

The COVID-19 Treatment Guidelines Panel's Statement on the Emergency Use Authorization of the Casirivimab Plus Imdevimab Combination for the Treatment of COVID-19

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Casirivimab (previously REGN10933) and imdevimab (previously REGN10987) are two recombinant human monoclonal antibodies that bind to nonoverlapping epitopes of the spike protein receptor-binding domain (RBD) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The casirivimab plus imdevimab combination blocks the binding of the RBD to the host cell and is being evaluated for the treatment of COVID-19.

On November 21, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) to make the casirivimab plus imdevimab combination available for the treatment of nonhospitalized patients with mild to moderate COVID-19 who are at high risk for progressing to severe disease and/or hospitalization (see the specific EUA criteria for use of the combination below).¹ The issuance of an EUA does not constitute FDA approval of a product.

The FDA has also issued an EUA for bamlanivimab, another SARS-CoV-2 neutralizing antibody, for the same patient population. Please see the COVID-19 Treatment Guidelines Panel's (the Panel's) previously issued [statement on the bamlanivimab EUA](#).

The Panel reviewed the clinical trial data included in the EUA as supporting evidence for the use of casirivimab plus imdevimab for the treatment for mild to moderate COVID-19 in nonhospitalized patients.¹

Based on the available evidence, the Panel has determined the following:

- At this time, there are insufficient data to recommend either for or against the use of casirivimab plus imdevimab for the treatment of outpatients with mild to moderate COVID-19.
- The casirivimab plus imdevimab combination **should not be considered** the standard of care for the treatment of patients with COVID-19.
- Health care providers are encouraged to discuss participation in SARS-CoV-2 neutralizing antibody clinical trials with patients who have mild to moderate COVID-19.
- Given the possibility of a limited supply of the casirivimab plus imdevimab combination, as well as challenges distributing and administering the drugs, patients at highest risk for COVID-19 progression should be prioritized for use of the drugs through the EUA. In addition, efforts should be made to ensure that communities most affected by COVID-19 have equitable access to casirivimab plus imdevimab.
- Casirivimab plus imdevimab should not be withheld from a pregnant individual who has a condition that poses a high risk of progression to severe COVID-19 if the clinician thinks that the potential benefit of the drug combination outweighs potential risk (see the criteria for EUA use of casirivimab plus imdevimab below).
- Patients who are hospitalized for COVID-19 **should not receive** casirivimab plus imdevimab outside of a clinical trial.
- There are currently no comparative data to determine whether there are differences in clinical efficacy or safety between casirivimab plus imdevimab and bamlanivimab.

Clinical Trial Data

The clinical trial data presented below have not yet been published in a medical journal. Results and data from this trial provided supporting evidence for the casirivimab plus imdevimab EUA. The following data are drawn from the FDA EUA.

R10933-10987-COV-2067 is a Phase 1 and 2, randomized, double-blind, placebo-controlled trial conducted at 96 centers in the United States to evaluate the safety and efficacy of casirivimab plus imdevimab for the treatment of mild to moderate COVID-19 in an outpatient setting. Participants received a single intravenous infusion of the casirivimab plus imdevimab combination within 3 days of having a positive SARS-CoV-2 virologic test result. Participants who were hospitalized because of COVID-19 before or at randomization were excluded from the study. According to the EUA, 799 participants were randomized to receive one of two doses of the casirivimab plus imdevimab combination, either the 2,400 mg dose (casirivimab 1,200 mg and imdevimab 1,200 mg) (n = 266) or the 8,000 mg dose (casirivimab 4,000 mg and imdevimab 4,000 mg) (n = 267), or placebo (n = 266).¹

The median age of the participants at baseline was 42 years (7% were aged ≥ 65 years); 85% were White, 50% were Hispanic/Latinx, and 9% were Black. Thirty-four percent of the study participants were considered at high risk for progressing to severe COVID-19 and/or hospitalization (as defined by the EUA criteria outlined below). The median duration of symptoms was 3 days.

The prespecified primary endpoint was the time-weighted average change in nasopharyngeal SARS-CoV-2 level from baseline to Day 7, as measured in a modified full analysis set of participants with detectable virus at baseline (n = 665). This change was greater among the overall group of participants who received casirivimab plus imdevimab (i.e., either the 2,400 mg or 8,000 mg dose of the combination) than among the placebo-treated participants ($-0.36 \log_{10}$ copies/mL; $P < 0.0001$).

A prespecified secondary clinical endpoint was a composite of medically attended visits related to COVID-19 including hospitalization or emergency department, urgent care, or physician office/telemedicine visits within 28 days of treatment. The proportion of patients who had medically attended visits related to COVID-19 was lower among the patients treated with casirivimab plus imdevimab (2.8% for the pooled doses) than among the placebo-treated patients (6.5%).² A post hoc analysis of hospitalization or emergency department visit within 28 days of treatment found that the proportion of patients in which these events occurred was lower for the individual and pooled doses of casirivimab plus imdevimab than for placebo. However, the number of participants in each group who met this endpoint was small, and the contribution of hospitalization versus emergency department visit is not provided:

- Placebo: 10 of 231 participants (4%)
- Pooled casirivimab plus imdevimab doses: 8 of 434 participants (2%)
 - Casirivimab plus imdevimab 2,400 mg: 4 of 215 participants (2%)
 - Casirivimab plus imdevimab 8,000 mg: 4 of 219 participants (2%)

In a post hoc analysis of participants at higher risk for hospitalization (using the definition of high risk in the EUA, and thus approximating the population that would be recommended for treatment with casirivimab plus imdevimab per the EUA), four of 151 participants (3%) in the pooled casirivimab plus imdevimab arms versus seven of 78 participants (9%) in the placebo group were hospitalized or had emergency department visits.

The median time to symptom improvement was 5 days for participants who received casirivimab plus imdevimab and 6 days for those who received placebo.

The safety profile of casirivimab plus imdevimab at both the low and the high dose was reportedly similar to that of the placebo. According to the EUA, among 799 participants in the R10933-10987-COV-2067 trial who received casirivimab plus imdevimab, four infusion-related reactions of Grade 2 severity or higher were reported in the 8,000 mg casirivimab plus imdevimab arm. In two of the participants, the infusion-related reactions resulted in permanent discontinuation of the infusion. One participant had an anaphylactic reaction that resolved with treatment.

The analysis of the R10933-10987-COV-2067 study suggests a potential clinical benefit of casirivimab plus imdevimab for outpatients with mild to moderate COVID-19. However, the relatively small number of participants in this early phase trial and the low number of hospitalizations or emergency department visits make it difficult to draw definitive conclusions about the clinical benefit of casirivimab plus imdevimab. The Panel believes that more data are needed to assess the impact of casirivimab plus imdevimab on the disease course of COVID-19 in patients with specific characteristics and/or conditions and will update recommendations as more information becomes available.

High-Risk Criteria for Emergency Use Authorization of the Casirivimab Plus Imdevimab Combination

The FDA EUA allows for the use of casirivimab plus imdevimab for the treatment of COVID-19 in nonhospitalized adults and children aged ≥ 12 years and weighing ≥ 40 kg who are at high risk for progressing to severe COVID-19 and/or hospitalization. High-risk individuals specified in the EUA are those who meet at least one of the following criteria:

- Body mass index (BMI) ≥ 35
- Chronic kidney disease
- Diabetes mellitus
- Immunocompromising condition
- Currently receiving immunosuppressive treatment
- Aged ≥ 65 years
- Aged ≥ 55 years and have:
 - Cardiovascular disease, *or*
 - Hypertension, *or*
 - Chronic obstructive pulmonary disease/other chronic respiratory disease
- Aged 12 to 17 years and have:
 - BMI ≥ 85 th percentile for their age and gender based on the [Centers for Disease Control and Prevention growth charts](#); *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 or a reactive airway or other chronic respiratory disease that requires daily medication for control
- Casirivimab and imdevimab are 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 an underlying non-COVID-19 related-comorbidity.
- Benefit of treatment with casirivimab plus imdevimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 who require high-flow oxygen or mechanical ventilation.

References

1. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of casirivimab and imdevimab. 2020. Available at: <https://www.fda.gov/media/143892/download>. Accessed November 13, 2020.
2. Regeneron. Regeneron's COVID-19 outpatient trial prospectively demonstrates that REGN-COV2 antibody cocktail significantly reduced virus levels and need for further medical attention. 2020. Available at: <https://investor.regeneron.com/news-releases/news-release-details/regenerons-covid-19-outpatient-trial-prospectively-demonstrates>. Accessed November 30, 2020.