We are currently updating this section of the Guidelines based on the Food and Drug Administration's Emergency Use Authorization for bamlanivimab plus etesevimab for the treatment of mild to moderate COVID-19 in certain outpatients. Until these updates are released, please see the COVID-19 Treatment Guidelines Panel's Statement on the Emergency Use Authorization of the Bamlanivimab Plus Etesevimab Combination for the Treatment of COVID-19.

Anti-SARS-CoV-2 Monoclonal Antibodies

Last Updated: February 11, 2021

Bamlanivimab and the combination of casirivimab plus imdevimab are anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) monoclonal antibodies available through Food and Drug Administration (FDA) Emergency Use Authorizations (EUAs) for the treatment of outpatients with mild to moderate COVID-19 who are high risk for progressing to severe disease and/or hospitalization.

Based on the clinical trial data to date (summarized below), the COVID-19 Treatment Guidelines Panel (the Panel) has determined the following:

- There are currently insufficient data to recommend either for or against the use of bamlanivimab or the casirivimab plus imdevimab combination for the treatment of outpatients with mild to moderate COVID-19. The preliminary data on the use of these agents are from Phase 1 and 2 clinical trials that included relatively few participants and reported only a small number of clinical events related to COVID-19. Final results from large Phase 3 randomized controlled trials will further inform the Panel's recommendations on the use of these monoclonal antibodies.
- Health care providers are encouraged to discuss participation in anti-SARS-CoV-2 monoclonal antibody clinical trials, if available, with their patients.
- For high-risk patients who meet EUA criteria for treatment with these monoclonal antibodies, it is appropriate to discuss the potential benefits and risks of the products as part of shared decision making between the patient and the clinician.
- Bamlanivimab and the casirivimab plus imdevimab combination should not be considered standard of care for the treatment of patients with COVID-19.
- There are currently no comparative data to determine whether there are differences in clinical efficacy or safety between bamlanivimab and the casirivimab plus imdevimab combination.
- Patients who are hospitalized because of COVID-19 should not receive bamlanivimab or the casirivimab plus imdevimab combination outside of a clinical trial, although use of the agents can be considered for patients hospitalized for an indication other than COVID-19 who meet EUA use criteria.

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Background

The SARS-CoV-2 genome encodes four major structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) and nonstructural and accessory proteins. The S protein is further divided into two subunits, S1 and S2, that mediate host cell attachment and invasion.

Through its receptor-binding domain (RBD), S1 attaches to angiotensin-converting enzyme 2 (ACE2) on the host cell; this initiates a conformational change in S2 resulting in virus-host cell membrane fusion and viral entry.[1]

A significant proportion of individuals with COVID-19 produce neutralizing antibodies to SARS-CoV-2 about 10 days after disease onset, with higher antibody levels observed in those with severe disease.[2] The neutralizing activity of COVID-19 patients' plasma was correlated with the magnitude of antibody responses to SARS-CoV-2 S and N proteins. Monoclonal antibodies targeting the S protein therefore have the potential to prevent SARS-CoV-2 infection and to improve symptomatology and limit progression to severe disease in patients with mild to moderate COVID-19.

Several monoclonal antibodies to SARS-CoV-2 have been developed and characterized.[3-7] Evaluation of their efficacy for the treatment and prevention of COVID-19 is ongoing. In November 2020, the FDA issued two EUAs, one for bamlanivimab and one for the combination of casirivimab plus imdevimab. The EUAs allow for use of the drugs in nonhospitalized patients (aged ≥12 years and weighing ≥40 kg) with laboratory confirmed SARS-CoV-2 infection and mild to moderate COVID-19 who are at high risk for progressing to severe disease and/or hospitalization. Administration of the drugs is recommended as soon as possible after a positive SARS-CoV-2 test result and within 10 days of symptom onset. The issuance of an EUA does not constitute FDA approval.

Bamlanivimab (also known as LY-CoV555 and LY3819253) is a neutralizing monoclonal antibody that targets the RBD of the spike protein of SARS-CoV-2. It is administered intravenously as a one-time dose of bamlanivimab 700 mg.

Casirivimab (previously REGN10933) and imdevimab (previously REGN10987) are recombinant human monoclonal antibodies that bind to nonoverlapping epitopes of the spike protein RBD of SARS-CoV-2. The combination of these two antibodies blocks the binding of the RBD to the host cell. The monoclonal antibodies are administered intravenously together as a combined one-time dose of casirivimab 1,200 mg and imdevimab 1,200 mg.

Clinical Trial Data to Date

Bamlanivimab

The Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies (BLAZE-1) study is a randomized controlled Phase 2 trial comparing three doses of bamlanivimab to placebo.[8] An interim analysis of this study suggested a potential clinical benefit of bamlanivimab for outpatients with mild to moderate COVID-19 who received the antibody infusion a median of 4 days after symptom onset. In the pooled bamlanivimab arms, five of 309 participants (1.6%) were hospitalized or had emergency department visits versus nine of 143 participants (6.3%) in the placebo arm. In a subset analysis of patients at high risk for hospitalization (using an expanded definition that approximates the bamlanivimab EUA criteria for treatment), four of 136 participants (2.9%) in the pooled bamlanivimab arms versus seven of 69 participants (10.1%) in the placebo arm were hospitalized or had emergency department visits.[9]

Casirivimab Plus Imdevimab

The R10933-10987-COV-2067 study is a randomized controlled Phase 1 and 2 trial comparing two doses of casirivimab plus imdevimab to placebo. An interim analysis of this study suggested a potential clinical benefit of casirivimab plus imdevimab for outpatients with mild to moderate COVID-19 who received an infusion of the drug combination a median of 3 days after symptom onset.[10] In a post hoc analysis submitted to the FDA for the EUA application, eight of 434 participants (2%) in the pooled casirivimab plus imdevimab arms versus 10 of 231 participants (4%) in the placebo arm were hospitalized or had emergency department visits within 28 days of treatment. Among the participants at higher risk for hospitalization (using the EUA definition of high risk and thus approximating the population that would be recommended for treatment), four of 151 participants (3%) in the pooled casirivimab plus imdevimab arms versus seven of 78 participants (9%) in the placebo arm were hospitalized or had emergency department visits.

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A published interim analysis of a subset of 275 participants from the R10933-10987-COV-2067 trial suggests that casirivimab plus imdevimab may have a greater effect in participants who test negative for SARS-CoV-2 serum antibodies (endogenous antibodies) at baseline. In this analysis, the proportion of participants who had at least one COVID-19-related medical visit (including hospitalization or emergency department, urgent care, or physician office/telemedicine visit) was lower in the casirivimab plus imdevimab group (6 of 182 participants [3%] for the pooled doses) than in the placebo group (6 of 93 participants [6%]). In the subgroup of participants who were serum antibody negative at baseline, the intergroup difference in patients with medical visits was greater (5 of 80 participants [6%] in the pooled antibody group and 5 of 33 participants [15%] in the placebo group).[11]

Please see Clinical Data: Anti-SARS-CoV-2 Monoclonal Antibodies for additional information.

Based on these study results, the FDA issued EUAs for the use of these monoclonal antibodies in nonhospitalized patients with mild to moderate COVID-19 who are at high risk for progressing to severe disease and/or hospitalization.

The FDA EUAs do not authorize the use of these antibodies for patients who are hospitalized for COVID-19, although their use can be considered for patients who are hospitalized for a non-COVID-19 indication and meet EUA criteria for use of the products. A substudy of A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients With COVID-19 (ACTIV-3) randomized patients hospitalized with COVID-19 to bamlanivimab 7,000 mg or placebo, each in addition to remdesivir. On October 26, 2020, following a prespecified interim futility analysis, enrollment into this study was stopped due to lack of clinical benefit.[12] Among 314 adult hospitalized patients (163 in the bamlanivimab arm and 151 in the placebo arm), pulmonary outcomes were similar at Day 5 (odds ratio of being in a more favorable category in the bamlanivimab arm than in the placebo arm 0.85; 95% CI, 0.56–1.29; $P = 0.45$). The time to hospital discharge was also similar in the two arms (rate ratio 0.97; 95% CI, 0.78–1.20).[13] Patients who are hospitalized for COVID-19 should not receive bamlanivimab or casirivimab plus imdevimab except in a clinical trial. The FDA EUAs do permit the use of these monoclonal antibodies for patients who are hospitalized for an indication other than COVID-19 provided that they have mild to moderate COVID-19 and are at high risk for progressing to severe disease and/or hospitalization.[14,15]

Rationale for the Panel's Recommendations

In the studies described above, the number of participants was small, and only a limited number of clinical events (e.g., hospitalizations or emergency department visits) were reported. Given the low number of clinical events, it is difficult to draw definitive conclusions about the efficacy of these anti-SARS-CoV-2 antibodies. In addition, if there is a clinical benefit, there is uncertainty as to which patients are most likely to benefit from these antibodies. Although the published data from the bamlanivimab trial indicate that approximately two-thirds of the patients had a high-risk condition, only 10.7% of those in the antibody arm and 14% of those in the placebo arm were aged ≥65 years. In the trial supporting the EUA for casirivimab plus imdevimab (see above), only 34% of the participants were considered high risk. Additional clinical trial data are needed to provide further evidence on the safety and efficacy of these agents and to identify the populations in which the potential benefit will be the greatest.

Please see Table 3a for additional information.

Monitoring

- Bamlanivimab or casirivimab plus imdevimab should only be administered in health care settings by qualified health care providers who have immediate access to medications to treat severe infusion reactions and to emergency medical services.
- Patients should be monitored during infusion of the agents and then observed for at least 1 hour after the infusion is completed.
- No dosage adjustments are required for body weight, renal impairment, or mild hepatic impairment.

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Adverse Effects

- In the BLAZE-1 trial, the most common adverse events of bamlanivimab were nausea, diarrhea, dizziness, headache, pruritis, and vomiting. The safety profile of bamlanivimab at all three doses was reportedly similar to that of the placebo.
- Hypersensitivity, including anaphylaxis and infusion reactions, may occur. According to the EUA for bamlanivimab, among >850 participants in ongoing trials who have received bamlanivimab, one anaphylactic reaction and one serious infusion-related reaction occurred and both required treatment, which in one case included epinephrine.
- According to the EUA fact sheet for casirivimab plus imdevimab, among the 533 participants who received casirivimab plus imdevimab in the R10933-10987-COV-2067 trial, one participant had an anaphylaxis reaction that required treatment with epinephrine, and four participants who received the 8,000 mg dose of the combination (casirivimab 4,000 mg and imdevimab 4,000 mg) had an infusion reaction of grade 2 severity or higher, which, in two cases, resulted in permanent discontinuation of the infusion.

Drug-Drug Interactions

- Drug-drug interactions are unlikely between bamlanivimab or casirivimab plus imdevimab and medications that are renally excreted or that are cytochrome P450 substrates, inhibitors, or inducers.
- Please see Table 3b for more information.
- For persons who received bamlanivimab or casirivimab plus imdevimab for treatment, vaccination with an mRNA COVID-19 vaccine should be deferred for at least 90 days as a precautionary measure to avoid interference of the antibody treatment with vaccine-induced immune responses.[16]

Considerations in Pregnancy

- As immunoglobulin (Ig) G monoclonal antibodies, bamlanivimab and casirivimab plus imdevimab would be expected to cross the placenta. There are no available data on the use of bamlanivimab or casirivimab plus imdevimab during pregnancy; however, IgG products are generally not withheld because of pregnancy when their use is indicated .
- Bamlanivimab and casirivimab plus imdevimab should not be withheld from a pregnant individual with COVID-19 who has a condition that poses a high risk of progression to severe COVID-19, and the patient and provider determine that the potential benefit of the drug outweighs potential risk (see the EUA criteria for the use of bamlanivimab and casirivimab plus imdevimab below).
- Inclusion of pregnant people in clinical trials should be encouraged to inform decisions regarding administration of anti-SARS-CoV-2 antibodies to individuals in this population.

Considerations in Children

- Most children with mild or moderate COVID-19, even those with risk factors specified in the EUAs for bamlanivimab or casirivimab plus imdevimab, will not progress to more severe illness and will recover without specific therapy.
- Risk factors for hospitalization in children with COVID-19 have not been clearly defined to the same extent as in adults, making it difficult to identify those at the highest risk of hospitalization and those who would be likely to benefit from use of bamlanivimab or casirivimab plus imdevimab.
- The use of bamlanivimab or casirivimab plus imdevimab for children who meet the EUA criteria can be considered on a case-by-case basis in consultation with a pediatric infectious disease specialist. Additional guidance is provided in a recent publication endorsed by the Pediatric Infectious Diseases Society.[17]
- Additional data on clinical outcomes in children who receive bamlanivimab or casirivimab plus imdevimab for the treatment of COVID-19, including in those with specific risk factors, are needed.

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Clinical Trials

- Several clinical trials that are evaluating bamlanivimab, casirivimab plus imdevimab, and other monoclonal antibodies, alone or in combination, for the treatment of COVID-19 are

underway or in development. Please see *ClinicalTrials.gov* for the latest information on bamlanivimab clinical trials and casirivimab plus imdevimab clinical trials.

- Health care providers are encouraged to discuss participation in anti-SARS-CoV-2 monoclonal antibody clinical trials with patients who have mild to moderate COVID-19.

Drug Availability

- Bamlanivimab and casirivimab plus imdevimab are available through FDA EUAs for outpatients with mild to moderate COVID-19 who are at high risk for progression to severe disease and/or hospitalization.
- Given the possibility of a limited supply of bamlanivimab and casirivimab plus imdevimab, as well as challenges of distributing and administering the drug, patients at highest risk for COVID-19 progression should be prioritized for use through the EUA. In addition, efforts should be made to ensure that communities most affected by COVID-19 have equitable access to bamlanivimab and casirivimab plus imdevimab.

High-Risk Criteria for Emergency Use Authorization of Bamlanivimab or Casirivimab Plus Imdevimab

The FDA EUAs allow for the use of bamlanivimab or casirivimab plus imdevimab for the treatment of mild to moderate COVID-19 in nonhospitalized adults and children aged ≥12 years and weighing ≥40 kg and who are at high risk for progressing to severe COVID-19 and/or hospitalization. High-risk criteria specified in the EUA are:

- Body mass index (BMI) ≥35
- Chronic kidney disease
- Diabetes mellitus
- Immunocompromising condition
- Currently receiving immunosuppressive treatment
- Aged ≥65 years
- Aged ≥55 years, *and*
  - Cardiovascular disease, *or*
  - Hypertension, *or*
  - Chronic obstructive pulmonary disease or another chronic respiratory disease.
- Aged 12 to 17 years, *and*
  - BMI ≥85th percentile for their age and gender based on 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, reactive airway, or other chronic respiratory disease that requires daily medication for control.

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