The COVID-19 Treatment Guidelines Panel's Statement on the Emergency Use Authorization of Casirivimab Plus Imdevimab as Post-Exposure Prophylaxis for SARS-CoV-2 Infection

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Vaccination remains the most effective way to prevent SARS-CoV-2 infection. However, despite widespread availability of SARS-CoV-2 vaccines, a number of individuals are either not fully vaccinated or cannot mount adequate responses to the vaccine. Some of these people, if infected, are at high risk of progression to serious COVID-19. On July 30, 2021, the Food and Drug Administration (FDA) expanded the Emergency Use Authorization (EUA) indication for the anti-SARS-CoV-2 monoclonal antibodies casirivimab plus imdevimab to allow this combination to be used as post-exposure prophylaxis (PEP) for selected individuals, as described below.

The authorized dosage is casirivimab 600 mg plus imdevimab 600 mg administered as four subcutaneous (SQ) injections (2.5 mL per injection) at four different sites, or as a single intravenous (IV) infusion (for a list of individuals who are considered to be at high risk of progressing to severe COVID-19, see the FDA EUA). Casirivimab plus imdevimab should be administered as soon as possible after exposure.

Summary Recommendations and Considerations

Recommendation for Individuals With Symptoms That Are Consistent With COVID-19

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends that individuals who have recently been exposed to SARS-CoV-2 and have symptoms that are consistent with COVID-19 be evaluated for SARS-CoV-2 infection by either a nucleic acid amplification test (NAAT) or antigen testing **(AIII)**.
  - Individuals with positive SARS-CoV-2 NAAT or antigen test results who meet the Emergency Use Authorization (EUA) criteria for therapeutic use of anti-SARS-CoV-2 monoclonal antibodies should be referred for treatment (see Anti-SARS-CoV-2 Monoclonal Antibodies).
  - Those with negative test results should be considered for post-exposure prophylaxis (PEP) as discussed below.

Recommendations for Post-Exposure Prophylaxis

- The Panel recommends using **casirivimab 600 mg plus imdevimab 600 mg** administered as subcutaneous (SQ) injections **(AI)** or an intravenous (IV) infusion **(BIII)** as PEP for people who are at high risk for progression to severe COVID-19 if infected with SARS-CoV-2[a] **AND** who have the following vaccination status **AND** exposure history.
  - *Vaccination Status:*
    - Not fully vaccinated (defined as people who were never vaccinated or those who received the second vaccine dose in a two-dose series or a single-dose vaccine <2 weeks ago); *or*
    - Fully vaccinated, but not expected to mount an adequate immune response (e.g., those with immunocompromising conditions, including those who are taking immunosuppressive medications)

AND

  - *Exposure History to SARS-CoV-2:*
    - Had a recent exposure to an individual with SARS-CoV-2 infection that is consistent with the Centers for Disease Control and Prevention (CDC) close contact criteria;[b] *or*
    - At high risk of exposure to an individual with SARS-CoV-2 infection because of recent occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (e.g., nursing homes, prisons)

Timing and Doses of Casirivimab Plus Imdevimab

- The doses should be administered as soon as possible and preferably within 7 days of high-risk exposure **(AIII)**.

Summary Recommendations and Considerations, continued
• **Casirivimab 600 mg plus imdevimab 600 mg** should be given as four SQ injections (2.5 mL per injection) at four different sites **(AI)** or as a single IV infusion **(AIII)**. The patient should be observed for at least 1 hour after the injections or infusion. • There is insufficient evidence for the Panel to recommend either for or against repeat dosing every 4 weeks for those who received PEP and who continue to have high-risk exposures.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

[a] For a list of individuals who are considered to be at high risk of progressing to severe COVID-19, see the Food and Drug Administration EUA. It should be noted that the relative risk is not identical for all risk factors listed in the EUA. The presence of multiple risk factors in an individual is associated with a higher risk of progression. Providers should use clinical judgement when determining a patient's risk of progression.

[b] For the CDC definition of close contact, visit the CDC Glossary of Key Terms.

The strength of the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for using these anti-SARS-CoV-2 monoclonal antibodies for PEP varies based on the available evidence to date:

- **AI** for the population represented in the clinical trial, where the analysis included asymptomatic people with a negative SARS-CoV-2 test result (nucleic acid amplification test [NAAT] or antigen) who were exposed to someone in their household with a positive SARS-CoV-2 test result from a sample that was collected within the previous 96 hours, and who anticipated ongoing exposure over at least the next 28 days.
- **AIII** for individuals who meet the EUA criteria but not the clinical trial criteria.

Rationale

The Panel's recommendations for the use of casirivimab plus imdevimab for PEP are based on the available data from the EUA and the COVID-19 Phase 3 Prevention Trial.[1,2] The clinical trial included a population that was, in part, distinct from those authorized through the EUA. These differences account for the Panel's different ratings in different clinical scenarios.

The differences between the clinical trial and the EUA include the following:

- Enrollment in the trial was not limited to those who were at increased risk of severe COVID-19; however, at least 30% of patients met the study's prespecified high-risk criteria, and 75% met the expanded criteria included in the EUA.
- Enrollment in the trial was limited to those with household contacts, where the index patients had SARS-CoV-2 infections that were confirmed by samples that were collected during the preceding 96 hours. The enrolled participants also intended to continue living with the index patients for at least 28 days of follow-up.
- The trial only enrolled asymptomatic individuals. Among these individuals, 12.6% were SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) positive and 3.7% had an undetermined status.
- The trial randomized people with unknown SARS-CoV-2 serostatus but excluded individuals who were subsequently found to be seropositive (i.e., those who had evidence of prior COVID-19 infection) at baseline from the primary analysis. The absolute risk of infection was considerably lower in the seropositive individuals than in the seronegative individuals, but there remained an

81% relative risk reduction of infection among those who were given casirivimab plus imdevimab compared to those who received placebo in this group.

- The trial used SQ injections as the only route of administration.
- The EUA allows for repeat dosing of casirivimab 300 mg plus imdevimab 300 mg once every 4 weeks by SQ injections or IV infusion for those who meet the EUA criteria for PEP and have ongoing exposures. There are no data from the COVID-19 Phase 3 Prevention Trial or other studies on the utility of repeat dosing for individuals who continue to have high-risk exposures.

Clinical Trial Data on Casirivimab Plus Imdevimab as Post-Exposure Prophylaxis

The pivotal trial that demonstrated the efficacy of casirivimab plus imdevimab as PEP was a randomized, double-blind, placebo-controlled, Phase 3 trial that was conducted at 112 sites in the United States, Romania, and Moldova.[2] The trial enrolled individuals aged ≥12 years who were exposed to a household contact (the index patient) who had a positive SARS-CoV-2 RT-PCR result from a nasopharyngeal (NP) swab specimen that was collected within the previous 96 hours. Study participants were asymptomatic, had a negative RT-PCR result for SARS-CoV-2 from an NP swab, and intended to live with the index patient for the 28-day duration of follow-up.

Participants were randomized 1:1 to receive casirivimab 600 mg plus imdevimab 600 mg or placebo administered as four SQ injections (2.5 mL per injection) at different sites in the abdomen or thigh. NP swabs were collected weekly. The primary efficacy endpoint was the proportion of participants who developed symptomatic, RT-PCR-confirmed SARS-CoV-2 infection during the 28 days of follow-up. Additional key efficacy endpoints included asymptomatic infection and the quantity and duration of viral shedding detected by NP swabs.

The primary analysis included 1,505 participants (753 in the casirivimab plus imdevimab arm and 752 in the placebo arm) who had negative SARS-CoV-2 RT-PCR results at baseline and who were subsequently found to be serum SARS-CoV-2 antibody negative. The mean age was 42.9 years, 45.9% of patients were male, and 9.3% of patients were Black or African American and 40.5% were Hispanic/Latino. The protocol-specified risk factors for progression to severe COVID-19 were present in 30.5% of patients, with approximately 75% meeting the revised EUA high-risk criteria.

The use of casirivimab plus imdevimab resulted in a significant reduction in the risk of symptomatic SARS-CoV-2 infection compared with placebo (81.4% risk reduction: 11 of 753 patients [1.5%] vs. 59 of 752 patients [7.8%]; OR 0.17; $P < 0.001$). This risk reduction was present throughout the follow-up period, starting from the first week and continuing through Week 4. Using asymptomatic and symptomatic infection as an endpoint, the use of casirivimab plus imdevimab was associated with a significant reduction in risk compared to placebo (66.4% risk reduction; 36 of 753 patients [4.8%] vs. 107 of 752 patients [14.2%]; OR 0.31; 95% CI, 0.21–0.46; $P < 0.0001$). Among the subset of patients who were found to be seropositive at baseline (and were therefore excluded from the primary analysis), the number of patients who reached the study endpoints was small, and there was no significant difference in the number of patients who reached the endpoints between the casirivimab plus imdevimab arm (1 of 235 patients [0.4%]) and the placebo arm (5 of 222 patients [2.3%]; OR 0.19; 95% CI, 0.02–1.68; $P = 0.14$).

Hospitalizations were rare, with none in the casirivimab plus imdevimab arm and four in the placebo arm. The study also demonstrated that if a patient's SARS-CoV-2 RT-PCR result became positive during the trial, the duration of detection was shorter in the casirivimab plus imdevimab arm than in the placebo arm (mean of 1.1 vs. 2.2 weeks), and the duration of symptoms per person was shorter as well (mean of 1.2 vs. 3.2 weeks). Safety was comparable between the arms, with no difference in the frequency of non-

COVID-19-related adverse events or serious adverse events.

Considerations in Pregnant and Lactating People

Anti-SARS-CoV-2 monoclonal antibodies as PEP should not be withheld from pregnant or lactating individuals who have been exposed to SARS-CoV-2, especially those with additional conditions that increase their risk of progressing to severe disease. Pregnant or lactating patients and their providers should determine whether the potential benefits of the drugs outweigh the potential risks.

Considerations in Children

Though data from the clinical trial suggest that casirivimab plus imdevimab is effective in adolescents, only 68 participants aged 12 to 17 years were enrolled in the study. The rate of severe COVID-19 in the general adolescent population is lower than the rate of severe disease in adults. Therefore, there is insufficient evidence to recommend the routine use of monoclonal antibodies as PEP in pediatric patients. Certain high-risk populations, such as those who are highly immunocompromised or those who are unvaccinated and have multiple comorbidities and medical-related technology dependence, may benefit from PEP in the setting of high-risk SARS-CoV-2 exposure (e.g., exposure from a household contact, prolonged indoor exposure without masks), and the use of casirivimab plus imdevimab could be considered for these patients on a case-by-case basis.

References

1. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of REGEN-COV (casirivimab and imdevimab). 2021. Available at: https://www.fda.gov/media/145611/download.
2. O'Brien MP, Forleo-Neto E, Musser BJ, et al. Subcutaneous REGEN-COV antibody combination to prevent COVID-19. *N Engl J Med*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34347950.