

The COVID-19 Treatment Guidelines Panel’s Statement on the Emergency Use Authorization of Anti-SARS-CoV-2 Monoclonal Antibodies for the Treatment of COVID-19

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Anti-SARS-CoV-2 monoclonal antibodies that target the SARS-CoV-2 spike protein and block virus entry into cells have been evaluated for the treatment of COVID-19. To date, the Food and Drug Administration (FDA) has issued Emergency Use Authorizations (EUAs) for the following anti-SARS-CoV-2 monoclonal antibodies and combinations: bamlanivimab alone, bamlanivimab plus etesevimab, and casirivimab plus imdevimab.

Data are emerging on the currently available anti-SARS-CoV-2 monoclonal antibodies, including preliminary data from a Phase 3 trial of casirivimab plus imdevimab, and on the in vitro susceptibility of SARS-CoV-2 variants to anti-SARS-CoV-2 monoclonal antibodies. After reviewing the available data, the COVID-19 Treatment Guidelines Panel (the Panel) has updated its recommendations on the use of anti-SARS-CoV-2 monoclonal antibodies in outpatients with mild to moderate COVID-19 who are at high risk of disease progression. In addition, the Panel notes that, because of an increasing number of reports of variants that are resistant to bamlanivimab alone, this product will no longer be distributed by the U.S. government.¹

Summary Recommendations and Considerations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using one of the following combination anti-SARS-CoV-2 monoclonal antibodies to treat outpatients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by the Emergency Use Authorization (EUA) criteria (listed in alphabetical order):
 - **Bamlanivimab 700 mg plus etesevimab 1,400 mg (AIIa); or**
 - **Casirivimab 1,200 mg plus imdevimab 1,200 mg (AIIa).**
- Treatment should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 antigen or nucleic acid amplification test (NAAT) and within 10 days of symptom onset.
- There are no comparative data to determine whether there are differences in clinical efficacy or safety between bamlanivimab plus etesevimab and casirivimab plus imdevimab.
 - There are SARS-CoV-2 variants, particularly those that contain the mutation E484K (see below), that reduce the virus’ susceptibility to bamlanivimab and, to a lesser extent, casirivimab and etesevimab in vitro; however, the clinical impact of these mutations is not known.
 - In regions where SARS-CoV-2 variants with reduced in vitro susceptibility to bamlanivimab plus etesevimab are common, some Panel members would preferentially use casirivimab plus imdevimab while acknowledging that it is not known whether in vitro susceptibility data correlate with clinical outcomes.
- Because clinical outcome data are limited and there are concerns regarding decreased susceptibility of variants, the Panel **recommends against** the use of **bamlanivimab monotherapy (AIII)**.
 - If combination products are not available, the use of bamlanivimab monotherapy can be considered for people who meet the EUA criteria on a case-by-case basis.
- The Panel **recommends against** the use of **anti-SARS-CoV-2 monoclonal antibodies** for patients who are hospitalized because of COVID-19, except in a clinical trial (**AIIa**). However, their use 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.

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

SARS-CoV-2 Variants of Concern or Interest and Their Susceptibility to Anti-SARS-CoV-2 Monoclonal Antibodies

In laboratory studies, some SARS-CoV-2 variants of concern or interest that harbor certain mutations have markedly reduced susceptibility to bamlanivimab and may have lower sensitivity to etesevimab and casirivimab. However, the impact of these mutations on the clinical response to antibody combinations is uncertain, and the prevalence of these variants in different regions may vary.² Of note:

- The B.1.1.7 variant of concern, which is increasing in frequency in the United States, retains in vitro susceptibility to the anti-SARS-CoV-2 monoclonal antibodies that are currently available through EUAs.³⁻⁵
- The B.1.351 variant of concern has been infrequently detected among the SARS-CoV-2 samples sequenced in the United States to date. This variant includes the E484K mutation, which results in a marked reduction in in vitro susceptibility to bamlanivimab.^{4,6,7} In vitro studies suggest that bamlanivimab plus etesevimab has markedly reduced activity against the B.1.351 variant.³ In vitro studies also suggest that the K417N mutation, which is present in this variant along with the E484K mutation, reduces casirivimab activity, although the combination of casirivimab and imdevimab appears to retain activity.⁵
- The P.1 variant of concern has been infrequently detected among the SARS-CoV-2 samples sequenced in the United States to date. This variant includes the E484K mutation, which results in a marked reduction in in vitro susceptibility to bamlanivimab.^{3,7} In vitro studies suggest that bamlanivimab plus etesevimab also has markedly reduced activity against the P.1 variant.^{3,6,8} In vitro studies also suggest that the K417T mutation, which is present in this variant along with the E484K mutation, reduces casirivimab activity, although the combination of casirivimab and imdevimab appears to retain activity.⁵
- The B.1.429/B.1.427 variants of concern (also called 20C/CAL.20C) that are circulating in parts of the United States, including California, Arizona, and Nevada, have the L452R mutation. This mutation is associated with a marked reduction in in vitro susceptibility to bamlanivimab. There appears to be a modest in vitro decrease in susceptibility to the combination of bamlanivimab and etesevimab, although the clinical implications of this finding are not known.³
- The B.1.526 variant of interest is circulating in parts of the United States, such as New York. It commonly has the E484K mutation, which is associated with a marked reduction in in vitro susceptibility to bamlanivimab.³ There appears to also be reduced in vitro susceptibility to the combination of bamlanivimab and etesevimab, although the clinical implications of this finding are not known.³ In vitro studies suggest that the E484K mutation may reduce casirivimab activity, although the combination of casirivimab and imdevimab appears to retain activity.⁵

Ongoing [population-based genomic surveillance](#) of the types and frequencies of circulating SARS-CoV-2 variants and studies on the susceptibility of different variants to available anti-SARS-CoV-2 monoclonal antibodies will be important in defining the utility of specific monoclonal antibodies in the future.

Rationale for Recommending Bamlanivimab Plus Etesevimab

In the Phase 3 Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies (BLAZE-1) trial, all the participants met the criteria for being at high risk for progressing to severe COVID-19 and/or hospitalization (as defined in the EUA). A total of 1,035 participants were randomized to receive 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 women, 87% were White, 29% were Hispanic/Latinx, and 8% were Black or African American. The mean duration of symptoms at study enrollment 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. Endpoint events occurred in 11 of 518 participants (2%) in the bamlanivimab plus etesevimab arm and in 36 of 517 participants (7%) in the placebo arm. 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 ($P < 0.001$). There were no deaths in the bamlanivimab plus etesevimab arm, and 10 deaths occurred in the placebo arm (10 of 517 participants [2%] died; $P < 0.001$).

Secondary virologic endpoints included SARS-CoV-2 levels on nasopharyngeal (NP) swab assays at different time points. Study participants who received bamlanivimab plus etesevimab had a greater and more rapid decline in virus levels than those who received placebo. The proportion of participants with persistently high viral loads (defined as a 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 ($P < 0.000001$).

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

- The doses authorized in the EUA are bamlanivimab 700 mg plus etesevimab 1,400 mg, which are different from the doses of bamlanivimab 2,800 mg plus etesevimab 2,800 mg used in the Phase 3 BLAZE-1 study. The lower dose was authorized by the FDA based on preliminary data from BLAZE-4, a double-blind, placebo-controlled, randomized Phase 2 trial.³ The available data 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.
- The results of the Phase 3 BLAZE-1 trial have not been peer reviewed and published.
- The Panel's recommendations are based on preliminary results only, and the details on the study design, follow-up, and methods are currently limited. When peer-reviewed data for the Phase 3 BLAZE-1 trial become publicly available, the Panel will review the results and update the recommendations if necessary.

Rationale for Recommending Casirivimab Plus Imdevimab

The updated recommendation for the use of casirivimab plus imdevimab is based on Phase 3 results from the [R10933-10987-COV-2067](#) study (the information from this study is currently available only in a press release, and there is currently no peer-reviewed preprint or publication).^{9,10} This trial compared 1,355 participants who received casirivimab 1,200 mg plus imdevimab 1,200 mg to 1,341 participants who received placebo.

The modified full analysis set (mFAS) included participants who had a positive SARS-CoV-2 polymerase chain reaction result from an NP swab at randomization and one or more risk factors for severe COVID-19. In the mFAS cohort:

- The median participant age at baseline was 50 years. Across the arms, 35% of the participants were Hispanic/Latinx and 5% were Black or African American. The median duration of symptoms prior to enrollment was 3 days.
- COVID-19-related hospitalizations or death from any cause were reported in 18 of 1,355 participants (1.3%) in the casirivimab plus imdevimab arm and 62 of 1,341 participants (4.6%)

in the placebo arm ($P < 0.0001$). This represents a 3.3% absolute reduction and a 71% relative reduction in hospitalization or death in the casirivimab plus imdevimab treatment participants.

In the full analysis set, there was 1 death out of 1,849 participants in the casirivimab plus imdevimab arm and 5 deaths out of 1,843 participants in the placebo arm.

Recommendations for casirivimab plus imdevimab should be considered in the context of the following limitations:

- The results of this clinical trial have not been peer reviewed and published.
- The Panel's recommendation is based on preliminary results only, and the details on the study design, follow-up, and methods are limited. When peer-reviewed data for this trial become publicly available, the Panel will review the results and update the recommendations if necessary.

Rationale for Recommending Against the Use of Bamlanivimab Monotherapy

As noted above, several circulating SARS-CoV-2 variants have mutations that are associated with reduced in vitro susceptibility to certain anti-SARS-CoV-2 monoclonal antibodies that are available through EUAs. In laboratory studies, [some SARS-CoV-2 variants of concern or interest](#) that harbor certain mutations have markedly reduced susceptibility to bamlanivimab alone and possibly lower sensitivity to etesevimab and casirivimab. Reduced in vitro susceptibility to both antibodies in a combination regimen is currently uncommon. Because this field is moving quickly, and real-time testing for variants and mutations is not currently available, it seems prudent to use therapeutic options for which reduced susceptibility to the entire regimen is less likely. Therefore, the Panel **recommends against** the use of **bamlanivimab monotherapy (AIII)**. If combination products are not available, the use of bamlanivimab monotherapy can be considered for people who meet the EUA criteria on a case-by-case basis.

Rationale for Recommending Against the Use of Anti-SARS-CoV-2 Monoclonal Antibodies in Patients Who Are Hospitalized for COVID-19

The FDA EUAs do not authorize the use of these antibodies in patients who are hospitalized for COVID-19, although their use could be considered for patients who are hospitalized for a non-COVID-19 indication and who meet the EUA criteria for the use of these products. See [Anti-SARS-CoV-2 Monoclonal Antibodies](#) for further discussion of the clinical trial data for hospitalized patients.

Anti-SARS-CoV-2 monoclonal antibodies may be available through expanded access programs for the treatment of immunocompromised patients who are hospitalized because of COVID-19. It is not yet known whether these antibodies provide clinical benefits in people with B-cell immunodeficiency or other immunodeficiencies.

Vaccination

SARS-CoV-2 vaccination should be deferred for at least 90 days in people who have received anti-SARS-CoV-2 monoclonal antibodies. This is a precautionary measure, as the antibody treatment may interfere with vaccine-induced immune responses.¹¹

For people who develop COVID-19 after receiving SARS-CoV-2 vaccination, prior vaccination should not affect treatment decisions, including the use of and timing of treatment with monoclonal antibodies.¹¹

High-Risk Criteria in the Emergency Use Authorizations for Anti-SARS-CoV-2 Monoclonal Antibodies

The FDA EUAs for all available anti-SARS-CoV-2 monoclonal antibodies and combinations have the same criteria for use: they allow for the use of the monoclonal antibodies 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.³

High-risk individuals as 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 (e.g., cerebral palsy); *or*
 - A medically related technological dependence that is not related to COVID-19 (e.g., tracheostomy, gastrostomy, positive pressure ventilation); *or*
 - Asthma or a reactive airway or other chronic respiratory disease that requires daily medication for control.

References

1. Public Health Emergency. Outpatient monoclonal antibody treatment for COVID-19 made available under emergency use authorization. March 24, 2021, update on COVID-19 variants and impact on bamlanivimab distribution. 2021. Available at: <https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Bamlanivimab/Pages/default.aspx>. Accessed April 5, 2021.
2. Centers for Disease Control and Prevention. SARS-CoV-2 variant classifications and definitions. 2021. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html>. Accessed April 5, 2021.
3. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of bamlanivimab and etesevimab. 2021. Available at: <https://www.fda.gov/media/145802/download>.
4. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of bamlanivimab. 2020. Available at: <https://www.fda.gov/media/143603/download>.
5. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of

- REGEN-COV (casirivimab with imdevimab). 2020. Available at: <https://www.fda.gov/media/145611/download>.
6. Wang P, Liu L, Iketani S, et al. Increased resistance of SARS-CoV-2 variants B.1.315 and B.1.1.7 to antibody neutralization. *bioRxiv*. 2021;Preprint. Available at: <https://www.biorxiv.org/content/10.1101/2021.01.25.428137v2>.
 7. Wang P, Nair MS, Liu L, et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. *Nature*. 2021;Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33684923>.
 8. Wang P, Wang M, Yu J, et al. Increased resistance of SARS-CoV-2 variant P.1 to antibody neutralization. *bioRxiv*. 2021;Preprint. Available at: <https://www.biorxiv.org/content/10.1101/2021.03.01.433466v1>.
 9. Phase 3 trial shows REGEN-COV (casirivimab with imdevimab) antibody cocktail reduced hospitalization or death by 70% in non-hospitalized COVID-19 patients. News release. Regeneron. March 23, 2021. Available at: <https://investor.regeneron.com/news-releases/news-release-details/phase-3-trial-shows-regen-covtm-casirivimab-imdevimab-antibody>. Accessed April 5, 2021.
 10. Regeneron. COV-2067 Phase 3 trial in high-risk outpatients shows that REGEN-COV (2400 mg and 1200 mg IV doses) significantly reduces risk of hospitalization or death while also shortening symptom duration. 2021. Available at: <https://investor.regeneron.com/static-files/6ab24e8d-9733-4d91-8511-76e56b540723>.
 11. Centers for Disease Control and Prevention. Interim clinical considerations for use of COVID-19 vaccines currently authorized in the United States. 2021. Available at: <https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html>. Accessed April 7, 2021.