.

VLPs pseudotyped with the SARS-CoV-2 spike of variant strains with reduced susceptibility to cilgavimab included those with R346K+E484K+N501Y (Mu, 21-fold), and those with reduced susceptibility to tixagevimab included those harboring E484K (Alpha, 18.5-fold; Beta, 3.5- to 15-fold; Zeta, 7.3-fold). Similar results were observed, where data were available, in neutralization assays using authentic SARS-CoV-2 variant strains.

VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BA.1 or BA.1.1 (BA.1+R346K) showed reduced susceptibility to tixagevimab (>600- to >1,000-fold or 460-fold, respectively) and to cilgavimab (>700- to >1,000-fold or >500-fold, respectively). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BA.2 or BA.2.12.1 showed reduced susceptibility to tixagevimab (>1,000-fold or >500-fold, respectively) but not to cilgavimab (1.9-fold or 2-fold, respectively). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BA.2.75 or BA.2.75.2 showed reduced susceptibility to tixagevimab (7- to 53-fold or >3,333- to >10,000-fold, respectively) and to cilgavimab (6- to 40-fold or >769- to >5,000-fold, respectively). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BA.3 showed reduced susceptibility to tixagevimab (>5,000-fold) but not to cilgavimab (4-fold). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BA.4/BA.5 showed reduced susceptibility to tixagevimab (>10,000-fold) and cilgavimab (7.5- to 9-fold). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BA.4.6 showed reduced susceptibility to tixagevimab (>1,000-fold) and to cilgavimab (>1,000-fold). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BF.7 or BJ.1 showed reduced susceptibility to tixagevimab (>3,333- to >10,000-fold or 85- to 172-fold, respectively) and to cilgavimab (>769- to >5,000-fold or >769- to >5,000-fold, respectively). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BQ.1 or BQ.1.1 showed reduced susceptibility to tixagevimab (>1,250- to >10,000-fold) and to cilgavimab (>667- to >5,000-fold). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BA.5.2.6 or BF.11 showed reduced susceptibility to tixagevimab (>333-fold) and to cilgavimab (>77-fold). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BN.1 or XBB showed reduced susceptibility to tixagevimab (24- to 44-fold or >2,600- to >10,000-fold, respectively) and to cilgavimab (>3,700- to >5,000-fold or >565- to >5,000-fold, respectively). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron XBB.1.5 showed reduced susceptibility to tixagevimab (>10,000-fold) and to cilgavimab (>2,900-fold). The effects of the individual substitutions in Omicron spike glycoproteins on neutralization susceptibility are being investigated.

The neutralizing activity of tixagevimab and cilgavimab in combination was tested against pseudotyped VLPs and/or authentic SARS-CoV-2 variant strains harboring all spike substitutions identified in Alpha (B.1.1.7, 0.5- to 5.2-fold), Beta (B.1.351, 1.0- to 3.8-fold), Gamma (P.1, 0.4- to 2.0-fold), Delta (B.1.617.2, 0.6- to 1.2-fold), and Delta [+K417N] (AY.1/ AY.2, 1.0-fold) variants of concern, and Eta (B.1.525, 3.1-fold), Iota (B.1.526, 0.3- to 3.4-fold), Kappa (B.1.617.1, 0.5- to 3.4-fold) Lambda (C.37, 0.7-fold), and Mu (B.1.621, 7.5-fold) variants of interest. Tixagevimab and cilgavimab in combination was also tested against Epsilon (B.1.427 / B.1.429, 0.8- to 3.5-fold), R.1 (3.5-fold), B.1.1.519 (1.4-fold), C.36.3 (2.3-fold), B.1.214.2 (0.8-fold), and B.1.619.1 (3.3-fold) variant alerts for further monitoring and B.1.616 (0.5-fold), A.23.1 (0.4-fold), A.27 (0.8-fold), and AV.1 (5.9-fold) variants de-escalated from further monitoring (Table 6).

Preliminary data for the neutralizing activities of tixagevimab and cilgavimab in combination against circulating Omicron subvariants are available. VLPs pseudotyped with the SARS-CoV-2 spike of

Omicron BA.1 or BA.1.1 (BA.1+R346K) showed reduced neutralizing activity (132- to 183-fold or 424-fold, respectively), Omicron BA.2 showed no change in neutralizing activity (3.2-fold). VLPs pseudotyped with the spike of Omicron BA.2.12.1, BA.2.75, BA.2.75.2, BA.3, BA.4/BA.5, or BA.4.6 showed 5-fold, 2.4- to 15-fold, >5,000- to >10,000-fold, 16-fold, 33- to 65-fold, or >1,000-fold reductions in neutralizing activity, respectively. VLPs pseudotyped with the spike of Omicron BF.7, BJ.1, BQ.1 or BQ.1.1 showed >5,000- to >10,000-fold, 228- to 424-fold, >2,000- to >10,000-fold or >2,000- to >10,000-fold reductions in neutralizing activity, respectively. VLPs pseudotyped with the spike of Omicron BA.5.2.6, BF.11, BN.1, XBB, or XBB.1.5 showed >500-fold, >500-fold, 68-fold, >1,400- to >10,000-fold, or >5,000-fold reductions in neutralizing activity, respectively. Authentic Omicron BA.1, BA.1.1, BA.2, or BA.5 viruses showed 12- to 30-fold, 176-fold, 5.4-fold, or 2.8- to 16-fold reductions in susceptibility, respectively.

Data collection is ongoing to better understand how the reductions in activity seen in pseudotyped VLP assays or authentic SARS-CoV-2 assays may correlate with clinical outcomes. Emerging Omicron subvariants that are resistant to neutralization by cilgavimab harbor the spike substitution R346T or K444T, while those resistant to neutralization by tixagevimab harbor the spike substitution F486S or F486V. EVUSHELD is unlikely to neutralize SARS-CoV-2 Omicron subvariants harboring R346T or K444T in combination with F486S or F486V.

Table 6 EVUSHELD Pseudotyped Virus-Like Particles and Authentic SARS-CoV-2 Neutralization Data for SARS-CoV-2 Variants

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested	Fold Reduction in Susceptibility* (Pseudotyped VLPs†)	Fold Reduction in Susceptibility* (Authentic virus‡)
B.1.1.7	UK	Alpha	N501Y	0.5- to 5.2-fold	No Change§
B.1.351	South Africa	Beta	K417N+E484K+N501Y	No Change§	No Change§
P.1	Brazil	Gamma	K417T+E484K+N501Y	No Change§	No Change§
B.1.617.2	India	Delta	L452R+T478K	No Change§	No Change§
AY.1/ AY.2	India	Delta [+K417N]	K417N+L452R+T478K	No Change§	No Change§
BA.1	Botswana	Omicron (BA.1)	G339D+S371L+S373P+ S375F+K417N+N440K+ G446S+S477N+T478K+ E484A+Q493R+G496S+ Q489R+N501Y+Y505H	132- to 183-fold#	12- to 30-fold
BA.1.1	Multiple country origin	Omicron (BA.1.1) [+R346K]	BA.1+R346K	424-fold	176-fold
BA.2	Multiple country origin	Omicron (BA.2)	G339D+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ S477N+T478K+E484A+ Q493R+Q498R+N501Y+ Y505H	No Change§	5.4-fold
BA.2.12.1	United States	Omicron (BA.2.12.1)	BA.2+L452Q	5-fold	ND
BA.2.75	India	Omicron (BA.2.75)	G339H+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ G446S+N460K+S477N+ T478K+E484A+Q498R+ N501Y+ Y505H	2.4- to 15-fold	ND

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested	Fold Reduction in Susceptibility* (Pseudotyped VLPs†)	Fold Reduction in Susceptibility* (Authentic virus‡)
BA.2.75.2	India	Omicron (BA.2.75.2)	BA.2.75+R346T+F486S	>5000-fold[Þ]	ND
BA.3	Multiple country origin	Omicron (BA.3)	G339D+S371F+S373P+ S375F+D405N+K417N+ N440K+G446S+S477N+ T478K+E484A+Q493R+ Q498R+N501Y+Y505H	16-fold	ND
BA.4	Multiple country origin	Omicron (BA.4)	G339D+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ L452R+S477N+T478K+ E484A+F486V+Q498R+ N501Y+Y505H	33- to 65-fold	ND
BA.4.6	United States	Omicron (BA.4.6)	BA.4+R346T	>1000-fold[Þ]	ND
BA.5	Multiple country origin	Omicron (BA.5)	G339D+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ L452R+S477N+T478K+ E484A+F486V+Q498R+ N501Y+Y505H	33- to 65-fold	2.8- to 16-fold
BA.5.2.6	Multiple country origin	Omicron (BA.5.2.6)	G339D+R346T+S371F+ S373P+S375F+T376A+ D405N+R408S+K417N+ N440K+L452R+S477N+ T478K+E484A+F486V+ Q498R+N501Y+Y505H	>500-fold	ND
BF.7	United States/Belgium	Omicron (BF.7)	BA.4+R346T	>5000-fold[Þ]	ND
BF.11	Multiple country origin	Omicron (BF.11)	G339D+R346T+S371F+ S373P+ S375F+T376A+ D405N+R408S+K417N+ N440K+L452R+S477N+ T478K+E484A+F486V+ Q498R+N501Y+Y505H	>500-fold	ND
BJ.1	Multiple country origin	Omicron (BJ.1)	G339H+R346T+L368I+ S371F+S373P+S375F+ T376A+D405N+R408S+ K417N+N440K+V445P+ G446S+S477N+T478K+ V483A+E484A+F490V+ Q493R+Q498R+N501Y+ Y505H	228- to 424-fold	ND
BN.1	Multiple country origin	Omicron (BN.1)	G339D+R346T+K356T+ S371F+S373P+S375F+ D405N+ R408S+ K417N+N440K+G446S+ N460K+S477N+T478K+ E484A+F490S+ Q493R+Q498R+Y505H	68-fold	ND
BQ.1	Nigeria	Omicron (BQ.1)	BA.5+K444T+N460K	>2000-fold[Þ]	ND
BQ.1.1	Multiple country origin	Omicron (BQ.1.1)	BA.5+R346T+K444T+ N460K	>2000-fold[Þ]	ND

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested	Fold Reduction in Susceptibility* (Pseudotyped VLPs†)	Fold Reduction in Susceptibility* (Authentic virus‡)
XBB	Multiple country origin	Omicron (XBB)	G339H+R346T+L368I+ S371F+S373P+S375F+ T376A+D405N+R408S+ K417N+N440K+V445P+ G446S+N460K+S477N+ T478K+ E484A+F486S+ F490S+Q498R+N501Y+ Y505H	>1400-fold[þ]	ND
XBB.1.5	Multiple country origin	Omicron (XBB.1.5)	G339H+R346T+L368I+ S371F+S373P+S375F+ T376A+D405N+R408S+ K417N+N440K+V445P+ G446S+N460K+S477N+ T478K+E484A+F486P+ F490S+Q498R+N501Y +Y505H	>5000-fold[þ]	ND
B.1.525	Multiple country origin	Eta	E484K	No Change§	ND
B.1.526	United States	Iota	E484K	No Change§	No Change§
B.1.617.1	India	Kappa	L452R+E484Q	No Change§	No Change§
C.37	Peru	Lambda	L452Q+F490S	No Change§	ND
B.1.621	Colombia	Mu	R346K+E484K +N501Y	7.5-fold	ND
B.1.427 / B.1.429	United States	Epsilon	L452R	No Change§	No Change§
R.1	Multiple country origin	-	E484K	No Change§	ND
B.1.1.519	Multiple country origin	-	T478K	No Change§	ND
C.36.3	Multiple country origin	-	R346S:L452R	No Change§	ND
B.1.214.2	Multiple country origin	-	Q414K:N450K	No Change§	ND
B.1.619.1	Multiple country origin	-	N440K:E484K	No Change§	ND
P.2	Brazil	Zeta	E484K	No Change§	ND
B.1.616	France	-	V483A	No Change§	ND
A.23.1	UK	-	V367F	No Change§	ND
A.27	Multiple country origin	-	L452R+N501Y	No Change§	ND
AV.1	Multiple country origin	-	N439K+E484K	5.9-fold	ND

* Range of reduced potency across multiple variants of each lineage using research-grade pseudotyped VLP neutralization assays; mean fold change in half maximal effective concentration (EC_{50}) of mAb required for a 50% reduction in infection compared to wild type reference strain

† Pseudotyped virus-like particles expressing the entire SARS-CoV-2 spike variant protein and individual characteristic spike substitutions except L452Q were tested including Alpha (+L455F, E484K, F490S, Q493R, and/or S494P), and Delta (+K417N) harboring additional indicated RBD substitutions that are no longer detected or detected at extremely low levels within these lineages

‡ Authentic SARS-CoV-2 expressing the entire variant spike protein were tested including Alpha (+E484K or S494P) harboring additional indicated RBD substitutions that are no longer detected or detected at extremely low levels within these lineages

§ No change: <5-fold reduction in susceptibility

EC_{50} value = 1.13 – 1.83 nM (171 - 277 ng/mL)

[þ] Tixagevimab and cilgavimab together are unlikely to be active against this variant.

ND, not determined; RBD, receptor binding domain

It is not known how pseudotyped VLPs or authentic SARS-CoV-2 neutralization susceptibility data correlate with clinical outcome.

In PROVENT, illness visit sequencing data were available for 21 of 33 subjects with SARS-CoV-2 infection (6 who received tixagevimab and cilgavimab and 15 placebo). Fourteen subjects were infected with variants of concern or variants of interest, including 8 subjects with Alpha (B.1.1.7) (8 who received placebo), 1 subject with Beta (B.1.351) (1 who received tixagevimab and cilgavimab), 3 subjects with Delta (B.1.617.2) (3 who received placebo), and 2 subjects with Epsilon (B.1.429) (2 who received tixagevimab and cilgavimab). Seven additional subjects were infected with B.1.375 (1 who received tixagevimab and cilgavimab) or the A_1 set of lineages containing a constellation of spike protein substitutions including D614G and P681H or Q677P (3 who received tixagevimab and cilgavimab and 3 placebo). Additional spike protein RBD substitutions detected at low frequency (between 3% and 24%) included V503F in the tixagevimab and cilgavimab group.

In STORM CHASER, illness visit sequencing data was available for 19 of 19 subjects with SARS-CoV-2 infections (12 of 12 who received tixagevimab and cilgavimab and 7 of 7 placebo). At an allele fraction ≥25%, 12 of 19 subjects were infected with variants of concern or variants of interest, including 9 subjects with Alpha (B.1.1.7) (5 who received tixagevimab and cilgavimab and 4 placebo) and 3 subjects with Epsilon (B.1.427 / B.1.429) (2 who received tixagevimab and cilgavimab and 1 placebo). Seven additional subjects were infected with B.1.1.519 (1 who received tixagevimab and cilgavimab) or the A_1 set of lineages containing a constellation of spike protein substitutions including D614G and D138H, Q675H, Q677H, or V1176F (4 who received tixagevimab and cilgavimab and 2 placebo). Additional spike protein RBD substitutions detected at an allele fraction ≥3% included S325P, Del342, C361W, Del428, F429V, and F515C in the tixagevimab and cilgavimab group.

Evaluation of neutralization susceptibility of variants identified through global surveillance and in subjects who received tixagevimab and cilgavimab is ongoing.

It is possible that variants resistant to tixagevimab and cilgavimab could have cross-resistance to other monoclonal antibodies targeting the RBD of SARS-CoV-2. The combination of tixagevimab and cilgavimab retained activity against pseudotyped VLPs harboring individual SARS-CoV-2 spike substitutions (K417E/N, D420N, K444Q, V445A, Y453F, L455F, N460K/S/T, E484D/K/Q, F486V, F490S, Q493K/R, and S494P) identified in neutralization escape variants of other monoclonal antibodies targeting the RBD of SARS-CoV-2 spike protein.

12.6 Immunogenicity

There are no immunogenicity data available for the currently authorized dosing regimen (EVUSHELD [300 mg of tixagevimab and 300 mg cilgavimab] administered every 6 months).

There was no apparent clinically significant effect of anti-EVUSHELD antibodies (ADA) on the safety or effectiveness of EVUSHELD in PROVENT (EVUSHELD [150 mg of tixagevimab and 150 mg cilgavimab]), but data are limited at this time. There is up to a 26% decrease, on average, in serum concentrations of EVUSHELD over time through 183 days post-administration in subjects with positive ADA after the initial dose compared to subjects who tested negative for ADA after the initial dose; the clinical significance of this decrease is unknown.

In PROVENT, following a single IM dose of EVUSHELD (150 mg of tixagevimab and 150 mg cilgavimab) (baseline: study Day 1) through study Day 183, treatment-emergent anti-tixagevimab, anti-cilgavimab and anti-EVUSHELD antibodies were detected in 3% (101/3152), 4% (113/3068) and 5% (156/3158) ADA-evaluable participants, respectively, who received EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab). The average Day 8, 29, and 183 serum concentrations of EVUSHELD were approximately 0%, 12%, and 26% lower, respectively, in subjects who tested positive for ADA after the initial dose versus subjects who tested negative for ADA after the initial dose.

In the PROVENT repeat dose sub-study, following a subsequent single IM dose of EVUSHELD (150 mg of tixagevimab and 150 mg cilgavimab) (baseline: sub-study Day 1) through sub-study Day 29, treatment-emergent anti-tixagevimab, anti-cilgavimab and anti-EVUSHELD antibodies were detected in 0% (0/49), 10% (5/49) and 10% (5/49) ADA-evaluable subjects, respectively. The average Day 29 concentration of EVUSHELD was approximately 14% lower in subjects who tested positive for ADA after the second dose versus subjects who tested negative for ADA after the second dose. The time between repeat doses was 10 to 14 months (first IM dose administered in the original PROVENT study to second IM dose administered in the PROVENT sub-study).

The observed incidence of ADA is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described above with the incidence of ADA in other studies.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, genotoxicity, and reproductive toxicology studies have not been conducted with tixagevimab and cilgavimab.

13.2 Animal Toxicology and Pharmacology

In a toxicology study in cynomolgus monkeys, tixagevimab and cilgavimab had no adverse effects when administered via IM injection.

In tissue cross-reactivity studies with tixagevimab and cilgavimab using human adult and fetal tissues no binding of clinical concern was detected.

Tixagevimab and cilgavimab have been assessed in rhesus macaque and cynomolgus macaque models of SARS-CoV-2 infection. Prophylactic administration of tixagevimab and cilgavimab (N= 4 rhesus macaque; N= 3 cynomolgus macaque) three days prior to infection prevented SARS-CoV-2 infection of the upper and lower respiratory tracts in dose-dependent manner. Prophylactic administration of 4 mg/kg tixagevimab and cilgavimab resulted in a 7-$\log_{10}$ reduction in viral sub-genomic messenger RNA (sgmRNA) in nasopharyngeal swabs and 5 to 6-$\log_{10}$ reduction in sgmRNA or infectious virus titer in bronchoalveolar lavage samples at Day 2 post-challenge in all animals relative to placebo-treated animals. Compared to placebo, prophylactic administration of tixagevimab and cilgavimab (N= 3 cynomolgus macaque) reduced lung injury associated with SARS-CoV-2 infection.

The applicability of these findings to a clinical setting is not known.

14 CLINICAL STUDIES

The data supporting this EUA are based on analyses from the Phase III trials PROVENT (NCT04625725) and STORM CHASER (NCT04625972). Both trials are evaluating the safety and efficacy of EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) for the prophylaxis SARS-CoV-2 symptomatic illness (COVID-19).

Efficacy Data from PROVENT

PROVENT is an ongoing Phase III, randomized (2:1), double-blind, placebo-controlled clinical trial studying EVUSHELD for the pre-exposure prophylaxis of COVID-19 in adults ≥18 years of age. All subjects were either ≥60 years of age, had a pre-specified co-morbidity (obesity, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, immunocompromised state, or previous history of severe or serious adverse event after receiving any approved vaccine), or were at increased risk of SARS-CoV-2 infection due to their living situation or occupation. Subjects could not have previously received a COVID-19 vaccine. Subjects received a single dose (administered as two IM injections) of EVUSHELD or placebo. The study excluded subjects with a history of laboratory-confirmed SARS-CoV-2 infection or SARS-CoV-2 antibody positivity at screening. Once COVID-19 vaccines were locally available, subjects were permitted on request to unblind to make an informed decision on vaccine timing and to receive COVID-19 vaccination.

The baseline demographics were balanced across the EVUSHELD and placebo arms. The median age was 57 years (with 43% of subjects aged 60 years or older), 46% of subjects were female, 73% were White, 3% were Asian 17% were Black/African American, and 15% were Hispanic/Latino. Of the 5,197 subjects, 78% had baseline co-morbidities or characteristics associated with an increased risk for severe COVID-19, including obesity (42%), diabetes (14%), cardiovascular disease (8%), cancer, including a history of cancer (7%), chronic obstructive pulmonary disease (5%), chronic kidney disease (5%), chronic liver disease (5%), immunosuppressive medications (3%) and immunosuppressive disease (<1%).

For the primary endpoint, a subject was defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurred after administration and prior to Day 183. The primary analysis included 5,172 subjects who were SARS-CoV-2 RT-PCR-negative at baseline, of which 3,441 received EVUSHELD and 1,731 received placebo. Only events that occurred prior to unblinding or vaccine receipt were included. EVUSHELD receipt resulted in a statistically significant (p-value <0.001) 77% reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness (COVID-19) when compared to placebo (Table 7). At the time of analysis the median follow-up time post-administration was 83 days (range 3 to 166 days).

Similar results were observed for EVUSHELD recipients compared to placebo recipients in the reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness or death from any cause (12/3,441 versus 19/1,731, respectively) with relative risk reduction of 69% (95% CI: 36, 85; p-value= 0.002), and in the reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness regardless of unblinding or vaccine receipt (10/3,441 versus 22/1,731, respectively) with relative risk reduction of 77% (95% CI: 52, 89 ; p-value <0.001).

Table 7 Incidence of Symptomatic COVID-19 in Adults (PROVENT)

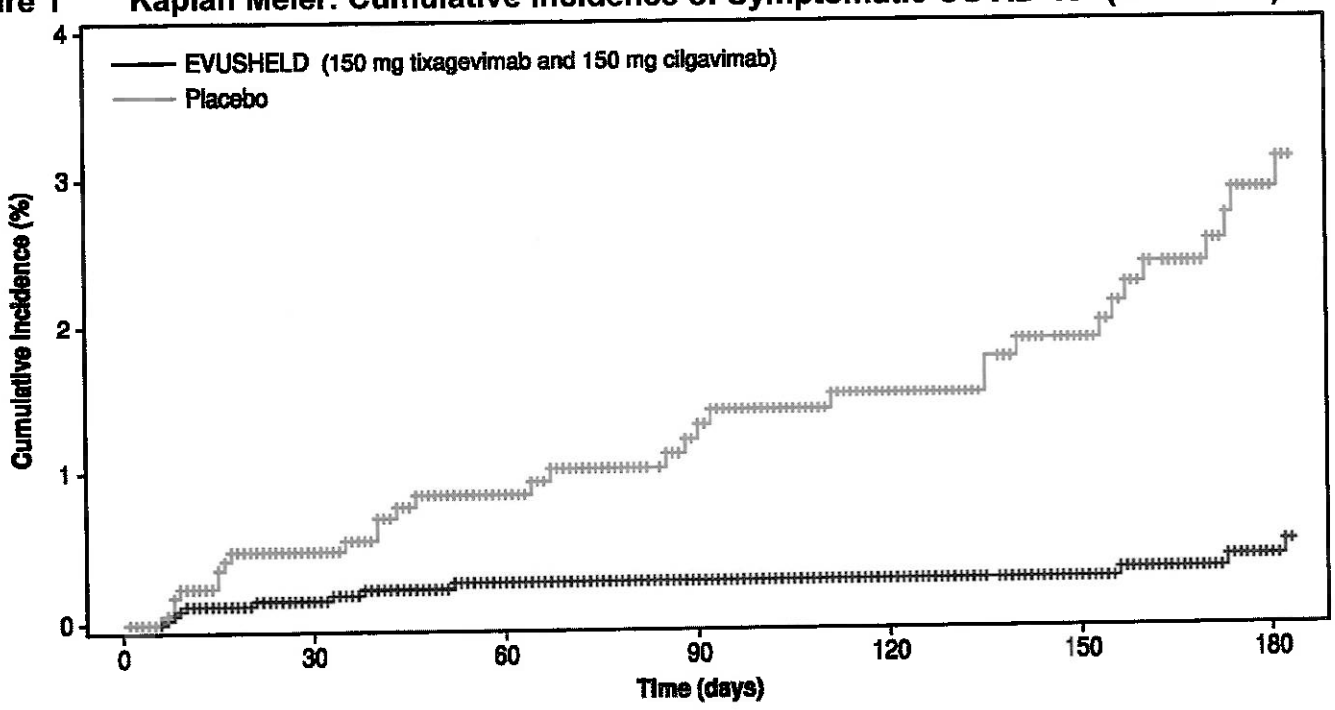
	N*	Number of events, n (%)	Relative Risk Reduction, % (95% CI)
EVUSHELD†	3,441	8 (0.2%)	77% (46, 90)
Placebo	1,731	17 (1.0%)	

N = number of subjects in analysis; CI = Confidence Interval
* subjects were censored after receiving the vaccine or being unblinded to consider the vaccine, whichever occurred earlier
† EVUSHELD dose (150 mg tixagevimab and 150 mg cilgavimab)

Among subjects who received EVUSHELD, there were no severe/critical COVID-19 events (defined as SARS-CoV-2 RT-PCR-positive symptomatic illness characterized by a minimum of either pneumonia [fever, cough, tachypnoea or dyspnea, and lung infiltrates] or hypoxemia [SpO_2 <90% in room air and/or severe respiratory distress] and a WHO Clinical Progression Scale score of 5 or higher) compared to one event (0.1%) among subjects who received placebo.

An additional data cut was conducted to provide post-hoc updated efficacy and safety analysis, the median follow-up was 6.5 months for subjects in both EVUSHELD and placebo arms. The relative risk reduction of SARS-CoV-2 RT-PCR-positive symptomatic illness was 83% (95% CI: 66, 91) with 11/3,441 (0.3%) events in the EVUSHELD arm and 31/1,731 (1.8%) events in the placebo arm, see Figure 1. These results are consistent with the duration of protection predicted by population PK modelling. Among subjects who received EVUSHELD there were no severe/critical COVID-19 events compared to five events among subjects who received placebo.

Figure 1 Kaplan Meier: Cumulative Incidence of Symptomatic COVID-19* (PROVENT)



Number of participants at risk							
EVUSHELD	3441	2957	2393	2054	1815	1667	1044
Placebo	1731	1483	1177	991	856	774	472

* Subjects who do not experience a primary endpoint event (and had not discontinued) are censored at Day 183. Subjects who were unblinded/vaccinated prior to an event are also censored at the earlier time of unblinding/vaccination.

Efficacy Data from STORM CHASER

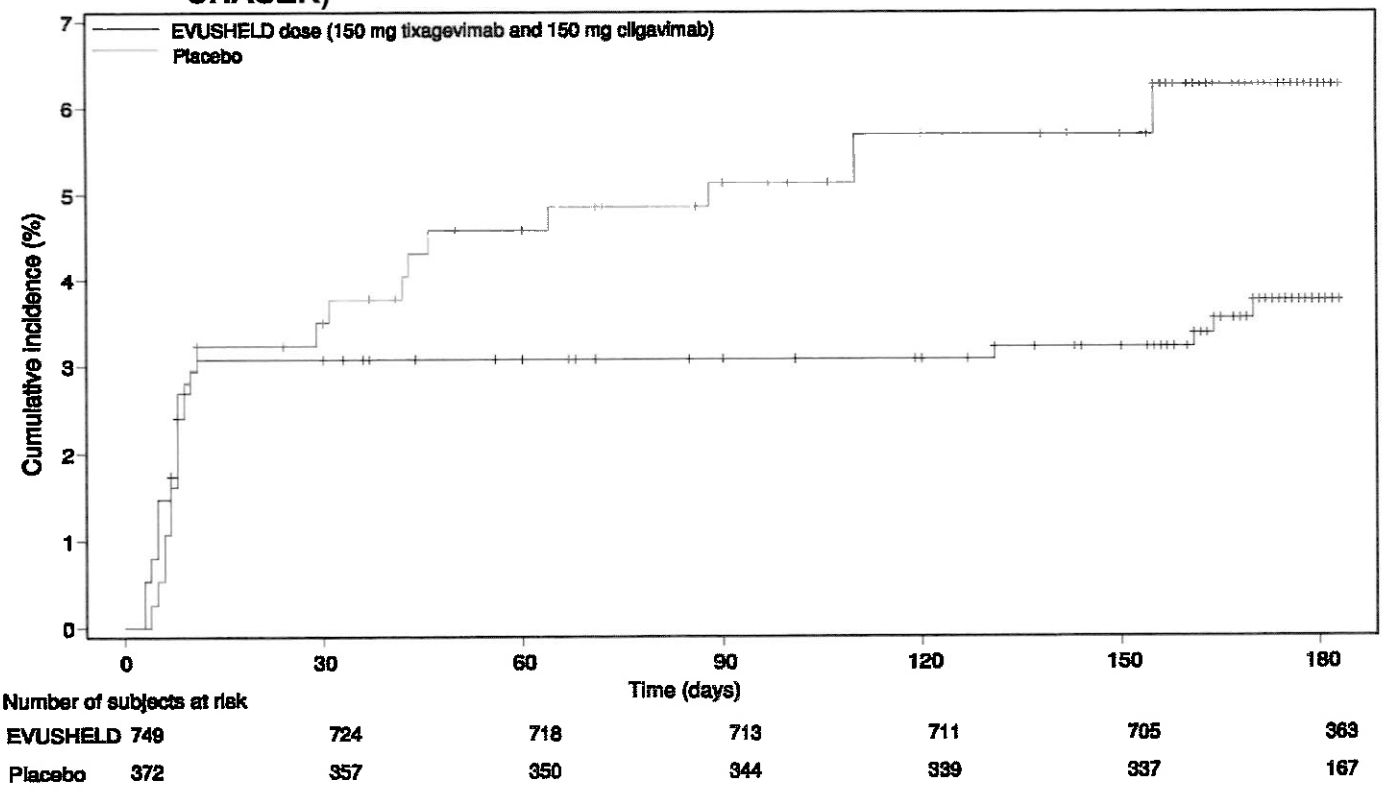
STORM CHASER is an ongoing Phase III randomized (2:1), double-blind, placebo-controlled clinical trial of EVUSHELD for the post-exposure prophylaxis of COVID-19 in adults ≥18 years of age. Subjects who had not previously received a COVID-19 vaccine were enrolled following potential exposure (within 8 days) to an identified individual with a laboratory-confirmed SARS-CoV-2 infection (symptomatic or asymptomatic). Subjects received a single dose (administered as two IM injections) of EVUSHELD or placebo. The study excluded subjects with a history of laboratory-confirmed SARS-CoV-2 infection or SARS-CoV-2 antibody positivity at screening. Once COVID-19 vaccines were locally available, subjects were permitted on request to unblind to make an informed decision on vaccine timing and to receive COVID-19 vaccination.

Of the 1,121 subjects who were randomized and received EVUSHELD (N= 749) or placebo (N= 372), 48 subjects were positive for SARS-CoV-2 (RT-PCR analysis of nasopharyngeal swabs) at baseline.

The primary efficacy analysis, comparison of the incidence of a subject's first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post-dose and before Day 183, did not demonstrate a statistically significant effect for EVUSHELD versus placebo with 23 cases of symptomatic COVID-19 in the EVUSHELD arm (3.1%) and 17 cases in the placebo arm (4.6%) (relative risk reduction of 33%, 95% CI: -26, 65). At the time of analysis the median follow-up time post-administration was 49 days (range 5 to 115 days).

The study did not demonstrate benefit for EVUSHELD in preventing symptomatic COVID-19 in the first 30 days after randomization, leading to the limitation of use for post-exposure prophylaxis *[see Emergency Use Authorization (1)]*. However, there was a higher proportion of symptomatic COVID-19 cases among placebo recipients after Day 29 (see Figure 2 below, data from the post-hoc updated efficacy analysis with a median follow-up time of 6.5 months). EVUSHELD is not authorized for post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2.

Figure 2 Kaplan Meier: Cumulative Incidence of Symptomatic COVID-19* (STORM CHASER)



* Subjects who do not experience a primary endpoint event (and had not discontinued) are censored at Day 183.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Each EVUSHELD co-packaged carton contains two vials (Table 8):

- 1 single-dose vial of tixagevimab injection as a sterile, preservative-free, clear to opalescent and colorless to slightly yellow solution.
- 1 single-dose vial of cilgavimab injection as a sterile, preservative-free, clear to opalescent and colorless to slightly yellow solution.

Table 8 EVUSHELD co-packaged carton contents

Carton (2 vials per pack)	**Components**	
	1 vial of Tixagevimab 150 mg/1.5 mL (100 mg/mL) **(dark grey cap)**	**1 vial of Cilgavimab** 150 mg/1.5 mL (100 mg/mL) **(white cap)**
NDC 0310-7442-02	NDC 0310-8895-01	NDC 0310-1061-01
NDC 0310-8861-02		

Storage and Handling

Store unopened vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Discard any unused portion.

DO NOT FREEZE. DO NOT SHAKE.

17 PATIENT COUNSELING INFORMATION

As a prescribing healthcare practitioner, you must communicate to the patient, parent and caregiver information consistent with the "FACT SHEET FOR PATIENTS, PARENTS OR CAREGIVERS" and provide them with a copy of this Fact Sheet prior to administration of EVUSHELD.

Dosing
Inform individuals that they will need to receive additional doses of EVUSHELD every 6 months if ongoing protection is needed *[see Dosage and Administration (2.1), and Clinical Pharmacology (12.3)]*.

Risk for COVID-19 Due to SARS-CoV-2 Viral Variants Not Neutralized by EVUSHELD
Certain SARS-CoV-2 viral variants may not be neutralized by monoclonal antibodies such as tixagevimab and cilgavimab, the components of EVUSHELD. EVUSHELD may not be effective at preventing COVID-19 caused by these SARS-CoV-2 viral variants. Inform individuals of the increased risk, compared to other variants, for COVID-19 due to SARS-CoV-2 viral variants not neutralized by EVUSHELD. If signs and symptoms of COVID-19 occur, advise individuals to test for COVID-19 and seek medical attention, including starting treatment for COVID-19 as appropriate *[see Warnings and Precautions (5.3)]*.

Cardiovascular Events
Inform individuals that a higher proportion of subjects who received EVUSHELD versus placebo reported cardiovascular serious adverse events (myocardial infarctions and heart failure). Advise individuals to seek immediate medical attention if they experience any signs or symptoms suggestive of a cardiovascular event *[see Warnings and Precautions (5.5)]*.

For additional information, please visit the website or call the telephone number provided below.

To access the most recent EVUSHELD Fact Sheets, please scan the QR code provided below.

Website	Telephone number
http://www.evusheld.com	1-800-236-9933

18 MANUFACTURER INFORMATION

Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

U.S. FOOD & DRUG ADMINISTRATION

October 27, 2022

Eli Lilly and Company
Attention: Christine Phillips, PhD, RAC
Advisor Global Regulatory Affairs - US
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

RE: Emergency Use Authorization 111

Dear Ms. Phillips:

This letter is in response to Eli Lilly and Company's ("Lilly") request that the Food and Drug Administration (FDA or Agency) issue an Emergency Use Authorization (EUA) for the emergency use of bebtelovimab for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in certain adults and pediatric patients who are at high-risk for progression to severe COVID-19, including hospitalization or death, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §360bbb-3).

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19).[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[2]

On February 11, 2022, the FDA issued an EUA for the emergency use of bebtelovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high-risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

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[1] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3.* February 4, 2020.

[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).

Bebtelovimab is a neutralizing IgG1 monoclonal antibody that binds to an epitope within the receptor binding domain of the spike protein of SARS-CoV-2. Bebtelovimab is not FDA-approved for any uses, including use as treatment for COVID-19.

FDA subsequently reissued the Letter of Authorization (LOA) on August 5, 2022.[3]

On October 27, 2022, having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the August 5, 2022 letter in its entirety, to incorporate clarifying revisions to Condition W of this letter. Condition V was also revised to require that all printed matter, advertising and promotional materials relating to the use of bebtelovimab under this authorization be submitted to FDA for consideration at least 14 calendar days prior to initial dissemination or first use.

Based on the review of the data from the BLAZE-4 clinical trial (NCT04634409), a Phase 1/2 randomized, single-dose clinical trial studying bebtelovimab for the treatment of non-hospitalized patients with mild-to-moderate COVID-19, as well as available pharmacokinetic data and nonclinical viral neutralization data for Omicron and other variants of concern, it is reasonable to believe that bebtelovimab may be effective for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high-risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate, as described in the Scope of Authorization (Section II), and when used under the conditions described in this authorization, the known and potential benefits of bebtelovimab outweigh the known and potential risks of such product.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of bebtelovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high-risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of bebtelovimab for treatment of mild-to-moderate COVID-19, when administered as described in the Scope of Authorization (Section II), meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

1. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that bebtelovimab may be effective for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who

[3] In its August 5, 2022 revision, FDA revised the LOA with revisions to the scope of authorization no longer requiring directed distribution of bebtelovimab by the United States Government.

are at high-risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (section II), and that, when used under the conditions described in this authorization, the known and potential benefits of bebtelovimab outweigh the known and potential risks of such product; and

3. There is no adequate, approved, and available alternative[4] to the emergency use of bebtelovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric (12 years of age and older weighing at least 40 kg) patients as further described in the Scope of Authorization (section II).[5]

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Bebtelovimab may only be used for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg):
    - With positive results of direct SARS-CoV-2 viral testing, and
    - Who are at high-risk[6] for progression to severe COVID, including hospitalization or death, and
    - For whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

- Bebtelovimab is **not** authorized for use in the following patient populations[7]:
    - Adults or pediatric patients who are hospitalized due to COVID-19, or
    - Adults or pediatric patients who require oxygen therapy and/or respiratory support due to COVID-19, or
    - Adults or pediatric patients who require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 in those patients on chronic oxygen therapy and/or oxygen support due to underlying non-COVID-19-related comorbidity;

- Bebtelovimab is **not** authorized for treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible

[4] Although Veklury (remdesivir) is an approved alternative to treat COVID-19 in adults and pediatric patients within the scope of this authorization, FDA does not consider it to be an adequate alternative for certain patients for whom it may not be feasible or practical (e.g., it requires a 3-day treatment duration).
[5] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.
[6] For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html.
[7] Treatment with bebtelovimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bebtelovimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

SARS-CoV-2 variant, based on available information including variant susceptibility to these drugs and regional variant frequency.[8]

- Bebtelovimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary;

- The use of bebtelovimab covered by this authorization must be in accordance with the authorized Fact Sheets.

Product Description

Bebtelovimab injection (NDC 0002-7589-01) is a sterile, preservative-free clear to opalescent and colorless to slightly yellow to slightly brown solution supplied in a single-dose vial. Each carton contains a single vial of bebtelovimab, which is labeled "For Use Under Emergency Use Authorization (EUA)".

The authorized storage and handling information is included in the authorized Fact Sheet for Healthcare Providers.

Bebtelovimab is authorized for emergency use with the following product-specific information required to be made available to healthcare providers and to patients, parents, and caregivers, respectively, through Lilly's website www.LillyAntibody.com/bebtelovimab (referred to as the "authorized labeling"):

- Fact Sheet for Healthcare Providers: Emergency Use Authorization (EUA) for bebtelovimab
- Fact Sheet for Patients, Parents, and Caregivers: Emergency Use Authorization (EUA) of bebtelovimab for Coronavirus Disease 2019 (COVID-19)

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of bebtelovimab, when used for the treatment of COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh the known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that bebtelovimab may be effective for the treatment of COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

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[8] FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility (see, e.g., section 12.4 of authorized Fact Sheet for Health Care Providers), and CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions. FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that bebtelovimab (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of bebtelovimab under this EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), bebtelovimab is authorized for the treatment of COVID-19 as described in this Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

Lilly and Authorized Distributors[9]

A. Lilly and authorized distributor(s) will ensure that the authorized bebtelovimab is distributed and the authorized labeling (i.e., Fact Sheets) will be made available to healthcare facilities and/or healthcare providers consistent with the terms of this letter.

B. Lilly and authorized distributor(s) will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., U.S. government agencies, state and local government authorities, authorized distributors, healthcare facilities, healthcare providers) involved in distributing or receiving bebtelovimab. Lilly will provide to all relevant stakeholders a copy of this Letter of Authorization and communicate any subsequent amendments that might be made to this Letter of Authorization and its authorized accompanying materials (i.e., Fact Sheets).

C. Lilly may request changes to this authorization, including to the authorized Fact Sheets for bebtelovimab. Any request for changes to this EUA must be submitted to the Office of Infectious Diseases/Office of New Drugs/Center for Drug Evaluation and Research. Such changes require appropriate authorization prior to implementation.[10]

[9] "Authorized Distributor(s)" are identified by Lilly as an entity or entities allowed to distribute the authorized bebtelovimab.

[10] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study; (8) new strengths of the authorized product, new product sources (e.g., of active pharmaceutical ingredient) or of product components. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), (7), or (8), review and concurrence is required from the Counter-Terrorism and

D. Lilly may develop and disseminate instructional and educational materials (e.g., materials providing information on product administration and/or patient monitoring) that are consistent with the authorized emergency use of bebtelovimab as described in this Letter of Authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs. Any instructional and educational materials that are inconsistent with the authorized labeling for bebtelovimab are prohibited. If the Agency notifies Lilly that any instructional and educational materials are inconsistent with the authorized labeling, Lilly must cease distribution of such instructional and educational materials. Furthermore, as part of its notification, the Agency may also require Lilly to issue corrective communication(s).

E. Lilly will report to FDA all serious adverse events and medication errors potentially related to bebtelovimab use that are reported to Lilly using either of the following options.

Option 1: Submit reports through the Safety Reporting Portal (SRP) as described on the FDA SRP web page.

Option 2: Submit reports directly through the Electronic Submissions Gateway (ESG) as described on the FAERS electronic submissions web page.

Submitted reports under both options must state: "Bebtelovimab use for COVID-19 under Emergency Use Authorization (EUA)." For reports submitted under Option 1, include this language at the beginning of the question "Describe Event" for further analysis. For reports submitted under Option 2, include this language at the beginning of the "Case Narrative" field.

F. All manufacturing, packaging, and testing sites for both drug substance and drug product used for EUA supply will comply with current good manufacturing practice requirements of Section 501(a)(2)(B) of the Act.

G. Lilly will submit information to the Agency within three working days of receipt of any information concerning significant quality problems with distributed drug product of bebtelovimab that includes the following:

- Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or
- Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the established specifications.

Emergency Coordination Staff/Office of the Center Director/CDER and the Office of Counterterrorism and Emerging Threats/Office of the Chief Scientist.

If a significant quality problem affects unreleased product and may also impact product(s) previously released and distributed, then information must be submitted for all potentially impacted lots.

Lilly will include in its notification to the Agency whether the batch, or batches, in question will be recalled. If FDA requests that these, or any other batches, at any time, be recalled, Lilly must recall them.

If not included in its initial notification, Lilly must submit information confirming that Lilly has identified the root cause of the significant quality problems, taken corrective action, and provide a justification confirming that the corrective action is appropriate and effective. Lilly must submit this information as soon as possible but no later than 45 calendar days from the initial notification.

H. Lilly will manufacture bebtelovimab to meet all quality standards and per the manufacturing process and control strategy as detailed in Lilly's EUA request. Lilly will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product, without notification to and concurrence by the Agency as described under condition D.

I. Lilly will list bebtelovimab with a unique product NDC under the marketing category of Emergency Use Authorization. Further, the listing will include each establishment where manufacturing is performed for the drug and the type of operation performed at each such establishment.

J. Through a process of inventory control, Lilly and authorized distributor(s) will maintain records regarding distribution of bebtelovimab (i.e., lot numbers, quantity, receiving site, receipt date).

K. Lilly will establish a process for monitoring genomic database(s) for the emergence of global viral variants of SARS-CoV-2. A summary of Lilly's process should be submitted to the Agency as soon as practicable, but no later than 30 calendar days of the issuance of this letter, and within 30 calendar days of any material changes to such process. Lilly will provide reports to the Agency on a monthly basis summarizing any findings as a result of its monitoring activities and, as needed, any follow-up assessments planned or conducted.

L. FDA may require Lilly to assess the activity of the authorized bebtelovimab against any global SARS-CoV-2 variant(s) of interest (e.g., variants that are prevalent or becoming prevalent that harbor substitutions in the target protein or in protein(s) that interact with the target protein). Lilly will perform the required assessment in a manner and timeframe agreed upon by Lilly and the Agency. Lilly will submit to FDA a preliminary summary report immediately upon completion of its assessment followed by a detailed study report within 30 calendar days of study completion. Lilly will submit any relevant proposal(s) to revise the authorized labeling based on the results of its assessment, as may be necessary or appropriate based on the foregoing assessment.

M. Lilly shall provide samples as requested of the authorized bebtelovimab to the HHS for evaluation of activity against emerging global viral variants of SARS-CoV-2, including specific amino acid substitution(s) of interest (e.g., variants that are highly prevalent or that harbor substitutions in the target protein) within 5 business days of any request made by HHS. Analyses performed with the supplied quantity of authorized bebtelovimab may include, but are not limited to, cell culture potency assays, protein binding assays, cell culture variant assays (pseudotyped virus-like particles and/or authentic virus), and *in vivo* efficacy assays.

N. Lilly must provide the following information to the Agency:

1. Lilly will submit a study report to FDA characterizing the development of SARS-CoV-2 resistance to bebtelovimab in cell culture passage experiments no later than 30 days of the completion of these experiments.
2. Lilly will submit to FDA all sequencing data assessing bebtelovimab, including sequencing of any participant samples from the full analysis population from PYAH arms 9-14 that have not yet been completed no later than March 31, 2022.
3. Lilly will submit a proposed clinical trial protocol to further evaluate bebtelovimab for the treatment of mild-to-moderate COVID-19 in non-hospitalized patients no later than March 1, 2022.

O. Lilly and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

Healthcare Facilities to Whom Bebtelovimab Is Distributed and Healthcare Providers Administering bebtelovimab

P. Healthcare facilities and healthcare providers will ensure that they are aware of the letter of authorization, and the terms herein, and that the authorized Fact Sheets are made available to healthcare providers and to patients and caregivers, respectively, through appropriate means, prior to administration of bebtelovimab as described in the Scope of Authorization (Section II) under this EUA.

Q. Healthcare facilities and healthcare providers receiving bebtelovimab will track all serious adverse events and medication errors that are considered to be potentially related to bebtelovimab use and must report these to FDA in accordance with the Fact Sheet for Healthcare Providers. Complete and submit a MedWatch form (www.fda.gov/medwatch/report.htm), or complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178) (these forms can be found via link above). Call 1-800-FDA-1088 for questions. Submitted reports must state, "Bebtelovimab use for COVID-19 under Emergency Use Authorization" at the beginning of the question "Describe Event" for further analysis.

R. Healthcare facilities and healthcare providers will ensure that appropriate storage is maintained until the product is administered consistent with the terms of this letter and the authorized labeling.

S. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensing and administration of bebtelovimab for the use authorized in this letter (i.e., lot numbers, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered).

T. Healthcare facilities will ensure that any records associated with this EUA are maintained until notified by Lilly and/or FDA. Such records will be made available to Lilly, HHS, and FDA for inspection upon request.

U. Healthcare facilities and providers will report therapeutics information and utilization data as directed by HHS.

Conditions Related to Printed Matter, Advertising, and Promotion

V. All descriptive printed matter, advertising, and promotional materials relating to the use of bebtelovimab under this authorization shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in Section 502(a) and (n) of the Act, as applicable, and FDA implementing regulations. References to "approved labeling", "permitted labeling" or similar terms in these requirements shall be understood to refer to the authorized labeling for the use of bebtelovimab under this authorization. In addition, such materials shall:

- Be tailored to the intended audience.
- Not take the form of reminder advertisements, as that term is described in 21 CFR 202.1(e)(2)(i), 21 CFR 200.200 and 21 CFR 201.100(f).
- Present the same risk information relating to the major side effects and contraindications concurrently in the audio and visual parts of the presentation for advertising and promotional materials in audio-visual format.
- Be accompanied by the authorized labeling, if the promotional materials are not subject to Section 502(n) of the Act.
- Be submitted to FDA accompanied by Form FDA-2253 for consideration at least 14 calendar days prior to initial dissemination or first use.

W. Lilly may disseminate descriptive printed matter, advertising, and promotional materials relating to the emergency use of bebtelovimab that provide accurate descriptions of safety results and efficacy results on a clinical endpoint(s) from the clinical trial(s) summarized in the authorized labeling. Such materials must include any limitations of the clinical trial data as described in the authorized labeling. Lilly may not imply that bebtelovimab is FDA-approved for its authorized use by making statements such as "bebtelovimab is safe and effective for the treatment of COVID-19."

X. All descriptive printed matter, advertising, and promotional material, relating to the use of bebtelovimab under this authorization clearly and conspicuously shall state that:

- Bebtelovimab has not been approved, but has been authorized for emergency use by FDA under an EUA, for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high-risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate; and

- The emergency use of bebtelovimab is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

If the Agency notifies Lilly that any descriptive printed matter, advertising or promotional materials do not meet the terms set forth in conditions V through X of this EUA, Lilly must cease distribution of such descriptive printed matter, advertising, or promotional materials in accordance with the Agency's notification. Furthermore, as part of its notification, the Agency may also require Lilly to issue corrective communication(s).

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

--/S/--

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR BEBTELOVIMAB

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use BEBTELOVIMAB under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for BEBTELOVIMAB.

BEBTELOVIMAB injection for intravenous use
Original EUA Authorized Date: 02/2022
Revised EUA Authorized Date: 11/2022

----------RECENT MAJOR CHANGES----------

Dosage and Administration, Dose Preparation and Administration (2.3): updated administration materials	03/2022
Use in Specific Populations, Pregnancy (8.1): added hypersensitivity reactions in pregnant women	05/2022
Clinical Pharmacology, Microbiology (12.4): updated neutralizing data	11/2022

----------EMERGENCY USE AUTHORIZATION----------

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of bebtelovimab for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg):

- with positive results of direct SARS-CoV-2 viral testing, **and**
- who are at high risk for progression to severe COVID-19, including hospitalization or death, **and**
- for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate. (14.4)

LIMITATIONS OF AUTHORIZED USE

- Bebtelovimab is not authorized for treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to this drug and regional variant frequency.
  - FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility, and CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions. (12.4)
  - FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs
- Bebtelovimab is not authorized for use in patients who:
  - are hospitalized due to COVID-19, OR
  - require oxygen therapy and/or respiratory support due to COVID-19, OR
  - require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 and are on chronic oxygen therapy and/or respiratory support due to underlying non-COVID-19 related comorbidity.

Bebtelovimab is not approved for any use, including for use as treatment of COVID-19. (1)

Bebtelovimab is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of bebtelovimab under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

See Full Fact Sheet for Healthcare Providers for the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19.

----------DOSAGE AND ADMINISTRATION----------

The dosage in adults (18 years and older) and pediatric patients (≥12 years of age and weighing at least 40 kg) is bebtelovimab 175 mg administered as a single intravenous injection over at least 30 seconds. Administer bebtelovimab as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 7 days of symptom onset. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 175 mg/2 mL (87.5 mg/mL) in a single-dose vial. (3)

----------CONTRAINDICATIONS----------

No contraindications have been identified based on the limited available data for the emergency use of bebtelovimab authorized under this EUA. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions: Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of other SARS-CoV-2 monoclonal antibodies and could occur with administration of bebtelovimab. If clinically significant hypersensitivity reactions occur, discontinue and initiate appropriate supportive care. Infusion-related reactions may occur up to 24 hours post injection. These reactions may be severe or life threatening. (5.1)
- Clinical Worsening After SARS-CoV-2 Monoclonal Antibody Administration: Clinical worsening of COVID-19 after administration of SARS-CoV-2 monoclonal antibody treatment has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to SARS-CoV-2 monoclonal antibody use or were due to progression of COVID-19. (5.2)
- Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19: Treatment with bebtelovimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bebtelovimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. (5.3)

----------ADVERSE REACTIONS----------

Most common adverse reactions are infusion-related reactions (0.3%), pruritus (0.3%), and rash (0.8%). (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to bebtelovimab (1) by submitting FDA Form 3500 online, (2) by downloading this form and then submitting by mail or fax, or (3) contacting the FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to Eli Lilly and Company, Global Patient Safety: Fax: 1-317-277-0853; E-mail: mailindata_gsmtindy@lilly.com; or call 1-855-LillyC19 (1-855-545-5921) to report adverse events. (6.4).

----------DRUG INTERACTIONS----------

Bebtelovimab is not renally excreted or metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely. (7)

See FACT SHEET FOR PATIENTS, PARENTS, AND CAREGIVERS.

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* Sections or subsections omitted from the EUA are not listed

FULL FACT SHEET FOR HEALTHCARE PROVIDERS

1 EMERGENCY USE AUTHORIZATION

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of bebtelovimab for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg):

- with positive results of direct SARS-CoV-2 viral testing, **and**
- who are at high risk[1] for progression to severe COVID-19, including hospitalization or death, **and**
- for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate *[see Clinical Studies (14.4)]*.

LIMITATIONS OF AUTHORIZED USE

- Bebtelovimab is not authorized for treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to this drug and regional variant frequency.
    - FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.[2]
- Bebtelovimab is not authorized for use in patients, who:
    - are hospitalized due to COVID-19, OR
    - require oxygen therapy and/or respiratory support due to COVID-19, OR
    - require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 and are on chronic oxygen therapy and/or respiratory support due to underlying non-COVID-19 related comorbidity.

Treatment with bebtelovimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bebtelovimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation *[see Warnings and Precautions (5.3)]*.

Bebtelovimab is not FDA-approved for any use, including for use as treatment of COVID-19 *[see Emergency Use Authorization (1)]*.

Bebtelovimab is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of bebtelovimab under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Justification for Emergency Use of Drugs During the COVID-19 Pandemic

There is currently an outbreak of Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2, a novel coronavirus. The Secretary of HHS has declared that:

[1] For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

[2] FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility *[see Microbiology (12.4)]*, and CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions.

- A public health emergency related to COVID-19 has existed since January 27, 2020.
- Circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic (March 27, 2020 declaration).

An EUA is a FDA authorization for the emergency use of an unapproved product or unapproved use of an approved product (i.e., drug, biological product, or device) in the United States under certain circumstances including, but not limited to, when the Secretary of HHS declares that there is a public health emergency that affects the national security or the health and security of United States citizens living abroad, and that involves biological agent(s) or a disease or condition that may be attributable to such agent(s). Criteria for issuing an EUA include:

- The biological agent(s) can cause a serious or life-threatening disease or condition;
- Based on the totality of the available scientific evidence (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that
    - the product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition; and
    - The known and potential benefits of the product - when used to diagnose, prevent, or treat such disease or condition - outweigh the known and potential risks of the product, taking into consideration the material threat posed by the biological agent(s);
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the serious or life-threatening disease or condition.

Information Regarding Available Alternatives for the EUA Authorized Use

Veklury (remdesivir) is FDA-approved for the treatment of COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, who are not hospitalized and have mild-to-moderate COVID-19, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Veklury is administered via intravenous infusion for a total treatment duration of 3 days.

Although Veklury is an approved alternative treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, FDA does not consider Veklury to be an adequate alternative to bebtelovimab for this authorized use because it may not be feasible or practical for certain patients (e.g., it requires a 3-day treatment duration).

Other therapeutics are currently authorized for the same use as bebtelovimab. For additional information on all products authorized for treatment or prevention of COVID-19, please see https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

For information on clinical studies of bebtelovimab and other therapies for the treatment of COVID-19, see www.clinicaltrials.gov.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

The dosage in adults (18 years and older) and pediatric patients (≥12 years of age and weighing at least 40 kg) is bebtelovimab 175 mg.

Administer bebtelovimab as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 7 days of symptom onset.

Bebtelovimab must be administered as a single intravenous injection over at least 30 seconds.

2.2 Dosage Adjustment in Specific Populations

No dosage adjustment is recommended in pregnant or lactating individuals, in geriatrics, in individuals with renal impairment, or in individuals with mild hepatic impairment *[see Clinical Pharmacology (12.3)]*.

2.3 Dose Preparation and Administration

General Information

- Bebtelovimab should be prepared by a qualified healthcare professional using aseptic technique.
- Inspect bebtelovimab vial visually for particulate matter and discoloration. Bebtelovimab is clear to opalescent and colorless to slightly yellow to slightly brown solution. Discard the vial if the solution is cloudy, discolored or visible particles are observed.
- Bebtelovimab may only be administered in settings in which healthcare providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.
- **Clinically monitor patients for possible infusion-related reactions during administration and observe patients for at least 1 hour after injection is complete.**

Materials Needed for Administration

- 1 bebtelovimab vial (175 mg/2 mL)
- 1 disposable polypropylene dosing syringe capable of holding 2 mL
- 0.9% Sodium Chloride Injection for flushing
- Optional: 1 syringe extension set made of polyethylene or polyvinylchloride with or without di-ethylhexylphthalate (DEHP)

Preparation

- Remove bebtelovimab vial from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake vial. Inspect the vial.**
- Withdraw 2 mL from the vial into the disposable syringe.
- Discard any product remaining in the vial.
- This product is preservative-free and therefore, should be administered immediately.

- If immediate administration is not possible, store the syringe for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) and up to 7 hours at room temperature (20°C to 25°C [68°F to 77°F]). If refrigerated, allow the prepared syringe to equilibrate to room temperature for approximately 20 minutes prior to administration.
- If used, attach and prime the syringe extension set.
- Administer the entire contents of the syringe via IV injection over at least 30 seconds.
- After the entire contents of the syringe have been administered, **flush the injection line** with 0.9% Sodium Chloride to ensure delivery of the required dose.

3 DOSAGE FORMS AND STRENGTHS

Bebtelovimab is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow to slightly brown solution available as:

- Injection: 175 mg/2 mL (87.5 mg/mL) in a single-dose vial

4 CONTRAINDICATIONS

No contraindications have been identified based on the limited available data for the emergency use of bebtelovimab authorized under this EUA.

5 WARNINGS AND PRECAUTIONS

There are limited clinical data available for bebtelovimab. Serious and unexpected adverse events may occur that have not been previously reported with bebtelovimab use.

5.1 Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of other SARS-CoV-2 monoclonal antibodies and could occur with administration of bebtelovimab. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related reactions, which may occur up to 24 hours after the injection, have been observed in clinical trials of bebtelovimab when administered with other monoclonal antibodies and may occur with use of bebtelovimab alone. These reactions may be severe or life threatening.

Signs and symptoms of infusion-related reactions may include:

- fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vasovagal reactions (e.g., pre-syncope, syncope), dizziness and diaphoresis.

Administer appropriate medications and/or supportive care if an infusion-related reaction occurs.

Hypersensitivity reactions occurring more than 24 hours after the injection have also been reported with the use of SARS-CoV-2 monoclonal antibodies under Emergency Use Authorization.

5.2 Clinical Worsening After SARS-CoV-2 Monoclonal Antibody Administration

Clinical worsening of COVID-19 after administration of SARS-CoV-2 monoclonal antibody treatment has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to SARS-CoV-2 monoclonal antibody use or were due to progression of COVID-19.

5.3 Limitations of Benefit and Potential for Risk in Patients with Severe COVID 19

Treatment with bebtelovimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bebtelovimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Therefore, bebtelovimab is not authorized for use in patients, regardless of age, who:

- are hospitalized due to COVID-19, OR
- require oxygen therapy and/or respiratory support due to COVID-19, OR
- require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 and are on chronic oxygen therapy and/or respiratory support due to underlying non-COVID-19 related comorbidity.

6 ADVERSE REACTIONS

6.1 Adverse Reactions from Clinical Studies

The following adverse reactions have been observed in the clinical studies of bebtelovimab that supported the EUA. The adverse reaction rates observed in these clinical studies cannot be directly compared to rates in the clinical studies of other products and may not reflect the rates observed in clinical practice. Additional adverse events associated with bebtelovimab may become apparent with more widespread use.

The safety of bebtelovimab is primarily based on exposure of 602 ambulatory (non-hospitalized) subjects who received doses of bebtelovimab, alone or in combination with bamlanivimab and etesevimab, in the phase 1 and phase 2 portions of BLAZE-4, a randomized, single-dose clinical trial.

The following adverse reactions (i.e., adverse events assessed as causally related) have been observed in those who have received bebtelovimab, alone or in combination with bamlanivimab and etesevimab, at the authorized dose or higher:

- Infusion-related reactions (n=2, 0.3%)
- Pruritus (n=2, 0.3%)
- Rash (n=5, 0.8%)

The most common treatment-emergent adverse events observed in subjects treated with bebtelovimab, alone or in combination with bamlanivimab and etesevimab, at the authorized dose or higher, included nausea (0.8%) and vomiting (0.7%).

6.4 Required Reporting for Serious Adverse Events and Medication Errors

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events* and medication errors potentially related to bebtelovimab

within 7 calendar days from the healthcare provider's awareness of the event, using FDA Form 3500 (for information on how to access this form, see below). The FDA requires that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race)
- A statement "Bebtelovimab use for COVID-19 under Emergency Use Authorization (EUA)" under the "**Describe Event, Problem, or Product Use/Medication Error**" heading
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes).
- Patient's preexisting medical conditions and use of concomitant products
- Information about the product (e.g., dosage, route of administration, NDC #).

Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax to 1-800-FDA-0178, or
- Call 1-800-FDA-1088 to request a reporting form

In addition, please provide a copy of all FDA MedWatch forms to:

Eli Lilly and Company, Global Patient Safety
Fax: 1-317-277-0853
E-mail: mailindata_gsmtindy@lilly.com
Or call Eli Lilly and Company at 1-855-LillyC19 (1-855-545-5921) to report adverse events.

The prescribing health care provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of bebtelovimab.

*Serious adverse events are defined as:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- Other important medical event, which may require a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

7 DRUG INTERACTIONS

Bebtelovimab is not renally excreted or metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Severe hypersensitivity reactions and infusion-related reactions, have been observed with administration of bebtelovimab, including in pregnant patients *[see Warnings and Precautions (5.1)]*. There are risks to the mother and fetus associated with untreated COVID-19 in pregnancy as well as potential risks to the fetus associated with severe maternal hypersensitivity and infusion-related reactions *(see Clinical Considerations)*.

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Bebtelovimab should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy *(see Clinical Considerations)*.

Data

Nonclinical reproductive toxicity studies have not been performed with bebtelovimab. In tissue cross reactivity studies using human fetal tissues, no binding of clinical concern was detected for bebtelovimab. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, bebtelovimab has the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of bebtelovimab provides any treatment benefit or risk to the developing fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo-fetal risk

COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

Maternal Adverse Reactions

Pregnant patients who develop severe hypersensitivity and infusion-related reactions should be managed appropriately, including obstetrical care *[see Warnings and Precautions (5.1)]*.

8.2 Lactation

Risk Summary

There are no available data on the presence of bebtelovimab in human or animal milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for bebtelovimab and any potential adverse effects on the breastfed child from bebtelovimab or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

8.4 Pediatric Use

Bebtelovimab is not authorized for use in pediatric individuals under 12 years of age or weighing less than 40 kg. The safety and effectiveness of bebtelovimab have not been assessed in pediatric patients. The recommended dosing regimen in patients 12 years to less than 18 years of age, weighing at least 40 kg, is expected to result in comparable serum exposures of bebtelovimab as those observed in adults.

8.5 Geriatric Use

Of the 602 patients receiving bebtelovimab in BLAZE-4, 10.5% were 65 years of age and older and 3.3% were 75 years of age and older. Based on population PK analyses of samples from 573 patients over an age range of 14 to 89 years, there was no impact of age on PK. Therefore, there is no difference in the PK of bebtelovimab in geriatric patients compared to younger patients.

10 OVERDOSAGE

Doses up to 1750 mg of bebtelovimab (10 times the authorized dose of bebtelovimab) have been administered in clinical trials without dose-limiting toxicity. Treatment of overdose with bebtelovimab should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with bebtelovimab.

11 DESCRIPTION

Bebtelovimab is a human immunoglobulin G-1 (IgG1 variant) monoclonal antibody consisting of 2 identical light chain polypeptides composed of 215 amino acids each and 2 identical heavy chain polypeptides composed of 449 amino acids produced by a Chinese Hamster Ovary (CHO) stable bulk culture or cell line with a molecular weight of 144 kDa.

Bebtelovimab injection is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow to slightly brown solution in a single-dose vial for intravenous injection.

Each mL contains 87.5 mg of bebtelovimab, L-histidine (0.4 mg), L-histidine hydrochloride monohydrate (0.6 mg), sodium chloride (2.9 mg), sucrose (60 mg), polysorbate 80 (0.5 mg), and Water for Injection. The bebtelovimab solution has a pH range of 5.5-6.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bebtelovimab is a recombinant neutralizing human IgG1λ monoclonal antibody (mAb) to the spike protein of SARS-CoV-2 and is unmodified in the Fc region. Bebtelovimab binds the spike protein with a dissociation constant K_D = 0.046 to 0.075 nM and blocks spike protein attachment to the human ACE2 receptor with an IC_{50} value of 0.39 nM (0.056 mcg/mL).

12.2 Pharmacodynamics

The exposure-response relationships of bebtelovimab for viral loads and clinical outcomes are unknown.

12.3 Pharmacokinetics

A summary of PK parameters of bebtelovimab following administration of a single dose of 175 mg bebtelovimab is provided in Table 1.

Table 1: Pharmacokinetic Parameters of Bebtelovimab Administered IV in Adults and Pediatric Patients (12 years of age and older weighing at least 40 kg)

	Bebtelovimab (175 mg) N=585
Systemic Exposure	
Geometric Mean (%CV) C_{max}, mcg/mL	59.9 (31.9)
Geometric Mean (%CV) $C_{day\ 29}$, mcg/mL	4.55 (70.9)
Geometric Mean (%CV) AUC_{inf}, mcg day/mL	539 (41.5)
Distribution	
Geometric Mean (%CV) Vss (L)	4.55 (25.8)
Elimination	
Geometric Mean (%CV) Elimination Half-Life (day)	11.5 (27.0)
Geometric Mean (%CV) Clearance (L/day)	0.325 (41.5)

Abbreviations: CV = coefficient of variation; C_{max} = maximum concentration; $C_{day,29}$ = drug concentration on day 29; AUC_{inf} = area under the concentration versus time curve from zero to infinity; Vss = steady-state volume of distribution.

Specific Populations:
The PK profile of bebtelovimab was not affected by age, sex, race, or baseline viral load based on a population PK analysis. Body weight had no clinically relevant effect on the PK of bebtelovimab in adults with COVID-19 over the body weight range of 45 kg to 194 kg.

Patients with renal impairment
Renal impairment is not expected to impact the PK of bebtelovimab, since mAbs with molecular weight >69 kDa are known not to undergo renal elimination. Similarly, dialysis is not expected to impact the PK of bebtelovimab.

Patients with hepatic impairment
Bebtelovimab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as other IgG monoclonal antibodies and human endogenous IgG antibodies.

Based on population PK analysis, there is no significant difference in PK of bebtelovimab in patients with mild hepatic impairment compared to patients with normal hepatic function. Bebtelovimab has not been studied in patients with moderate or severe hepatic impairment.

Drug Interactions:
Bebtelovimab is not renally excreted or metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

12.4 Microbiology

Antiviral Activity
The cell culture neutralization activity of bebtelovimab against SARS-CoV-2 was measured in a dose-response model quantifying plaque reduction using cultured Vero E6 cells. Bebtelovimab neutralized the USA/WA/1/2020 isolate of SARS-CoV-2 with an estimated EC_{50} value = 0.044 nM (6.4 ng/mL).

Bebtelovimab demonstrated antibody-dependent cell-mediated cytotoxicity on Jurkat reporter cells expressing FcγRIIIa following engagement with target cells expressing spike protein. Bebtelovimab did not elicit complement-dependent cytotoxicity activity in cell-based assays.

Antibody Dependent Enhancement (ADE) of Infection
The risk that bebtelovimab could mediate viral uptake and replication by immune cells was studied in THP-1 and Raji cell lines and primary human macrophages. In general, experiments with bebtelovimab did not demonstrate productive viral infection in immune cells exposed to SARS-CoV-2 at concentrations of mAb down to 60,000-fold below the approximate EC_{50} value for neutralization.

Antiviral Resistance
There is a potential risk of treatment failure due to the development of viral variants that are resistant to bebtelovimab.

Nonclinical selection studies using a directed evolution of a yeast displayed Spike RBD identified that substitutions at residues K444, V445, G446, and P499 interfered with bebtelovimab's ability to block the Spike RBD:ACE-2 interaction. Pseudotyped virus-like particle (VLP) neutralization assays confirmed a 5-fold or greater reduction in susceptibility to bebtelovimab of viral variants with the following substitutions: K444E (>862), K444N (>1,901-fold), K444Q (208-fold), K444T (>1,814-fold), V445A (111-fold), V445F (369-fold), V445G (>730-fold), G446D (69-fold), G446R (7-fold), G446V (8-fold), P499H (>1,606-fold), P499R (>1,870-fold), and P499S (25-fold). In the context of Delta spike protein, G446V substitution had reduced susceptibility of 16.4-fold.

Pseudotyped VLP assessment using the full-length spike genes from different variant lineages indicate that bebtelovimab retains activity (<5-fold reduction) against the Alpha (B.1.1.7, UK origin), Beta (B.1.351, South Africa origin), Gamma (P.1, Brazil origin), Delta (B.1.617.2, India origin), Delta [+K417N] (AY.1/AY.2, India origin), Epsilon (B.1.427/B.1.429, California origin), Iota (B.1.526, New York origin), Kappa (B.1.617.1, India origin), Lambda (C.37, Peru origin), Omicron (B.1.1.529/BA.1, South Africa origin), Omicron [+R346K] (BA.1.1), Omicron BA.2, Omicron BA.2 [+L452Q] (BA.2.12.1), Omicron BA.2 [+D339H, G446S, N460K, R493Q (reversion)] (BA.2.75), Omicron BA.2 [BA.2.75+R346T+F486S] (BA.2.75.2), Omicron BA.4/BA.5, and Omicron BA.4 [+R346T] (BA.4.6/BF.7) variant lineages (Table 2). The Mu (B.1.621, Colombia origin) variant showed a reduction in susceptibility to bebtelovimab of 5.3-fold. The Omicron BA.5 [+N444T, N460K] (BQ.1),

and Omicron BA.5 [+R346T, N444T, N460K] (BQ.1.1) variants showed a large reduction in susceptibility to bebtelovimab of >672-fold.

Table 2: Bebtelovimab Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Spike Protein Variants

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested[a]	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y	No change[b]
B.1.351	South Africa	Beta	K417N + E484K + N501Y	No change[b]
P.1	Brazil	Gamma	K417T + E484K + N501Y	No change[b]
B.1.617.2/AY.3	India	Delta	L452R + T478K	No change[b]
AY.1/AY.2 (B.1.617.2 sublineages)	India	Delta [+K417N]	L452R + T478K + K417N	No change[b]
B.1.427/B.1.429	USA (California)	Epsilon	L452R	No change[b]
B.1.526[c]	USA (New York)	Iota	E484K	No change[b]
B.1.617.1	India	Kappa	L452R + E484Q	No change[b]
C.37	Peru	Lambda	L452Q + F490S	No change[b]
B.1.621	Colombia	Mu	R346K + E484K + N501Y	5.3
B.1.1.529/BA.1	South Africa	Omicron [BA.1]	G339D + S371L + S373P + S375F + K417N + N440K + G446S + S477N + T478K + E484A + Q493R + G496S + Q498R + N501Y + Y505H	No change[b]
BA.1.1	South Africa	Omicron [+R346K]	BA.1 + R346K	No change[b]
BA.2	South Africa	Omicron [BA.2]	G339D + S371F + S373P + S375F + T376A + D405N + R408S + K417N + N440K + S477N + T478K + E484A + Q493R + Q498R + N501Y + Y505H	No change[b]
BA.2.12.1	USA	Omicron [BA.2+L452Q]	BA.2 + L452Q	No change[b]
BA.2.75	India	Omicron [BA.2+D339H, G446S, N460K, R493Q (reversion)]	BA.2 + D339H + G446S + N460K + R493Q (reversion)	No change[b]
BA.2.75.2	India	Omicron [BA.2.75+R346T+F486S]	BA.2.75 + R346T + F486S	No change[b]
BA.4/BA.5	South Africa	Omicron [BA.4/BA.5]	G339D + S371F + S373P + S375F + T376A + D405N + R408S + K417N +	No change[b]

			N440K + L452R + S477N + T478K + E484A + F486V + Q498R + N501Y + Y505H	
BA.4.6/BF.7	USA/Belgium	Omicron [BA.4+R346T]	BA.4 + R346T	No change[b]
BQ.1	Nigeria	Omicron [BA.5+K444T+N460K]	BA.5 + K444T + N460K	>672[d]
BQ.1.1	Multiple	Omicron [BA.5+R346T+K444T+N460K]	BA.5 + R346T + K444T + N460K	>672[d]

[a] Key substitutions occurring in the receptor binding domain of spike protein are listed. Pseudotyped VLP contained the full-length spike protein reflective of the consensus sequence for each of the variant lineages with the exception of BA.2.75.2 which is a full-length spike of BA.2.75+R346T+F486S substitutions.

[b] No change: <5-fold reduction in susceptibility.

[c] Isolates of the B.1.526 lineage harbor several spike protein amino acid substitutions, and not all isolates contain the E484K substitution (as of February 2021).

[d] Bebtelovimab is unlikely to be active against this variant.

In authentic SARS-CoV-2 assays, bebtelovimab retained activity (<5-fold reduction) against variant virus isolates from the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2/AY.3), Omicron (B.1.1.529/BA.1), Omicron [+R346K] (BA.1.1), Omicron BA.2, Omicron BA.2 [+L452Q] (BA.2.12.1), Omicron BA.2 [+D339H, G446S, N460K, R493Q (reversion)] (BA.2.75), Omicron BA.4, Omicron BA.4 [+R346T] (BA.4.6), and Omicron BA.5 lineages, as well as SARS-CoV-2 (USA/WA/1/2020 isolate) engineered to express the L452R substitution present in the Epsilon (B.1.427/B.1.429) lineage or the E484K substitution present in the Iota (B.1.526) lineage (Table 3).

Table 3: Authentic[a] SARS-CoV-2 Neutralization Data for Bebtelovimab

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested[b]	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y	No change[c]
B.1.351	South Africa	Beta	K417N, E484K, N501Y	No change[c,d]
P.1	Brazil	Gamma	K417T, E484K, N501Y	No change[c]
B.1.617.2/AY.3	India	Delta	L452R, T478K	No change[c,d]
B.1.427/B.1.429	USA (California)	Epsilon	L452R	No change[c]
B.1.526[e]	USA (New York)	Iota	E484K	No change[c]
B.1.1.529/BA.1	South Africa	Omicron	G339D + S371L + S373P + S375F + K417N + N440K + G446S + S477N + T478K + E484A + Q493R + G496S + Q498R + N501Y + Y505H	No change[c,d]
BA.1.1	South Africa	Omicron [+R346K]	BA.1 + R346K	No change[c]
BA.2	South Africa	Omicron [BA.2]	G339D + S371F + S373P + S375F + T376A + D405N + R408S + K417N + N440K + S477N + T478K + E484A + Q493R + Q498R + N501Y + Y505H	No change[c,d]
BA.2.12.1	USA	Omicron [BA.2+L452Q]	BA.2 + L452Q	No change[c]
BA.2.75	India	Omicron [BA.2+D339H, G446S, N460K, R493Q (reversion)]	BA.2 + D339H + G446S + N460K + R493Q (reversion)	No change[c,d]
BA.4	South Africa	Omicron [BA.4]	G339D + S371F + S373P + S375F + T376A + D405N + R408S + K417N + N440K + L452R + S477N + T478K + E484A + F486V + Q498R + N501Y + Y505H	No change[c]
BA.4.6	USA	Omicron [BA.4+R346T]	BA.4 + R346T	No change[c]
BA.5	South Africa	Omicron [BA.4/BA.5]	G339D + S371F + S373P + S375F + T376A + D405N + R408S + K417N + N440K + L452R + S477N + T478K + E484A + F486V + Q498R + N501Y + Y505H	No change[c]

[a] The B.1.1.7, B.1.351, B.1.617.2, B.1.1.529/BA.1, and BA.2 variants were assessed using cell culture-expanded virus isolates and tested using a plaque reduction assay; the B.1.351, P.1, B.1.617.2, B.1.1.529/BA.1, BA.1.1, BA.2, BA.2.12.1, BA.2.75, BA.4, BA.4.6, and BA.5 variants were assessed using cell culture-expanded isolates and tested using a microneutralization assay with a CPE-based endpoint titer to determine the $IC_{>99}$; the B.1.526/E484K, B.1.427/B.1.429/L452R, and BA.2.75 spike substitutions were assessed using recombinant SARS-CoV-2 (USA/WA/1/2020 isolate with E484K, L452R, or full spike of BA.2.75) and tested using a plaque reduction assay.

[b] Key substitutions occurring in receptor binding domain of spike protein which are associated with each lineage.

[c] No change: <5-fold reduction in susceptibility when compared to ancestral control isolate using the same methodology.

[d] These viral variants have been tested with two different neutralization methodologies, both yielding <5-fold reductions in susceptibility.

[e] Isolates of the B.1.526 lineage harbor several spike protein amino acid substitutions, and not all isolates contain the E484K substitution (as of February 2021).

Genotypic analysis and phenotypic testing are ongoing to monitor for potential bebtelovimab-resistance-associated spike variations in clinical trials. Baseline sequencing data are available for 611 of the subjects in the BLAZE-4 (Arms 9-14) Study. Of these, 552 (90.3%) were infected with a variant of interest or concern, as designated by the WHO. No subject was infected with virus of the Omicron lineage or sub-lineages. The majority of subjects in the trial were infected with Delta (49.9%) and Alpha (28.6%). These were distributed across the treatment groups with Delta and Alpha infection rates of 60.2% and 23.1% in placebo, 31.3% and 41.8% in bebtelovimab alone arms, and 58.3% and 21.9% in the bebtelovimab with bamlanivimab and etesevimab arms, respectively. Gamma and Mu infections comprised 5.6% and 3.8% of the total infections respectively. Subjects infected with Beta, Delta [+K417N], Iota, and Lambda variants were the minority with 0.5%, 0.8%, 0.7%, and 0.5% total infections, respectively. All other subjects in the trial had SARS-CoV-2 infections from either non-WHO classified viruses (3.3%), or the lineage was not able to be determined based on the baseline sequence data (6.4%). Detection of viral variants with a 5-fold or greater reduction in susceptibility to bebtelovimab at baseline has been rare, with only one G446V substitution (8-fold shift) observed transiently out of 611 subjects in the BLAZE-4 (Arms 9-14) study that had baseline sequencing available (0.2%, 1/611).

Analysis of treatment-emergent variants focused on changes at amino acid positions with known phenotypically confirmed bebtelovimab-associated variations (i.e., K444, V445, G446, and P499) in serial viral samples obtained in the BLAZE-4 (Arms 9-14) bebtelovimab Phase 2 Study. Treatment-emergent substitutions detected at ≥15% or ≥50% allele fractions at these positions included K444E/N, V445G, G446V, and P499H/R. These substitutions resulted in a 5-fold or greater reduction in susceptibility to bebtelovimab in pseudotyped VLP assays: K444E (>862), K444N (>1,901-fold), V445G (>730-fold), G446V (8-fold), P499H (>1,606-fold), and P499R (>1,870-fold). Additional treatment-emergent substitutions detected at ≥15% or >50% allele fractions outside the epitope in at least 2 subjects included C379F (n=2) and G404C (n=2), seen in bebtelovimab in combination with bamlanivimab and etesevimab arms.

Considering all substitutions detected at ≥15% allele fraction at positions K444, V445, G446, and P499, 5.5% (11/199) of subjects treated with bebtelovimab alone harbored a variant that was treatment-emergent. This was more frequent than observed in the placebo arm (0%, 0/112), or when bebtelovimab was administered together with bamlanivimab and etesevimab (0.3%, 1/312). The appearance of these treatment-emergent bebtelovimab resistance-associated substitutions was associated with higher viral loads in the subjects in whom they were detected, but none of these subjects were hospitalized. The majority of the variants were first detected on Day 5 (n=3) and Day 7 (n=6) following treatment initiation.

It is possible that bebtelovimab resistance-associated variants could have cross-resistance to other mAbs targeting the receptor binding domain of SARS-CoV-2. The clinical impact is not known.

Immune Response Attenuation

There is a theoretical risk that antibody administration may attenuate the endogenous immune response to SARS-CoV-2 and make patients more susceptible to re-infection.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis, mutagenesis, and reproductive toxicology studies with bebtelovimab have not been conducted.

13.2 Animal Toxicology and/or Pharmacology

In toxicology studies, bebtelovimab had no adverse effects when administered intravenously to rats.

In tissue cross reactivity studies using human adult and fetal tissues, no binding of clinical concern was detected for bebtelovimab.

Antiviral Activity In Vivo
Prophylactic administration of bebtelovimab to male Syrian golden hamsters (n=5 to 8 per group) resulted in 2 to 4 $\log_{10}$ decreases in viral genomic RNA and viral replication (subgenomic RNA) from lung tissue, as well as decreases in lung weight and improvements in body weight compared to controls.

The applicability of these findings to a treatment setting is not known.

14 CLINICAL STUDIES

The data supporting this EUA for treatment of mild-to-moderate COVID-19 are primarily based on analyses of data from the Phase 2 portion of the BLAZE-4 trial (NCT04634409) that enrolled both low risk and high risk subjects (treatment arms 9-14). This trial evaluated the clinical efficacy data from subjects receiving 175 mg bebtelovimab alone and together with 700 mg bamlanivimab and 1,400 mg of etesevimab.

BLAZE-4 is a Phase 1/2, randomized, single-dose clinical trial evaluating treatment of subjects with mild-to-moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized). Efficacy of bebtelovimab, alone and together with bamlanivimab and etesevimab, was evaluated in low risk adults (i.e., those not at high-risk to progress to severe COVID-19) in a randomized part of the trial which included a placebo control arm (treatment arms 9-11). Low risk adults were randomized with a 1:1:1 ratio. High-risk adults and pediatric subjects (12 years of age and older weighing at least 40 kg) received open-label active treatments. One cohort of high risk subjects was randomized with 2:1 ratio (treatment arms 12 and 13). Another cohort of high risk subject was enrolled with no randomization (treatment arm 14). The trial enrolled subjects who were not hospitalized and had 1 or more COVID-19 symptoms that were at least mild in severity. Treatment was initiated within 3 days of obtaining the clinical sample for the first positive SARS-CoV-2 viral infection determination.

BLAZE-4 was conducted prior to the emergence of the Omicron variant. No subject in BLAZE-4 was infected with virus of the Omicron lineage or sub-lineages. The majority of participants in the trial were infected with Delta (49.8%) and Alpha (28.6%).

14.1 Phase 2 Data from the Placebo-Controlled Portion of BLAZE-4 (Low Risk Subjects; Treatment Arms 9-11)

In this portion of the trial, adult subjects were treated with a single infusion of bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg (N=127), 175 mg bebtelovimab alone (N=125), or placebo (N=128). The majority (96.8%) of the subjects enrolled in these treatment arms did not meet the criteria for high-risk.

At baseline, median age was 35 years (with 1 placebo subject aged 65 or older); 56% of subjects were female, 79% were White, 36% were Hispanic or Latino, and 19% were Black or African American. Subjects had mild (74%) to moderate (26%) COVID-19; the mean duration of symptoms was 3.6 days; mean viral load by cycle threshold (CT) was 24.63 at baseline. The baseline demographics and disease characteristics were well balanced across treatment arms with the exception of baseline serology status. A higher percentage of subjects in the placebo arm were positive for baseline serology (15% vs. 9% for bamlanivimab, etesevimab, and bebtelovimab together, and 7% for bebtelovimab alone). Participants enrolled in these treatment arms had not received SARS-CoV-2 vaccine at baseline.

The primary endpoint was the proportion of subjects with persistently high viral load (PHVL) by Day 7. PHVL occurred in 26 subjects treated with placebo (21%) as compared to 16 (13%) subjects treated with bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg together [p=0.098], and 17 (14%) subjects treated with bebtelovimab 175 mg alone [p=0.147], a 38% (95% CI: -9%, 65%) and 34% (95% CI: -15%, 62%) relative reduction, respectively.

Secondary endpoints included mean change in viral load from baseline to Day 3, 5, 7, and 11 (Figure 1).

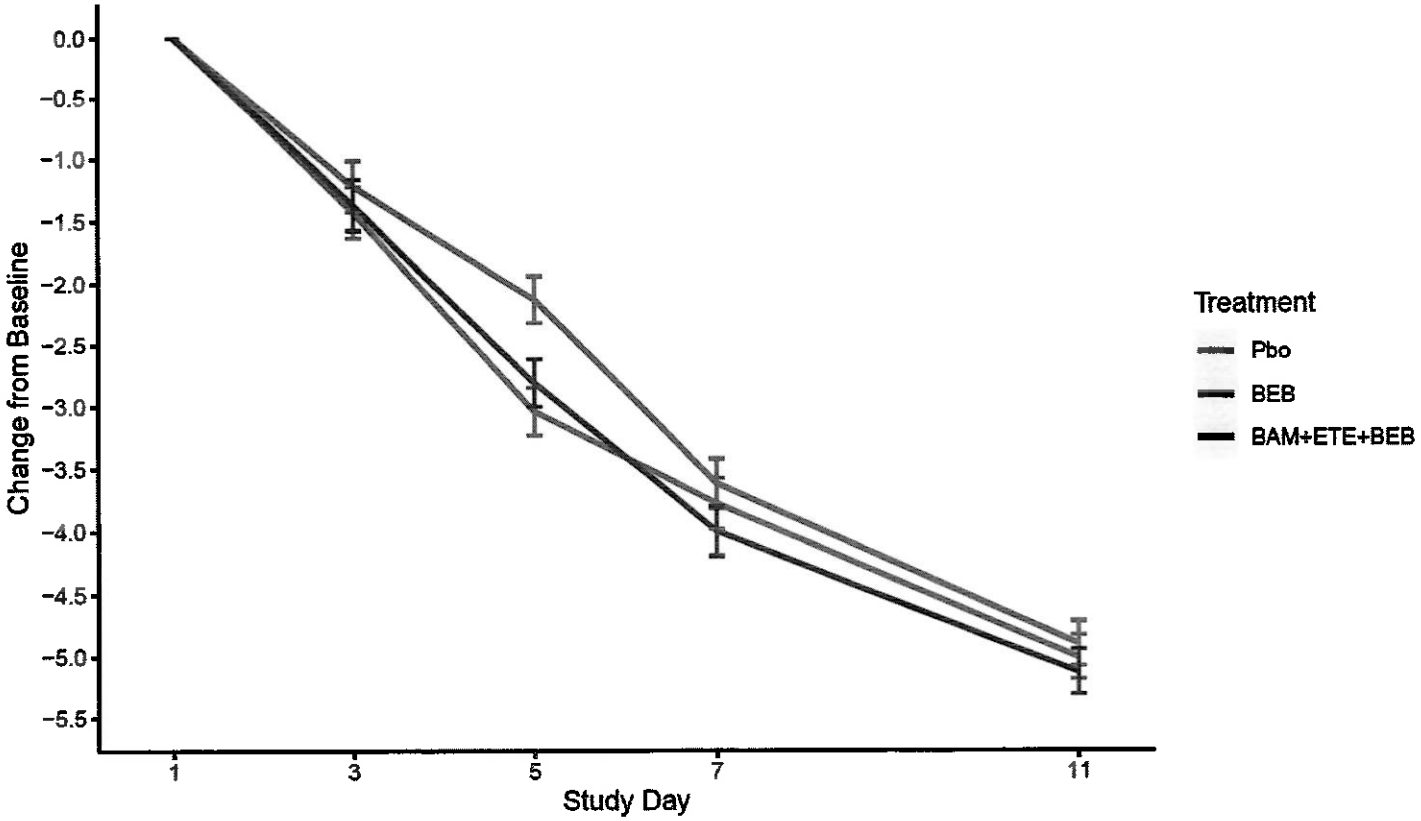

Figure 1: SARS-CoV-2 Viral Load Change from Baseline (Mean ± SE) by Visit from the Placebo-Controlled Portion of BLAZE-4 in Low Risk Adults (700 mg bamlanivimab, 1,400 mg etesevimab, 175 mg bebtelovimab together and 175 mg bebtelovimab alone).

For the secondary endpoint of COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death by any cause by Day 29, these events occurred in 2 (1.6%) subjects treated with placebo as compared with 3 (2.4%) events in subjects treated with bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg together and 2 (1.6%) events in subjects treated with bebtelovimab 175 mg alone. There was 1 subject treated with bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg together who died on Day 5. Conclusions are limited as COVID-19 related hospitalization and death rates are expected to be low in a low risk population.

The median time to sustained symptom resolution as recorded in a trial specific daily symptom diary was 7 days (95%CI: 6, 8 days) for subjects treated with bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg together [p=0.289] and 6 days (95% CI: 5, 7 days) for subjects treated with bebtelovimab 175 mg alone [p=0.003] as compared with 8 days (95% CI: 7, 9 days) for subjects treated with placebo. Symptoms assessed were cough, shortness of breath, feeling feverish, fatigue, body aches and pains, sore throat, chills, and headache. Sustained symptom resolution was defined as absence of any of these symptoms, except for allowance of mild fatigue and cough, in two consecutive assessments.

14.2 Phase 2 Data from the Randomized, Open-Label Portion of BLAZE-4 (High Risk Subjects; Treatment Arms 12-13)

In this portion of the trial, subjects were treated with a single infusion of bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg (N=50) or 175 mg bebtelovimab alone (N=100). The majority (91.3%) of the subjects enrolled in these dose arms meet the criteria for high-risk.

At baseline, median age was 50 years (with 28 subjects aged 65 or older); 52% of subjects were female, 75% were White, 18% were Hispanic or Latino, and 18% were Black or African American. Subjects had mild (75%) to moderate (25%) COVID-19; the mean duration of symptoms was 4.7 days; mean viral load by cycle threshold (CT) was 26.66 at baseline; and 20.7% of subjects had at least one dose of a COVID-19 vaccine. There were 2 pediatric patients enrolled (ages 14 and 17), one in each treatment arm. The baseline demographics and disease characteristics were well balanced across treatment groups.

The primary objective for these treatment arms was to characterize the safety profile of bebtelovimab 175 mg by evaluating adverse events and serious adverse events. Efficacy endpoints included the proportion of subjects with COVID-19 related hospitalization or death by any cause by Day 29, mean change in viral load from baseline to Days 3, 5, 7, and 11 and time to sustained symptom resolution.

The proportion of subjects with COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death by any cause was assessed by Day 29. Events occurred in 2 (4%) subjects treated with bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg together and 3 (3%) subjects treated with bebtelovimab 175 mg alone. There was 1 subject treated with bebtelovimab 175 mg alone who died on Day 34.

Mean changes in viral load from baseline to Day 3, 5, 7, and 11 are shown in Figure 2.

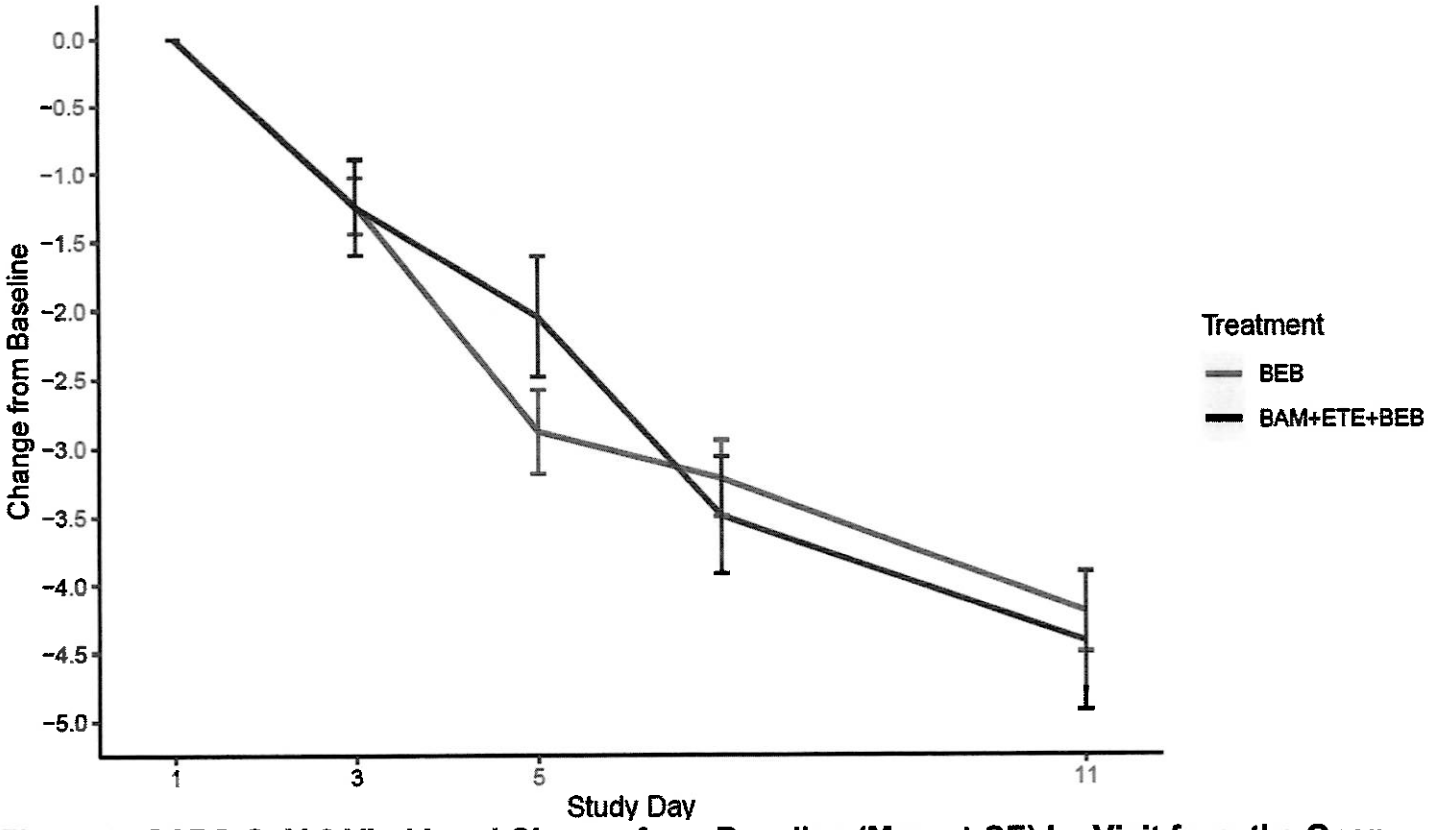

Figure 2: SARS-CoV-2 Viral Load Change from Baseline (Mean ± SE) by Visit from the Open-Label Portion of BLAZE-4 (700 mg bamlanivimab, 1,400 mg etesevimab, 175 mg bebtelovimab together and 175 mg bebtelovimab alone).

The median time to sustained symptom resolution as recorded in a trial specific daily symptom diary was 7 days for subjects treated with bebtelovimab 175 mg alone.

14.3 Phase 2 Data from the Non-Randomized, Open-Label Portion of BLAZE-4 (High Risk Subjects; Treatment Arm 14)

In this portion of the trial, subjects were treated with a single infusion of bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg (N=176). The majority (97.7%) of the subjects enrolled meet the criteria for high-risk.

At baseline, median age was 51 years (with 35 subjects aged 65 or older); 56% of subjects were female, 80% were White, 28% were Hispanic or Latino, and 16% were Black or African American. Subjects had mild (73%) to moderate (27%) COVID-19; the mean duration of symptoms was 4 days; mean viral load by cycle threshold (CT) was 23.45 at baseline; and 31% of subjects had at least one dose of a COVID-19 vaccine. There were 2 pediatric patients enrolled (ages 14 and 15).

The primary objective for this treatment arm was to characterize the safety profile of bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg by evaluating adverse events and serious adverse events. Efficacy endpoints included the proportion of subjects with COVID-19 related hospitalization or death by any cause by Day 29, mean change in viral load from baseline to Days 3, 5, 7, and 11, and time to sustained symptom resolution.

The proportion of subjects with COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death by any cause was assessed by Day 29. Events occurred in 3 subjects (1.7%), and no subjects died.

Mean changes in viral load from baseline to Day 3, 5, 7, and 11 were -1.4, -3.1, -4.0, and -5.4, respectively.

The median time to sustained symptom resolution as recorded in a trial specific daily symptom diary was 8 days.

14.4. Overall Benefit-Risk Assessment and Limitations of Data Supporting the Benefits of the Product

Based on the data from BLAZE-4, bebtelovimab has been shown to improve symptoms in patients with mild-to-moderate COVID-19. Additionally, a reduction in SARS-CoV-2 viral load on Day 5 was observed relative to placebo, though the clinical significance of this is unclear. The placebo-controlled phase 2 data are limited by enrollment of only subjects without risk factors for progression to severe COVID-19, and the trial was not powered or designed to determine a difference in the clinical outcomes of hospitalization or death between the placebo and bebtelovimab treatment arms *[see Clinical Studies (14.1)]*. Bebtelovimab has been studied in individuals who have risk factors for progression to severe COVID-19, but the efficacy analyses are limited due to the lack of a concurrent placebo control arm for this population *[see Clinical Studies (14.2, 14.3)]*.

However, based on the totality of scientific evidence available, including the available Phase 2 and pharmacokinetic data, along with the nonclinical viral neutralization data for Omicron and other variants of concern, it is reasonable to believe that bebtelovimab may be effective for the treatment of patients with mild-to-moderate COVID-19 to reduce the risk of progression to hospitalization or death. In addition, the mechanism of action for bebtelovimab is similar to other neutralizing SARS-CoV-2 monoclonal antibodies, including bamlanivimab and etesevimab, that have data from Phase 3 clinical trials showing a reduction in hospitalization or death in high risk patients infected with other SARS-CoV-2 variants. The safety profile of bebtelovimab is acceptable with monitorable risks and is comparable to other SARS-CoV-2 monoclonal antibodies, including bamlanivimab and etesevimab. Considered together, these data support that the known and potential benefits of treatment with bebtelovimab outweigh the known and potential risks in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

Clinical data summarized above were similar for bebtelovimab alone as compared to the combination of bamlanivimab, etesevimab and bebtelovimab administered together. Bebtelovimab retains activity against currently circulating variants *[see Microbiology (12.4)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Bebtelovimab injection is a sterile, preservative-free clear to opalescent and colorless to slightly yellow to slightly brown solution supplied in a single-dose vial.

Antibody	Concentration	Package Size	NDC
Bebtelovimab	175 mg/2 mL (87.5 mg/mL)	One vial per carton	0002-7589-01

Storage and Handling
Bebtelovimab is preservative-free. Discard unused portion.

Store unopened vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.

DO NOT FREEZE, SHAKE, OR EXPOSE TO DIRECT LIGHT.

17 PATIENT COUNSELING INFORMATION

As a healthcare practitioner, you must communicate to the patient and/or caregiver information consistent with the "FACT SHEET FOR PATIENTS, PARENTS AND CAREGIVERS" and provide them with a copy of this Fact Sheet prior to administration of bebtelovimab. However, if providing this information will delay the administration of bebtelovimab to a degree that would endanger the life of a patient, the information must be provided to the parent and/or caregiver as soon as feasible after bebtelovimab administration.

Remind patients treated with bebtelovimab that they should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect "high touch" surfaces, and frequent handwashing) according to CDC guidelines.

For additional information visit: www.LillyAntibody.com/bebtelovimab

If you have questions, please contact: 1-855-LillyC19 (1-855-545-5921)

18 MANUFACTURER INFORMATION

Eli Lilly and Company, Indianapolis, IN 46285, USA

Literature revised November 04, 2022

A2.0-BEB-0008-EUA HCP-2001104

U.S. FOOD & DRUG ADMINISTRATION

Frequently Asked Questions on the Emergency Use Authorization of Bebtelovimab for the Treatment of COVID-19

Q. What is an Emergency Use Authorization (EUA)?
A: Under section 564 of the Federal Food, Drug & Cosmetic Act, the FDA may, pursuant to a declaration by the HHS Secretary based on one of four types of determinations, authorize an unapproved product or unapproved uses of an approved product for emergency use. In issuing an EUA, the FDA must determine, among other things, that, based on the totality of scientific evidence available, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by a chemical, biological, radiological, or nuclear agent; that the known and potential benefits, when used to treat, diagnose or prevent such disease or condition, outweigh the known and potential risks for the product; and that there are no adequate, approved, and available alternatives. Emergency use authorization is NOT the same as FDA approval or licensure.

Q. What does this EUA authorize? Are there limitations of the authorized use under this EUA?
A. This EUA authorizes bebtelovimab, manufactured by Eli Lilly and Company (Lilly) for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

Bebtelovimab is not authorized for treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to these drugs and regional variant frequency.

- FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility [*see Microbiology (12.4)* in the Fact Sheet for Health Care Providers], and CDC regional variant frequency data.
- FDA's determination and any updates will be available at Emergency Use Authorizations for Drugs and Non-Vaccine Biological Products.

Bebtelovimab is not authorized for use in patients who:

- are hospitalized due to COVID-19 OR
- require oxygen therapy and/or respiratory support due to COVID-19, OR
- require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 and are on chronic oxygen therapy and/or respiratory support due to underlying non-COVID-19 related comorbidity.

Treatment with bebtelovimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bebtelovimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

Q. How are the monoclonal antibody therapies affected by the SAR-CoV-2 viral variants in the U.S.?

A: Circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies. The frequency of these variants is being monitored by the FDA, Centers for Disease Control and Prevention (CDC), and other stakeholders. Health care providers should review the Antiviral Resistance information in the authorized Fact Sheets for each monoclonal antibody therapy (see Section 12.4 for bebtelovimab) available under an EUA for details regarding specific variants and resistance.

Health care providers should also refer to the CDC website on Variant Proportions, and information from state and local health authorities regarding reports of viral variants of importance in their region to guide treatment decisions.

Q: What does direct SARS-CoV-2 viral testing mean?
A: Direct SARS-CoV-2 viral tests diagnose current COVID-19 infection. Direct SARS-CoV-2 viral tests include two types of diagnostic tests for COVID-19:

- Molecular tests, such as reverse transcription polymerase chain reaction (RT-PCR) tests, that detect the virus's genetic material.
- Antigen tests that detect specific proteins from the virus.

Antibody tests should not be used to diagnose COVID-19 and are not direct SARS-CoV-2 viral tests. Antibody tests look for antibodies that the immune system makes in response to the SARS-CoV-2 virus.

Q. How is high risk defined under the EUA?
A. Information for health care providers about medical conditions that place a patient with mild-to-moderate COVID-19 at increased risk for disease progression or death can be found at the CDC website Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals. Healthcare providers should consider the benefit-risk for an individual patient.

A general overview of medical conditions that make it more likely an individual will get very sick from COVID-19 and resources for the general public can be found on the CDC website People with Certain Medical Conditions.

Q. Can adults weighing less than 40 kg receive bebtelovimab?
A: Yes. Bebtelovimab is authorized for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Adults can be treated regardless of their weight; pediatric patients must be at least 12 years of age and weigh at least 40 kg.

Q. When should bebtelovimab be administered to a patient?
A. The EUA authorizes bebtelovimab to be administered by a qualified healthcare provider as a single intravenous infusion (IV) as soon as possible after positive viral test for COVID-19 and within seven (7) days of symptom onset. Bebtelovimab must be administered as a single IV infusion over at least 30 seconds. More information about administration is available in the Fact Sheet for Health Care Providers.

Q: Does "within seven (7) days of symptom onset" mean that a patient should have shown symptoms to receive bebtelovimab for its treatment use?
A. Yes. Symptom onset is the point at which a patient starts exhibiting symptoms. Patients should be treated as soon as possible after a positive viral test for SARS-CoV-2 **and** within seven (7) days of COVID-19 symptom onset. If a patient has a positive viral test for SARS-CoV-2 but does not show symptoms, they do not meet the definition of mild-to-moderate disease.

For more information on mild-to-moderate COVID-19, refer to the National Institutes of Health's website at: Clinical Spectrum | COVID-19 Treatment Guidelines (nih.gov).

Q. Does the EUA permit the use of bebtelovimab as authorized in patients hospitalized *for reasons other* than COVID-19?
A. If a patient is hospitalized *for reasons other* than COVID-19, such as for an elective orthopedic procedure, and the patient reports mild-to-moderate symptoms of COVID-19, confirmed with positive results of a direct SARS-CoV-2 viral test, then treatment with bebtelovimab is authorized, if the patient is also at high risk for progression to severe COVID-19, including hospitalization or death, and the terms and conditions of the authorization are met, as detailed in the Fact Sheet for Health Care Providers.

Bebtelovimab is not authorized for use in patients:

- who are hospitalized *due to* COVID-19, or
- who require oxygen therapy and/or respiratory support *due to* COVID-19, or
- who require an increase in baseline oxygen flow rate and/or respiratory support *due to* COVID-19 (in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity).

Q. Where are infusions of bebtelovimab available?
A. HHS maintains a COVID-19 Therapeutic Locator for product procured and distributed by the U.S. government. You may also wish to contact your health care provider for additional treatment locations in your area.

Bebtelovimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and have the ability to activate the emergency medical system, if necessary. Please speak with your doctor or contact your local or state public health department for more information.

Q. Is bebtelovimab approved by the FDA to treat COVID-19?
A. No. Bebtelovimab is an investigational drug. It is not currently FDA-approved to treat any diseases or conditions, including COVID-19.

Q. Is bebtelovimab a monoclonal antibody? What are monoclonal antibodies?
A. Yes, Bebtelovimab is a monoclonal antibody. Monoclonal antibodies are laboratory-produced molecules engineered to serve as substitute antibodies that can restore, enhance or mimic the immune system's attack on pathogens. Bebtelovimab is designed to block viral entry into human cells, thus neutralizing the virus.

Q. Are there data showing bebtelovimab might benefit patients with COVID-19?
A. Yes. These data and a detailed discussion of FDA's overall benefit risk assessment for bebtelovimab can be found in Section 14 of the authorized Fact Sheet for Health Care Providers.

To summarize, the clinical data are from a phase 2, randomized, single-dose clinical trial evaluating the efficacy of bebtelovimab alone and bebtelovimab combined with other monoclonal antibodies for treating mild-to-moderate COVID-19.

- The placebo-controlled portion of the trial enrolled 380 low-risk patients (i.e., patients without risk factors for progression to severe COVID-19). Patients in this part of the trial were randomized to receive a single infusion of bebtelovimab alone, bebtelovimab with other monoclonal antibodies, or a placebo. Treatment with bebtelovimab resulted in a reduction in time to sustained symptom resolution compared to placebo. Reduction in viral load relative to placebo was also seen on Day 5 after treatment.

- In another part of the trial involving mostly high-risk individuals (i.e., patients with risk factors for progression to severe COVID-19), 150 patients were randomized to receive a single infusion of bebtelovimab alone or a single infusion of bebtelovimab with other monoclonal antibodies. An additional 176 high-risk patients received bebtelovimab with other monoclonal antibodies in an open-label treatment arm (a type of clinical trial in which the specific treatment is disclosed to trial participants).

- The rates of COVID-19 related hospitalization and death through Day 29 seen in those who received bebtelovimab alone or with other monoclonal antibodies were generally lower than the placebo rate reported in prior trials of other monoclonal antibodies in high risk patients. Conclusions are limited as these data are from different trials that were conducted when different viral variants were circulating and baseline risk factors varied.

Q. Are there side effects (adverse events) of bebtelovimab?
A. Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of other SARS-CoV-2 monoclonal antibodies and could occur with administration of bebtelovimab. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related reactions, which may occur up to 24 hours after the injection, have been observed in clinical trials of bebtelovimab when administered with other monoclonal antibodies and may occur with use of bebtelovimab alone. These reactions may be severe or life threatening.

Signs and symptoms of infusion-related reactions may include:

fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vasovagal reactions (e.g., pre-syncope, syncope), dizziness and diaphoresis (excessive sweating). There have been reports of clinical worsening of COVID-19 after administration of COVID-19 monoclonal antibodies under EUA; signs or symptoms may include fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), fatigue, and

altered mental status. Some of these events required hospitalization. It is not known if these events were related to COVID-19 monoclonal antibody use or were due to progression of COVID-19.

The following adverse reactions (i.e., adverse events assessed as causally related) have been observed in those who have received bebtelovimab alone or when administered with other monoclonal antibodies at the authorized dose or higher:

- Infusion-related reactions (n=2, 0.3%)
- Itching (n=2, 0.3%)
- Rash (n=5, 0.8%)

The most common treatment-emergent adverse events observed in subjects treated with bebtelovimab, alone or in combination with bamlanivimab and etesevimab, at the authorized dose or higher included nausea (0.8%) and vomiting (0.7%).

These are not all the possible side effects of bebtelovimab. Serious and unexpected side effects may happen. It is possible that all of the risks are not known at this time.

Q. How can bebtelovimab be obtained for use under the EUA?
A. Starting August 15, 2022, bebtelovimab is available for states/territories and providers to purchase commercially through Lilly's authorized distributor. Additional information on bebtelovimab's transition from U.S. government distributed supply to commercially available supply can be found on HHS/ASPR's Bebtelovimab Therapeutics Update. For questions regarding access to bebtelovimab, please contact c19therapies@amerisourcebergen.com.

Q. Are there reporting requirements for healthcare facilities and providers as part of the EUA?
A. Yes. As part of the EUA, FDA requires health care providers who prescribe bebtelovimab to report all medication errors and serious adverse events considered to be potentially related to bebtelovimab through FDA's MedWatch Adverse Event Reporting program. Providers can complete and submit the report online; or download and complete the form, then submit it via fax at 1-800-FDA-0178. This requirement is outlined in the EUA's Fact Sheet for Health Care Providers. FDA MedWatch forms should also be provided to Lilly.

Q. Do patient outcomes need to be reported under the EUA?
A. No, reporting of patient outcomes is not required under the EUA. However, reporting of all medication errors and serious adverse events considered to be potentially related to bebtelovimab is required.

Q. Does the EUA authorize bebtelovimab to be used to prevent COVID-19?
A. No. Bebtelovimab is not authorized for the prevention of COVID-19.

Q. Can health care providers share the Fact Sheet for Patient, Parents, and Caregivers electronically?
A. The letter of authorization for bebtelovimab permits Lilly and its authorized distributors to make the Fact Sheets available to healthcare facilities and health care providers through electronic means.

Q. Can I be vaccinated for COVID-19 if I was treated with a monoclonal antibody for COVID-19?

A. Health care providers should refer to recommendations of the Advisory Committee on Immunization Practices regarding vaccination.

FDA U.S. FOOD & DRUG ADMINISTRATION

January 24, 2022

Regeneron Pharmaceuticals, Inc.
Attention: Yunji Kim, PharmD
Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591

RE: Emergency Use Authorization 091

Dear Dr. Kim:

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19).[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[2]

On November 21, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of REGEN-COV (casirivimab and imdevimab, administered together)[3] for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization. Casirivimab and imdevimab are recombinant human IgG1 monoclonal antibodies that target the receptor binding domain of the spike protein of SARS-CoV-2. They are investigational drugs and are not approved for any indication.

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[1] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3.* February 4, 2020.

[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).

[3] The November 21, 2020 EUA referred to the authorized product as "casirivimab and imdevimab, administered together". Regeneron subsequently requested, and FDA concurred, that the authorized labeling be revised to add references to authorized products' trade name, "REGEN-COV".

FDA reissued the Letter of Authorization on the following dates: February 3, 2021,[4] February 25, 2021,[5] June 3, 2021,[6] July 30, 2021,[7] September 9, 2021,[8] and November 17, 2021.[9]

On January 24, 2022, again having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the November 17, 2021 letter in its entirety, to further limit the use of REGEN-COV for treatment of COVID-19 or as post-exposure prophylaxis of COVID-19 to exclude geographic regions where, based on available information including variant susceptibility to this drug and regional variant frequency, infection or exposure is likely due to a variant that is non-susceptible to REGEN-COV. Corresponding revisions have also been made to the authorized Fact Sheets.

Based on the review of the analysis of phase 3 data from COV-2067[10] (NCT04425629), a phase 1/2/3 randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of a single intravenous infusion of 600 mg casirivimab and 600 mg imdevimab in outpatients (non-hospitalized) with SARS-CoV-2 infection, it is reasonable to believe that REGEN-COV may be effective for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral

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[4] In the February 3, 2021 revision, FDA revised the condition on requesting changes to this authorization, including changes to the authorized Fact Sheets. New conditions were also incorporated relating to the development of instructional or educational materials, as well as certain mandatory reporting requirements for healthcare facilities and providers. In addition to certain editorial and/or clarifying revisions, the Fact Sheet for Healthcare Providers was revised to include information on the new mandatory reporting requirements on therapeutics information and utilization data for healthcare facilities and providers. Updated safety information and details on possible side effects were also incorporated into the authorized Fact Sheets.

[5] In the February 25, 2021 revision, FDA revised the condition on instructional and educational materials. New conditions were also incorporated on the establishment of a process for monitoring genomic databases for the emergence of global viral variants of SARS-CoV-2 and the assessment, if requested by FDA, of the activity of the authorized REGEN-COV against any global SARS-CoV-2 variant(s) of interest.

[6] In the June 3, 2021 revision, FDA revised the authorized use statement for REGEN-COV. Additionally, FDA authorized a change in dosing of REGEN-COV from 2400 mg (1200 mg casirivimab and 1200 mg imdevimab) to 1200 mg (600 mg casirivimab and 600 mg imdevimab), and the addition of a new presentation consisting of a single vial containing casirivimab and imdevimab co-formulated in a 1:1 ratio for either intravenous infusion or subcutaneous injection. New conditions were incorporated on the provision of samples of the authorized REGEN-COV to the U.S. Department of Health and Human Services, upon request, and the submission of certain genomic sequencing and virology information to the FDA by a specified date. Revisions to existing conditions on advertising and promotion and manufacturing practices and other editorial changes were also incorporated.

[7] In the July 30, 2021 revision, FDA authorized REGEN-COV for emergency use as post-exposure prophylaxis for COVID-19 in certain adults and pediatric individuals. Clarifying revisions to the conditions on good manufacturing practices as well as advertising and promotion were also incorporated.

[8] In the September 9, 2021 revision, FDA authorized a co-packaged presentation of REGEN-COV which consists of individual vials of both casirivimab and imdevimab inside a single carton. FDA also authorized a document entitled *Casirivimab and Imdevimab Co-Packaged Product Quick Reference Guide* that must accompany in hardcopy format the authorized co-packaged formulation of REGEN-COV that is labeled "For pandemic use". Revisions to the Fact Sheet for Healthcare Providers associated with the co-packaged presentation of REGEN-COV and clarifying revisions on the preparation of more than one dose from a single-dose vial were also incorporated.

[9] In the November 17, 2021 revision, FDA revised the product description in this Letter of Authorization with updated storage and handling information for the authorized dose pack bags of REGEN-COV, co-packaged REGEN-COV, and subcutaneous injection presentation of REGEN-COV. Corresponding revisions on storage and handling of the subcutaneous injection presentation of REGEN-COV and minor revisions to section 15 ("Virology") were also incorporated in the Fact Sheet for Healthcare Providers.

[10] Referred to as trial R10933-10987-COV-2067 in previous iterations of this Letter of Authorization.

testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and that, when used under the conditions described in this authorization, the known and potential benefits of REGEN-COV outweigh the known and potential risks of such product.

Additionally, based on the review of the topline analysis of phase 3 data from COV-2069 (NCT04452318), a phase 3 randomized, double-blind, placebo-controlled trial in household contacts with close exposure to a household member known to be infected with SARS-CoV-2 (index case), but who were themselves asymptomatic; and the analysis of phase 1 data from COV-2093 (NCT 04519437), an ongoing, phase 1, randomized, double-blind, placebo-controlled clinical trial assessing the safety and pharmacokinetics of repeat subcutaneous doses of REGEN-COV in subjects who are SARS-CoV-2 negative at baseline, it is reasonable to believe that REGEN-COV may be effective for use as post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (Section II), and that, when used under such conditions, the known and potential benefits of REGEN-COV outweigh the known and potential risks of such product.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of REGEN-COV for treatment and as post-exposure prophylaxis of COVID-19, as described in the Scope of Authorization (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of REGEN-COV for treatment and as post-exposure prophylaxis of COVID-19, when administered as described in the Scope of Authorization (Section II), meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

1. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe the following:

    - REGEN-COV may be effective for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, as further described in the Scope of Authorization (Section II)

    - REGEN-COV may be effective for use as post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, as further described in the Scope of Authorization (Section II)

And that, when used under the conditions described in the Scope of Authorization (Section II), the known and potential benefits of REGEN-COV outweigh the known and potential risks of such products; and

3. There is no adequate, approved, and available alternative to the emergency use of REGEN-COV for treatment and as post-exposure prophylaxis of COVID-19, as described in the Scope of Authorization (Section II).[11]

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Distribution of the authorized REGEN-COV will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Regeneron will supply REGEN-COV to authorized distributor(s)[12], who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed;

Treatment of COVID-19

- REGEN-COV will be used only by healthcare providers to treat mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19, including hospitalization or death;

  The monoclonal antibodies that comprise REGEN-COV, casirivimab and imdevimab, may only be administered together;

- REGEN-COV is **not** authorized for use in the following patient populations[13]:
  - Adults or pediatric patients who are hospitalized due to COVID-19, or
  - Adults or pediatric patients who require oxygen therapy due to COVID-19, or
  - Adults or pediatric patients who require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity.

- REGEN-COV is **not** authorized for treatment of mild to moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible

[11] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.
[12] "Authorized Distributor(s)" are identified by Regeneron as an entity or entities allowed to distribute authorized REGEN-COV.
[13] Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

SARS-CoV-2 variant, based on available information including variant susceptibility to this drug and regional variant frequency.[14]

- REGEN-COV may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

- REGEN-COV is authorized for intravenous infusion. Subcutaneous injection is authorized as an alternative route of administration when intravenous infusion is not feasible and would lead to delay in treatment.

- The use of REGEN-COV covered by this authorization must be in accordance with the authorized Fact Sheets.

Post-Exposure Prophylaxis

- REGEN-COV may only be used in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

    - not fully vaccinated[15] **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications[16]) **and**
        - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[17] **or**
        - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other

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[14] FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility (see, e.g., section 15 of authorized Fact Sheet for Healthcare Providers), and the CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions. FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.

[15] Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as the Johnson & Johnson/ Janssen vaccine). See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated.

[16] See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html

[17] Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example). See this website for additional details: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html

individuals in the same institutional setting (for example, nursing homes, prisons).

- The monoclonal antibodies that comprise REGEN-COV, casirivimab and imdevimab, may only be administered together;

- REGEN-COV is **not** authorized for post-exposure prophylaxis of COVID-19 in geographic regions where exposure is likely to have been to a non-susceptible SARS-CoV-2 variant, based on available information including variant susceptibility to these drugs and regional variant frequency.[18]

- REGEN-COV may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

- REGEN-COV is authorized for either intravenous infusion or subcutaneous injection when administered for post-exposure prophylaxis under this authorization.

- The use of REGEN-COV covered by this authorization must be in accordance with the authorized Fact Sheets.

- Post-exposure prophylaxis with REGEN-COV (casirivimab with imdevimab) is **not** intended to be a substitute for vaccination against COVID-19.

- REGEN-COV is **not** authorized for pre-exposure prophylaxis for prevention of COVID-19.

Product Description

Casirivimab and imdevimab are recombinant neutralizing human IgG1 monoclonal antibodies that target the receptor binding domain of the spike protein of SARS-CoV-2. REGEN-COV is available in three distinct presentations: (1) REGEN-COV co-packaged in an individual carton, (2) REGEN-COV in dose pack bags, and (3) co-formulated solution of REGEN-COV.[19]

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[18] Supra at Note 14.

[19] Individual vials of casirivimab and imdevimab distributed in interstate commerce prior to the reissuance of this letter on February 3, 2021 remain authorized for emergency use. FDA is not requiring that such product be repackaged given the public health need for the product. The use of the individual vials of casirivimab and imdevimab must be consistent with the terms and conditions of this authorization. Individual vial labels for casirivimab and imdevimab and carton labeling may be clearly marked with either "Caution: New Drug - Limited by Federal (or United States) law to investigational use" or with "For use under Emergency Use Authorization (EUA)". Some vial labels and carton labeling of casirivimab and imdevimab may be instead labeled with the Investigational New Drug (IND) clinical trial code name as "REGN10933" and "REGN10987", respectively.

(1) *Co-packaged REGEN-COV:* Co-packaged REGEN-COV is comprised of one vial each of both casirivimab and imdevimab inside a single carton. Individual vial and carton container labeling for casirivimab and imdevimab covered in the authorized co-packaged presentation will be clearly marked with either "For pandemic use" or "For Use under Emergency Use Authorization."

Casirivimab is available as 300 mg/2.5 mL (120 mg/mL) or 1332 mg/11.1 mL (120 mg/mL) sterile, preservative-free aqueous solution to be diluted prior to infusion. Imdevimab is available as 300 mg/2.5 mL (120 mg/mL) or 1332 mg/11.1 mL (120 mg/mL) sterile, preservative-free aqueous solution to be diluted prior to infusion. Co-packaged REGEN-COV supplied in the 1332 mg/11.1 mL strength presentation will include a sufficient number of vials of casirivimab and imdevimab to prepare more than one dose.

The authorized storage and handling information for the co-packaged REGEN-COV is included in the authorized Fact Sheet for Healthcare Providers.

(2) *Dose pack bags:* Dose pack bags of REGEN-COV will include a sufficient number of vials of casirivimab and imdevimab to prepare more than one dose. Individual vials and carton container labeling for casirivimab and imdevimab included in dose pack bags are clearly marked "For Use under Emergency Use Authorization." Casirivimab and imdevimab are recombinant neutralizing human IgG1 monoclonal antibodies that target the receptor binding domain of the spike protein of SARS-CoV-2.

Casirivimab is available as 300 mg/2.5 mL (120 mg/mL) or 1332 mg/11.1 mL (120 mg/mL) sterile, preservative-free aqueous solution to be diluted prior to infusion. Imdevimab is available as 300 mg/2.5 mL (120 mg/mL) or 1332 mg/11.1 mL (120 mg/mL) sterile, preservative-free aqueous solution to be diluted prior to infusion.

The authorized storage and handling information for the dose pack bags of REGEN-COV is included in the authorized Fact Sheet for Healthcare Providers.

(3) *Co-formulated solution of REGEN-COV*: The co-formulated solution of REGEN-COV contains two antibodies in a 1:1 ratio in a single dose vial consisting of 600 mg casirivimab and 600 mg of imdevimab per 10 mL (60 mg/60 mg per mL). Individual vials of co-formulated REGEN-COV are clearly marked "For Use under Emergency Use Authorization."

Co-formulated casirivimab and imdevimab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution. Co-formulated REGEN-COV may be administered via intravenous infusion or subcutaneous injection.

The authorized storage and handling information for the co-formulated solution of REGEN-COV is included in the authorized Fact Sheet for Healthcare Providers.

Any presentation of REGEN-COV described above may be prepared for intravenous infusion or subcutaneous injection.[20]

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[20] Certain carton labeling for the co-packaged presentation of REGEN-COV is labeled as "casirivimab and

REGEN-COV is authorized for emergency use with the following product-specific information required to be made available to healthcare providers and patients/caregivers, respectively, through Regeneron's website at www.REGENCOV.com:

- Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of REGEN-COV (casirivimab and imdevimab)

- Fact Sheet for Patients, Parents and Caregivers: Emergency Use Authorization (EUA) of REGEN-COV (casirivimab and imdevimab) for Coronavirus Disease 2019 (COVID-19)

The co-packaged presentation of REGEN-COV that is labeled "For pandemic use" is also authorized for emergency use with the document entitled *Casirivimab and Imdevimab Co-Packaged Product Quick Reference Guide*, which must accompany this authorized co-packaged presentation of REGEN-COV in hardcopy format.

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of REGEN-COV, when used for treatment and as post-exposure prophylaxis of COVID-19 as described in this Scope of Authorization (Section II), outweigh the known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that REGEN-COV may be effective for treatment and as post-exposure prophylaxis of COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that REGEN-COV (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of your product under an EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), REGEN-COV is authorized for treatment and as post-exposure prophylaxis of COVID-19 as described in this Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

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imdevimab 120 mg/mL concentrate for solution for infusion. The vials in the carton for the co-packaged presentation of REGEN-COV may be used to prepare and administer REGEN-COV for either intravenous infusion or subcutaneous injection despite this labeling.

Regeneron and Authorized Distributors

A. Regeneron and authorized distributor(s) will ensure that the authorized REGEN-COV is distributed as directed by the U.S. government, and the authorized labeling (i.e., Fact Sheets) will be made available to healthcare facilities and/or healthcare providers consistent with the terms of this letter.

B. Regeneron and authorized distributor(s) will ensure that appropriate storage and cold chain is maintained until the product is delivered to healthcare facilities and/or healthcare providers.

C. Regeneron and authorized distributor(s) will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., U.S. government agencies, state and local government authorities, authorized distributors, healthcare facilities, healthcare providers) involved in distributing or receiving authorized REGEN-COV. Regeneron will provide to all relevant stakeholders a copy of this letter of authorization and communicate any subsequent amendments that might be made to this letter of authorization and its authorized accompanying materials (i.e., Fact Sheets).

D. Regeneron may request changes to this authorization, including to the authorized Fact Sheets for REGEN-COV. Any request for changes to this EUA must be submitted to the Office of Infectious Diseases/Office of New Drugs/Center for Drug Evaluation and Research. Such changes require appropriate authorization prior to implementation.[21]

E. Regeneron may develop and disseminate instructional and educational materials (e.g., materials providing information on product administration and/or patient monitoring) that are consistent with the authorized emergency use of REGEN-COV as described in this letter of authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs. Any instructional and educational materials that are inconsistent with the authorized labeling for REGEN-COV are prohibited. Should the Agency become aware of any instructional or educational materials that are inconsistent with the authorized labeling for REGEN-COV, the Agency will require Regeneron to cease distribution of such instructional and educational materials.

[21] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study; (8) new strengths of the authorized product, new product sources (e.g., of active pharmaceutical ingredient) or of product components. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), (7), or (8), review and concurrence is required from the Counter-Terrorism and Emergency Coordination Staff/Office of the Center Director/CDER and the Office of Counterterrorism and Emerging Threats/Office of the Chief Scientist.

F. Regeneron will report to FDA serious adverse events and all medication errors associated with the use of the authorized REGEN-COV that are reported to Regeneron using either of the following options.

Option 1: Submit reports through the Safety Reporting Portal (SRP) as described on the FDA SRP web page.

Option 2: Submit reports directly through the Electronic Submissions Gateway (ESG) as described on the FAERS electronic submissions web page.

Submitted reports under both options must state: "REGEN-COV use for COVID-19 under Emergency Use Authorization (EUA)." For reports submitted under Option 1, include this language at the beginning of the question "Describe Event" for further analysis. For reports submitted under Option 2, include this language at the beginning of the "Case Narrative" field.

G. All manufacturing, packaging, and testing sites for both drug substance and drug product will comply with current good manufacturing practice requirements of Section 501(a)(2)(B) of the Act.

H. Regeneron will submit information to the Agency within three working days of receipt of any information concerning significant quality problems with distributed drug product of REGEN-COV that includes the following:

- Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or
- Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the product to meet the established specifications.

If a significant quality problem affects unreleased product and may also impact product(s) previously released and distributed, then information must be submitted for all potentially impacted lots.

Regeneron will include in its notification to the Agency whether the batch, or batches, in question will be recalled. If FDA requests that these, or any other batches, at any time, be recalled, Regeneron must recall them.

If not included in its initial notification, Regeneron must submit information confirming that Regeneron has identified the root cause of the significant quality problems and taken corrective action, and provide a justification confirming that the corrective action is appropriate. Regeneron must submit this information as soon as possible but no later than 45 calendar days from the initial notification.

I. Regeneron will manufacture REGEN-COV to meet all quality standards and per the manufacturing process and control strategy as detailed in Regeneron's EUA request.

Regeneron will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product, without notification to and concurrence by the Agency as described under condition D.

J. Regeneron will list the single dose pack bag, the co-packaged product, and the co-formulated product containing casirivimab and imdevimab with unique NDC product codes from each other and the NDC product codes of the single ingredient listings under the marketing category of Unapproved Drug-Other. As applicable, different vial sizes should be identified by a different package NDC within the product NDC. Further, the listing will include each establishment where manufacturing is performed for the drug and the type of operation performed at such establishment.

K. Through a process of inventory control, Regeneron and authorized distributor(s) will maintain records regarding distribution of the authorized casirivimab and imdevimab (i.e., lot numbers, quantity, receiving site, receipt date).

L. Regeneron and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

M. Regeneron will establish a process for monitoring genomic database(s) for the emergence of global viral variants of SARS-CoV-2. A summary of Regeneron's process should be submitted to the Agency as soon as practicable, but no later than 30 calendar days of the issuance of this letter, and within 30 calendar days of any material changes to such process. Regeneron will provide reports to the Agency on a monthly basis summarizing any findings as a result of its monitoring activities and, as needed, any follow-up assessments planned or conducted.

N. FDA may require Regeneron to assess the activity of the authorized REGEN-COV against any global SARS-CoV-2 variant(s) of interest (e.g., variants that are prevalent or becoming prevalent that harbor substitutions in the target protein or in protein(s) that interact with the target protein). Regeneron will perform the required assessment in a manner and timeframe agreed upon by Regeneron and the Agency. Regeneron will submit to FDA a preliminary summary report immediately upon completion of its assessment followed by a detailed study report within 30 calendar days of study completion. Regeneron will submit any relevant proposal(s) to revise the authorized labeling based on the results of its assessment, as may be necessary or appropriate based on the foregoing assessment.

O. Regeneron shall provide samples as requested of the authorized REGEN-COV to the U.S. Department of Health and Human Services (HHS) for evaluation of activity against emerging global viral variants of SARS-CoV-2, including specific amino acid substitution(s) of interest (e.g., variants that are highly prevalent or that harbor substitutions in the target protein) within 5 business days of any request made by HHS. Analyses performed with the supplied quantity of authorized REGEN-COV may include, but are not limited to, cell culture potency assays, protein binding assays, cell culture variant assays (pseudotyped virus-like particles and/or authentic virus), and *in vivo* efficacy assays.

P. Regeneron will submit to FDA all sequencing data assessing REGEN-COV, including sequencing of any participant samples from the full analysis population from COV-2067 that have not yet been completed no later than July 30, 2021. Regeneron will provide the Agency with a frequency table reporting all substitutions detected for all participants at all available time points at a frequency ≥5%.

Q. Regeneron will submit to FDA all SARS-CoV-2 nasopharyngeal viral shedding and blood viral load data, including quantitation of viral load for any participant samples from the full analysis population for which REGEN-COV is currently authorized from COV-2067 that have not yet been completed, no later than July 30, 2021.

Healthcare Facilities to Whom the Authorized REGEN-COV Is Distributed and Healthcare Providers Administering the Authorized Casirivimab and Imdevimab

R. Healthcare facilities and healthcare providers will ensure that they are aware of the letter of authorization, and the terms herein, and that the authorized Fact Sheets are made available to healthcare providers and to patients and caregivers, respectively, through appropriate means, prior to administration of REGEN-COV.

S. Healthcare facilities and healthcare providers receiving REGEN-COV will track serious adverse events and medication errors that are considered to be potentially attributable to REGEN-COV use and must report these to FDA in accordance with the Fact Sheet for Healthcare Providers. Complete and submit a MedWatch form (www.fda.gov/medwatch/report.htm), or Complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178) (these forms can be found via link above). Call 1-800-FDA-1088 for questions. Submitted reports must state, "REGEN-COV use for COVID-19 under Emergency Use Authorization" at the beginning of the question "Describe Event" for further analysis.

T. Healthcare facilities and healthcare providers will ensure that appropriate storage and cold chain is maintained until the product is administered consistent with the terms of this letter.

U. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensed authorized REGEN-COV (i.e., lot numbers, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered).

V. Healthcare facilities will ensure that any records associated with this EUA are maintained until notified by Regeneron and/or FDA. Such records will be made available to Regeneron, HHS, and FDA for inspection upon request.

W. Healthcare facilities and providers will report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

Conditions Related to Printed Matter, Advertising and Promotion

X. All descriptive printed matter, advertising, and promotional materials relating to the use of the REGEN-COV under this authorization shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in section 502(a) and (n) of the Act and FDA implementing regulations, as applicable. References to "approved labeling", "permitted labeling" or similar terms in these requirements shall be understood to refer to the authorized labeling for the use of REGEN-COV under this authorization. In addition, such materials shall:

- Be tailored to the intended audience.
- Not take the form of reminder advertisements, as that term is described in 21 CFR 202.1(e)(2)(i), 21 CFR 200.200 and 21 CFR 201.100(f).
- Present the same risk information relating to the major side effects and contraindications concurrently in the audio and visual parts of the presentation for advertising and promotional materials in audio-visual format.
- Be accompanied by the authorized labeling, if the promotional materials are not subject to Section 502(n) of the Act.
- Be submitted to FDA accompanied by Form FDA-2253 at the time of initial dissemination or first use.

If the Agency notifies Regeneron that any descriptive printed matter, advertising or promotional materials do not meet the terms set forth in conditions X-Z of this EUA, Regeneron must cease distribution of such descriptive printed matter, advertising, or promotional materials in accordance with the Agency's notification. Furthermore, as part of its notification, the Agency may also require Regeneron to issue corrective communication(s).

Y. No descriptive printed matter, advertising, or promotional materials relating to the use of REGEN-COV under this authorization may represent or suggest that REGEN-COV is safe or effective when used for the treatment of COVID-19 or when used as post-exposure prophylaxis as described in the Scope of Authorization (Section II).

Z. All descriptive printed matter, advertising, and promotional material, relating to the use of the REGEN-COV under this authorization shall clearly and conspicuously state that:

- REGEN-COV has not been approved, but has been authorized for emergency use by FDA under an EUA, for treatment and as post-exposure prophylaxis of COVID-19 in certain adults and pediatric individuals (12 years of age and older weighing at least 40 kg) with high risk for progression to severe COVID-19, including hospitalization or death, and

- The emergency use of REGEN-COV is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19

pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

--/S/--

Jacqueline A. O'Shaughnessy, Ph.D.
Acting Chief Scientist
Food and Drug Administration

FACT SHEET FOR HEALTH CARE PROVIDERS
EMERGENCY USE AUTHORIZATION (EUA) OF REGEN-COV®
(casirivimab and imdevimab)

AUTHORIZED USE

TREATMENT

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adult and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Limitations of Authorized Use

- REGEN-COV is not authorized for treatment of mild to moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information such as variant susceptibility to this drug and regional variant frequency.
    - FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.[1]
- REGEN-COV (casirivimab and imdevimab) is not authorized for use in patients:
    - who are hospitalized due to COVID-19, OR
    - who require oxygen therapy due to COVID-19, OR
    - who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.
- Monoclonal antibodies, such as REGEN-COV, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

POST-EXPOSURE PROPHYLAXIS

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated[2] **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with

[1] FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility *[see Microbiology/Resistance Information (15)]*, and CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions.

[2] Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as Johnson & Johnson's Janssen vaccine). See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated

immunocompromising conditions including those taking immunosuppressive medications[3]) **and**

- have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[4] **or**
- who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

Limitations of Authorized Use

- REGEN-COV is not authorized for post-exposure prophylaxis of COVID-19 in geographic regions where exposure is likely to have been to a non-susceptible SARS-CoV-2 variant, based on available information including variant susceptibility to this drug and regional variant frequency.
  - FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.[5]
- Post-exposure prophylaxis with REGEN-COV (casirivimab and imdevimab) is not a substitute for vaccination against COVID-19.
- REGEN-COV (casirivimab and imdevimab) is not authorized for pre-exposure prophylaxis for prevention of COVID-19.

RECENT MAJOR CHANGES

- Limitations of Authorized Use: updated Limitations of Authorized Use for treatment and post-exposure prophylaxis — Revised 1/2022
- Box-Removed SARS-CoV-2 viral variant section — Revised 1/2022
- Antiviral Resistance (Section 15): addition of information on susceptibility of SARS-CoV-2 variants to REGEN-COV (Tables 9 and 10) and updates based on latest viral surveillance report — Revised 12/2021, 8/2021
- Dosage and Administration (Section 2.4) and How Supplied/ Storage and Handling (Section 19): updated storage temperature range and duration — Revised 11/2021
- Dosage and Administration (Box, Section 2.4, Section 3, Section 19): addition of co-packaged carton — Revised 09/2021
- Dosage and Administration (Section 2.4): addition of 5% Dextrose as diluent — Revised 09/2021
- Authorized Use: addition of new indication for post-exposure

[3] See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html

[4] Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example). See this website for additional details: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html

[5] FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility *[see Microbiology/Resistance Information (15)]*, and CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions.

prophylaxis of COVID-19 — Revised 07/2021

- Dosage and Administration (Box, and Section 2.2): updated authorized dosage for post-exposure prophylaxis of COVID-19 — Revised 07/2021
- Authorized Use: expanded the definition of progression of severe COVID-19 to include death — Revised 06/2021
- Dosage and Administration (Box, and Section 2.2): updated authorized dosage — Revised 06/2021
- Dosage and Administration (Box, Section 2.2 and 2.4): updated with subcutaneous route of administration as an alternative for those who cannot receive intravenous infusion — Revised 06/2021
- Dosage and Administration (Box, Section 2.2 and 2.4): updated with co-formulation — Revised 06/2021
- Warnings: Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions (Section 5.1): addition of vasovagal reactions — Revised 06/2021
- Overall Safety Summary, Clinical Trials Experience (Section 6.1): addition of Phase 3 results and safety with subcutaneous dosing — Revised 06/2021
- Clinical Trial Results and Supporting Data for EUA, Mild to Moderate COVID-19 (Section 18.1): addition of Phase 3 data for the authorized dose — Revised 06/2021
- Dosage and Administration (Box and Section 2.1): updated high risk criteria for patient selection — Revised 05/2021
- Dose Preparation and Administration Instructions (Section 2.4): provides updated minimum infusion times based on size of infusion bag used — Revised 03/2021
- New proprietary name: REGEN-COV — Revised 02/2021
- Warnings: Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions (Section 5.1) – addition of new symptoms — Revised 02/2021
- Warnings: Clinical Worsening After REGEN-COV Administration (Section 5.2) – new warning added — Revised 02/2021

REGEN-COV has been authorized by FDA for the emergency uses described above.

REGEN-COV is not FDA-approved for these uses.

REGEN-COV is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of REGEN-COV under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Treatment

This EUA is for the use of the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, for the treatment of mild to moderate COVID-19 in adult and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death *[see Limitations of Authorized Use (1.1)]*.

Post-Exposure Prophylaxis

This EUA is for the use of the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- **not fully vaccinated[2] or who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications[3]) and**
  - **have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Center for Disease Control and Prevention (CDC)[4] or who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons)** ***[see Limitations of Authorized Use (1.2)].***

Criteria for Identifying High Risk Individuals

The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example, age ≥65 years of age)
- Obesity or being overweight (for example, BMI >25 kg/m^2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19))

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of REGEN-COV under the EUA is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID, see the CDC website:

https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

Available Dosage Forms of REGEN-COV:

REGEN-COV (casirivimab and imdevimab) is available as:

1. A single vial which contains two antibodies co-formulated in a 1:1 ratio of casirivimab and imdevimab or
2. Individual antibody solutions in separate vials, which may be supplied in separate cartons or together in a single carton (also referred to as a co-packaged carton), or in a dose pack.

Routes of Administration for REGEN-COV:

REGEN-COV may be administered by intravenous infusion or subcutaneous injection.

FOR TREATMENT, INTRAVENOUS INFUSION IS STRONGLY RECOMMENDED. SUBCUTANEOUS INJECTION IS AN ALTERNATIVE ROUTE OF ADMINISTRATION WHEN INTRAVENOUS INFUSION IS NOT FEASIBLE AND WOULD LEAD TO DELAY IN TREATMENT.

FOR POST-EXPOSURE PROPHYLAXIS, EITHER SUBCUTANEOUS INJECTION OR INTRAVENOUS INFUSION CAN BE USED.

Treatment Dosage

- The authorized dosage is 600 mg of casirivimab and 600 mg of imdevimab administered together as a single intravenous infusion or by subcutaneous injection as soon as possible after positive SARS-CoV-2 viral testing and within 10 days of symptom onset *[see Dosage and Administration (2.2) and Clinical Trial Results and Supporting Data for EUA (18.1)]*.
- The authorized dosage of 600 mg of casirivimab and 600 mg of imdevimab for subcutaneous administration for treatment is selected based on the totality of the scientific evidence, incorporating clinical data, viral load reduction data (pharmacodynamics) and pharmacokinetic data *[see Clinical Pharmacology (14.2) and (14.3)]*.

Post-exposure Prophylaxis Dosage

- The authorized dosage is 600 mg of casirivimab and 600 mg of imdevimab administered by subcutaneous injection or together as a single intravenous infusion as soon as possible following exposure to SARS-CoV-2.
- For individuals in whom repeat dosing is determined to be appropriate for ongoing exposure to SARS-CoV-2 for longer than 4 weeks and who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination, the initial dose is 600 mg of casirivimab and 600 mg of imdevimab by subcutaneous injection or intravenous infusion followed by subsequent repeat dosing of 300 mg of casirivimab and 300 mg of imdevimab by subcutaneous injection or intravenous infusion once every 4 weeks for the duration of ongoing exposure.

- The authorized dosage including dosage for repeat dosing is based on the totality of the scientific evidence including clinical pharmacology data and clinical trial data *[see Clinical Trial Results and Supporting Data for EUA (18.2) and Clinical Pharmacology (14.3)].*

For Intravenous Infusion:

- Co-formulated casirivimab and imdevimab solution in a vial and casirivimab and imdevimab solutions in individual vials must be diluted prior to intravenous administration.
- Administer casirivimab and imdevimab together as a single intravenous infusion via pump or gravity (see Table 1, Table 2, Table 3 and Table 4).
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

For Subcutaneous Injection:

- Administer casirivimab and imdevimab using the co-formulated solution in a vial or using the individual vials (see Table 5 and Table 6).
- Clinically monitor patients after injections and observe patients for at least 1 hour after injections.
- For treatment, subcutaneous injection is an alternative route of administration when intravenous administration is not feasible and would lead to delay in treatment. For post-exposure prophylaxis, either subcutaneous injection or intravenous infusion can be administered.

REGEN-COV may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion or hypersensitivity reactions, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

Health care providers must submit a report on **ALL MEDICATION ERRORS and ALL SERIOUS ADVERSE EVENTS** potentially related to REGEN-COV. See Sections 8 and 9 of the Full EUA Prescribing Information for reporting instructions below.

- Patients treated with REGEN-COV should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect "high touch" surfaces, and frequent handwashing) according to CDC guidelines.

The authorized dosage may be updated as additional data from clinical trials becomes available.

For information on clinical trials that are testing the use of REGEN-COV in COVID-19, please see www.clinicaltrials.gov.

Contraindications

REGEN-COV is contraindicated in individuals with previous severe hypersensitivity reactions, including anaphylaxis, to REGEN-COV *[see Warnings and Precautions (5.1)]*.

Dosing

Patient Selection for Treatment and Post-Exposure Prophylaxis

This section provides essential information on the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied in individual vials to be administered together in adult and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death for:

- Treatment of mild to moderate COVID-19 in adult and pediatric patients with positive results of direct SARS-CoV-2 viral testing *[see Limitations of Authorized Use (1.1)]*.
- Post-exposure prophylaxis of COVID-19 in high risk individuals who are:
    - not fully vaccinated[2] **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications[3]) **and**
        - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[4] **or**
        - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

Criteria for Identifying High Risk Individuals

The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example, age ≥65 years of age)
- Obesity or being overweight (for example, BMI >25 kg/m^2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19))

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of REGEN-COV under the EUA is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

Dosage

Treatment:
The dosage in adult and pediatric patients (12 years of age and older weighing at least 40 kg) is 600 mg of casirivimab and 600 mg of imdevimab administered together as a single intravenous infusion or by subcutaneous injection. Casirivimab and imdevimab should be given together as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset.

Post-Exposure Prophylaxis:
The dosage in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) is 600 mg of casirivimab and 600 mg of imdevimab administered by subcutaneous injection or together as a single intravenous infusion. Casirivimab and imdevimab should be given together as soon as possible following exposure to SARS-CoV-2.

For individuals in whom repeat dosing is determined to be appropriate for ongoing exposure to SARS-CoV-2 for longer than 4 weeks and who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination, the initial dose is 600 mg of casirivimab and 600 mg of imdevimab by subcutaneous injection or intravenous infusion followed by subsequent repeat dosing of 300 mg of casirivimab and 300 mg of imdevimab by subcutaneous injection or intravenous infusion once every 4 weeks for the duration of ongoing exposure.

For Intravenous Infusion:
- Casirivimab and imdevimab solution co-formulated in a vial and in individual vials, including co-packaged carton and dose pack, must be diluted prior to intravenous administration.
- Administer casirivimab and imdevimab together as a single intravenous infusion via pump or gravity (see Table 1, Table 2, Table 3 and Table 4).
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

For Subcutaneous Injection:
- Administer casirivimab and imdevimab using the co-formulated vial or using the individual vials by subcutaneous injection (see Table 5 and Table 6).
- Clinically monitor patients after injections and observe patients for at least 1 hour.

Dosage Adjustment in Specific Populations

No dosage adjustment is recommended in pregnant or lactating women and in patients with renal impairment *[see Full EUA Prescribing Information, Use in Specific Populations (11)]*.

Preparation and Administration

There are TWO different formulations of REGEN-COV:

- Casirivimab and imdevimab co-formulated solution containing two antibodies in a 1:1 ratio in a vial.
- Casirivimab and imdevimab available as individual antibody solutions in separate vials supplied as follows:
  - Individual vials in individual cartons, or
  - together in a single carton (as referred to as a co-packaged carton), or
  - in a dose pack. The dose pack contains individual vials of casirivimab and imdevimab, configurations that may vary in vial size, strength and appearance and are available in dose pack configurations that include 2, 5, and 8 cartons *[see Full EUA Prescribing Information, How Supplied/Storage and Handling (19)]*.

For treatment, intravenous infusion is strongly recommended. Subcutaneous injection is an alternative route of administration when intravenous infusion is not feasible and would lead to delay in treatment.

For post-exposure prophylaxis, either subcutaneous injection or intravenous infusion can be used.

There are differences in the way the two formulations are prepared. Carefully follow the preparation procedures below.

- Casirivimab and imdevimab co-formulated solution in a vial and casirivimab or imdevimab as individual antibody solutions in separate 11.1 mL vials may be used to prepare more than one dose simultaneously as appropriate, either in intravenous bags or in syringes for subcutaneous injection. Discard any product remaining in the vial.
- Store unopened casirivimab and imdevimab vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Unopened vials may be stored in the original carton at room temperature [up to 25°C (77°F)] and must be used within 30 days. If not used in the 30 days, discard vials.

Under the EUA, a single-dose vial may be used to prepare more than one dose.

Preparation for Intravenous Infusion

For treatment, the preferred route of administration for casirivimab and imdevimab is by intravenous infusion after dilution.

Casirivimab and imdevimab solution for intravenous infusion should be prepared by a qualified healthcare professional using aseptic technique:

1. Remove the casirivimab and imdevimab vials from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake the vials.**
2. Inspect casirivimab and imdevimab vials visually for particulate matter and discoloration prior to administration. Should either be observed, the vial must be discarded and replaced with a new vial.
   - The solution for each vial should be clear to slightly opalescent, colorless to pale yellow.

3. Obtain a prefilled intravenous infusion bag containing either 50 mL, 100 mL, 150 mL, or 250 mL of either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.
4. Withdraw the appropriate amount of casirivimab and imdevimab from each respective vial(s) and inject into a prefilled infusion bag containing either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP (see Table 1 and Table 2). If using one vial to prepare more than one infusion bag, then prepare all infusion bags at the same time. The product is preservative-free, therefore do not store unused solution in vial(s).
5. Gently invert infusion bag by hand approximately 10 times to mix. **Do not shake**.
6. This product is preservative-free and therefore, the diluted infusion solution should be administered immediately (see Table 3 and Table 4).
    - If immediate administration is not possible, store the diluted casirivimab and imdevimab infusion solution in the refrigerator between 2°C to 8°C (36°F to 46°F) for no more than 36 hours or at room temperature up to 25°C (77°F) for no more than 4 hours. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.

Table 1: Recommended Dilution Instructions for 600 mg of Casirivimab and 600 mg of Imdevimab for Intravenous Infusion

<table>
<tr><th>Size of Prefilled 0.9% Sodium Chloride or 5% Dextrose Infusion Bag</th><th>Preparing Using Co-Formulated Casirivimab and Imdevimab Vial</th><th>Preparing Casirivimab and Imdevimab Using Individual Vials[a]</th></tr>
<tr><td>50 mL</td><td rowspan="4">Add 10 mL of co-formulated casirivimab and imdevimab (1 vial) into a prefilled 0.9% Sodium Chloride or 5% Dextrose infusion bag and administer as instructed below</td><td rowspan="4">Add:
• 5 mL of casirivimab (may use 2 vials of 2.5 mL OR 1 vial of 11.1 mL) and
• 5 mL of imdevimab (may use 2 vials of 2.5 mL OR 1 vial of 11.1 mL)
and inject into a prefilled 0.9% Sodium Chloride or 5% Dextrose infusion bag and administer as instructed below</td></tr>
<tr><td>100 mL</td></tr>
<tr><td>150 mL</td></tr>
<tr><td>250 mL</td></tr>
</table>

[a] 600 mg of casirivimab and 600 mg of imdevimab are added to the same infusion bag and administered together as a single intravenous infusion.

Table 2: Recommended Dilution Instructions for 300 mg of Casirivimab and 300 mg of Imdevimab for Intravenous Infusion for Repeat Dosing[a]

Size of Prefilled 0.9% Sodium Chloride or 5%	Preparing Using Co-Formulated Casirivimab and Imdevimab Vial	Preparing Casirivimab and Imdevimab Using Individual Vials[b]

Dextrose Infusion Bag		
50 mL	Add 5 mL of co-formulated casirivimab and imdevimab into a prefilled 0.9% Sodium Chloride or 5% Dextrose infusion bag and administer as instructed below	Add: • 2.5 mL of casirivimab (may use 1 vial of 2.5 mL OR 1 vial of 11.1 mL) and • 2.5 mL of imdevimab (may use 1 vial of 2.5 mL OR 1 vial of 11.1 mL) and inject into a prefilled 0.9% Sodium Chloride or 5% Dextrose infusion bag and administer as instructed below
100 mL		
150 mL		
250 mL		

[a] Subsequent repeat dosing every 4 weeks after initial 600 mg casirivimab and 600 mg imdevimab dosing for the duration of ongoing exposure.

[b] 300 mg of casirivimab and 300 mg of imdevimab are added to the same infusion bag and administered together as a single intravenous infusion.

Administration by Intravenous Infusion

Casirivimab and imdevimab infusion solution should be administered by a qualified healthcare professional using aseptic technique.

- Gather the recommended materials for infusion:
  - Polyvinyl chloride (PVC), polyethylene (PE)-lined PVC, or polyurethane (PU) infusion set
  - In-line or add-on 0.2 micron polyethersulfone (PES) filter
- Attach the infusion set to the intravenous bag.
- Prime the infusion set.
- Administer the entire infusion solution in the bag via pump or gravity through an intravenous line containing a sterile, in-line or add-on 0.2-micron polyethersulfone (PES) filter (see Table 3 and Table 4). Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.
- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of casirivimab and imdevimab injection with intravenous solutions and medications other than 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP is not known.
- After infusion is complete, flush the tubing with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to ensure delivery of the required dose.
- Discard unused product.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.

Table 3: Recommended Administration Rate for 600 mg of Casirivimab and 600 mg of Imdevimab for Intravenous Infusion

Size of Prefilled 0.9% Sodium Chloride or 5% Dextrose Infusion Bag used	Maximum Infusion Rate	Minimum Infusion Time
50 mL[a]	180 mL/hr	20 minutes
100 mL	310 mL/hr	21 minutes
150 mL	310 mL/hr	31 minutes
250 mL	310 mL/hr	50 minutes

[a] The minimum infusion time for patients administered casirivimab and imdevimab together using the 50 mL prefilled 0.9% Sodium Chloride or 5% Dextrose infusion bag must be at least 20 minutes to ensure safe use.

Table 4: Recommended Administration Rate for 300 mg of Casirivimab and 300 mg of Imdevimab for Intravenous Infusion for Repeat Dosing[a]

Size of Prefilled 0.9% Sodium Chloride or 5% Dextrose Infusion Bag used	Maximum Infusion Rate	Minimum Infusion Time
50 mL[b]	165 mL/hr	20 minutes
100 mL	310 mL/hr	20 minutes
150 mL	310 mL/hr	30 minutes
250 mL	310 mL/hr	49 minutes

[a] Subsequent repeat dosing every 4 weeks after initial 600 mg casirivimab and 600 mg imdevimab dosing for the duration of ongoing exposure.
[b] The minimum infusion time for patients administered casirivimab and imdevimab together using the 50 mL prefilled 0.9% Sodium Chloride or 5% Dextrose infusion bag must be at least 20 minutes to ensure safe use.

Preparation for Subcutaneous Injection

Remove the casirivimab and imdevimab vial(s) from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake the vials.**

Inspect casirivimab and imdevimab vial(s) visually for particulate matter and discoloration prior to administration. Should either be observed, the vial must be discarded and replaced with a new vial. The solution for each vial should be clear to slightly opalescent, colorless to pale yellow.

1. Casirivimab and imdevimab should be prepared using the appropriate number of syringes (see Table 5 and Table 6). Obtain 3 mL or 5 mL polypropylene Luer Lock syringes with luer connection and 21-gauge 1½ inch transfer needles.
2. Withdraw the appropriate amount of solution into each syringe (see Table 5 and Table 6). Prepare all syringes at the same time.
3. Replace the 21-gauge transfer needle with a 25-gauge or 27-gauge needle for subcutaneous injection.
4. This product is preservative-free and therefore, the prepared syringes should be administered immediately. If immediate administration is not possible, store the prepared casirivimab and imdevimab syringes in the refrigerator between 2°C to 8°C (36°F to 46°F) for no more than 24 hours, or at room temperature up to 25°C (77°F) for no more than 8 hours. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 20 minutes prior to administration.

Table 5: Preparation of 600 mg of Casirivimab and 600 mg of Imdevimab for Subcutaneous Injections

Prepare 600 mg of Casirivimab and 600 mg of Imdevimab	Preparation of 4 Syringes
Using Casirivimab and Imdevimab Co-formulated Vial	Withdraw 2.5 mL solution per syringe into FOUR separate syringes.
Using Casirivimab and Imdevimab Individual Vials	• **Casirivimab:** Withdraw 2.5 mL solution per syringe into TWO separate syringes. • **Imdevimab:** Withdraw 2.5 mL solution per syringe into TWO separate syringes. For total of 4 syringes.

Table 6: Preparation of 300 mg of Casirivimab and 300 mg of Imdevimab for Subcutaneous Injections for Repeat Dosing[a]

Prepare 300 mg of Casirivimab and 300 mg of Imdevimab	Preparation of 2 Syringes
Using Casirivimab and Imdevimab Co-formulated Vial	Withdraw 2.5 mL solution per syringe into TWO separate syringes.
Using Casirivimab and Imdevimab Individual Vials	• **Casirivimab:** Withdraw 2.5 mL solution into ONE syringe. • **Imdevimab:** Withdraw 2.5 mL solution into ONE syringe. For total of 2 syringes.

[a] Subsequent repeat dosing every 4 weeks after initial 600 mg casirivimab and 600 mg imdevimab dosing for the duration of ongoing exposure.

Administration for Subcutaneous Injection

- For the administration of 600 mg of casirivimab and 600 mg of imdevimab, gather 4 syringes (see Table 5) and prepare for subcutaneous injections.
- For the administration of 300 mg of casirivimab and 300 mg of imdevimab, gather 2 syringes (see Table 6) and prepare for subcutaneous injections.
- Administer the subcutaneous injections consecutively, each at a different injection site, into the thigh, back of the upper arm, or abdomen, except for 2 inches (5 cm) around the navel. The waistline should be avoided.
- When administering the subcutaneous injections, it is recommended that providers use different quadrants of the abdomen or upper thighs or back of the upper arms to space apart each 2.5 mL subcutaneous injection of casirivimab and imdevimab. DO NOT inject into skin that is tender, damaged, bruised, or scarred.
- Clinically monitor patients after injections and observe patients for at least 1 hour.

Storage

Store unopened casirivimab and imdevimab vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Unopened vials may be stored in the original carton at room temperature [up to 25°C (77°F)] and must be used within 30 days. If not used in the 30 days, discard vials.

Warnings

There are limited clinical data available for REGEN-COV (casirivimab and imdevimab). Serious and unexpected adverse events may occur that have not been previously reported with REGEN-COV use.

Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of REGEN-COV (casirivimab and imdevimab). If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy.

Infusion-related reactions, occurring during the infusion and up to 24 hours after the infusion, have been observed with administration of REGEN-COV. These reactions may be severe or life-threatening.

Signs and symptoms of infusion-related reactions may include:

- fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vasovagal reactions (e.g., pre-syncope, syncope), dizziness, and diaphoresis.

Consider slowing or stopping the infusion and administer appropriate medications and/or supportive care if an infusion-related reaction occurs.

Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of REGEN-COV under Emergency Use Authorization.

Clinical Worsening After REGEN-COV Administration

Clinical worsening of COVID-19 after administration of REGEN-COV has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to REGEN-COV use or were due to progression of COVID-19.

Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19

Monoclonal antibodies, such as REGEN-COV, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Therefore, REGEN-COV is not authorized for use in patients *[see Limitations of Authorized Use (1.1)]*:

- who are hospitalized due to COVID-19, OR
- who require oxygen therapy due to COVID-19, OR
- who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

Side Effects

Adverse events have been reported with REGEN-COV (casirivimab and imdevimab) [*see Full EUA Prescribing Information, Clinical Trials Experience (6.1)*].

Additional adverse events associated with REGEN-COV, some of which may be serious, may become apparent with more widespread use.

INSTRUCTIONS FOR HEALTH CARE PROVIDERS

As the health care provider, you must communicate to your patient or parent/caregiver, as age appropriate, information consistent with the "Fact Sheet for Patients, Parents and Caregivers" (and provide a copy of the Fact Sheet) prior to the patient receiving REGEN-COV (casirivimab and imdevimab), including:

- FDA has authorized the emergency use of REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, for the treatment of mild to moderate COVID-19 in adult and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death *[see Limitations of Authorized Use (1.1)]*.
- FDA has authorized the emergency use of REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated[2] **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications[3]) **and**
  - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Center for Disease Control and Prevention (CDC)[4] **or**
  - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

- The patient or parent/caregiver has the option to accept or refuse REGEN-COV.
- The significant known and potential risks and benefits of REGEN-COV, and the extent to which such risks and benefits are unknown.
- Information on available alternative treatments and the risks and benefits of those alternatives, including clinical trials.
- Patients treated with REGEN-COV should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect "high touch" surfaces, and frequent handwashing) according to CDC guidelines.

For information on clinical trials that are testing the use of REGEN-COV related to COVID-19, please see www.clinicaltrials.gov.

MANDATORY REQUIREMENTS FOR REGEN-COV UNDER EMERGENCY USE AUTHORIZATION:

In order to mitigate the risks of using this unapproved product under EUA and to optimize the potential benefit of REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, the following items are required. Use of REGEN-COV under this EUA is limited to the following (all requirements **must** be met):

1. Treatment of mild to moderate COVID-19 in adult and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for severe COVID-19, including hospitalization or death *[see Limitations of Authorized Use (1.1)]*.
2. Post-exposure prophylaxis of COVID-19 in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:
   a. not fully vaccinated[2] **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications[3]) and
      - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Center for Disease Control and Prevention (CDC)[4] **or**
      - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in

other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

3. As the health care provider, communicate to your patient or parent/caregiver, as age appropriate, information consistent with the "Fact Sheet for Patients, Parents and Caregivers" prior to the patient receiving REGEN-COV. Health care providers (to the extent practicable given the circumstances of the emergency) must document in the patient's medical record that the patient/caregiver has been:
   a. Given the "Fact Sheet for Patients, Parents and Caregivers",
   b. Informed of alternatives to receiving REGEN-COV, and
   c. Informed that REGEN-COV is an unapproved drug that is authorized for use under this Emergency Use Authorization.
4. Patients with known hypersensitivity to any ingredient of REGEN-COV must not receive REGEN-COV.
5. The prescribing health care provider and/or the provider's designee are/is responsible for mandatory reporting of all medication errors and serious adverse events* potentially related to REGEN-COV treatment within 7 calendar days from the onset of the event. The reports must include unique identifiers and the words "REGEN-COV use for COVID-19 under Emergency Use Authorization (EUA)" in the description section of the report.

   - Submit adverse event reports to FDA MedWatch using one of the following methods:
     - Complete and submit the report online: www.fda.gov/medwatch/report.htm, or
     - Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
       - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
       - Fax (1-800-FDA-0178), or
     - Call 1-800-FDA-1088 to request a reporting form
     - Submitted reports must include in the field name, "Describe Event, Problem, or Product Use/Medication Error" a statement "REGEN-COV use for COVID-19 under Emergency Use Authorization (EUA)."

   *Serious Adverse Events are defined as:
   - death;
   - a life-threatening adverse event;
   - inpatient hospitalization or prolongation of existing hospitalization;
   - a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
   - a congenital anomaly/birth defect;
   - a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

6. The prescribing health care provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of REGEN-COV.

7. OTHER REPORTING REQUIREMENTS
    - Healthcare facilities and providers must report therapeutics information and utilization data through HHS Protect, Teletracking or National Healthcare Safety Network (NHSN) as directed by the U.S. Department of Health and Human Services.

    - In addition, please provide a copy of all FDA MedWatch forms to:
      Regeneron Pharmaceuticals, Inc
      Fax: 1-888-876-2736
      E-mail: medical.information@regeneron.com
      Or call Regeneron Pharmaceuticals at 1-844-734-6643 to report adverse events.

APPROVED AVAILABLE ALTERNATIVES

Veklury (remdesivir) is FDA-approved for the treatment of COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, who are not hospitalized and have mild-to-moderate COVID-19, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Veklury is administered via intravenous infusion for a total treatment duration of 3 days.

Although Veklury is an approved alternative treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, FDA does not consider Veklury to be an adequate alternative to REGEN-COV for this authorized use because it may not be feasible or practical for certain patients (e.g., it requires a 3-day treatment duration).

There is no adequate, approved and available alternative to REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated[2] **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications[3]) **and**
    - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per CDC[4] **or**
    - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

Additional information on COVID-19 treatments can be found at https://www.cdc.gov/coronavirus/2019-ncov/index.html. The health care provider should visit https://clinicaltrials.gov/ to determine whether the patient may be eligible for enrollment in a clinical trial.

AUTHORITY FOR ISSUANCE OF THE EUA

The Secretary of the Department of Health and Human Services (HHS) has declared a public health emergency that justifies the emergency use of drugs and biological products during the COVID-19 pandemic.

FDA has issued this EUA, requested by Regeneron Pharmaceuticals, Inc. for the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, for the treatment of mild to moderate COVID-19 in adult and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death.[6] As a health care provider, you must comply with the mandatory requirements of the EUA (see above).

FDA has issued this EUA, requested by Regeneron Pharmaceuticals, Inc. for the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated[2] **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications[3]) **and**
    - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[4] **or**
      who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

Although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, may be effective for the treatment of COVID-19 or for post-exposure prophylaxis of COVID-19 in individuals as specified in this Fact Sheet. You may be contacted and asked to provide information to help with the assessment of the use of the product during this emergency.

This EUA for REGEN-COV will end when the Secretary determines that the circumstances justifying the EUA no longer exist or when there is a change in the approval status of the product such that an EUA may no longer be needed.

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[6] The health care provider should visit https://clinicaltrials.gov/ to determine whether there is an active clinical trial for the product in this disease/condition and whether enrollment of the patient(s) in a clinical trial is more appropriate than product use under this EUA.

CONTACT INFORMATION

For additional information visit www.REGENCOV.com
If you have questions, please contact Regeneron at 1-844-734-6643.

END SHORT VERSION FACT SHEET
Long Version Begins on Next Page

FULL EUA PRESCRIBING INFORMATION

FULL EUA PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

1 AUTHORIZED USE

1.1 TREATMENT

REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, is authorized for use under an EUA for the treatment of mild to moderate COVID-19 in adult and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Limitations of Authorized Use

- REGEN-COV is not authorized for treatment of mild to moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information such as variant susceptibility to this drug and regional variant frequency.
  - FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.[7]
- REGEN-COV (casirivimab and imdevimab) is not authorized for use in patients:
  - who are hospitalized due to COVID-19, OR
  - who require oxygen therapy due to COVID-19, OR

[7] FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility *[see Microbiology/Resistance Information (15)]*, and CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions.

- who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.
- Monoclonal antibodies, such as REGEN-COV, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation *[see Warnings and Precautions (5.2)]*.

1.2 POST-EXPOSURE PROPHYLAXIS

REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, is authorized for use under an EUA for the post-exposure prophylaxis of COVID-19 in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated[8] **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications[9]) **and**
  - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[10] **or**
  - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons).

Limitations of Authorized Use

- REGEN-COV is not authorized for post-exposure prophylaxis of COVID-19 in geographic regions where exposure is likely to have been to a non-susceptible SARS-CoV-2 variant, based on available information including variant susceptibility to this drug and regional variant frequency.
  - FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.[11]

- Post-exposure prophylaxis with REGEN-COV (casirivimab and imdevimab) is not a substitute for vaccination against COVID-19.

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[8] Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as Johnson & Johnson's Janssen vaccine). See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated

[9] See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html

[10] Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example). See this website for additional details: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html

[11] FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility *[see Microbiology/Resistance Information (15)]*, and CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions.

- REGEN-COV (casirivimab and imdevimab) is not authorized for pre-exposure prophylaxis for prevention of COVID-19.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

The optimal dosing regimen for treatment of COVID-19 has not yet been established.
The recommended dosing regimen may be updated as data from clinical trials become available.

Patient Selection for Treatment and Post-Exposure Prophylaxis

Treatment:
This section provides essential information on the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, for the treatment of adult and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death *[see Limitations of Authorized Use (1.1)]*.

Post-Exposure Prophylaxis:
This section provides essential information on the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied in individual vials to be administered together, in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for the post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated[2] **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications[3]) **and**
  - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[4] **or**
  - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) *[see Limitations of Authorized Use (1.2)]*.

The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example, age ≥65 years of age)
- Obesity or being overweight (for example, BMI >25 kg/m^2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- Pregnancy
- Chronic kidney disease

- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19))

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of REGEN-COV under the EUA is not limited to the medical conditions or factors listed above.

For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

2.2 Dosage

Treatment:
The dosage in adult and pediatric patients (12 years of age and older weighing at least 40 kg) is 600 mg of casirivimab and 600 mg of imdevimab administered together as a single intravenous infusion or by subcutaneous injection. Casirivimab and imdevimab should be given together as soon as possible after a positive viral test for SARS-CoV-2 and within 10 days of symptom onset.

Post-Exposure Prophylaxis:
The dosage in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) is 600 mg of casirivimab and 600 mg of imdevimab administered by subcutaneous injection or together as a single intravenous infusion. Casirivimab and imdevimab should be given together as soon as possible following exposure to SARS-CoV-2.

For individuals whom repeat dosing is determined to be appropriate for ongoing exposure to SARS-CoV-2 for longer than 4 weeks and who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination, the initial dose is 600 mg of casirivimab and 600 mg of imdevimab by subcutaneous injection or intravenous infusion followed by subsequent repeat dosing of 300 mg of casirivimab and 300 mg of imdevimab by subcutaneous injection or intravenous infusion once every 4 weeks for the duration of ongoing exposure.

For Intravenous Infusion:

- Casirivimab and imdevimab solution co-formulated in a vial and in individual vials, including co-packaged carton and dose pack, must be diluted prior to intravenous administration.
- Administer casirivimab and imdevimab together as a single intravenous infusion via pump or gravity (see Table 1, Table 2, Table 3 and Table 4).
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

For Subcutaneous Injection:

- Administer casirivimab and imdevimab using the co-formulated vial or using the individual vials by subcutaneous injection (see Table 5 and Table 6).
- Clinically monitor patients after injections and observe patients for at least 1hour.

2.3 Dose Adjustment in Specific Populations

Pregnancy or Lactation

No dosage adjustment is recommended in pregnant or lactating women *[see Use in Specific Populations (11.1, 11.2)]*.

Pediatric Use

No dosage adjustment is recommended in pediatric patients who weigh at least 40 kg and are older than 12 years of age. REGEN-COV (casirivimab and imdevimab) is not recommended for pediatric patients weighing less than 40 kg or those less than 12 years of age *[see Use in Specific Populations (11.3)]*.

Renal Impairment

No dosage adjustment is recommended in patients with renal impairment *[see Use in Specific Populations (11.5)]*.

2.4 Dose Preparation and Administration

There are TWO different formulations of REGEN-COV:

- Casirivimab and imdevimab co-formulated solution containing two antibodies in a 1:1 ratio in a vial.
- Casirivimab and imdevimab available as individual antibody solutions in separate vials supplied as follows:
    - Individual vials in individual cartons, or
    - together in a single carton (also referred to as a co-packaged carton), or
    - in a dose pack. The dose pack contains individual vials of casirivimab and imdevimab, configurations that may vary in vial size, strength and appearance and are available in dose pack configurations that include 2, 5, and 8 cartons *[see Full EUA Prescribing Information, How Supplied/Storage and Handling (19)]*.

For treatment, intravenous infusion is strongly recommended. Subcutaneous injection is an alternative route of administration when intravenous infusion is not feasible and would lead to delay in treatment.

For post-exposure prophylaxis, either subcutaneous injection or intravenous infusion can be used.

There are differences in the way the two formulations are prepared. Carefully follow the preparation procedures below.

- Casirivimab and imdevimab co-formulated solution in a vial and casirivimab or imdevimab as individual antibody solutions in separate 11.1 mL vials may be used to prepare more than one dose simultaneously as appropriate, either in intravenous bags or in syringes for subcutaneous injection. Discard any product remaining in the vial.
- Store unopened casirivimab and imdevimab vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Unopened vials may be stored in the original carton at room temperature [up to 25°C (77°F)] and must be used within 30 days. If not used in the 30 days, discard vials.

Under the EUA, a single-dose vial may be used to prepare more than one dose.

Preparation for Intravenous Infusion

For treatment, the preferred route of administration for casirivimab and imdevimab is by intravenous infusion after dilution.

Casirivimab and imdevimab solution for intravenous infusion should be prepared by a qualified healthcare professional using aseptic technique:

1. Remove the casirivimab and imdevimab vials from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake the vials**.
2. Inspect casirivimab and imdevimab vials visually for particulate matter and discoloration prior to administration. Should either be observed, the vial must be discarded and replaced with a new vial.
   - The solution for each vial should be clear to slightly opalescent, colorless to pale yellow.
3. Obtain a prefilled intravenous infusion bag containing either 50 mL, 100 mL, 150 mL, or 250 mL of either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.
4. Withdraw the appropriate amount of casirivimab and imdevimab from each respective vial(s) and inject into a prefilled infusion bag containing either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP, (see Table 1 and Table 2). If using one vial to prepare more than one infusion bag, then prepare all infusion bags at the same time. The product is preservative-free, therefore do not store unused solution in vial(s).
5. Gently invert infusion bag by hand approximately 10 times to mix. **Do not shake**.

6. This product is preservative-free and therefore, the diluted infusion solution should be administered immediately (see Table 3 and Table 4).
   - If immediate administration is not possible, store the diluted casirivimab and imdevimab infusion solution in the refrigerator between 2°C to 8°C (36°F to 46°F) for no more than 36 hours or at room temperature up to 25°C (77°F) for no more than 4 hours. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.

Table 1: Recommended Dilution Instructions for 600 mg of Casirivimab and 600 mg of Imdevimab for Intravenous Infusion

Size of Prefilled 0.9% Sodium Chloride or 5% Dextrose Infusion Bag	Preparing Using Co-Formulated Casirivimab and Imdevimab Vial	Preparing Casirivimab and Imdevimab Using Individual Vials[a]
50 mL	Add 10 mL of co-formulated casirivimab and imdevimab (1 vial) into a prefilled 0.9% Sodium Chloride or 5% Dextrose infusion bag and administer as instructed below	Add: • 5 mL of casirivimab (may use 2 vials of 2.5 mL OR 1 vial of 11.1 mL) and • 5 mL of imdevimab (may use 2 vials of 2.5 mL OR 1 vial of 11.1 mL) and inject into a prefilled 0.9% Sodium Chloride or 5% Dextrose infusion bag and administer as instructed below
100 mL		
150 mL		
250 mL		

[a] 600 mg of casirivimab and 600 mg of imdevimab are added to the same infusion bag and administered together as a single intravenous infusion.

Table 2: Recommended Dilution Instructions for 300 mg of Casirivimab and 300 mg of Imdevimab for Intravenous Infusion for Repeat Dosing[a]

Size of Prefilled 0.9% Sodium Chloride or 5% Dextrose Infusion Bag	Preparing Using Co-Formulated Casirivimab and Imdevimab Vial	Preparing Casirivimab and Imdevimab Using Individual Vials[b]
50 mL	Add 5 mL of co-formulated casirivimab and imdevimab into a prefilled 0.9% Sodium Chloride or	Add: • 2.5 mL of casirivimab (may use 1 vial of 2.5

100 mL	5% Dextrose infusion bag and administer as instructed below	mL OR 1 vial of 11.1 mL) and • 2.5 mL of imdevimab (may use 1 vial of 2.5 mL OR 1 vial of 11.1 mL) and inject into a prefilled 0.9% Sodium Chloride or 5% Dextrose infusion bag and administer as instructed below
150 mL		
250 mL		

[a] Subsequent repeat dosing every 4 weeks after initial 600 mg casirivimab and 600 mg imdevimab dosing for the duration of ongoing exposure.

[b] 300 mg of casirivimab and 300 mg of imdevimab are added to the same infusion bag and administered together as a single intravenous infusion.

Administration by Intravenous Infusion

Casirivimab and imdevimab infusion solution should be administered by a qualified healthcare professional using aseptic technique.

- Gather the recommended materials for infusion:
  - Polyvinyl chloride (PVC), polyethylene (PE)-lined PVC, or polyurethane (PU) infusion set
  - In-line or add-on 0.2 micron polyethersulfone (PES) filter
- Attach the infusion set to the intravenous bag.
- Prime the infusion set.
- Administer the entire infusion solution in the bag via pump or gravity through an intravenous line containing a sterile, in-line or add-on 0.2-micron polyethersulfone (PES) filter (see Table 3 and Table 4). Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.
- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of casirivimab and imdevimab injection with intravenous solutions and medications other than 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP is not known.
- After infusion is complete, **flush the tubing** with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to ensure delivery of the required dose.
- Discard unused product.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.

Table 3: Recommended Administration Rate for 600 mg of Casirivimab and 600 mg of Imdevimab for Intravenous Infusion

Size of Prefilled 0.9% Sodium Chloride or 5% Dextrose Infusion Bag used	Maximum Infusion Rate	Minimum Infusion Time
50 mL[a]	180 mL/hr	20 minutes
100 mL	310 mL/hr	21 minutes
150 mL	310 mL/hr	31 minutes
250 mL	310 mL/hr	50 minutes

[a] The minimum infusion time for patients administered casirivimab and imdevimab together using the 50 mL prefilled 0.9% Sodium Chloride or 5% Dextrose infusion bag must be at least 20 minutes to ensure safe use.

Table 4: Recommended Administration Rate for 300 mg of Casirivimab and 300 mg of Imdevimab for Intravenous Infusion for Repeat Dosing[a]

Size of Prefilled 0.9% Sodium Chloride or 5% Dextrose Infusion Bag used	Maximum Infusion Rate	Minimum Infusion Time
50 mL[b]	165 mL/hr	20 minutes
100 mL	310 mL/hr	20 minutes
150 mL	310 mL/hr	30 minutes
250 mL	310 mL/hr	49 minutes

[a] Subsequent repeat dosing every 4 weeks after initial 600 mg casirivimab and 600 mg imdevimab dosing for the duration of ongoing exposure.
[b] The minimum infusion time for patients administered casirivimab and imdevimab together using the 50 mL prefilled 0.9% Sodium Chloride or 5% Dextrose infusion bag must be at least 20 minutes to ensure safe use.

Preparation for Subcutaneous Injection

Remove the casirivimab and imdevimab vial(s) from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake the vials.**

Inspect casirivimab and imdevimab vial(s) visually for particulate matter and discoloration prior to administration. Should either be observed, the vial must be discarded and replaced with a new vial. The solution for each vial should be clear to slightly opalescent, colorless to pale yellow.

1. Casirivimab and imdevimab should be prepared using the appropriate number of syringes (see Table 5 and Table 6). Obtain 3 mL or 5 mL polypropylene Luer Lock syringes with luer connection and 21-gauge 1½ inch transfer needles.
2. Withdraw the appropriate amount of solution into each syringe (see Table 5 and Table 6). Prepare all syringes at the same time.
3. Replace the 21-gauge transfer needle with a 25-gauge or 27-gauge needle for subcutaneous injection.

4. This product is preservative-free and therefore, the prepared syringes should be administered immediately. If immediate administration is not possible, store the prepared casirivimab and imdevimab syringes in the refrigerator between 2°C to 8°C (36°F to 46°F) for no more than 24 hours, or at room temperature up to 25°C (77°F) for no more than 8 hours. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 20 minutes prior to administration.

Table 5: Preparation of 600 mg of Casirivimab and 600 mg of Imdevimab for Subcutaneous Injections

Prepare 600 mg of Casirivimab and 600 mg of Imdevimab	**Preparation of 4 Syringes**
Using Casirivimab and Imdevimab Co-formulated Vial	Withdraw 2.5 mL solution per syringe into FOUR separate syringes.
Using Casirivimab and Imdevimab Individual Vials	• **Casirivimab:** Withdraw 2.5 mL solution per syringe into TWO separate syringes. • **Imdevimab:** Withdraw 2.5 mL solution per syringe into TWO separate syringes. For total of 4 syringes.

Table 6: Preparation of 300 mg of Casirivimab and 300 mg of Imdevimab for Subcutaneous Injections for Repeat Dosing[a]

Prepare 300 mg of Casirivimab and 300 mg of Imdevimab	**Preparation of 2 Syringes**
Using Casirivimab and Imdevimab Co-formulated Vial	Withdraw 2.5 mL solution per syringe into TWO separate syringes.

Using Casirivimab and Imdevimab Individual Vials	• **Casirivimab:** Withdraw 2.5 mL solution into ONE syringe. • **Imdevimab:** Withdraw 2.5 mL solution into ONE syringe. For total of 2 syringes.

[a] Subsequent repeat dosing every 4 weeks after initial 600 mg casirivimab and 600 mg imdevimab dosing for the duration of ongoing exposure.

Administration for Subcutaneous Injection

- For the administration of 600 mg of casirivimab and 600 mg of imdevimab, gather 4 syringes (see Table 5) and prepare for subcutaneous injections.
- For the administration of 300 mg of casirivimab and 300 mg of imdevimab, gather 2 syringes (see Table 6) and prepare for subcutaneous injections.
- Administer the subcutaneous injections consecutively, each at a different injection site, into the thigh, back of the upper arm, or abdomen, except for 2 inches (5 cm) around the navel. The waistline should be avoided.
- When administering the subcutaneous injections, it is recommended that providers use different quadrants of the abdomen or upper thighs or back of the upper arms to space apart each 2.5 mL subcutaneous injection of casirivimab and imdevimab. DO NOT inject into skin that is tender, damaged, bruised, or scarred.
- Clinically monitor patients after injections and observe patients for at least 1 hour.

3 DOSAGE FORMS AND STRENGTHS

REGEN-COV (casirivimab and imdevimab) is available as:

1. A single vial which contains two antibodies co-formulated in a 1:1 ratio of casirivimab and imdevimab. Co-formulated casirivimab and imdevimab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution available as:
    - Injection: 600 mg of casirivimab and 600 mg of imdevimab per 10 mL (60 mg/60 mg per mL) in a single-dose[12] vial

2. Individual antibody solutions in separate single-dose[4] vials, which may be supplied in separate cartons or together in a single carton (also referred to as a co-packaged carton), or as dose pack.
    - Casirivimab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution available as:

[12] Under the EUA, a single-dose vial may be used to prepare more than one dose.

- Injection: 300 mg/2.5 mL (120 mg/mL) or 1,332 mg/11.1 mL (120 mg/mL)

- Imdevimab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution available as:
  - Injection: 300 mg/2.5 mL (120 mg/mL) or 1,332 mg/11.1 mL (120 mg/mL)

- Each REGEN-COV dose pack contains 1,200 mg of casirivimab [REGN10933] and 1,200 mg of imdevimab [REGN10987] *[see How Supplied/Storage and Handling (19)]*. Casirivimab and imdevimab vial labels and carton labeling may instead be labeled REGN10933 and REGN10987, respectively.

4 CONTRAINDICATIONS

REGEN-COV is contraindicated in individuals with previous severe hypersensitivity reactions, including anaphylaxis, to REGEN-COV *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

There are limited clinical data available for REGEN-COV (casirivimab and imdevimab). Serious and unexpected adverse events may occur that have not been previously reported with REGEN-COV use.

5.1 Hypersensitivity including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported with administration of REGEN-COV (casirivimab and imdevimab). If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related reactions, occurring during the infusion and up to 24 hours after the infusion, have been observed with administration of REGEN-COV. These reactions may be severe or life threatening.
Signs and symptoms of infusion related reactions may include:

- fever, difficulty breathing, reduced oxygen saturation, chills, nausea, arrhythmia (e.g., atrial fibrillation, tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vasovagal reactions (e.g., pre-syncope, syncope), dizziness, fatigue, and diaphoresis *[see Overall Safety Summary (6.1)]*.

If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care.

Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of REGEN-COV under Emergency Use Authorization.

5.2 Clinical Worsening After REGEN-COV Administration

Clinical worsening of COVID-19 after administration of REGEN-COV has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to REGEN-COV use or were due to progression of COVID-19.

5.3 Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19

Monoclonal antibodies, such as REGEN-COV, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Therefore, REGEN-COV is not authorized for use in patients *[see Limitations of Authorized Use (1.1)]*:

- who are hospitalized due to COVID-19, OR
- who require oxygen therapy due to COVID-19, OR
- who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

6 OVERALL SAFETY SUMMARY

6.1 Clinical Trials Experience

Overall, approximately 16,000 subjects have been exposed to REGEN-COV (casirivimab and imdevimab) in clinical trials in hospitalized and non-hospitalized subjects. Approximately 13,500 subjects received intravenous infusions and 2,500 subjects received subcutaneous injections.

The safety of REGEN-COV (casirivimab and imdevimab) is based on analyses from COV-2067, a Phase 1/2/3 trial of ambulatory (non-hospitalized) subjects with COVID-19; COV-2069, a Phase 3 post-exposure prophylaxis trial for prevention of COVID-19; and COV-2093, a Phase 1 trial evaluating the safety and pharmacokinetics of REGEN-COV repeat subcutaneous dosing every 4 weeks for 24 weeks.

COV-2067

This is a randomized, double-blind, placebo-controlled clinical trial in subjects with mild to moderate COVID-19 who had a sample collected for the first positive SARS-CoV-2 viral infection determination within 3 days prior to the start of the infusion. In the phase 3 portion of the trial, subjects were treated with a single intravenous infusion of 600 mg of casirivimab and 600 mg of imdevimab (n=827), or 1,200 mg of casirivimab and 1,200 mg of imdevimab (n=1,849), or 4,000 mg of casirivimab and 4,000 mg of imdevimab (n=1,012), or placebo (n=1,843). REGEN-COV is not authorized at the 4,000 mg of casirivimab and 4,000 mg of imdevimab dose. The 1,200 mg of casirivimab and 1,200 mg of imdevimab is no longer authorized under this EUA *[see Clinical Trial Results and Supporting Data for EUA (18)]*.

In pooled phase 1/2/3 analysis, infusion-related reactions (adverse event assessed as causally related by the investigator) of grade 2 or higher severity have been observed in 10/4,206 (0.2%) of those who received REGEN-COV at the authorized dose or a higher dose *[see Warnings and Precautions (5.1)]*.

Overall, in Phase 1/2/3, three subjects receiving the 8,000 mg dose of REGEN-COV, and one subject receiving the 1,200 mg of casirivimab and 1,200 mg of imdevimab infusion-related reactions (urticaria, pruritus, flushing, pyrexia, shortness of breath, chest tightness, nausea, vomiting, rash) which resulted in permanent discontinuation of the infusion. All events resolved [*see Warnings and Precautions (5.1)*].

Anaphylactic reactions have been reported in the clinical program in subjects receiving REGEN-COV. The events began within 1 hour of completion of the infusion, and in at least one case required treatment including epinephrine. The events resolved.

COV-2069

This is a randomized, double-blind, placebo-controlled clinical trial assessing the efficacy and safety of REGEN-COV (casirivimab and imdevimab) for post-exposure prophylaxis of COVID-19 in household contacts of individuals infected with SARS-CoV-2. Subjects who were SARS-CoV-2 negative at baseline were enrolled in Cohort A and received a single dose of 600 mg of casirivimab and 600 mg of imdevimab subcutaneously (n=1,311) or placebo (n=1,306).

Adverse events were reported in 265 subjects (20%) in the REGEN-COV group and 379 subjects (29%) in the placebo group. Injection site reactions (all grade 1 and 2) occurred in 55 subjects (4%) in the REGEN-COV group and 19 subjects (2%) in the placebo group. The most common signs and symptoms of injection site reactions which occurred in at least 1% of subjects in the REGEN-COV group were erythema and pruritus. Hypersensitivity reactions occurred in 2 subjects (0.2%) in the REGEN-COV group and all hypersensitivity reactions were grade 1 in severity. There were no cases of anaphylaxis.

Subjects who were SARS-CoV-2 positive at baseline were enrolled in Cohort B and received a single dose of 600 mg of casirivimab and 600 mg of imdevimab subcutaneously (n=155) or placebo (n=156).

Adverse events were reported in 52 subjects (34%) in the REGEN-COV group and 75 subjects (48%) in the placebo group. Injection site reactions, all of which were grade 1 or 2, occurred in 6 subjects (4%) in the REGEN-COV group and 1 subject (1%) in the placebo group. The most common signs and symptoms of injection site reactions which occurred in at least 1% of subjects in the REGN-COV group were ecchymosis and erythema. There were no cases of hypersensitivity reaction or anaphylaxis.

COV-2093

This is a randomized double-blind, placebo-controlled Phase 1 trial evaluating the safety, pharmacokinetic and immunogenicity of repeated doses of 600 mg of casirivimab and 600 mg of imdevimab administered subcutaneously in healthy adult subjects. In COV-2093, subjects were

randomized 3:1 to REGEN-COV (n=729) or placebo (n=240) administered every 4 weeks for 24 weeks. Adverse events were reported in 380 subjects (52%) in the REGEN-COV group and 111 subjects (46%) in the placebo group. Injection site reactions occurred in 12% and 4% of subjects following single dose administration in the REGEN-COV and placebo groups, respectively; the remaining safety findings following subcutaneous administration in the REGEN-COV group were similar to the safety findings observed with intravenous administration of REGEN-COV in COV-2067.

With repeat dosing, injection site reactions occurred in 252 subjects (35%) in the REGEN-COV group and 38 subjects (16%) in the placebo group; all injection site reactions were grade 1 or 2 in severity. Hypersensitivity reactions occurred in 8 subjects (1%) in the REGEN-COV group; and all hypersensitivity reactions were grade 1 or 2 in severity. There were no cases of anaphylaxis.

The authorized dosage for repeat dosing for post-exposure prophylaxis of COVID-19 for certain individuals who remain at high risk of exposure for longer than 4 weeks is the initial dose of 600 mg casirivimab and 600 mg imdevimab followed by 300 mg of casirivimab and 300 mg of imdevimab administered every 4 weeks *[see Dosage and Administration (2.2)]*.

7 PATIENT MONITORING RECOMMENDATIONS

Clinically monitor patients during dose administration and observe patients for at least 1 hour after intravenous infusion or subcutaneous dosing is complete *[see Warnings and Precautions (5.1) and Clinical Trials Experience (6.1)]*.

8 ADVERSE REACTIONS AND MEDICATION ERRORS REPORTING REQUIREMENTS AND INSTRUCTIONS

Clinical trials evaluating the safety of REGEN-COV (casirivimab and imdevimab) are ongoing *[see Overall Safety Summary (6)]*.

Completion of an FDA MedWatch Form to report all medication errors and serious adverse events* occurring during REGEN-COV use and considered to be potentially related to REGEN-COV is mandatory and must be done by the prescribing healthcare provider and/or the provider's designee. These adverse events must be reported within 7 calendar days from the onset of the event:

*Serious Adverse Events are defined as:

- death;
- a life-threatening adverse event;
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly/birth defect;

- a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

If a serious and unexpected adverse event occurs and appears to be associated with the use of REGEN-COV, the prescribing health care provider and/or the provider's designee must complete and submit a MedWatch form to FDA using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm, or
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax (1-800-FDA-0178), or
- Call 1-800-FDA-1088 to request a reporting form

IMPORTANT: When reporting adverse events or medication errors to MedWatch, please complete the entire form with detailed information. It is important that the information reported to FDA be as detailed and complete as possible. Information that must be included:

- Patient demographics (e.g., patient initials, date of birth)
- Pertinent medical history
- Pertinent details regarding admission and course of illness
- Concomitant medications
- Timing of adverse event(s) in relationship to administration of REGEN-COV
- Pertinent laboratory and virology information
- Outcome of the event and any additional follow-up information if it is available at the time of the MedWatch report. Subsequent reporting of follow-up information should be completed if additional details become available.

The following steps are highlighted to provide the necessary information for safety tracking:

1. In section A, box 1, provide the patient's initials in the Patient Identifier
2. In section A, box 2, provide the patient's date of birth or age
3. In section B, box 5, description of the event:
   a. Write "REGEN-COV use for COVID-19 under Emergency Use Authorization (EUA)" as the first line
   b. Provide a detailed report of medication error and/or adverse event. It is important to provide detailed information regarding the patient and adverse event/medication error for ongoing safety evaluation of this unapproved drug. Please see information to include listed above.
4. In section G, box 1, name and address:
   a. Provide the name and contact information of the prescribing health care provider or institutional designee who is responsible for the report
   b. Provide the address of the treating institution (NOT the health care provider's office address).

9 OTHER REPORTING REQUIREMENTS

Healthcare facilities and providers must report therapeutics information and utilization data through HHS Protect, Teletracking or National Healthcare Safety Network (NHSN) as directed by the U.S. Department of Health and Human Services.

In addition, please provide a copy of all FDA MedWatch forms to:
Regeneron Pharmaceuticals, Inc
Fax: 1-888-876-2736
E-mail: medical.information@regeneron.com
Or call Regeneron Pharmaceuticals at 1-844-734-6643 to report adverse events.

10 DRUG INTERACTIONS

REGEN-COV consists of 2 monoclonal antibodies (mAbs), casirivimab and imdevimab, which are not renally excreted or metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk Summary

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. REGEN-COV (casirivimab and imdevimab) should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

Nonclinical reproductive toxicity studies have not been conducted with casirivimab and imdevimab. In a tissue cross-reactivity study with casirivimab and imdevimab using human fetal tissues, no binding of clinical concern was detected. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, casirivimab and imdevimab have the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of casirivimab and imdevimab provides any treatment benefit or risk to the developing fetus. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy *(see Clinical Considerations)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk
COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

11.2 Lactation

Risk Summary

There are no available data on the presence of casirivimab and/or imdevimab in human milk or animal milk, the effects on the breastfed infant, or the effects of the drug on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for REGEN-COV (casirivimab and imdevimab) and any potential adverse effects on the breastfed child from REGEN-COV or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

11.3 Pediatric Use

REGEN-COV is not authorized for use in pediatric patients under 12 years of age or weighing less than 40 kg. The safety and effectiveness of casirivimab and imdevimab are being assessed in pediatric and adolescent patients in an ongoing clinical trial. The recommended dosing regimen is expected to result in comparable serum exposures of casirivimab and imdevimab in patients 12 years of age and older and weighing at least 40 kg as observed in adults, since adults with similar body weight have been included in Trials COV-2067, COV-2069, and COV-2093.

11.4 Geriatric Use

Of the 4,567 subjects with SARS-CoV-2 infection randomized in Trial COV-2067, 14% were 65 years or older, and 4% were 75 years of age or older. Of the 3,029 subjects randomized in Trial COV-2069, 9% were 65 years or older and 2% were 75 years of age or older. Of the 974 subjects randomized in Trial COV-2093, 13% were 65 years or older and 2% were 75 years of age or older. The difference in pharmacokinetics (PK) of casirivimab and imdevimab in geriatric patients compared to younger patients is unknown *[see Clinical Trial Results and Supporting Data for EUA (18.1)]*.

11.5 Renal Impairment

Casirivimab and imdevimab are not eliminated intact in the urine, thus renal impairment is not expected to affect the exposure of casirivimab and imdevimab.

11.6 Hepatic Impairment

The effect of hepatic impairment on PK of casirivimab and imdevimab is unknown.

11.7 Other Specific Populations

The effect of other covariates (e.g., sex, race, body weight, disease severity) on PK of casirivimab and imdevimab is unknown.

12 OVERDOSAGE

Doses up to 8,000 mg (4,000 mg each of casirivimab and imdevimab, greater than 3 times the recommended dose) have been administered in clinical trials without dose-limiting toxicity. Treatment of overdose should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with REGEN-COV (casirivimab and imdevimab).

13 PRODUCT DESCRIPTION

Casirivimab, a human immunoglobulin G-1 (IgG1) monoclonal antibody (mAb), is a covalent heterotetramer consisting of 2 heavy chains and 2 light chains produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture and has an approximate molecular weight of 145.23 kDa.

Casirivimab injection is a sterile, preservative-free, clear to slightly opalescent and colorless to pale yellow solution in a vial for subcutaneous use or intravenous infusion after dilution available as a 300 mg/2.5 mL (120 mg/mL) or 1,332 mg/11.1 mL (120 mg/mL) solution and must be administered with imdevimab. The vial stoppers are not made with natural rubber latex.

- Casirivimab: Each 2.5 mL of solution contains 300 mg of casirivimab, L-histidine (1.9 mg), L-histidine monohydrochloride monohydrate (2.7 mg), polysorbate 80 (2.5 mg), sucrose (200 mg), and Water for Injection, USP. The pH is 6.0.

- Casirivimab: Each 11.1 mL of solution contains 1,332 mg of casirivimab, L-histidine (8.3 mg), L-histidine monohydrochloride monohydrate (12.1 mg), polysorbate 80 (11.1 mg), sucrose (888 mg), and Water for Injection, USP. The pH is 6.0.

Imdevimab, a human IgG1 mAb, is a covalent heterotetramer consisting of 2 heavy chains and 2 light chains produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture and has an approximate molecular weight of 144.14 kDa.

Imdevimab injection is a sterile, preservative-free, clear to slightly opalescent and colorless to pale yellow solution in a vial for subcutaneous use or intravenous infusion after dilution available as a 300 mg/2.5 mL (120 mg/mL) or 1,332 mg/11.1 mL (120 mg/mL) solution and must be administered with casirivimab. The vial stoppers are not made with natural rubber latex.

- Imdevimab: Each 2.5 mL of solution contains 300 mg of imdevimab, L-histidine (1.9 mg), L-histidine monohydrochloride monohydrate (2.7 mg), polysorbate 80 (2.5 mg), sucrose (200 mg), and Water for Injection, USP. The pH is 6.0.

- Imdevimab: Each 11.1 mL of solution contains 1,332 mg of imdevimab, L-histidine (8.3 mg), L-histidine monohydrochloride monohydrate (12.1 mg), polysorbate 80 (11.1 mg), sucrose (888 mg), and Water for Injection, USP. The pH is 6.0.

REGEN-COV (casirivimab and imdevimab solution) injection is a sterile, preservative-free, clear to slightly opalescent, and colorless to pale yellow 10 mL solution in a vial for intravenous infusion after dilution. The vial stoppers are not made with natural rubber latex.

- Each 10 mL of solution contains 600 mg of casirivimab, 600 mg of imdevimab, L-histidine (7.4 mg), L-histidine monohydrochloride monohydrate (10.9 mg), polysorbate 80 (10.0 mg), sucrose (800 mg), and Water for Injection, USP. The pH is 6.0.

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

Casirivimab (IgG1κ) and imdevimab (IgG1λ) are two recombinant human mAbs which are unmodified in the Fc regions. Casirivimab and imdevimab bind to non-overlapping epitopes of the spike protein receptor binding domain (RBD) of SARS-CoV-2 with dissociation constants K_D = 45.8 pM and 46.7 pM, respectively. Casirivimab, imdevimab and casirivimab and imdevimab together blocked RBD binding to the human ACE2 receptor with IC_{50} values of 56.4 pM, 165 pM and 81.8 pM, respectively and prevents viral attachment to host cells [*see Microbiology/Resistance Information (15)*].

14.2 Pharmacodynamics

Trial COV-2067 evaluated REGEN-COV (casirivimab and imdevimab) with doses of up to 6.66 times the recommended dose (600 mg of casirivimab and 600 mg of imdevimab; 1,200 mg of casirivimab and 1,200 mg of imdevimab; 4,000 mg of casirivimab and 4,000 mg of imdevimab) in ambulatory patients with COVID-19. A flat dose-response relationship for efficacy was identified for REGEN-COV at all doses, based on viral load and clinical outcomes. Similar reductions in viral load (log10 copies/mL) were observed in subjects for the (600 mg of casirivimab and 600 mg of imdevimab) intravenous and (600 mg of casirivimab and 600 mg of imdevimab) subcutaneous doses; however, only limited clinical outcome data are available for the subcutaneous route of administration for the treatment of symptomatic patients.

14.3 Pharmacokinetics

Both casirivimab and imdevimab exhibited linear and dose-proportional pharmacokinetics (PK) between (600 mg of casirivimab and 600 mg of imdevimab) to (4,000 mg of casirivimab and 4,000 mg of imdevimab) doses of REGEN-COV (casirivimab and imdevimab) following intravenous administration of single dose. A summary of PK parameters after a single (600 mg of casirivimab and 600 mg of imdevimab) intravenous dose, for each antibody is provided in Table 7.

Table 7: Summary of PK Parameters for Casirivimab and Imdevimab After a Single 600 mg of Casirivimab and 600 mg of Imdevimab Intravenous Dose of REGEN-COV in Study COV-2067

PK Parameter[1]	Casirivimab	Imdevimab
C_{eoi} (mg/L)[2]	192 (80.9)	198 (84.8)
C_{28} (mg/L)[3]	46.2 (22.3)	38.5 (19.7)

[1] Mean (SD)
[2] concentration at end of 1-hour infusion
[3] observed concentration 28 days after dosing, i.e., on day 29, as defined in the protocol

A summary of PK parameters after a single 600 mg of casirivimab and 600 mg of imdevimab subcutaneous dose is shown in Table 8.

Table 8: Summary of PK Parameters for Casirivimab and Imdevimab After a Single 600 mg of Casirivimab and 600 mg of Imdevimab Subcutaneous Dose of REGEN-COV

PK Parameter[1,5]	Casirivimab	Imdevimab
C_{max} (mg/L)	55.6 (22.2)	52.7 (22.5)
t_{max} (day)[2]	8.00 (4.00, 87.0)	7.00 (4.00, 15.0)
AUC_{0-28} (mg•day/L)	1060 (363)	950 (362)
AUC_{inf} (mg•day/L)[3]	2580 (1349)	1990 (1141)
C_{28} (mg/L)[4]	30.7 (11.9)	24.8 (9.58)
Half-life (day)	31.8 (8.35)	26.9 (6.80)

[1] Mean (SD)
[2] Median (range)
[3] Value reported for subjects with $\%AUC_{inf}$ extrapolated <20%
[4] Observed concentration 28 days after dosing, i.e., on day 29
[5] Mean (SD) concentration at 24 hours (C_{24}) of casirivimab and imdevimab in serum with 1200 SC dosing, 22.5 (11.0) mg/L and 25.0 (16.4) mg/L, respectively

For the repeat dose prophylaxis intravenous and subcutaneous regimens, population pharmacokinetic simulations predicted that trough concentrations in serum at steady-state after an initial 600 mg casirivimab and 600 mg imdevimab intravenous or subcutaneous dose followed by monthly (every 4 weeks) 300 mg casirivimab and 300 mg imdevimab intravenous or

subcutaneous doses are similar to slightly higher than observed mean day 29 concentrations in serum for a single 600 mg casirivimab and 600 mg imdevimab subcutaneous dose.

Specific Populations

The effect of different covariates (e.g., age, sex, race, body weight, disease severity, hepatic impairment) on the PK of casirivimab and imdevimab is unknown. Renal impairment is not expected to impact the PK of casirivimab and imdevimab, since mAbs with molecular weight >69 kDa are known not to undergo renal elimination. Similarly, dialysis is not expected to impact the PK of casirivimab and imdevimab.

Drug-Drug Interactions

Casirivimab and imdevimab are mAbs which are not renally excreted or metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely *[see Drug Interactions (10)]*.

15 MICROBIOLOGY/RESISTANCE INFORMATION

Antiviral Activity

In a SARS-CoV-2 virus neutralization assay in Vero E6 cells, casirivimab, imdevimab, and casirivimab and imdevimab together neutralized SARS-CoV-2 (USA-WA1/2020 isolate) with EC_{50} values of 37.4 pM (0.006 µg/mL), 42.1 pM (0.006 µg/mL), and 31.0 pM (0.005 µg/mL), respectively.

Antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) were assessed using Jurkat target cells expressing SARS-CoV-2 spike protein. Casirivimab, imdevimab and casirivimab and imdevimab together mediated ADCC with human natural killer (NK) effector cells. Casirivimab, imdevimab and casirivimab and imdevimab together mediated ADCP with human macrophages. Casirivimab, imdevimab and casirivimab and imdevimab together did not mediate complement-dependent cytotoxicity in cell-based assays.

Antibody Dependent Enhancement (ADE) of Infection

The potential of casirivimab and of imdevimab to mediate viral entry was assessed in immune cell lines co-incubated with recombinant vesicular stomatitis virus (VSV) virus-like particles (VLP) pseudotyped with SARS-CoV-2 spike protein at concentrations of mAb(s) down to approximately 10-fold below the respective neutralization EC_{50} values. Casirivimab and imdevimab together and imdevimab alone, but not casirivimab alone, mediated entry of pseudotyped VLP into $Fc\gamma R2^+$ Raji and $Fc\gamma R1^+/Fc\gamma R2^+$ THP1 cells (maximum infection in total cells of 1.34% and 0.24%, respectively, for imdevimab; 0.69% and 0.06%, respectively for casirivimab and imdevimab together), but not any other cell lines tested (IM9, K562, Ramos and U937 cells).

Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to casirivimab and imdevimab administered together. Prescribing healthcare providers should consider the prevalence of SARS-CoV-2 variants in their area, where data are available, when considering treatment options.

Escape variants were identified following two passages in cell culture of recombinant VSV encoding SARS-CoV-2 spike protein in the presence of casirivimab or imdevimab individually, but not following two passages in the presence of casirivimab and imdevimab together. Variants which showed reduced susceptibility to casirivimab alone included those with spike protein amino acid substitutions K417E (182-fold), K417N (7-fold), K417R (61-fold), Y453F (>438-fold), L455F (80-fold), E484K (25-fold), F486V (>438-fold) and Q493K (>438-fold). Variants which showed reduced susceptibility to imdevimab alone included substitutions K444N (>755-fold), K444Q (>548-fold), K444T (>1,033-fold), and V445A (>548-fold). Casirivimab and imdevimab together showed reduced susceptibility to variants with K444T (6-fold) and V445A (5-fold) substitutions.

In neutralization assays using VSV VLP pseudotyped with spike protein variants identified in circulating SARS-CoV-2, variants with reduced susceptibility to casirivimab alone included those with E406D (51-fold), G476S (5-fold), E484Q (19-fold), G485D (5-fold), F486L (61-fold), F486S (>715-fold), Q493E (446-fold), Q493R (77-fold), and S494P (5-fold) substitutions, and variants with reduced susceptibility to imdevimab alone included those with P337L (5-fold), N439K (463-fold), N439V (4-fold), N440K (28-fold), K444L (153-fold), K444M (1,577-fold), G446V (135-fold), N450D (9-fold), Q498H (17-fold), P499S (206-fold) substitutions. The G476D substitution had an impact (4-fold) on casirivimab and imdevimab together. Substitutions tested concurrently which had reduced susceptibility to casirivimab and imdevimab together included N440K+E484K (21-fold), found in the B.1.619/B.1.625 lineages, and N439K+E484K (23-fold), found in the AV.1 lineage; variants harboring these concurrent substitutions have been detected rarely in the US.

Casirivimab and imdevimab individually and together retained neutralization activity against pseudotyped VLP expressing all spike protein substitutions found in the B.1.1.7 lineage (Alpha; UK origin) and against pseudotyped VLP expressing only N501Y found in B.1.1.7 and other circulating lineages (Table 9). Casirivimab and imdevimab together retained neutralization activity against pseudotyped VLP expressing all spike protein substitutions, or individual substitutions K417N, E484K or N501Y, found in the B.1.351 lineage (Beta; South Africa origin), and all spike protein substitutions or key substitutions K417T, E484K, or N501Y, found in the P.1 lineage (Gamma; Brazil origin), although casirivimab alone, but not imdevimab, had reduced activity against pseudotyped VLP expressing K417N (7-fold) or E484K (25-fold). The E484K substitution is also found in the B.1.526 lineage (Iota; USA [New York] origin). Casirivimab and imdevimab, individually and together, retained neutralization activity against the L452R substitution found in the B.1.427/B.1.429 lineages (Epsilon; USA [California] origin).

Casirivimab and imdevimab, individually and together, retained neutralization activity against pseudotyped VLP expressing L452R+T478K substitutions found in the B.1.617.2 and AY.3 lineages (Delta; India origin). Casirivimab and imdevimab together retained neutralization activity against pseudotyped VLP expressing L452R+E484Q substitutions, found in the B.1.617.1/B.1.617.3 lineages (Kappa/no designation; India origin), although casirivimab alone, but not imdevimab, had reduced activity against pseudotyped VLP expressing L452R+E484Q (7-fold). Casirivimab and imdevimab together retained activity against pseudotyped VLP expressing R346K+E484K+N501Y found in the B.1.621/B.1.621.1 (Mu; Colombia origin) lineage although casirivimab alone, but not imdevimab, had reduced activity against pseudotyped VLP expressing R346K+E484K+N501Y (23-fold).

Casirivimab and imdevimab, individually (>1732-fold and >754-fold, respectively) and together (>1013-fold), demonstrated reduced neutralization activity against VLP pseudotyped with the full spike protein sequence of the B.1.1.529/BA.1 (Omicron; South Africa origin) lineage.

Table 9: Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variant Substitutions with Casirivimab and Imdevimab Together

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y[a]	no change[d]
B.1.351	South Africa	Beta	K417N+E484K+N501Y[b]	no change[d]
P.1	Brazil	Gamma	K417T+E484K+N501Y[c]	no change[d]
B.1.617.2/AY.3	India	Delta	L452R+T478K	no change[d]
B.1.427/B.1.429	USA (California)	Epsilon	L452R	no change[d]
B.1.526[e]	USA (New York)	Iota	E484K	no change[d]
B.1.617.1/B.1.617.3	India	Kappa/no designation	L452R+E484Q	no change[d]
B.1.621/B.1.621.1	Colombia	Mu	R346K+E484K+N501Y	no change[d]
B.1.1.529/BA.1	South Africa	Omicron	G339D+S371L+S373P+ S375F+K417N+N440K, G446S+S477N+T478K+ E484A+Q493R+G496S+ Q498R+N501Y+Y505H[f]	>1013-fold[g]

[a] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: del69-70, del145, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H.

[b] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: D80Y, D215Y, del241-243, K417N, E484K, N501Y, D614G, A701V.

[c] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F.

[d] No change: ≤2-fold reduction in susceptibility.

[e] Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

[f] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: A67V, del69-70, T95I, G142D/del143-145, del211/L212I, ins214EPE, G339D, S371L, S373P,

S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F

[g] Casirivimab and imdevimab together are unlikely to be active against variants from this lineage

Abbreviations: del, deletion; ins, insertion

Due to the large reduction of pseudotyped VLP neutralization activity against spike protein from the B.1.1.529/BA.1 (Omicron;South Africa origin) variant, it is unlikely that casirivimab and imdevimab together will be active against this variant.

Casirivimab and imdevimab together retained activity against authentic SARS-CoV-2 variants of B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.617.1 (Kappa) lineages (Table 10), although casirivimab alone, but not imdevimab, had reduced activity against B.1.351 (5-fold), P.1 (>371-fold) and B.1.617.1 (6-fold) variants.

It is not known how pseudotyped VLP or authentic SARS-CoV-2 data correlate with clinical outcomes.

Table 10: Authentic SARS-CoV-2 Neutralization Data for Casirivimab and Imdevimab Together

SARS-CoV-2 Lineage	Country First Identified	WHO Nomenclature	Key Substitutions[a]	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y	no change[b]
B.1.351	South Africa	Beta	K417N+E484K+N501Y	no change[b]
P.1	Brazil	Gamma	K417T+E484K+N501Y	no change[b]
B.1.617.2	India	Delta	L452R+T478K	no change[b]
B.1.617.1	India	Kappa	L452R+E484Q	no change[b]

[a] Key substitutions occurring in receptor binding domain of spike protein which are associated with each lineage

[b] No change: ≤2-fold reduction in susceptibility.

In clinical trial COV-2067, interim data indicated only one variant (G446V) occurring at an allele fraction ≥15%, which was detected in 3/66 subjects who had nucleotide sequencing data, each at a single time point (two at baseline in subjects from placebo and 2,400 mg casirivimab and imdevimab groups, and one at Day 25 in a subject from the 8,000 mg casirivimab and imdevimab group). The G446V variant had reduced susceptibility to imdevimab of 135-fold compared to wild-type in a pseudotyped VSV VLP neutralization assay but retained susceptibility to casirivimab alone and casirivimab and imdevimab together.

It is possible that resistance-associated variants to casirivimab and imdevimab together could have cross-resistance to other mAbs targeting the receptor binding domain of SARS-CoV-2. The clinical impact is not known.

Immune Response Attenuation

There is a theoretical risk that antibody administration may attenuate the endogenous immune response to SARS-CoV-2 and make patients more susceptible to re-infection.

16 NONCLINICAL TOXICOLOGY

Carcinogenicity, genotoxicity, and reproductive toxicology studies have not been conducted with casirivimab and imdevimab.

In a toxicology study in cynomolgus monkeys, casirivimab and imdevimab had no adverse effects when administered intravenously or subcutaneously. Non-adverse liver findings (minor transient increases in AST and ALT) were observed.

In tissue cross-reactivity studies with casirivimab and imdevimab using human adult and fetal tissues, no binding of clinical concern was detected.

17 ANIMAL PHARMACOLOGIC AND EFFICACY DATA

Casirivimab and imdevimab administered together has been assessed in rhesus macaque and Syrian golden hamster treatment models of SARS-CoV-2 infection. Therapeutic administration of casirivimab and imdevimab together at 25 mg/kg or 150 mg/kg into rhesus macaques (n=4 for each dosing group) 1-day post infection resulted in approximately 1-2 $\log_{10}$ reductions in genomic and sub-genomic viral RNA in nasopharyngeal swabs and oral swabs at Day 4 post-challenge in most animals, and reduced lung pathology relative to placebo-treated animals. Therapeutic administration of casirivimab and imdevimab together at 5 mg/kg and 50 mg/kg doses to hamsters 1-day post infection resulted in reduced weight loss relative to placebo treated animals. In the prophylactic setting in rhesus macaques, administration of 50 mg/kg casirivimab and imdevimab together prior to challenge with SARS-CoV-2 demonstrated reduction in viral RNA via nasopharyngeal, oral swabs and bronchioalveolar lavage fluid, as well as a reduction in lung inflammation. In the prophylactic setting in hamsters, administration of 0.5 mg/kg, 5 mg/kg, or 50 mg/kg casirivimab and imdevimab together prior to challenge with SARS-CoV-2 protected against weight loss, and reduced percentage of lung area showing pneumonia pathology and severity of lung inflammation, indicative of reduced morbidity in this model. The applicability of these findings to a clinical setting is not known.

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

18.1 Treatment of Mild to Moderate COVID-19 (COV-2067)

The data supporting this EUA are based on the analysis of Phase 1/2/3 from trial, COV-2067 (NCT04425629). This is a randomized, double-blinded, placebo-controlled clinical trial evaluating REGEN-COV (casirivimab and imdevimab) for the treatment of subjects with mild to moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized). Cohort 1 enrolled adult subjects who were not hospitalized and had 1 or more COVID-19 symptoms that were at least mild in severity. Treatment was initiated within 3 days of obtaining a positive

SARS-CoV-2 viral infection determination. Subjects in the Phase 3 primary efficacy analysis met the criteria for high risk for progression to severe COVID-19, as shown in Section 2.

In the Phase 3 trial, 4,567 subjects with at least one risk factor for severe COVID-19 were randomized to a single intravenous infusion of 600 mg of casirivimab and 600 mg of imdevimab (n=838), 1,200 mg of casirivimab and 1,200 mg of imdevimab (n=1,529), 4,000 mg of casirivimab and 4,000 mg of imdevimab (n=700), or placebo (n=1,500) groups. The two REGEN-COV doses at the start of Phase 3 were 4,000 mg and 1,200 mg of each component; however, based on Phase 1/2 efficacy analyses showing that the 4,000 mg and 1,200 mg doses of each component were similar, the Phase 3 portion of the protocol was amended to compare 1,200 mg dose of each component vs. placebo and 600 mg dose of each component vs. placebo. Comparisons were between subjects randomized to the specific REGEN-COV dose and subjects who were concurrently randomized to placebo.

At baseline, in all randomized subjects with at least one risk factor, the median age was 50 years (with 13% of subjects ages 65 years or older), 52% of the subjects were female, 84% were White, 36% were Hispanic or Latino, and 5% were Black or African American. In subjects with available baseline symptom data, 15% had mild symptoms, 42% had moderate, 42% had severe symptoms, and 2% reported no symptoms at baseline; the median duration of symptoms was 3 days; mean viral load was 6.2 $\log_{10}$ copies/mL at baseline. The baseline demographics and disease characteristics were well balanced across the casirivimab and imdevimab and placebo treatment groups.

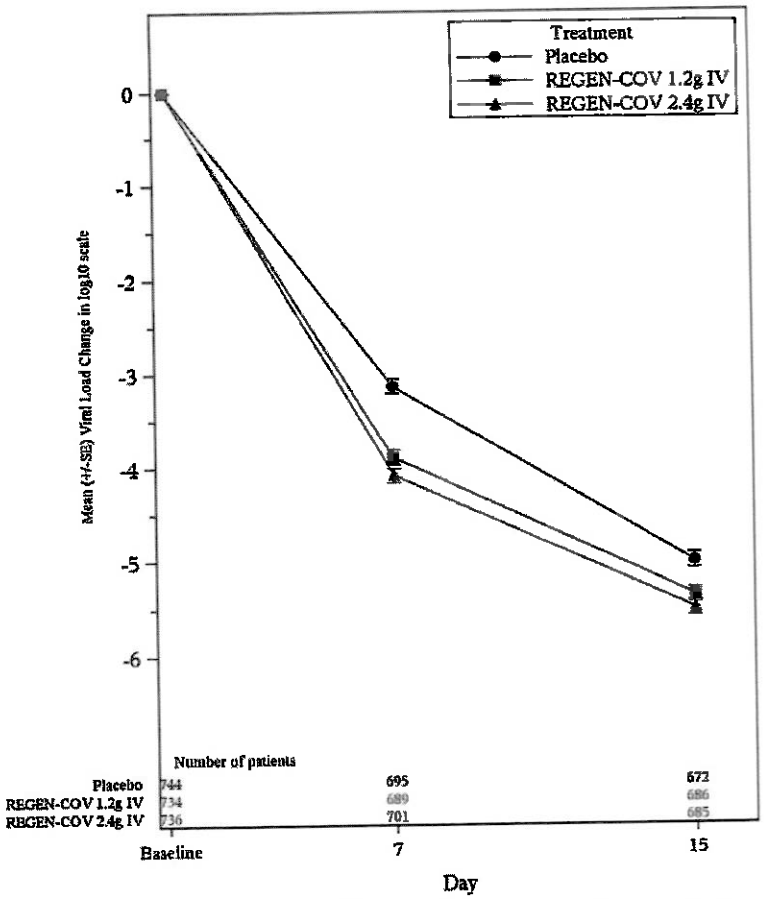
The primary endpoint was the proportion of subjects with ≥1 COVID-19-related hospitalization or all-cause death through Day 29, in subjects with a positive SARS-CoV-2 RT-qPCR result from nasopharyngeal (NP) swab at randomization, and with at least one risk factor for severe COVID-19, i.e., the modified full analysis set (mFAS). In the mFAS, events (COVID-19-related hospitalization or all-cause death through Day 29) occurred in 7 (1.0%) subjects treated with 600 mg of casirivimab and 600 mg of imdevimab compared to 24 (3%) subjects concurrently randomized to placebo, demonstrating a 70% reduction in COVID-19-related hospitalization or all-cause death compared to placebo (p=0.0024). Events occurred in 18 (1.3%) subjects treated with 1,200 mg of casirivimab and 1,200 mg of imdevimab compared to 62 (5%) subjects concurrently randomized to placebo, demonstrating a 71% reduction compared to placebo (REGEN-COV 1% vs placebo 5%, p<0.0001). In the 1,200 mg analysis, there was 1 death each in the REGEN-COV and placebo arm (p=1.0); and in 2,400 mg analysis, there were 1 and 3 deaths, respectively, in the REGEN-COV and placebo arms (p=0.3721). Overall, similar effects were observed for 600 mg of casirivimab and 600 mg of imdevimab and 1,200 mg of casirivimab and 1,200 mg of imdevimab doses, indicating the absence of a dose effect; therefore the 600 mg of casirivimab and 600 mg of imdevimab dose is authorized and the 1,200 mg of casirivimab and 1,200 mg of imdevimab dose is no longer authorized under this EUA (See Table 11). Results were consistent across subgroups of patients defined by nasopharyngeal viral load >10^6 copies/mL at baseline or serologic status.

Table 11: Proportion of subjects with ≥1 COVID-19-related hospitalization or all-cause death through day 29 (COV-2067)

	600 mg of casirivimab and 600 mg of imdevimab (intravenous)	**Placebo**	**1,200 mg of casirivimab and 1,200 mg of imdevimab (intravenous)**	**Placebo**
	n=736	n=748	n=1,355	n=1,341
# of subjects with at least 1 event (COVID-19-related hospitalization or all-cause death)	7 (1.0%)	24 (3.2%)	18 (1.3%)	62 (4.6%)
Risk reduction	70% (p=0.0024)		71% (p<0.0001)	

Treatment with REGEN-COV resulted in a statistically significant reduction in the LS mean viral load (log_{10} copies/mL) from baseline to Day 7 compared to placebo (-0.71 log_{10} copies/mL for 600 mg dose of casirivimab and 600 mg of imdevimab and -0.86 log_{10} copies/mL for 2,400 mg; $p<0.0001$). Reductions were observed in the overall mFAS population and in other subgroups, including those with baseline viral load $>10^6$ copies/mL or who were seronegative at baseline. Consistent effects were observed for the individual doses, indicating the absence of a dose effect. Figure 1 shows the mean change from baseline in SARS-COV-2 viral load to Day 15.

Figure 1: Change from Baseline in SARS-COV-2 Viral Load (log_{10} copies/mL) to Day 15 (COV-2067)



REGEN-COV 1.2 g IV = 600 mg of casirivimab and 600 mg of imdevimab administered intravenously
REGEN-COV 2.4 g IV = 1,200 mg of casirivimab and 1,200 mg of imdevimab administered intravenously

The median time to symptom resolution, as recorded in a trial-specific daily symptom diary, was 10 days for REGEN-COV-treated subjects, as compared with 14 days for placebo-treated subjects (p=0.0001 for 600 mg of casirivimab and 600 mg of imdevimab vs. placebo; p<0.0001 for 1,200 mg of casirivimab and 1,200 mg of imdevimab vs. placebo). Symptoms assessed were fever, chills, sore throat, cough, shortness of breath/difficulty breathing, nausea, vomiting, diarrhea, headache, red/watery eyes, body aches, loss of taste/smell, fatigue, loss of appetite, confusion, dizziness, pressure/tight chest, chest pain, stomachache, rash, sneezing, sputum/phlegm, runny nose. Time to COVID-19 symptom resolution was defined as time from randomization to the first day during which the subject scored 'no symptom' (score of 0) on all of the above symptoms except cough, fatigue, and headache, which could have been 'mild/moderate symptom' (score of 1) or 'no symptom' (score of 0).

18.2 Post-exposure Prophylaxis of COVID-19 (COV-2069)

The data supporting this EUA for post-exposure prophylaxis of COVID-19 are based on the efficacy analysis of data from the Phase 3 COV-2069 trial (NCT04452318). This is a randomized, double-blind, placebo-controlled clinical trial studying REGEN-COV (casirivimab

and imdevimab) for post-exposure prophylaxis of COVID-19 in household contacts of individuals infected with SARS-CoV-2 (index case).

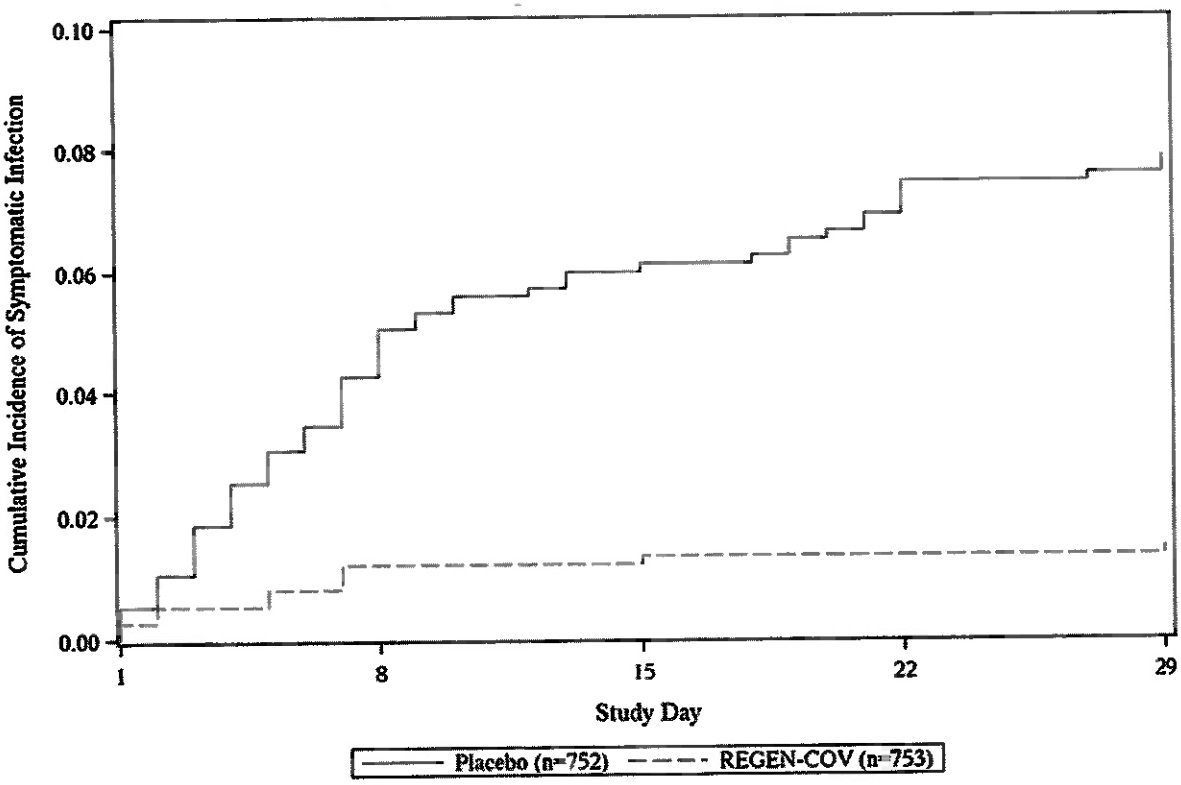
The trial enrolled subjects who were asymptomatic and who lived in the same household with a SARS-CoV-2 infected patient. Subjects were randomized 1:1 to a single dose of 600 mg of casirivimab and 600 mg of imdevimab or placebo administered subcutaneously within 96 hours of collection of the index cases' positive SARS-CoV-2 diagnostic test sample.

Subjects with a negative SARS-CoV-2 RT-qPCR test result at baseline (n=2,067) were enrolled and randomized in Cohort A. The primary analysis population included subjects who were SARS-CoV-2 RT-qPCR negative and seronegative at baseline. Of the 1,505 subjects in the primary analysis population, 753 subjects were randomized to receive REGEN-COV and 752 subjects were randomized to placebo. Following randomization and dosing, subjects had SARS-CoV-2 RT-qPCR testing via a nasopharyngeal swab every 7 days as well as weekly interviews with the investigator for assessment of COVID-19 symptoms during the 28-day efficacy assessment period. No data were collected on the type or extent of exposure to the index case.

For the primary analysis population at baseline, the median age was 44 years (with 9% of subjects ages 65 years or older), 54% of the subjects were female, 86% were White, 41% were Hispanic or Latino, and 9% were Black. The baseline demographics and disease characteristics were well balanced across the casirivimab and imdevimab and placebo treatment groups.

The primary efficacy endpoint was the proportion of subjects who developed RT qPCR-confirmed COVID-19 through Day 29. In the primary analysis population (RT-qPCR negative and seronegative at baseline), there was an 81% risk reduction in the development of COVID-19 with REGEN-COV treatment versus placebo [11/753 (1%) and 59/752 (8%); adjusted odds ratio 0.17; $p<0.0001$]. Figure 2 shows the cumulative incidence of COVID-19 through Day 29. Similar results were obtained in a sensitivity analysis that included RT-qPCR negative subjects at baseline, regardless of baseline serological status, where there was an 82% risk reduction in RT-qPCR-confirmed COVID-19 with REGEN-COV treatment versus placebo. There was a 66% risk reduction in the proportion of participants with any RT-qPCR-confirmed SARS-CoV-2 infection (symptomatic or asymptomatic) with REGEN-COV treatment versus placebo [36/753 (5%) and 107/752 (14%); adjusted odds ratio 0.31; $p<0.0001$].

Figure 2: Cumulative Incidence of Symptomatic COVID-19 (COV-2069 Cohort A)



In a post-hoc analysis in the subgroup of subjects who met the criteria for high risk for progression to severe COVID-19 (as shown in Section 2), there was a 76% risk reduction in COVID-19 with REGEN-COV treatment versus placebo [10/570 (2%) vs 42/567 (7%); adjusted odds ratio 0.22; p<0.0001].

In Cohort B, asymptomatic subjects with a positive SARS-CoV-2 RT-qPCR test result at baseline (n=311) were enrolled and randomized 1:1 to REGEN-COV or placebo. In a post-hoc analysis of the overall combined Cohort A and Cohort B (regardless of serology status at baseline), there was a 62% risk reduction in COVID-19 with REGEN-COV treatment versus placebo [46/1201 (4%) vs 119/1177 (10%); adjusted odds ratio 0.35; p<0.0001].

19 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Co-formulated casirivimab and imdevimab injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution supplied in a vial. Refer to Table 12.

Casirivimab injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution supplied in a vial. Refer to Table 13.

Imdevimab injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution supplied in a vial. Refer to Table 13.

REGEN-COV (casirivimab and imdevimab) injection is available as:

1. **A single vial which contains two antibodies co-formulated in a 1:1 ratio of casirivimab and imdevimab** (Table 12).
2. **Individual antibody solutions in separate vials, which may be supplied in separate cartons** (Table 13) **or together in a single carton (also referred to as a co-packaged carton)** (Table 14)**, or in a dose pack** (Table 15)**.**

Table 12: Co-Formulated Casirivimab and Imdevimab

Antibody	Concentration	Package Size	NDC Number
REGEN-COV (casirivimab and imdevimab)	600 mg/600 mg per 10 mL (60 mg/60 mg per mL)	1 vial per carton	61755-039-01

INDIVIDUAL CASIRIVIMAB AND IMDEVIMAB SOLUTIONS MUST BE ADMINISTERED TOGETHER.

Table 13: Individual Package Size

Antibody	Concentration	Package Size	NDC Number
Casirivimab REGN10933	1,332 mg/11.1 mL (120 mg/mL)	1 vial per carton	61755-024-01
	300 mg/2.5 mL (120 mg/mL)	1 vial per carton	61755-026-01
Imdevimab REGN10987	1,332 mg/11.1 mL (120 mg/mL)	1 vial per carton	61755-025-01
	300 mg/2.5 mL (120 mg/mL)	1 vial per carton	61755-027-01

Each co-packaged carton contains 1 vial of casirivimab and 1 vial of imdevimab. Refer to Table 14.

Table 14: Casirivimab and Imdevimab Co-Packaged Carton

Co-Packaged Carton Contents	Co-Packaged Components	Concentration	Co-Packaged Carton NDC Number
2 Vials	**1 vial of casirivimab** (NDC 61755-024-00)	1,332 mg/11.1 mL (120 mg/mL)	61755-042-02
	1 vial of imdevimab (NDC 61755-025-00)	1,332 mg/11.1 mL (120 mg/mL)	

2 Vials	**1 vial of casirivimab** (NDC 61755-026-00)	300 mg/2.5 mL (120 mg/mL)	61755-045-02
	1 vial of imdevimab (NDC 61755-027-00)	300 mg/2.5 mL (120 mg/mL)	

Each REGEN-COV dose pack contains sufficient number of vials of casirivimab [REGN10933] and imdevimab [REGN10987] to prepare up to two treatment doses (600 mg of casirivimab and 600 mg of imdevimab). Refer to Table 15.

Table 15: Dose Pack Providing 1,200 mg Casirivimab and 1,200 mg Imdevimab

REGEN-COV Dose Pack Size	REGEN-COV Dose Pack Components	Concentration	REGEN-COV Dose Pack NDC Number
2 Cartons	**1 vial of casirivimab REGN10933** (NDC 61755-024-01)	1,332 mg/11.1 mL (120 mg/mL)	61755-035-02
	1 vial of imdevimab REGN10987 (NDC 61755-025-01)	1,332 mg/11.1 mL (120 mg/mL)	
8 Cartons	**4 vials of casirivimab REGN10933** (NDC 61755-026-01)	300 mg/2.5 mL (120 mg/mL)	61755-036-08
	4 vials of imdevimab REGN10987 (NDC 61755-027-01)	300 mg/2.5 mL (120 mg/mL)	
5 Cartons	**1 vial of casirivimab REGN10933** (NDC 61755-024-01)	1,332 mg/11.1 mL (120 mg/mL)	61755-037-05
	4 vials of imdevimab REGN10987 (NDC 61755-027-01)	300 mg/2.5 mL (120 mg/mL)	
5 Cartons	**4 vials of casirivimab REGN10933** (NDC 61755-026-01)	300 mg/2.5 mL (120 mg/mL)	61755-038-05
	1 vial of imdevimab REGN10987 (NDC 61755-025-01)	1,332 mg/11.1 mL (120 mg/mL)	

Storage and Handling

Casirivimab is preservative-free. Discard any unused portion.
Imdevimab is preservative-free. Discard any unused portion.

Store unopened casirivimab and imdevimab vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Unopened vials may be stored in the original carton at room temperature [up to 25°C (77°F)] and must be used within 30 days. If not used in the 30 days, discard vials.

DO NOT FREEZE. DO NOT SHAKE. DO NOT EXPOSE TO DIRECT LIGHT.

Solution in vial requires dilution prior to intravenous administration. The prepared infusion solution is intended to be used immediately. If immediate administration is not possible, store diluted casirivimab and imdevimab infusion solution in the refrigerator at 2°C to 8°C (36°F to 46°F) for no more than 36 hours or at room temperature up to 25°C (77°F) for no more than 4 hours. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.

The prepared syringes should be administered immediately. If immediate administration is not possible, store the prepared casirivimab and imdevimab syringes in the refrigerator between 2°C to 8°C (36°F to 46°F) for no more than 24 hours, or at room temperature up to 25°C (77°F) for no more than 8 hours. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 20 minutes prior to administration.

20 PATIENT COUNSELING INFORMATION

Patients treated with REGEN-COV (casirivimab and imdevimab) should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect "high touch" surfaces, and frequent handwashing) according to CDC guidelines. Also see Fact Sheet for Patients, Parents and Caregivers.

21 CONTACT INFORMATION

For additional information visit www.REGENCOV.com
If you have questions, please contact Regeneron at 1-844-734-6643.

REGENERON

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U.S. FOOD & DRUG ADMINISTRATION

Frequently Asked Questions on the Emergency Use Authorization of REGEN-COV (Casirivimab and Imdevimab)

As of January 24, 2022, due to the high frequency of the Omicron variant, REGEN-COV is not currently authorized for use in any U.S. region because of markedly reduced activity against the omicron variant. Therefore, this drug may not be administered for treatment or post-exposure prevention of COVID-19 under the Emergency Use Authorization until further notice by the Agency. FDA will continue to closely monitor the SARS-CoV-2 variants using resources such as using the CDC's Variant website, and will determine whether use in a geographic region is consistent with the scope of authorization for REGEN-COV. FDA's determination and any updates will be available at Emergency Use Authorizations for Drugs and Non-Vaccine Biological Products.

Q. What is an Emergency Use Authorization (EUA)?
A: Under section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), when the Secretary of Health and Human Services declares that an emergency use authorization is appropriate, FDA may authorize unapproved medical products or unapproved uses of approved medical products for emergency use. In issuing an EUA, the FDA must determine, among other things, that, based on the totality of the scientific evidence available, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by a chemical, biological, radiological, or nuclear agent; that the known and potential benefits, when used to treat, diagnose or prevent such disease or condition, outweigh the known and potential risks for the product; and that there are no adequate, approved, and available alternatives. Emergency use authorization is NOT the same as FDA approval or licensure.

Q. What does this EUA authorize? What are the limitations of authorized use?
A. This EUA authorizes the emergency use of the investigational drug product REGEN-COV (casirivimab and imdevimab) for both treatment and as post-exposure prophylaxis:

Treatment

Treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adult and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Limitations of Authorized Use for Treatment

- REGEN-COV is not authorized for treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information such as variant susceptibility to this drug and regional variant frequency.
    - FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility [see Microbiology/Resistance Information (15) in Fact Sheet for Health Care Providers], and CDC regional variant frequency data. FDA's determination and any updates will be available at Emergency Use Authorizations for Drugs and Non-Vaccine Biological Products.

- REGEN-COV (casirivimab with imdevimab) is not authorized for use in patients:
  - who are hospitalized due to COVID-19, OR
  - who require oxygen therapy due to COVID-19, OR
  - who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying nonCOVID-19 related comorbidity.
- Monoclonal antibodies, such as REGENCOV, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

Post-Exposure Prophylaxis

For use as post-exposure prophylaxis of COVID-19 in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications) **and**
  - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC) **or**
  - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing home or prisons).

In general, people are considered fully vaccinated two weeks after their second dose in a two-dose series (the Pfizer or Moderna vaccines) **OR** two weeks after a single-dose vaccine (the Janssen vaccine).

The CDC defines close contact as someone who has been within six feet of an infected person (laboratory-confirmed or a clinically compatible illness) for a cumulative total of 15 minutes or more over a 24-hour period.

Limitations of Authorized Use for Post-Exposure Prophylaxis

- REGEN-COV is not authorized for post-exposure prophylaxis COVID-19 in geographic regions where exposure is likely to have been to a non-susceptible SARS-CoV-2 variant, based on available information including variant susceptibility to this drug and regional variant frequency.
  - FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility *[*see Microbiology/Resistance Information (15) in Fact Sheet for Health Care Providers*]*, and CDC regional variant frequency data. FDA's determination and any updates will be available at Emergency Use Authorizations for Drugs and Non-Vaccine Biological Products.
- Post-exposure prophylaxis with REGEN-COV is not a substitute for vaccination against COVID-19. FDA has authorized three vaccines, and approved two, to prevent COVID-19 and serious clinical outcomes caused by COVID-19, including hospitalization and death. FDA urges you to get

vaccinated, if you are eligible. Learn more about FDA-authorized COVID-19 vaccines. Find a COVID-19 vaccine near you at vaccines.gov.

- REGEN-COV is not authorized for pre-exposure prophylaxis for prevention of COVID-19.

Q. Why has FDA not revoked the authorization for REGEN-COV due to the omicron variant?
A. FDA may revoke an EUA if, for example, the statutory criteria for authorization under section 564(c) of the Federal Food, Drug, and Cosmetic Act are no longer met. The Agency recognizes that REGEN-COV may retain activity against future circulating SARS-CoV-2 variants other than the Omicron variant, and that the pattern of circulating variants of SARS-CoV-2 throughout the United States may also shift over time.

Based on the totality of scientific evidence available at this time, FDA has determined that the statutory criteria continue to be met, including that the known and potential benefits of REGEN-COV outweigh the known and potential risks, when used consistent with the terms and conditions of the authorization to:

- treat a patient with mild-to-moderate COVID-19 likely caused by a variant that is susceptible to this therapy, or
- when used as post-exposure prophylaxis of COVID-19 in an individual likely exposed to a susceptible variant to this therapy.

As such, FDA is not revoking the authorization for REGEN-COV at this time, but is instead limiting the authorization of use.

Q. Does the EUA permit the use of REGEN-COV as authorized in patients hospitalized *for reasons other* than COVID-19?
A: REGEN-COV co-formulated product and REGEN-COV supplied as individual vials to be administered together is authorized for emergency use for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19, including hospitalization or death.

If a patient is hospitalized *for reasons other* than COVID-19, such as for an elective orthopedic procedure, and the patient reports mild-to-moderate symptoms of COVID-19, confirmed with positive results of a direct SARS-CoV-2 viral test, then treatment with REGEN-COV may be appropriate, if the patient is also at high risk for progressing to severe COVID-19, including hospitalization or death, and the terms and conditions of the authorization are met, as detailed in the Fact Sheet for Health Care Providers.

REGEN-COV is not authorized for use in patients:

- who are hospitalized *due to* COVID-19, or
- who require oxygen therapy *due to* COVID-19, or
- who require an increase in baseline oxygen flow rate *due to* COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

Q: What does direct SARS-CoV-2 viral testing mean?
A. Direct SARS-CoV-2 viral tests diagnose active COVID-19 infection. Direct SARS-CoV-2 viral tests include two types of diagnostic tests for COVID-19:

- Molecular tests, such as reverse transcription polymerase chain reaction (RT-PCR) tests, that detect the virus's genetic material.
- Antigen tests that detect specific proteins from the virus.

Antibody tests should not be used to diagnose COVID-19 and are not direct SARS-CoV-2 viral tests. Antibody tests look for antibodies that the immune system makes in response to the SARS-CoV-2 virus.

Q. What data supported the Agency's determination that REGEN-COV would not retain activity against the Omicron variant?
A. As conditions to the EUA for REGEN-COV, Regeneron is required to monitor and test the activity of REGEN-COV against variants of the virus that cause COVID-19. For the Omicron variant, Regeneron submitted testing data to FDA.

The authorized monoclonal antibodies need to bind to the spike protein of the virus in order to neutralize the virus. Following the emergence of the Omicron variant, Regeneron assessed the activity of their product(s) against this variant and submitted these data to the FDA for review. Neutralization assays using virus-like particles (VLP) expressing SARS-CoV-2 spike proteins showed that REGEN-COV had marked reductions in neutralization activity. Specifically, the ability of REGEN-COV to neutralize VLPs expressing the spike protein of the Omicron variant was dramatically lower as compared to that of VLPs expressing the spike protein from the original strain of the virus. Using a measurement called neutralization, there was greater than 1000-fold reduction in the activity. These data are shown in Section 15 of the Health Care Provider Fact Sheet.

Q. How is high risk defined under the EUA?
A. The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example age ≥65 years of age)
- Obesity or being overweight (for example, adults with BMI >25 kg/m2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19))

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19, and authorization of REGEN-COV under the EUA is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: People with Certain Medical Conditions. Healthcare providers should consider the benefit-risk for an individual patient.

Q: Can adults weighing less than 40 kg receive REGEN-COV?
A: Yes. REGEN-COV is authorized for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Adults can be treated regardless of their weight; pediatric patients must be at least 12 years of age and weigh at least 40 kg.

Q. Are casirivimab and imdevimab monoclonal antibodies? What are monoclonal antibodies?
A. Yes, casirivimab and imdevimab are monoclonal antibodies. Monoclonal antibodies are laboratory-produced molecules engineered to serve as substitute antibodies that can restore, enhance or mimic the immune system's attack on pathogens. Casirivimab and imdevimab, administered together, are designed to block viral attachment and entry into human cells, thus neutralizing the virus.

Q. When, and how, should REGEN-COV be administered to a patient for its treatment use?
A. The EUA authorizes REGEN-COV to be administered as soon as possible after a positive viral test for COVID-19 and within 10 days of symptom onset. REGEN-COV is authorized for intravenous infusion, and intravenous infusion is strongly recommended. Subcutaneous injection is authorized as an alternative route of administration when intravenous infusion is not feasible and would lead to delay in treatment.

More information about dosage and administration is available in the Fact Sheet for Health Care Providers.

Q: Does "within 10 days of symptom onset" mean that a patient should have shown symptoms to receive REGEN-COV for its treatment use?
A. Yes. Symptom onset is the point at which a patient starts exhibiting symptoms. Patients should be treated as soon as possible after a positive viral test for SARS-CoV-2 **and** within ten days of COVID-19 symptom onset. If a patient has a positive viral test for SARS-CoV-2 but does not show symptoms, they do not meet the definition of mild-to-moderate disease.

REGEN-COV is authorized for emergency use by FDA for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Patients with mild to moderate COVID-19 are those patients who are actively exhibiting certain symptoms of COVID-19 illness (such as, fever, cough, sore throat, headache, malaise, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell).

For more information on mild-to-moderate COVID-19, refer to the National Institutes of Health's website at: Clinical Spectrum | COVID-19 Treatment Guidelines (nih.gov).

Therefore, patients who are at high risk for progression to severe COVID-19, including hospitalization or death, with mild-to-moderate COVID-19 disease (i.e., symptoms consistent with mild-to-moderate illness at the time of treatment) and who are within 10 days of symptom onset are within the scope of the EUA.

Q. Is REGEN-COV approved by the FDA to treat or prevent COVID-19?
A. No. REGEN-COV is an investigational drug. It is not currently FDA-approved to treat or prevent any diseases or conditions, including COVID-19. REGEN-COV is only authorized under an EUA; it is not a replacement for vaccination against COVID-19.

Q. Are there data showing REGEN-COV may provide benefit for the treatment of certain patients with COVID-19 or as post-exposure prophylaxis of COVID-19?
A. Yes. The most important scientific evidence supporting the authorization for REGEN-COV for treatment of COVID-19 comes from the phase 3 portion of a randomized, double-blind, placebo-controlled clinical trial in 4,567 non-hospitalized adults with mild-to-moderate COVID-19 symptoms and at least one risk factor for severe COVID-19. Of these patients, 838 received a single intravenous infusion of 600 mg of casirivimab and 600 mg of imdevimab, 1,529 received 1,200 mg of casirivimab and 1,200 mg of imdevimab, 700 received 4,000 mg of casirivimab and 4,000 mg of imdevimab, and 1,500 received a placebo within three days of obtaining a positive SARS-CoV-2 viral test.

The data from this clinical trial showed that high risk outpatients with mild-to-moderate COVID-19 demonstrated a similar reduction in risk of hospitalization or death with either the lower doses or the higher doses of casirivimab and imdevimab, administered together, compared to placebo. In addition, patients that received either the lower doses or the higher doses of casirivimab and imdevimab administered together had a faster time to symptom resolution in the clinical trial.

The primary data supporting the post-exposure prophylaxis of COVID-19 are from a Phase 3 trial. The trial was a randomized, double-blind, placebo-controlled clinical trial studying a single dose of REGEN-COV for prevention of COVID-19 in household contacts of individuals infected with SARS-CoV-2. Cases were confirmed using real-time reverse transcription–polymerase chain reaction (RT-PCR), one of the most accurate laboratory methods for detecting, tracking, and studying COVID-19. An 81% reduction in confirmed symptomatic COVID-19 cases was observed with REGEN-COV compared to placebo at day 29 in cases who were RT-PCR negative and seronegative at baseline (the primary analysis population). In the overall trial population, there was a 62% reduction in RT-PCR confirmed symptomatic COVID-19 cases in the REGEN-COV group compared to placebo at day 29.

Details on the clinical trial results can be found in section 18 of the authorized Fact Sheet for Health Care Providers.

Q. What is the authorized dose and route of administration for REGEN-COV?
A. The authorized dose for REGEN-COV for both treatment and as post-exposure prophylaxis is 600 mg of casirivimab and 600 mg of imdevimab administered together.

- For *treatment*, intravenous infusion is strongly recommended; subcutaneous (under the skin) injection is authorized as an alternative route of administration when intravenous infusion is not feasible and would lead to delay in treatment.

- For *post-exposure prophylaxis*, either intravenous infusion or subcutaneous injection is appropriate. For individuals who remain at high risk of exposure to another individual with SARS-CoV-2 for longer than 4 weeks, and who are not expected to mount an adequate immune response to full SARS-CoV-2 vaccination, following an initial dose of 600 mg of casirivimab and 600 mg of imdevimab, repeat doses of 300 mg of casirivimab and 300 mg of imdevimab once every 4 weeks are appropriate for the duration of ongoing exposure.

Q. Are there side effects (adverse events) of REGEN-COV?
A. Approximately 16,000 non-hospitalized and hospitalized subjects with symptomatic COVID-19 received REGEN-COV intravenously in clinical trials at doses of 600 mg of casirivimab and 600 mg of imdevimab or higher doses. Approximately 2,500 subjects have received subcutaneous injections of 600 mg of casirivimab and 600 mg of imdevimab or higher doses.

Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of REGEN-COV. Infusion-related reactions have been observed with administration of REGEN-COV. In the clinical trial in non-hospitalized patients, these reactions have been rare [infusion-related reactions of at least moderate severity were observed in 10 subjects (0.2%) who received REGEN-COV intravenously at the authorized dose or a higher dose], but may be severe or life threatening.

Signs and symptoms of infusion-related reactions may include:

- fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vasovagal reactions (e.g., pre-syncope, syncope), dizziness.

Based on reporting of adverse events that occurred after administration of REGEN-COV, clinical worsening of COVID-19 after administration has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to REGEN-COV use or were due to progression of COVID-19.

In a separate trial in healthy (non-hospitalized) adults, 600 mg of casirivimab and 600 mg of imdevimab were administered together subcutaneously in approximately 700 subjects. Injection site reactions were the most commonly reported adverse events after subcutaneous administration; and the remaining side effects with subcutaneous administration were similar to those observed with intravenous administration. Injection site reactions were the commonly reported side effects with repeat dosing every 4 weeks for six months.

These are not all the possible side effects of REGEN-COV, as not a lot of people have received REGEN-COV. Serious and unexpected side effects may happen. REGEN-COV is still being studied so it is possible that all of the risks are not known at this time. REGEN-COV is contraindicated in individuals with a previous severe hypersensitivity reaction, including anaphylaxis, to REGEN-COV.

Q. Is there likely to be an increased risk of infusion-related reactions with shorter versus longer infusion times?
A. FDA does not anticipate an increased risk of infusion-related reactions with the shorter infusion times or use of different size saline bags for dilution authorized. The preparation and administration instructions, including the shorter durations of infusion with smaller volumes of diluent were based on data evaluated by FDA including product quality data and data from clinical trials.

Q. How can REGEN-COV be obtained for use under the EUA?
A. For questions on how to obtain REGEN-COV under current distribution procedures, please contact COVID19therapeutics@hhs.gov.

Q. Are there reporting requirements for healthcare facilities and providers as part of the EUA?
A. Yes. As part of the EUA, FDA requires health care providers who prescribe REGEN-COV to report all medication errors and serious adverse events considered to be potentially related to REGEN-COV through FDA's MedWatch Adverse Event Reporting program. Providers can complete and submit the report online; or download and complete the form, then submit it via fax at 1-800-FDA-0178. This requirement is outlined in the EUA's Fact Sheet for Health Care Providers. FDA MedWatch forms should also be provided to Regeneron.

Healthcare facilities and providers must report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services. Such information and data should be reported through HHS Protect, Teletracking or National Healthcare Safety Network.

Q. Do patient outcomes need to be reported under the EUA?
A. No, reporting of patient outcomes is not required under the EUA. However, reporting of all medication errors and serious adverse events considered to be potentially related to REGEN-COV is required.

Q. Can health care providers share the patient/caregiver Fact Sheet electronically?
A. The letter of authorization for REGEN-COV requires that Regeneron and its authorized distributors make the Fact Sheets available to healthcare facilities and health care providers through Regeneron's website.

The letter of authorization (LOA) requires that healthcare facilities and healthcare providers ensure that they are aware of the LOA. The Fact Sheets must be made available to healthcare providers and to patients and caregivers, respectively, through "appropriate means", prior to the administration of the authorized product. Electronic delivery of the Fact Sheet is an appropriate means. For example, Fact Sheets can be delivered to a patient, parent or caregiver as a PDF electronically prior to medication administration. Health care providers should confirm receipt of the Fact Sheet with the patient.

Q. How is REGEN-COV supplied?
A. REGEN-COV is available in three distinct presentations:

> *Co-packaged REGEN-COV:* Co-packaged REGEN-COV is comprised of one vial each of both casirivimab and imdevimab inside a single carton. Individual vial and carton container labeling for casirivimab and imdevimab covered in the authorized co-packaged presentation will be clearly marked with either "For pandemic use" or "For Use under Emergency Use Authorization."
>
> *Dose pack bags:* Dose pack bags will include a sufficient number of vials of casirivimab and imdevimab to prepare up to two treatment doses or up to four doses for repeat dose prophylaxis, if appropriate. Casirivimab and imdevimab are each supplied in individual single use vials. Individual vials and carton container labeling for casirivimab and imdevimab included in dose pack bags are clearly marked "For Use under Emergency Use Authorization."

Co-formulated solution of REGEN-COV: The co-formulated solution of REGEN-COV contains two antibodies in a 1:1 ratio in a single dose vial consisting of 600 mg casirivimab and 600 mg of imdevimab per 10 mL (60 mg/60 mg per mL). Individual vials of co-formulated REGEN-COV are clearly marked "For Use under Emergency Use Authorization."

Individual vials of 1,200 mg of casirivimab and 1,200 mg of imdevimab distributed prior to the reissuance of EUA letter of authorization remain authorized for emergency use. FDA is not requiring that such product be repackaged given the public health need for the product. The use of the individual vials of casirivimab and imdevimab must be consistent with the terms and conditions of the reissued authorization. Individual vial labels for casirivimab and imdevimab and carton labeling may be clearly marked with either "Caution: New Drug - Limited by Federal (or United States) law to investigational use" or with "For use under Emergency Use Authorization (EUA)". Some vial labels and carton labeling of casirivimab and imdevimab may be instead labeled with the Investigational New Drug (IND) clinical trial code name as "REGN10933" and "REGN10987", respectively.

Casirivimab and imdevimab must be administered together by either intravenous infusion only or subcutaneous injection. Intravenous infusion is strongly recommended for treating infected symptomatic outpatients; and subcutaneous injection is an alternative route of administration when intravenous infusion is not feasible and would lead to delay in treatment. For post-exposure prophylaxis, casirivimab and imdevimab can be administered either by the subcutaneous or the intravenous route.

See the Health Care Provider Fact Sheet for dose preparation and administration. Regeneron's Dear Health Care Provider Letter also provides additional information for health care providers regarding vial and carton labeling, as well as contact information for healthcare providers and patients who may have questions.

Q. Can I be vaccinated for COVID-19 if I received a monoclonal antibody for COVID-19?
A. Health care providers should refer to recommendations of the Advisory Committee on Immunization Practices concerning the timing of vaccination.

FDA updates Sotrovimab emergency use authorization

Update [4/5/2022] Sotrovimab is no longer authorized to treat COVID-19 in any U.S. region due to increases in the proportion of COVID-19 cases caused by the Omicron BA.2 sub-variant

This statement updates the statements below.

The Centers for Disease Control and Prevention (CDC) Nowcast data (https://covid.cdc.gov/covid-data-tracker/#variant-proportions) from April 5, 2022, estimates that the proportion of COVID-19 cases caused by the Omicron BA.2 variant is above 50% in all Health and Human Services (HHS) U.S. regions. Data included in the health care provider fact sheet (https://www.fda.gov/media/149534/download) show the authorized dose of sotrovimab is unlikely to be effective against the BA.2 sub-variant. Due to these data, sotrovimab is not authorized in any U.S. state or territory at this time.

Health care providers should use other approved or authorized products (https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs) as they choose appropriate treatment options for patients.

FDA will continue to monitor BA.2 in all U.S. regions and will provide follow-up communication when appropriate.

Update [3/30/2022] FDA limits use of Sotrovimab to treat COVID-19 in additional U.S. regions due to the BA.2 Omicron sub-variant

This statement updates the statements below.

The Centers for Disease Control and Prevention (CDC) Nowcast data (https://covid.cdc.gov/covid-data-tracker/#variant-proportions) from March 29, 2022 estimates that the proportion of COVID-19 cases caused by the Omicron BA.2 variant is above 50% in three additional Health and Human Services (HHS) regions (5, 9, and 10). Due to these data, FDA has added these regions to the list of states and territories where sotrovimab is not authorized at this time.

Sotrovimab is not authorized at this time in the following states and territories:

- Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont (Region 1) (as of 3/25/2022)

- New Jersey, New York, Puerto Rico, and the Virgin Islands (Region 2) (as of 3/25/2022)
- Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin (Region 5) (as of 3/30/2022)
- Arizona, California, Hawaii, Nevada, American Samoa, Commonwealth of the Northern Mariana Islands, Federated States of Micronesia, Guam, Marshall Islands, and Republic of Palau (Region 9) (as of 3/30/2022)
- Alaska, Idaho, Oregon, and Washington (Region 10) (as of 3/30/2022)

Sotrovimab remains authorized in U.S. regions where the CDC Nowcast point estimate for the proportion of the Omicron BA.2 variant remains below 50%. FDA will continue to monitor BA.2 in all U.S. regions and may revise the authorization further to ensure that patients with COVID-19 have effective treatments available. Health care providers in regions where sotrovimab remains authorized should strongly consider the use of other approved or authorized products (https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs), and monitor the frequency of BA.2 in their region (https://covid.cdc.gov/covid-data-tracker/#variant-proportions) as they choose appropriate treatment options for patients.

Update [3/25/2022] FDA limits use of Sotrovimab to treat COVID-19 in some U.S. regions due to the BA.2 Omicron sub-variant

This statement updates and replaces the original statement below from 2/25/22.

The U.S. Food and Drug Administration is continually monitoring how authorized and approved treatments for COVID-19 are affected by changing variants—currently Omicron and the Omicron sub-variants, such as BA.2. Today, considering the most recent data available, FDA is announcing that sotrovimab is no longer authorized for use at this time in the following states and territories:

- Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont (Health and Human Services [HHS] Region 1)
- New Jersey, New York, Puerto Rico, and the Virgin Islands (HHS Region 2)

New data included in the health care provider fact sheet (/media/149534/download?attachment) shows that the authorized dose of sotrovimab is unlikely to be effective against the BA.2 sub-variant. Based on Centers for Disease Control and Prevention Nowcast data, the BA.2 sub-variant is estimated to account for more than 50% of cases in the states and territories in Regions 1 and 2 listed above (https://covid.cdc.gov/covid-data-tracker/#variant-proportions) as of March 19, 2022.

There are several other therapies (https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs) – Paxlovid, Veklury (remdesivir), bebtelovimab, and Lagevrio (molnupiravir) – that are expected to be effective against the BA.2 sub-variant, and that are authorized or approved to treat certain patients with mild-to-moderate COVID-19 who are at high risk for progression to severe disease, including hospitalization or death. Health care providers should assess whether these treatments are right for their patients.

We will continue to monitor BA.2 in all U.S. regions and may revise the authorization further to ensure that patients with COVID-19 have effective treatments available. Health care providers should also monitor the frequency of BA.2 in their region (https://covid.cdc.gov/covid-data-tracker/#variant-proportions) as they choose appropriate treatment options for patients.

[2/25/2022] On February 23, 2022, FDA revised the emergency use authorization for sotrovimab to clarify that sotrovimab is not authorized for treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a variant that is not susceptible to this treatment. However, sotrovimab is currently authorized in all U.S. regions until further notice by FDA. For other limitations and conditions, refer to the emergency use authorization (EUA) (https://www.fda.gov/media/149532/download).

FDA will continue to monitor conditions to determine whether use in a geographic region is consistent with the scope of authorization, referring to available information, including information on variant susceptibility and CDC regional variant frequency data (https://covid.cdc.gov/covid-data-tracker/#variant-proportions).

This EUA authorizes sotrovimab for the treatment of mild-to-moderate COVID-19 in adults and certain pediatric patients with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Sotrovimab should be administered by a qualified health care provider as a single intravenous infusion (IV) as soon as possible after positive viral test for COVID-19 and within seven days of symptom onset.

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR SOTROVIMAB

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use SOTROVIMAB under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for SOTROVIMAB.

SOTROVIMAB injection, for intravenous use
Original EUA Authorized Date: 05/2021

----------RECENT MAJOR CHANGES----------

Clinical Pharmacology, Microbiology (12.4)	3/2023
Emergency Use Authorization, Limitations of Authorized Use (1)	2/2022
Dosage and Administration, Recommended Dosage (2.3)	2/2022
Dosage and Administration, Preparation and Administration (2.5)	2/2022

----------EUA FOR SOTROVIMAB----------

- The Secretary of Health and Human Services has issued an EUA for the emergency use of sotrovimab for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

However, sotrovimab is not approved for this use (i.e., sotrovimab has not been demonstrated to be safe and effective for this use).

Limitations of Use:

- Sotrovimab is not authorized for treatment of mild-to-moderate COVID-19 when infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to these drugs and regional variant frequency (1, 12.4).
  - FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.
- Sotrovimab is not authorized for use in patients who:
  - are hospitalized due to COVID-19, OR
  - require oxygen therapy and/or respiratory support due to COVID-19, OR
  - require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 in those patients on chronic oxygen.

See Full Fact Sheet for Healthcare Providers for the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19 (1).

----------DOSAGE AND ADMINISTRATION----------

- The recommended dosage of sotrovimab in patients 12 years of age and older weighing at least 40 kg is 500 mg administered as a single intravenous infusion. (2.2)
- See Full Prescribing Information for instructions on preparation and administration. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 500 mg/8 mL (62.5 mg/mL) single-dose vial. (3)

----------CONTRAINDICATIONS----------

History of anaphylaxis to sotrovimab or to any of the excipients in the formulation. (4)

----------WARNINGS AND PRECAUTIONS----------

Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions: Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of sotrovimab. If clinically significant hypersensitivity reactions or anaphylaxis occur, discontinue and initiate appropriate supportive care. Infusion-related reactions have occurred during the infusion and up to 24 hours post infusion. These reactions may be severe or life threatening. (5.1)

Clinical Worsening After SARS-CoV-2 Monoclonal Antibody Administration: Clinical worsening of COVID-19 after administration of SARS-CoV-2 monoclonal antibody treatment has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, tachycardia, bradycardia), fatigue, and altered mental status. (5.2)

Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19: Benefit of treatment with sotrovimab has not been observed in patients hospitalized due to COVID-19. SARS-CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. (5.3)

----------ADVERSE REACTIONS----------

The most common adverse reactions (incidence ≥1%) included rash, diarrhea, infusion-related reactions, and hypersensitivity adverse reactions. (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to sotrovimab (1) by submitting FDA Form 3500 online, (2) by downloading this form and then submitting by mail or fax, or (3) contacting the FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to GSK, Global Safety: Fax: 919-287-2902; E-mail: WW.GSKAEReportingUS@gsk.com; or call GSK at 1-866-475-2684 to report adverse events. (6.4)

----------DRUG INTERACTIONS----------

Clinical drug-drug interaction studies have not been performed with sotrovimab. Sotrovimab is not renally excreted or metabolized by cytochrome P450 (CYP) enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely. (7)

See PATIENT AND PARENTS/CAREGIVER FACT SHEET.

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* Sections or subsections omitted from the EUA are not listed

FULL FACT SHEET FOR HEALTHCARE PROVIDERS

1 EMERGENCY USE AUTHORIZATION

The Secretary of Health and Human Services (HHS) has issued an Emergency Use Authorization (EUA) for the emergency use of sotrovimab for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. However, sotrovimab is not approved for this use (i.e., sotrovimab has not been demonstrated to be safe and effective for this use).

LIMITATIONS OF AUTHORIZED USE

- Sotrovimab is not authorized for treatment of mild-to-moderate COVID-19 when infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to these drugs and regional variant frequency *[see Microbiology (12.4)]*.
  - FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.[1]
- Sotrovimab is not authorized for use in patients who:
  - are hospitalized due to COVID-19, OR
  - require oxygen therapy and/or respiratory support due to COVID-19, OR
  - require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 in those patients on chronic oxygen.

Benefit of treatment with sotrovimab has not been observed in patients hospitalized due to COVID-19. SARS-CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation *[see Warnings and Precautions (5.2)]*.

Sotrovimab is not FDA-approved for any use, including for the treatment of COVID-19.

Sotrovimab is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of sotrovimab under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Justification for Emergency Use of Drugs During the COVID-19 Pandemic

There is currently an outbreak of Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2, a novel coronavirus. The Secretary of HHS has declared that:

- A public health emergency related to COVID-19 has existed since January 27, 2020.
- Circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic (March 27, 2020 declaration).

An EUA is a Secretary of HHS authorization for the emergency use of an unapproved product or unapproved use of an approved product (i.e., drug, biological product, or device) in the United States under certain circumstances including, but not limited to, when the Secretary of HHS declares that

[1] FDA will monitor conditions to determine whether the use of sotrovimab is consistent with this scope of authorization, referring to available information, including information on variant susceptibility *[see Microbiology (12.4)]*, and the CDC national and/or regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions.

there is a public health emergency that affects the national security or the health and security of United States citizens living abroad, and that involves biological agent(s) or a disease or condition that may be attributable to such agent(s). Criteria for issuing an EUA include:

- The biological agent(s) can cause a serious or life-threatening disease or condition;
- Based on the totality of the available scientific evidence (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that
  - the product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition; and
  - the known and potential benefits of the product - when used to diagnose, prevent, or treat such disease or condition - outweigh the known and potential risks of the product, taking into consideration the material threat posed by the biological agent(s);
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the serious or life-threatening disease or condition.

Information Regarding Available Alternatives for the EUA Authorized Use

Veklury (remdesivir) is FDA-approved for the treatment of COVID-19 in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) who are hospitalized, or who are not hospitalized, have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death. Veklury is administered via intravenous infusion for a total treatment duration of 3 days in patients who are not hospitalized.

Although Veklury is an approved alternative treatment of mild-to-moderate COVID-19 in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) who are not hospitalized and have mild-to-moderate COVID-19, FDA does not consider Veklury to be an adequate alternative to sotrovimab for this authorized use because it may not be feasible or clinically appropriate for certain patients.

Other therapeutics are currently authorized under Emergency Use Authorization for the same use as sotrovimab. For additional information on all products authorized for treatment or prevention of COVID-19, please see https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

For information on clinical studies of sotrovimab and other therapies for the treatment of COVID-19, see www.clinicaltrials.gov.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Sotrovimab is authorized for the use in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death *[see Clinical Studies (14)]*.

Medical conditions or other factors that may place individual patients at higher risk for progression to severe COVID-19 are listed on the following CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html.

2.2 Important Administration Information

Sotrovimab should be administered intravenously within 7 days of symptom onset.

Sotrovimab should be administered by a qualified healthcare professional and administered only in settings which have immediate access to medications to treat a severe infusion reaction, such as

anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary *[see Warnings and Precautions (5.1)]*.

Sotrovimab is available as a concentrated solution and **must be diluted** prior to IV infusion.

Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

2.3 Recommended Dosage

The recommended dosage for emergency use of sotrovimab authorized under this EUA is 500 mg administered as a single IV infusion over 15 minutes for 50-mL infusion bag or 30 minutes for 100-mL infusion bag.

2.4 Dosage Adjustment in Special Populations

No dosage adjustment is recommended in pregnant or lactating women, in elderly patients, or in patients with renal impairment *[see Use in Specific Populations (8)]*.

Pediatric Use

No dosage adjustment is recommended in pediatric patients who weigh at least 40 kg and are 12 years of age and older.

Sotrovimab is not authorized for patients under 12 years of age or in pediatric patients weighing less than 40 kg *[see Use in Specific Populations (8.4)]*.

2.5 Preparation and Administration

Preparation

Sotrovimab is supplied in a single-dose vial and **must be diluted** prior to IV infusion.

Sotrovimab concentrate for solution for infusion should be prepared by a qualified healthcare professional using aseptic technique.

- Gather a polyvinyl chloride (PVC) or polyolefin (PO), sterile, prefilled 50-mL or 100-mL infusion bag containing 0.9% Sodium Chloride Injection or 5% Dextrose Injection.
- Remove one vial of sotrovimab (500 mg/8 mL) from refrigerated storage and allow to equilibrate to room temperature, protected from light, for approximately 15 minutes.
- Inspect the vial of sotrovimab visually for particulate matter and discoloration prior to administration. Should either be observed, the solution must be discarded, and fresh solution prepared. Sotrovimab is a clear, colorless or yellow to brown solution.
- Gently swirl the vial several times before use without creating air bubbles. **Do not shake the vial.**
- Withdraw 8 mL of sotrovimab from the vial and inject into the prefilled infusion bag.
- Discard vial (even if some product remains).
- Prior to the infusion, gently rock the infusion bag back and forth by hand 3 to 5 times. **Do not invert the infusion bag.** Avoid forming air bubbles.
- This product is preservative-free; therefore, the diluted infusion solution should be administered immediately. If immediate administration is not possible, store the diluted solution of sotrovimab up to 6 hours at room temperature (up to 25°C [77°F]) or refrigerated up to 24 hours (2°C to 8°C [36°F to 46°F]).

Administration

Sotrovimab infusion solution should be administered by a qualified healthcare professional *[see*

Warnings and Precautions (5.1)].

Sotrovimab may only be administered in settings in which healthcare providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary *[see Warnings and Precautions (5.1)]*.

- Gather the materials for IV infusion via infusion pump or gravity:
  - Polyvinyl chloride (PVC) or polyolefin (PO) infusion set, and
  - Use of a 0.2 micron polyethersulfone (PES) filter is strongly recommended.
- Attach the infusion set to the IV bag using standard bore tubing.
- Prime the infusion set.
- Administer the entire infusion over 15 minutes for 50-mL infusion bag or 30 minutes for 100-mL infusion bag. Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.
- Do not administer as an IV push or bolus.
- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of sotrovimab with IV solutions and medications other than 0.9% Sodium Chloride Injection and 5% Dextrose Injection is not known.
- Once infusion is complete, **flush the tubing** with 0.9% Sodium Chloride or 5% Dextrose to ensure delivery of the required dose.
- If the infusion must be discontinued due to an infusion reaction, discard unused product.
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

3 DOSAGE FORMS AND STRENGTHS

Sotrovimab is a sterile, preservative-free, clear, colorless or yellow to brown solution for IV infusion only available as:

- Injection: 500-mg/8-mL (62.5-mg/mL) solution in a single-dose vial

4 CONTRAINDICATIONS

Sotrovimab is contraindicated in patients who have a history of anaphylaxis to sotrovimab or to any of the excipients in the formulation.

5 WARNINGS AND PRECAUTIONS

There are limited clinical data available for sotrovimab. Serious and unexpected adverse events may occur that have not been previously reported with sotrovimab use.

5.1 Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of sotrovimab *[see Adverse Reactions (6.1)]*. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related reactions, occurring during the infusion and up to 24 hours after the infusion, have

been observed with administration of sotrovimab. These reactions may be severe or life threatening.

Signs and symptoms of infusion-related reactions may include *[see Adverse Reactions (6.1)]*:

- fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vaso-vagal reactions (e.g., pre-syncope, syncope), dizziness, and diaphoresis.

If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care. Clinically monitor patients for at least 1 hour after completion of the infusion for signs and symptoms of hypersensitivity.

Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of SARS-CoV-2 monoclonal antibodies under Emergency Use Authorization.

5.2 Clinical Worsening after SARS-CoV-2 Monoclonal Antibody Administration

Clinical worsening of COVID-19 after administration of SARS-CoV-2 monoclonal antibody treatment has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to SARS-CoV-2 monoclonal antibody use or were due to progression of COVID-19.

5.3 Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19

Benefit of treatment with sotrovimab has not been observed in patients hospitalized due to COVID-19. SARS-CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Therefore, sotrovimab is not authorized for use in the following patient populations *[see Limitations of Authorized Use (1)]*:

- Patients who are hospitalized due to COVID-19, OR
- Patients who require oxygen therapy and/or respiratory support due to COVID-19, OR
- Patients who require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 in those patients on chronic oxygen.

6 ADVERSE REACTIONS

The following serious adverse reaction is described in more detail in the *Warnings and Precautions* section of the labeling:

- Hypersensitivity including anaphylaxis and infusion related reactions *[see Warnings and Precautions (5.1)]*.

6.1 Adverse Reactions from Clinical Studies

The following adverse reactions have been observed in the clinical studies of sotrovimab that supported EUA. The adverse reaction rates observed in these clinical studies cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice. Additional adverse events associated with sotrovimab may become apparent with more widespread use.

The safety of sotrovimab in subjects with mild-to-moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized) is based on analyses from COMET-ICE and COMET-TAIL *[see Clinical Studies (14)]*.

In COMET-ICE, subjects received a single 500-mg IV infusion of sotrovimab (n = 523) or placebo (n = 526). In COMET-TAIL, subjects received a single 500-mg IV infusion of sotrovimab (n = 393).

Infusion-Related Reactions Including Hypersensitivity

Infusion-related reactions, including immediate hypersensitivity reactions, were observed in 1% of subjects treated with sotrovimab and 1% of subjects treated with placebo in COMET-ICE and in <1% of subjects treated with IV sotrovimab in COMET-TAIL. Reported events that started within 24 hours of study treatment were pyrexia, chills, dizziness, dyspnea, pruritus, rash, and infusion-related reactions; all events were Grade 1 (mild) or Grade 2 (moderate).

One case of anaphylaxis was reported following sotrovimab infusion in a separate study evaluating sotrovimab in hospitalized subjects; the infusion was immediately discontinued, and the subject received epinephrine. The event resolved but recurred within 2 hours; the subject received another dose of epinephrine and improved with no additional symptoms. Other serious infusion-related reactions (including immediate hypersensitivity reactions) reported following sotrovimab infusion in the hospitalized study included Grade 3 (serious) or Grade 4 (life-threatening) bronchospasm and shortness of breath. These events were also reported following infusion of placebo. Sotrovimab is not authorized for use in subjects hospitalized due to COVID-19 *[see Warnings and Precautions (5.3)]*.

Hypersensitivity adverse reactions (i.e., adverse events assessed as causally related) were observed in 2% of subjects treated with sotrovimab and 1% of subjects treated with placebo in COMET-ICE and in <1% of subjects treated with sotrovimab in COMET-TAIL. All were Grade 1 (mild) or Grade 2 (moderate), and none of the reactions in either trial led to permanent discontinuation of the infusions. One reaction led to pausing of the infusion *[see Warnings and Precautions (5.1)]*.

Common Adverse Events

The most common treatment-emergent adverse events observed in the sotrovimab treatment group in COMET-ICE were rash (1%) and diarrhea (2%), all of which were Grade 1 (mild) or Grade 2 (moderate). No other treatment-emergent adverse events were reported at a higher rate with sotrovimab compared to placebo.

6.2 Adverse Reactions from Spontaneous Reports

The following adverse reactions have been identified during post-authorization use of sotrovimab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders

Anaphylaxis *[see Contraindications (4), Warnings and Precautions (5.1)]*.

6.4 Required Reporting for Serious Adverse Events and Medication Errors

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events* and medication errors potentially related to sotrovimab within 7 calendar days from the healthcare provider's awareness of the event, using FDA Form 3500 (for information on how to access this form, see below). The FDA requires that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race)
- A statement "Sotrovimab use for COVID-19 under Emergency Use Authorization (EUA)" under the **"Describe Event, Problem, or Product Use/Medication Error"** heading
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the

event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes)

- Patient's preexisting medical conditions and use of concomitant products
- Information about the product (e.g., dosage, route of administration, NDC #)

Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online at www.fda.gov/medwatch/report.htm, or
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax to 1-800-FDA-0178, or
- Call 1-800-FDA-1088 to request a reporting form.
- In addition, please provide a copy of all FDA MedWatch forms to:

  GlaxoSmithKline, Global Safety
  Fax: 919-287-2902
  Email: WW.GSKAEReportingUS@gsk.com
  Or call GSK at 1-866-475-2684 to report adverse events.

The prescribing health care provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of sotrovimab.

*Serious adverse events are defined as:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- Other important medical event, which may require a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

7 DRUG INTERACTIONS

Clinical drug-drug interaction studies have not been performed with sotrovimab. Sotrovimab is not renally excreted or metabolized by cytochrome P450 (CYP) enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to sotrovimab during pregnancy. Pregnant and recently pregnant individuals can go to https://covid-pr.pregistry.com to enroll or call 1-800-616-3791 to obtain information about the registry.

Risk Summary

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcome. Sotrovimab should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy *(see Clinical Considerations)*.

Nonclinical reproductive toxicity studies have not been conducted with sotrovimab. In a cross-reactive binding assay using a protein array enriched for human embryofetal proteins, no off-target binding was detected for sotrovimab. Since sotrovimab is a recombinant human immunoglobulin G (IgG) containing the LS modification in the Fc domain, it has the potential for placental transfer from the mother to the developing fetus. The potential treatment benefit or risk of placental transfer of sotrovimab to the developing fetus is not known.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk

COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

8.2 Lactation

Risk Summary

There are no available data on the presence of sotrovimab in human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for sotrovimab and any potential adverse effects on the breastfed infant from sotrovimab or from the underlying maternal condition. Individuals with COVID-19 who are breastfeeding should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

8.4 Pediatric Use

Sotrovimab is not authorized for use in pediatric patients under 12 years of age or weighing less than 40 kg. The safety and effectiveness of sotrovimab have not been assessed in pediatric patients. The recommended dosing regimen in patients 12 years to less than 18 years of age, weighing at least 40 kg, is expected to result in comparable serum exposures of sotrovimab as those observed in adults.

8.5 Geriatric Use

Of the 528 subjects randomized to receive sotrovimab 500 mg in COMET-ICE, 20% were 65 years of age and older and 11% were over 70 years of age. Of the 378 subjects in the primary analysis

population receiving sotrovimab 500 mg in COMET-TAIL, 25% were 65 years of age or older and 8% were over 75 years of age. In these trials, no notable differences in PK or safety were observed in geriatric subjects as compared to subjects less than 65 years of age.

8.6 Renal Impairment

No clinical trials have been conducted to evaluate the effects of renal impairment on the PK of sotrovimab. Sotrovimab is not eliminated intact in the urine, thus renal impairment is not expected to affect the exposure of sotrovimab.

8.7 Hepatic Impairment

No clinical trials have been conducted to evaluate the effects of hepatic impairment on the PK of sotrovimab. The impact of hepatic impairment on the PK of sotrovimab is unknown.

10 OVERDOSAGE

There is no human experience of acute overdosage with sotrovimab.

There is no specific treatment for an overdose with sotrovimab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

11 DESCRIPTION

Sotrovimab is a human immunoglobulin G-1 (IgG1-kappa) monoclonal antibody consisting of 2 identical light chain (LC) polypeptides composed of 214 amino acids each and 2 identical heavy chain (HC) polypeptides, each composed of 457 amino acids. Sotrovimab is produced by a Chinese Hamster Ovary cell line and has a molecular weight of approximately 149 kDa.

Sotrovimab injection is a sterile, preservative-free, clear, colorless or yellow to brown solution supplied in a single-dose vial for IV infusion after dilution.

Each mL contains sotrovimab (62.5 mg), L-histidine (1.51 mg), L-histidine monohydrochloride (2.15 mg), L-methionine (0.75 mg), polysorbate 80 (0.4 mg), and sucrose (70 mg). The solution of sotrovimab has a pH of 6.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sotrovimab is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antiviral drug ***[see Microbiology (12.4)]***.

12.3 Pharmacokinetics

A summary of pharmacokinetic parameters following a single 500-mg IV infusion is presented in Table 1 based on population pharmacokinetic analyses:

Table 1. Summary of IV Sotrovimab Serum Pharmacokinetic Exposure Parameters

Parameter[a]	Sotrovimab (500 mg IV)
C_{max}, mcg/mL	170.1 (53.4)
C_{D28}, mcg/mL	39.7 (37.6)
AUC_{D0-28}[b], day*mcg/mL	1564 (34.4)

[a] Parameters are reported as geometric mean (Geometric %CV).

[b] Based on a population pharmacokinetic analysis using data from a total of 1984 subjects across 5 clinical trials.

The primary analysis in the clinical efficacy study COMET-ICE was conducted when the ancestral Wuhan-Hu-1 virus was predominant, with the most common SARS-CoV-2 variants being Alpha and Epsilon among participants in the study population, which was enrolled prior to the emergence of the Delta and Omicron variants (Table 3).

Specific Populations

Based on available population pharmacokinetic analyses of sotrovimab dosages of 500 mg or less, the pharmacokinetics of sotrovimab administered intravenously were not affected by age or sex; body weight was identified as a significant covariate on the pharmacokinetics of sotrovimab, but the impact is not anticipated to be clinically relevant.

Renal impairment is not expected to impact the pharmacokinetics of sotrovimab since mAbs with molecular weight >69 kDa do not undergo renal elimination. Similarly, dialysis is not expected to impact the pharmacokinetics of sotrovimab.

12.4 Microbiology

Mechanism of Action

Sotrovimab is a recombinant human IgG1-kappa mAb that binds to a conserved epitope on the spike protein receptor binding domain of SARS-CoV-2 with a dissociation constant of K_D = 0.21 nM but does not compete with human ACE2 receptor binding (IC_{50} value >33.6 nM [5 µg/mL]). Sotrovimab inhibits an undefined step that occurs after virus attachment and prior to fusion of the viral and cell membranes. The Fc domain of sotrovimab includes M428L and N434S amino acid substitutions (LS modification) that extend antibody half-life, but do not impact wild-type Fc-mediated effector functions in cell culture.

Antiviral Activity

The neutralization activity of sotrovimab against SARS-CoV-2 (isolate WA1/2020) was measured in a concentration response model using cultured Vero E6 cells. Sotrovimab neutralized SARS-CoV-2 with an average EC_{50} value of 0.67 nM (100.1 ng/mL).

Sotrovimab demonstrated cell culture FcγR activation using Jurkat reporter cells expressing FcγRIIa (low-affinity R131 and high affinity H131 alleles), FcγRIIIa (low-affinity F158 and high-affinity V158 alleles), and FcγRIIb. Sotrovimab exhibited antibody-dependent cell-mediated cytotoxicity (ADCC) in cell culture using isolated human natural killer (NK) cells following engagement with target cells expressing spike protein. Sotrovimab also elicited antibody-dependent cellular phagocytosis (ADCP) in cell-based assays using $CD14^+$ monocytes targeting cells expressing spike protein.

Antibody Dependent Enhancement (ADE) of Infection

The risk that sotrovimab could mediate viral uptake and replication by immune cells was studied in U937 cells, primary human monocytic dendritic cells, and peripheral blood mononuclear cells. This

experiment did not demonstrate productive viral infection in immune cells exposed to SARS-CoV-2 in the presence of concentrations of sotrovimab from 1-fold down to 1000-fold below the EC_{50} value.

The potential for ADE was also evaluated in a hamster model of SARS-CoV-2 using sotrovimab. Intraperitoneal administration prior to inoculation resulted in a dose-dependent improvement in all measured outcomes (body weight, total viral RNA in the lungs, or infectious virus levels based on $TCID_{50}$ measurements). No evidence of enhancement of disease was observed at any dose evaluated, including sub-neutralizing doses down to 0.05 mg/kg.

Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to sotrovimab.

Cell Culture Studies: Spike protein amino acid substitution E340A emerged in cell culture selection of resistant virus and had a >100-fold reduction in activity in a pseudotyped virus-like particle (VLP) assay. This substitution is in the conserved epitope of sotrovimab, which is comprised of 23 amino acids. Pseudotyped VLP assessments in cell culture were performed using Wuhan-Hu-1, Omicron BA.1, and Omicron BA.2 spike proteins. The epitope amino acid substitutions P337H/K/L/N/R/T, E340A/I/K/G/Q/S/V, T345P, K356T, and L441N in the Wuhan-Hu-1 spike, conferred reduced susceptibility to sotrovimab based on observed fold-increase in EC_{50} value shown in parentheses: P337H (5.1), P337K (>304), P337L (>192), P337N (5.6), P337R (>192), P337T (10.6), E340A (>100), E340G (18.2), E340I (>190), E340K (>297), E340Q (>50), E340S (68), E340V (>200), T345P (225), K356T (5.9), and L441N (72). Epitope substitutions P337H (>631), K356T (>631), P337S (>609), E340D (>609), and V341F (5.9) in the Omicron BA.1 spike variant, and P337H (>117), P337S (>117), P337T (>117), E340D (>117), E340G (>117), K356T (>117), and K440D (5.1) in the Omicron BA.2 spike variant conferred reduced susceptibility to sotrovimab based on the observed fold-increase in EC_{50} value shown in parenthesis relative to each spike viral variant.

Table 2 provides cell culture neutralization data for SARS-CoV-2 variants. The clinical relevance of the fold reductions in susceptibility >5 is unknown. There are no data evaluating variants with fold reductions >5 in randomized controlled clinical studies.

Table 2. Sotrovimab Neutralization Data for SARS-CoV-2

SARS-CoV-2 Variant		Key Substitutions Tested[a]	Fold Reduction in Susceptibility[b]	
Lineage	WHO Nomenclature		Pseudotyped VLP	Authentic Virus
B.1.1.7	Alpha	N501Y	No change	No change
B.1.351	Beta	K417N+E484K+N501Y	No change	No change
P.1	Gamma	K417T+E484K+N501Y	No change	No change
B.1.617.2	Delta	L452R+T478K	No change	No change
AY.1 and AY.2	Delta [+K417N]	K417N+L452R+T478K	No change	Not tested
AY.4.2	Delta [+]	L452R+T478K	No change	Not tested
B.1.427/B.1.429	Epsilon	L452R	No change	Not tested
B.1.526	Iota	E484K	No change	Not tested
B.1.617.1	Kappa	L452R+E484Q	No change	No change
C.37	Lambda	L452Q+F490S	No change	Not tested
B.1.621	Mu	R346K+E484K+N501Y	No change	Not tested

B.1.1.529/BA.1	Omicron	G339D+S371L+S373P+ S375F+K417N+N440K+ G446S+S477N+T478K+ E484A+Q493R+G496S+ Q498R+N501Y+Y505H	No change	No change
BA.1.1	Omicron	G339D+R346K+S371L+ S373P+S375F+K417N+ N440K+G446S+S477N+ T478K+E484A+Q493R+ G496S+Q498R+N501Y+ Y505H	No change	No change
BA.2	Omicron	G339D+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ S477N+T478K+E484A+ Q493R+Q498R+N501Y+ Y505H	16	15.7[c]
BA.2.12.1	Omicron	G339D+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ L452Q+S477N+T478K+ E484A+Q493R+Q498R+ N501Y+Y505H	16.6	25.1[c]
BA.2.75	Omicron	G339H+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ G446S+N460K+S477N+ T478K+E484A+Q498R+ N501Y+Y505H	8.3	Not tested
BA.2.75.2	Omicron	G339H+R346T+S371F+ S373P+S375F+T376A+ D405N+R408S+K417N+ N440K+G446S+N460K+ S477N+T478K+E484A+ F486S+Q498R+N501Y+ Y505H	10	Not tested
BA.3	Omicron	G339D+S371F+S373P+ S375F+D405N+K417N+ N440K+G446S+S477N+ T478K+E484A+Q493R+ Q498R+N501Y+Y505H	7.3	Not tested
BA.4	Omicron	G339D+S371F+S373P+ S375F+T376A+D405N+	21.3	48.4[c]

		R408S+K417N+N440K+ L452R+S477N+T478K+ E484A+F486V+Q498R+ N501Y+Y505H		
BA.4.6	Omicron	G339D+R346T+S371F+ S373P+S375F+T376A+ D405N+R408S+K417N+ N440K+L452R+S477N+ T478K+E484A+F486V+ Q498R+N501Y+Y505H	57.9	Not tested
BA.5	Omicron	G339D+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ L452R+S477N+T478K+ E484A+F486V+Q498R+ N501Y+Y505H	22.6	21.6[c]
BF.7/BA.5.2.6	Omicron	G339D+R346T+S371F+ S373P+S375F+T376A+ D405N+R408S+K417N+ N440K+L452R+S477N+ T478K+E484A+F486V+ Q498R+N501Y+Y505H	74.2	Not tested
BN.1	Omicron	G339H+R346T+K356T+ S371F+S373P+S375F+ T376A+D405N+R408S+ K417N+N440K+G446S+ N460K+S477N+T478K+ E484A+F490S+Q498R+ N501Y+Y505H	778	Not tested
BQ.1	Omicron	G339D+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ K444T+L452R+N460K+ S477N+T478K+E484A+ F486V+Q498R+N501Y+ Y505H	28.5	Not tested
BQ.1.1	Omicron	G339D+R346T+S371F+ S373P+S375F+T376A+ D405N+R408S+K417N+ N440K+K444T+L452R+ N460K+S477N+T478K+ E484A+F486V+Q498R+ N501Y+Y505H	94	Not tested

XBB/XBB.1	Omicron	G339H+R346T+L368I+ S371F+S373P+S375F+ T376A+D405N+R408S+ K417N+N440K+V445P+ G446S+N460K+S477N+ T478K+E484A+F486S+ F490S+Q498R+N501Y+ Y505H	6.5	Not tested
XBB.1.5	Omicron	G339H+R346T+L368I+ S371F+S373P+S375F+ T376A+D405N+R408S+ K417N+N440K+V445P+ G446S+N460K+S477N+ T478K+E484A+F486P+ F490S+Q498R+N501Y+ Y505H	11.3	33.3[c]
XD	None[d]	G339D+S371L+S373P+ S375F+K417N+N440K+ G446S+S477N+T478K+ E484A+Q493R+G496S+ Q498R+N501Y+Y505H	Not tested	No change

[a] Substitutions in the spike receptor binding domain relative to wild-type are listed.

[b] Based on EC_{50} fold change compared to wild-type. No change: ≤5-fold change in EC_{50} value compared to wild-type.

[c] Sotrovimab inhibited authentic virus isolates of Omicron BA.2, BA.2.12.1, BA.4, BA.5, and XBB.1.5 lineages with maximum percentage inhibition in the range of 80% to 100%.

[d] Variant has not been named by the WHO.

Clinical Studies: SARS-CoV-2 variants of concern or variants of interest (VOC/VOI) were detected in participants enrolled in COMET-ICE (Table 3).

Table 3. SARS-CoV-2 VOC/VOI Detected at ≥2% Prevalence in Sotrovimab-Treated Participants

Clinical Study	VOC/VOI	Prevalence, % (n/N)[a]	Participants Meeting Primary Clinical Endpoint[b]
COMET-ICE	Alpha (B.1.1.7)	10% (35/338)	1
	Epsilon (B.1.427/B.1.429)	5% (16/338)	1
	Gamma (P.1)	3% (9/338)	0

[a] n = number of sotrovimab-treated participants with the designated VOC/VOI; N = total number of sotrovimab-treated participants with SARS-CoV-2 spike sequence results.

[b] The primary clinical endpoint for progression was defined as hospitalization for >24 hours for acute management of any illness or death from any cause through Day 29.

SARS-CoV-2 viruses with baseline and treatment-emergent substitutions at amino acid positions associated with reduced susceptibility to sotrovimab in cell culture were observed in COMET-ICE

(Table 4). Of the 32 sotrovimab-treated participants with a substitution detected at amino acid positions 337 and/or 340 at any visit baseline or post-baseline, only 1 met the primary endpoint for progression of hospitalization for >24 hours for acute management of any illness or death from any cause through Day 29. This participant had E340K detected post-baseline and was infected with the Epsilon variant of SARS-CoV-2.

Table 4. Baseline and Treatment-Emergent Substitutions Detected in Sotrovimab-Treated Participants at Amino Acid Positions Associated with Reduced Susceptibility to Sotrovimab

	Baseline[a]		Treatment-Emergent[b]	
Clinical Study	Substitutions	Frequency, % (n/N)	Substitutions	Frequency, % (n/N)
COMET-ICE	P337H, E340A	1% (4/307)	P337L/R, E340A/K/V	14% (24/170)[c]

[a] n = number of sotrovimab-treated participants with a baseline substitution detected at spike amino acid positions 337 or 340; N = total number of sotrovimab-treated participants with baseline sequence results.

[b] n = number of sotrovimab-treated participants with treatment-emergent substitutions detected at spike amino acid positions 337 or 340; N = total number of sotrovimab-treated participants with paired baseline and post-baseline sequence results.

[c] Four participants with a post-baseline substitution at P337 or E340 and lacking a baseline sequence are not included.

Immune Response Attenuation

There is a theoretical risk that antibody administration may attenuate the endogenous immune response to SARS-CoV-2 and make patients more susceptible to re-infection.

12.6 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies may be misleading.

Treatment-emergent anti-drug antibodies (ADAs) to sotrovimab were detected in 13% (65/513) of participants, through week 24, in the COMET-ICE study. None of the participants with confirmed treatment-emergent ADAs had neutralizing antibodies against sotrovimab.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis, mutagenesis, and reproductive toxicology studies with sotrovimab have not been conducted.

In a toxicology study in monkeys, sotrovimab had no adverse effects when administered intravenously.

In tissue cross reactivity studies using human and monkey adult tissues, no binding of clinical concern was detected for sotrovimab.

13.2 Animal Toxicology and/or Pharmacology

In a Syrian Golden hamster model of SARS-CoV-2 infection, antiviral activity was demonstrated using a single dose of sotrovimab which was administered intraperitoneally at 24- or 48-hours prior to infection. Animals receiving 5 mg/kg or more of the antibody showed a significant improvement in body weight loss and significantly decreased total lung SARS-CoV-2 viral RNA compared to vehicle only and control antibody-treated animals. Levels of virus in the lung (as measured by $TCID_{50}$) were significantly decreased versus controls in hamsters receiving 0.5 mg/kg or more of the antibody.

Protection was also observed in the Syrian Golden hamster model using the SARS-CoV-2 B.1.351 (Beta, South Africa origin) variant. Significant reductions in total and replication competent virus were observed on Day 4 post-infection in animals receiving a single intraperitoneal dose of 0.5, 2, 5, or 15 mg/kg sotrovimab compared to isotype control antibody-treated animals.

14 CLINICAL STUDIES

The clinical data supporting this EUA are based on the analysis of the Phase 1/2/3 COMET-ICE trial (NCT04545060) with supporting data from the Phase 3 COMET-TAIL trial (NCT04913675).

COMET-ICE (Study 214367)

COMET-ICE was a randomized, multi-center, double-blind, placebo-controlled trial studying sotrovimab for the treatment of subjects with mild-to-moderate COVID-19 (subjects with COVID-19 symptoms who were not hospitalized). Eligible subjects were 18 years of age and older with at least one of the following comorbidities: diabetes, obesity (BMI >30), chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, or moderate to severe asthma; or were 55 years of age and older regardless of comorbidities. The trial included symptomatic subjects with SARS-CoV-2 infection as confirmed by local laboratory tests and/or point of care tests and symptom onset within 5 days of enrollment. The study was conducted when the wild-type Wuhan-Hu-1 virus was predominant, with the highest frequency of variants being Alpha and Epsilon *[see Microbiology (12.4)]*. Subjects with severe COVID-19 requiring supplemental oxygen or hospitalization and severely immunocompromised subjects were excluded from the trial.

A total of 1,057 eligible subjects were randomized to receive a single 500-mg infusion of sotrovimab (n = 528) or placebo (n = 529) over 1 hour (Intent to Treat [ITT] population at Day 29). At baseline, the median age was 53 years (range:17 to 96); 20% of subjects were 65 years of age or older and 11% were over 70 years of age; 46% of subjects were male; 87% were White, 8% Black or African American, 4% Asian, 65% Hispanic or Latino. Fifty-nine percent of subjects received sotrovimab or placebo within 3 days of COVID-19 symptom onset and 41% within 4 to 5 days. The four most common pre-defined risk factors or comorbidities were obesity (63%), 55 years of age or older (47%), diabetes requiring medication (22%), and moderate-to-severe asthma (17%). Overall, baseline demographic and disease characteristics were well balanced between the treatment arms.

The primary endpoint, progression of COVID-19 at Day 29, was reduced by 79% (adjusted relative risk reduction) in recipients of sotrovimab versus placebo. Table 5 provides the results for the primary and key secondary endpoint of COMET-ICE.

Table 5. Efficacy Results in Adults with Mild-to-Moderate COVID-19 in COMET-ICE at Day 29

	Sotrovimab 500 mg n = 528	Placebo n = 529
Progression of COVID-19 (defined as hospitalization for >24 hours for acute management of any illness or death from any cause) (Day 29)[a]		
Proportion (n, %)	6 (1.1%)	30 (5.7%)
Adjusted Relative Risk Reduction (95% CI)	79% (50%, 91%)	
All-cause mortality (up to Day 29)		
Proportion (n, %)	0	2 (<1%)

[a] The determination of primary efficacy was based on a planned interim analysis of 583 subjects, which had similar findings to those seen in the full population above. The adjusted relative risk reduction was 85% with a 97.24% CI of (44%, 96%) and p-value = 0.002.

Within the subset of the ITT population who had a central laboratory confirmed, virologically quantifiable nasopharyngeal swab at Day 1 and Day 8 (n = 639), the mean decline in viral RNA levels from baseline to Day 8 was greater in subjects treated with sotrovimab (-2.610 $\log_{10}$ copies/mL) compared to that in subjects treated with placebo (-2.358); mean difference = -0.251, 95% CI: (-0.415, -0.087).

COMET-TAIL (Study 217114)

COMET-TAIL was a randomized, multi-center, open label trial which evaluated the efficacy, safety, and tolerability of sotrovimab for the treatment of subjects with mild-to-moderate COVID-19 (subjects with COVID-19 symptoms who were not hospitalized). Eligible subjects were 12 years of age or older with at least one of the following comorbidities: diabetes, obesity (BMI ≥85th percentile for age/gender based on Centers for Disease Control and Prevention [CDC] growth charts for adolescents or BMI ≥30 for subjects ≥18 years old), chronic kidney disease, congenital heart disease, congestive heart failure (for subjects ≥18 years old), chronic lung diseases, sickle cell disease, neurodevelopmental disorders, immunosuppressive disease or receiving immunosuppressive medications, or chronic liver disease; or were 55 years of age or older regardless of comorbidities. The trial included symptomatic subjects with SARS-CoV-2 infection as confirmed by local laboratory tests and/or point of care tests and symptom onset within 7 days of enrollment. Subjects with severe COVID-19 requiring supplemental oxygen or hospitalization were excluded from the trial.

The ITT population consisted of 385 subjects randomized to receive a single 500-mg IV infusion of sotrovimab over 15 minutes. The primary analysis population, which excluded 7 subjects because they were fully vaccinated and immunocompetent (key inclusion/exclusion violation), consisted of 378 subjects.

In the primary analysis population at baseline, the median age was 51 years (range:15 to 90, including 2 subjects under 18 years); 25% of subjects were 65 years of age or older and 8% were over 75 years of age; 42% of subjects were male; 96% were White and 4% were Black or African American; 83% were Hispanic or Latino. Forty-eight percent (48%) of subjects received sotrovimab within 3 days of COVID-19 symptom onset, 37% within 4 to 5 days, and 14% within 6 to 7 days. The four most common pre-defined risk factors or comorbidities were obesity (63%), 55 years of age or older (42%), chronic lung disease (16%), and diabetes requiring medication (13%).

In the primary analysis population, 5 (1.3%) of 378 subjects had progression to COVID-19 defined as hospitalization for >24 hours for acute management of any illness or death due to any cause through Day 29. No deaths were reported through Day 29.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Sotrovimab injection 500 mg (62.5 mg/mL) is a sterile, preservative-free, clear, colorless or yellow to brown solution supplied in a carton containing one single-dose glass vial with a rubber vial stopper (not made with natural rubber latex) and a flip-off cap (NDC 0173-0901-86).

Storage and Handling

Sotrovimab is preservative-free. Discard unused portion.

Store unopened vials refrigerated at 2°C to 8°C (36°F to 46°F) in original carton. Do not freeze or shake. Protect from light.

The concentrate for solution of sotrovimab in the vial is preservative-free and requires dilution prior to IV administration. The diluted infusion solution of sotrovimab should be administered immediately. If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) or up to 6 hours at room temperature (up to 25°C [up to 77°F]) including transportation and infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 15 minutes prior to administration.

17 PATIENT COUNSELING INFORMATION

As a healthcare practitioner, you must communicate to the patient and/or caregiver information consistent with the "FACT SHEET FOR PATIENTS AND CAREGIVERS" and provide them with a copy of this Fact Sheet prior to administration of sotrovimab. However, if providing this information will delay the administration of sotrovimab to a degree that would endanger the life of a patient, the information must be provided to the parent and/or caregiver as soon as feasible after sotrovimab administration.

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of sotrovimab. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, advise patients to alert healthcare provider immediately. Inform patients that hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of SARS-CoV-2 monoclonal antibodies and to alert their healthcare provider immediately if signs and symptoms of hypersensitivity occur *[see Warnings and Precautions (5.1)]*.

Pregnancy Registry

Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in individuals exposed to sotrovimab during pregnancy *[see Use in Specific Populations (8.1)]*.

18 MANUFACTURER INFORMATION

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U.S. FOOD & DRUG ADMINISTRATION

Frequently Asked Questions on the Emergency Use Authorization of Sotrovimab

Q. What is an Emergency Use Authorization (EUA)?

A. Under section 564 of the Federal Food, Drug & Cosmetic Act, the FDA may, pursuant to a declaration by the HHS Secretary based on one of four types of determinations, authorize an unapproved product or unapproved uses of an approved product for emergency use. In issuing an EUA, the FDA must determine, among other things, that, based on the totality of scientific evidence available, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by a chemical, biological, radiological, or nuclear agent; that the known and potential benefits, when used to treat, diagnose or prevent such disease or condition, outweigh the known and potential risks for the product; and that there are no adequate, approved, and available alternatives. Emergency use authorization is NOT the same as FDA approval or licensure.

Q. What does this EUA authorize? Are there limitations of the authorized use under this EUA?

A. This EUA authorizes sotrovimab, manufactured by GlaxoSmithKline LLC, to be used only for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Limitations of Authorized Use

Sotrovimab is not authorized for use in:

- Adults and pediatric patients who are hospitalized due to COVID-19, or
- Adult and pediatric patients who require oxygen therapy and/or respiratory support due to COVID-19, or
- Adult and pediatric patients who require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 in those patients on chronic oxygen.

Benefit of treatment with sotrovimab has **not** been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as sotrovimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

Sotrovimab is not authorized for treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARSCoV-2 variant based on available information including variant susceptibility to these drugs and regional variant frequency.

- FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility [see Microbiology/Resistance Information (15) in the Fact Sheet for Health Care Providers], and CDC's regional variant frequency data.
- FDA's determination and any updates will be available at Emergency Use Authorizations for Drugs and Non-Vaccine Biological Products.

For other limitations and conditions, refer to the EUA.

Q. How are the monoclonal antibody therapies affected by the SARS-CoV-2 viral variants in the U.S.?
A. Circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies. The frequency of these variants is being monitored by the FDA, Centers for Disease Control and Prevention (CDC), and other stakeholders. Health care providers should review the Antiviral Resistance information in Section 15 of the authorized Fact Sheets for each monoclonal antibody therapy available under an EUA for details regarding specific variants and resistance. Health care providers should also refer to the CDC website on Variant Proportions, and information from state and local health authorities regarding reports of viral variants of importance in their region to guide treatment decisions.

Q. What does direct SARS-CoV-2 viral testing mean?
A. Direct SARS-CoV-2 viral tests diagnose active COVID-19 infection. Direct SARS-CoV-2 viral tests include two types of diagnostic tests for COVID-19:

- Molecular tests, such as reverse transcription polymerase chain reaction (RT-PCR) tests, that detect the virus's genetic material.
- Antigen tests that detect specific proteins from the virus.

Antibody tests should not be used to diagnose COVID-19 and are not direct SARS-CoV-2 viral tests. Antibody tests look for antibodies that the immune system makes in response to the SARS-CoV-2 virus.

Q. How is high risk defined under the EUA?
A. The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example age ≥65 years of age)
- Obesity or being overweight (for example, adults with BMI >25 kg/m^2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID-19])

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of sotrovimab under the EUA is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC

website: People with Certain Medical Conditions. Healthcare providers should consider the benefit-risk for an individual patient.

Q. Can adults weighing less than 40 kg receive sotrovimab?
A. Yes. Sotrovimab is authorized for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Adults can be treated regardless of their weight; pediatric patients must be at least 12 years of age and weigh at least 40 kg.

Q. When should sotrovimab be administered to a patient?
A. Sotrovimab should be administered by a qualified healthcare provider as a single intravenous infusion (IV) as soon as possible after positive viral test for COVID-19 **and** within seven (7) days of symptom onset. More information about administration is available in the Fact Sheet for Health Care Providers.

Q. Does "within seven (7) days of symptom onset" mean that a patient should have shown symptoms to receive sotrovimab for treatment of COVID-19?
A. Yes. Symptom onset is the point at which a patient starts exhibiting symptoms. Patients should be treated as soon as possible after a positive viral test for SARS-CoV-2 **and** within seven (7) days of COVID-19 symptom onset. If a patient has a positive viral test for SARS-CoV-2 but does not show symptoms, they do not meet the definition of mild-to-moderate disease. Patients with mild-to-moderate COVID-19 are those patients who are actively exhibiting certain symptoms of COVID-19 illness (such as, fever, cough, sore throat, headache, malaise, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell).

Therefore, patients with mild-to-moderate COVID-19 disease (i.e., symptoms consistent with mild-to-moderate illness at the time of treatment) who are at high risk for progression to severe COVID-19, including hospitalization or death, and who have positive results of direct SARS-CoV-2 viral testing and who are within seven (7) days of symptom onset are within the scope of the EUA.

For more information on mild-to-moderate COVID-19, refer to the National Institutes of Health's website at: Clinical Spectrum | COVID-19 Treatment Guidelines (nih.gov).

Q. Does the EUA permit the use of sotrovimab as authorized in patients hospitalized *for reasons other* than COVID-19?
A. Yes. If a patient is hospitalized *for reasons other* than COVID-19, such as for an elective orthopedic procedure, and the patient reports mild to moderate symptoms of COVID-19, confirmed with positive results of a direct SARS-CoV-2 viral test, then treatment with sotrovimab may be appropriate, if the patient is also at high risk for progression to severe COVID-19, including hospitalization or death, and the terms and conditions of the authorization are met, as detailed in the Fact Sheet for Health Care Providers.

Sotrovimab is not authorized for use in:

- Adults and pediatric patients who are hospitalized due to COVID-19, or
- Adult and pediatric patients who require oxygen therapy and/or respiratory support due to COVID-19, or
- Adult and pediatric patients who require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 in those patients on chronic oxygen.

Q. How can sotrovimab be obtained for use under the EUA?
A. For questions on how to obtain sotrovimab under current distribution procedures, please contact COVID19therapeutics@hhs.gov.

Q. Is sotrovimab approved by the FDA to treat COVID-19?
A. No. Sotrovimab is an investigational drug. It is not currently FDA-approved to treat any diseases or conditions, including COVID-19.

Q. Is sotrovimab a monoclonal antibody? What are monoclonal antibodies?
A. Yes, sotrovimab is a monoclonal antibody. Monoclonal antibodies are laboratory-produced molecules engineered to serve as substitute antibodies that can restore, enhance or mimic the immune system's attack on pathogens. Sotrovimab is designed to block viral entry into human cells, thus neutralizing the virus.

Q. Are there data showing sotrovimab might benefit patients with COVID-19?
A. The initial data supporting benefit for sotrovimab are based on an analysis of an ongoing, randomized, double-blind, placebo-controlled clinical trial in non-hospitalized adults with mild-to-moderate COVID-19 symptoms at increased risk for COVID-19 disease progression due to age or other medical conditions. Of the 1,057 patients enrolled, 528 were treated with a single 500-mg infusion of sotrovimab, and 529 received a placebo. Eligible subjects were 18 years of age and older with at least one of the following comorbidities: diabetes, obesity (BMI >30), chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, or moderate to severe asthma, or were 55 years of age and older regardless of comorbidities.

The primary endpoint, progression of COVID-19 at Day 29 (defined as hospitalization for greater than 24 hours for acute management of any illness or death from any cause) was reduced by 79% (adjusted relative risk reduction) in recipients of sotrovimab versus placebo (95% confidence interval [50%, 91%]).

Q. Are there clinical trials underway evaluating sotrovimab for COVID-19?
A. Yes. Clinical trials remain ongoing to study sotrovimab for the treatment of COVID-19.

Q. Are there side effects (adverse events) of sotrovimab?
A. Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of sotrovimab in clinical trials. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related reactions have been observed with administration of sotrovimab. Signs and symptoms of infusion-related reactions may include:

- fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, or dizziness.

There have been reports of clinical worsening of COVID-19 after administration of COVID-19 monoclonal antibodies under EUA; signs or symptoms may include fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), fatigue, and altered mental status.

Some of these events required hospitalization. It is not known if these events were related to COVID-19 monoclonal antibody use or were due to progression of COVID-19.

These are not all the possible side effects of sotrovimab. Serious and unexpected side effects may happen. Sotrovimab is still being studied so it is possible that all of the risks are not known at this time.

Q. How can sotrovimab be obtained for use under the EUA?
A. For questions on how to obtain sotrovimab under current distribution procedures, please contact COVID19therapeutics@hhs.gov.

Q. Are there reporting requirements for healthcare facilities and providers as part of the EUA?
A. Yes. As part of the EUA, FDA requires health care providers who prescribe sotrovimab to report all medication errors and serious adverse events considered to be potentially related to sotrovimab through FDA's MedWatch Adverse Event Reporting program. Providers can complete and submit the report online; or download and complete the form, then submit it via fax at 1-800-FDA-0178. This requirement is outlined in the EUA's Fact Sheet for Health Care Providers. FDA MedWatch forms should also be provided to GlaxoSmithKline.

Q. Do patient outcomes need to be reported under the EUA?
A. No, reporting of patient outcomes is not required under the EUA. However, reporting of all medication errors and serious adverse events considered to be potentially related to sotrovimab is required.

Q. Does the EUA authorize sotrovimab to be used to prevent COVID-19?
A. No. Sotrovimab is not authorized for the prevention of COVID-19.

Q. Can health care providers share the Fact Sheet for Patient, Parents, and Caregivers electronically?
A. The letter of authorization for sotrovimab permits GlaxoSmithKline and its authorized distributors make the Fact Sheets available to healthcare facilities and health care providers through electronic means.

Q. Can I be vaccinated for COVID-19 if I was treated with a monoclonal antibody for COVID-19?
A. Health care providers should refer to recommendations of the Advisory Committee on Immunization Practices regarding vaccination.