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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

Last Updated: March 2, 2021

Bamlanivimab and etesevimab are neutralizing monoclonal antibodies that bind to different but overlapping epitopes in the receptor-binding domain of the spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The bamlanivimab plus etesevimab combination blocks SARS-CoV-2 entry into host cells and is being evaluated for the treatment of COVID-19.

On February 9, 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) to make bamlanivimab 700 mg plus etesevimab 1,400 mg available for the treatment of outpatients with mild to moderate COVID-19 who are at high risk for progressing to severe disease and/or hospitalization (see the EUA criteria for use of the products below).¹ The issuance of an EUA does not constitute FDA approval of a product.

The FDA previously issued an EUA for bamlanivimab alone and another for the anti-SARS-CoV-2 monoclonal antibody combination casirivimab plus imdevimab, both for use in the same patient population as authorized for bamlanivimab plus etesevimab. See [Anti-SARS-CoV-2 Monoclonal Antibodies](#) for detailed descriptions of these other monoclonal antibody options.

The COVID-19 Treatment Guidelines Panel (the Panel) reviewed the clinical trial data included in the EUA for bamlanivimab plus etesevimab as evidence to support its use for the treatment of mild to moderate COVID-19 in high-risk outpatients.

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

- The Panel recommends the use of **bamlanivimab 700 mg plus etesevimab 1,400 mg** for the treatment of outpatients with mild to moderate COVID-19 who are at high risk of clinical progression as defined by the EUA criteria (see below) (**BIIa**). Treatment should be started as soon as possible after the patient has received a positive result on a SARS-CoV-2 antigen or nucleic acid amplification test and within 10 days of symptom onset (see the Panel's rationale for this recommendation below).
 - It is important to note that the authorized dose of bamlanivimab 700 mg plus etesevimab 1,400 mg is lower than the dose given to participants in the Phase 3 study that provides clinical data in support of this therapy. The authorized dose was extrapolated from data demonstrating its antiviral activity, as well as from in vitro studies and pharmacokinetic/pharmacodynamic modeling (see below).
 - Laboratory studies suggest that bamlanivimab and etesevimab have activity against the SARS-CoV-2 B.1.1.7 variant but have markedly reduced activity against the B.1.351 variant.^{1,2} At this time, the B.1.351 variant has rarely been detected amongst SARS-CoV-2 samples sequenced in the United States. Ongoing [population-based genomic surveillance](#) of the types and frequencies of circulating SARS-CoV-2 variants will be important in defining the utility of bamlanivimab plus etesevimab in the future.
- The Panel **recommends against** the use of bamlanivimab 700 mg plus etesevimab 1,400 mg for patients who are hospitalized because of COVID-19, except in a clinical trial. However,

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bamlanivimab 700 mg plus etesevimab 1,400 mg should be considered for persons with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 but who otherwise meet the EUA criteria.³

- Given the possibility of a limited supply of bamlanivimab plus etesevimab, as well as challenges of distributing and administering the drugs, priority should be given to patients who are at highest risk for COVID-19 progression based on the EUA criteria.^{4,5}
- Efforts should be made to ensure that communities most affected by COVID-19 have equitable access to bamlanivimab plus etesevimab.
- Bamlanivimab plus etesevimab 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 combination outweighs the potential risk (see the EUA criteria for use of bamlanivimab plus etesevimab below).
- There are insufficient pediatric data to recommend either for or against the use of bamlanivimab plus etesevimab or other monoclonal antibody products for children with COVID-19 who are not hospitalized but who have risk factors for severe disease. Based on adult studies, bamlanivimab plus etesevimab may be considered on a case-by-case basis for children who meet EUA criteria, especially those who meet more than one criterion or are aged ≥ 16 years. In such cases, consultation with a pediatric infectious disease specialist is recommended.

Rationale for the Panel's Recommendation

The EUA for bamlanivimab plus etesevimab for the treatment of outpatients with mild to moderate COVID-19 who are at high risk of progressing to severe COVID-19 and/or hospitalization is based on data from several studies, including the Blocking Viral Attachment and Cell Entry With SARS-CoV-2 Neutralizing Antibodies (BLAZE)-1 and BLAZE-4 trials. In particular, the supporting data is from BLAZE-1, a Phase 3 trial that included more than 1,000 randomized high-risk participants with almost 50 primary outcome clinical events (i.e., hospitalization or death). The number of clinical events reported for this study supporting the EUA for bamlanivimab plus etesevimab is greater than that currently reported for Phase 2 studies of bamlanivimab monotherapy or the casirivimab plus imdevimab combination (see [Anti-SARS-CoV-2 Monoclonal Antibodies](#)). Furthermore, the clinical events reported in the bamlanivimab monotherapy and the casirivimab plus imdevimab studies included emergency department visits, as well as hospitalizations and deaths. Based on the larger sample size and greater number of clinical events in the BLAZE-1 Phase 3 trial, the Panel has greater confidence in the currently available evidence for the clinical efficacy of the bamlanivimab plus etesevimab combination than in the evidence for the other monoclonal antibody options. For this reason, when available, bamlanivimab plus etesevimab should be used for high-risk outpatients according to the EUA. The Panel's recommendations on the use of bamlanivimab monotherapy and casirivimab plus imdevimab can be found in [Anti-SARS-CoV-2 Monoclonal Antibodies](#).

It is important to note that the authorized dose of bamlanivimab 700 mg plus etesevimab 1,400 mg is lower than the dose administered to participants in the BLAZE-1 Phase 3 trial. The authorized dose was extrapolated from data demonstrating its antiviral activity, as well as from in vitro studies and pharmacokinetic/pharmacodynamic modeling (see below).

Recommendations for the use of bamlanivimab plus etesevimab should be considered in the context of the following limitations:

- There are no clinical endpoint data for the EUA dose (see Dose below).
- The results of the BLAZE-1 Phase 3 trial have not been peer reviewed and published.
- There are incomplete data on potential predictors of response, such as the absence or presence of anti-SARS-CoV-2 antibodies in patients prior to treatment, or how SARS-CoV-2 variants will affect the antiviral activity of the products.

A benefit of treatment with bamlanivimab plus etesevimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 who require high-flow oxygen or mechanical ventilation.

Bamlanivimab plus etesevimab is not authorized for use in patients:

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- Who are hospitalized due to COVID-19; or
- Who require oxygen therapy due to COVID-19; or
- Who are on chronic oxygen therapy due to an underlying non-COVID-19-related comorbidity and, because of COVID-19, require an increase in oxygen flow rate from baseline.

The Panel will update these recommendations as data emerge from ongoing clinical trials, and the results that are summarized in the EUA become available in peer-reviewed publications.

Clinical Trial Data

Some of the clinical trial data presented below have not yet been published in a medical journal. These results and data are from trials that provide supporting evidence for the bamlanivimab plus etesevimab EUA. The following data are drawn from the FDA EUA Fact Sheet.¹

BLAZE-1 is a double-blind, placebo-controlled, Phase 2 and 3 randomized trial to evaluate the safety and efficacy of bamlanivimab plus etesevimab for the treatment of mild to moderate COVID-19 in an outpatient setting. Participants received a single intravenous (IV) infusion of bamlanivimab, bamlanivimab plus etesevimab, or placebo within 3 days of having a positive result on a SARS-CoV-2 virologic test. Participants were excluded if they had a saturation of oxygen (SpO₂) ≤93% on room air, respiratory rate ≥30 breaths/min, or heart rate ≥125 bpm.

Results From Phase 3 of the BLAZE-1 Trial

In Phase 3 of the study, all the participants met the criteria for being at high risk for progressing to severe COVID-19 and/or hospitalization (i.e., as defined in the EUA). A total of 1,035 participants were randomized to bamlanivimab 2,800 mg plus etesevimab 2,800 mg (n = 518) or placebo (n = 517).

- The median participant age at baseline was 56 years; 31% of the participants were aged ≥65 years. Across the arms, 52% of the participants were female, 87% were White, 29% were Hispanic/Latinx, and 8% were Black or African American. The mean duration of symptoms was 4 days, and 77% of the participants had mild COVID-19.
- The primary endpoint was the proportion of participants who had a COVID-19-related hospitalization (defined as ≥24 hours of acute care) or who died from any cause by Day 29. Compared to the placebo-treated participants, the participants who received bamlanivimab plus etesevimab had a 5% absolute reduction and a 70% relative reduction in COVID-19-related hospitalizations or death from any cause ($P < 0.001$). Endpoint events occurred in 11 of 518 (2%) participants in the bamlanivimab plus etesevimab arm and in 36 of 517 (7%) participants in the placebo arm.
- There were no deaths in the bamlanivimab plus etesevimab arm and 10 deaths in the placebo arm (10 of 517 [2%] participants died; $P < 0.001$).
- Secondary virologic endpoints included SARS-CoV-2 levels on nasopharyngeal swab assays at different time points. Study participants who received bamlanivimab plus etesevimab had a greater and more rapid virus level decline than those who received placebo. The proportion of participants with persistently high viral loads, defined as SARS-CoV-2 level $>5.27 \log_{10}$ copies/mL at Day 7, was 10% in the bamlanivimab plus etesevimab arm and 29% in the placebo arm ($P < 0.000001$).

Dose

The optimal dose of bamlanivimab plus etesevimab for the treatment of COVID-19 has not yet been established, and the dose currently recommended by the EUA may be revised as data from clinical trials emerge. The dose authorized in the EUA is bamlanivimab 700 mg plus etesevimab 1,400 mg administered together in a single infusion, which is different from the dose (bamlanivimab 2,800 mg plus etesevimab 2,800 mg, also administered as a single infusion) used in the BLAZE-1 Phase 3 study summarized above. The lower dose was authorized by the FDA based on preliminary data from BLAZE-4, a double-blind, placebo-controlled randomized Phase 2 trial for the treatment of adult outpatients with mild to moderate COVID-19 (excluding patients aged ≥65 years or having a body mass index [BMI] ≥35).¹ The available data (according to the EUA) reportedly demonstrate that the antiviral activity of bamlanivimab 700 mg plus etesevimab 1,400 mg is similar to that of bamlanivimab 2,800 mg plus etesevimab 2,800 mg. This finding,

which is supported by data from in vitro studies and pharmacokinetic/pharmacodynamic modeling, led to the expectation that the clinical effect of the authorized dose will be similar to that of the higher dose administered in the BLAZE-1 trial.

Other Considerations

SARS-CoV-2 Variants

The BLAZE studies summarized here were conducted before widespread circulation of SARS-CoV-2 variants that might be less sensitive to some monoclonal antibodies. In vitro studies suggest that bamlanivimab with etesevimab has activity against the B.1.1.7 variant but has markedly reduced activity against the B.1.351 variant.^{1,2} Although the clinical impact of these in vitro findings is unknown, data emerging from the ongoing clinical trials and EUA use will further inform recommendations on the use of bamlanivimab with etesevimab.

Vaccination

- For persons who have received anti-SARS-CoV-2 monoclonal antibodies, vaccination with a 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.⁶
- For persons who have received a COVID-19 vaccine and subsequently develop COVID-19, prior vaccination should not affect treatment decisions, including the use of and timing of treatment with monoclonal antibodies.⁶

High-Risk Criteria for Emergency Use Authorization of the Bamlanivimab Plus Etesevimab Combination

The FDA EUA allows for the use of bamlanivimab plus etesevimab 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.¹

High-risk individuals as specified in the EUA are those who meet at least one of the following criteria:

- 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.

References



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