Anti-SARS-CoV-2 Monoclonal Antibodies

Last Updated: August 18, 2022

The SARS-CoV-2 genome encodes 4 major structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N), as well as nonstructural and accessory proteins. The spike protein is further divided into 2 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 that results in virus-host cell membrane fusion and viral entry.1 Anti-SARS-CoV-2 monoclonal antibodies (mAbs) that target the spike protein have been shown to have clinical benefits in treating SARS-CoV-2 infection. The anticipated activity of the different anti-SARS-CoV-2 mAb therapies varies dramatically depending on the circulating variant. The recommendations and discussion below pertain only to anti-SARS-CoV-2 mAb products for the treatment of COVID-19. Currently, no product is available for post-exposure prophylaxis (PEP). For recommendations and discussion regarding the use of tixagevimab plus cilgavimab (Evusheld) as pre-exposure prophylaxis (PrEP), see Prevention of SARS-CoV-2 Infection.

The Omicron variant of concern (VOC) has become the dominant SARS-CoV-2 variant in the United States.2 This variant and its subvariants have markedly reduced in vitro susceptibility to several anti-SARS-CoV-2 mAbs, especially bamlanivimab plus etesevimab and casirivimab plus imdevimab. Sotrovimab is active against the Omicron BA.1 and BA.1.1 subvariants, but it has substantially decreased in vitro neutralization activity against the Omicron BA.2, BA.4, and BA.5 subvariants. Bebtelovimab retains in vitro neutralization activity against circulating Omicron subvariants.3-5

Recommendations

The COVID-19 Treatment Guidelines Panel’s (the Panel) recommendations for the use of anti-SARS-CoV-2 mAbs are based on current knowledge of the in vitro activities of the available products against the circulating SARS-CoV-2 variants and subvariants.

Bebtelovimab

• For nonhospitalized adults aged ≥18 years with mild to moderate COVID-19 who are at high risk of progressing to severe disease, the Panel recommends using **bebtelovimab 175 mg intravenous** (IV) injection as an alternative therapy ONLY when both ritonavir-boosted nirmatrelvir (Paxlovid) and remdesivir are not available, feasible to use, or clinically appropriate (CIII).

• Treatment should be initiated as soon as possible and within 7 days of symptom onset.

• See the Centers for Disease Control and Prevention (CDC) webpage People With Certain Medical Conditions for information on medical conditions that are associated with an increased risk of progression to severe COVID-19 and **Therapeutic Management of Nonhospitalized Adults With COVID-19** for further guidance on the use of bebtelovimab.

• For recommendations for nonhospitalized children, see **Therapeutic Management of Nonhospitalized Children With COVID-19**.

• Bebtelovimab is 1 of the treatment options that can be considered for adults aged ≥18 years with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 if they otherwise meet the Food and Drug Administration (FDA) Emergency Use Authorization (EUA) criteria for outpatient treatment.
Bamlanivimab Plus Etesevimab, Casirivimab Plus Imdevimab, and Sotrovimab

- Because the Omicron VOC is now the dominant variant in the United States, the Panel recommends against using bamlanivimab plus etesevimab, casirivimab plus imdevimab, or sotrovimab for the treatment of COVID-19 (AIII).

Additional Considerations

- For information on medical conditions and other factors that are associated with an increased risk of progression to severe COVID-19, see the CDC webpage People With Certain Medical Conditions. The decision to use anti-SARS-CoV-2 mAbs for a patient should be based on an individualized assessment of the risks and benefits. Not all of the conditions and factors considered to be high risk were well-represented in the clinical trials that provide support for the mAb EUAs.

- Some rare medical conditions that are not listed on the CDC webpage Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19 and other factors (e.g., race, ethnicity) may be associated with a high risk of progressing to severe COVID-19. It is important to note that the likelihood of developing severe COVID-19 increases when a person has multiple high-risk conditions or comorbidities.

- Previously published clinical trials that evaluated the use of anti-SARS-CoV-2 mAbs for the treatment of COVID-19 largely enrolled an unvaccinated participant population. The risk of progression to severe COVID-19 in high-risk patients is substantially greater for those who are not vaccinated against COVID-19 and those who are vaccinated but do not mount an adequate immune response to the vaccine due to an underlying immunocompromising condition.

- If indicated, treatment with anti-SARS-CoV-2 mAbs should be started as soon as possible after SARS-CoV-2 infection is confirmed by an antigen test or a nucleic acid amplification test and within 7 days of symptom onset.

- Anti-SARS-CoV-2 mAbs should be administered in a setting where severe hypersensitivity reactions, such as anaphylaxis, can be managed. Patients should be monitored for at least 1 hour after the injection.

- See Prioritization of Anti-SARS-CoV-2 Therapies for the Treatment and Prevention of COVID-19 When There Are Logistical or Supply Constraints for the Panel’s recommendations in situations where therapies for the treatment of mild to moderate COVID-19, including anti-SARS-CoV-2 mAbs, cannot be offered to all eligible patients.

- Data are limited on the combined use of antiviral agents and anti-SARS-CoV-2 mAbs for the treatment of nonhospitalized patients with COVID-19. Clinical trials are needed to determine whether this combination therapy has a role in the treatment of COVID-19.

- Patients who are severely immunocompromised may have prolonged SARS-CoV-2 replication, leading to more rapid viral evolution. There is a concern that using a single anti-SARS-CoV-2 mAb in these patients may result in the emergence of resistant virus. Additional studies are needed to assess this risk.

Anti-SARS-CoV-2 Monoclonal Antibodies That Have Received Emergency Use Authorizations

Five anti-SARS-CoV-2 mAb products have received EUAs from the FDA. The authorized anti-SARS-CoV-2 mAb products that are currently available for use are:

- Bebtelovimab: This recombinant neutralizing human mAb binds to the spike protein of SARS-CoV-2. Bebtelovimab retains in vitro neutralization activity against all circulating Omicron
subvariants, but there are no clinical efficacy data on the treatment of patients who are at high risk of progressing to severe COVID-19.\textsuperscript{3,5,13-15}

- \textit{Tixagevimab plus cilgavimab:} These recombinant human anti-SARS-CoV-2 mAbs bind to nonoverlapping epitopes of the spike protein RBD of SARS-CoV-2. Tixagevimab plus cilgavimab has retained in vitro neutralization activity against the Omicron BA.2 subvariant.\textsuperscript{16-19} Tixagevimab plus cilgavimab has modestly reduced in vitro neutralization activity against the Omicron BA.4 and BA.5 subvariants, but this combination is expected to be clinically active. Tixagevimab plus cilgavimab is authorized for use as PrEP in certain patients and should be given in repeat doses every 6 months if ongoing protection is needed. See \textit{Prevention of SARS-CoV-2 Infection} for more information.

The distribution of the following authorized anti-SARS-CoV-2 mAb products has paused in the United States. The Omicron VOC has markedly reduced in vitro susceptibility to these products; therefore, they are not expected to provide a clinical benefit for patients with COVID-19 caused by the Omicron VOC:\textsuperscript{20,21}

- \textit{Bamlanivimab plus etesevimab:} These neutralizing mAbs bind to different, but overlapping, epitopes of the spike protein RBD of SARS-CoV-2.
- \textit{Casirivimab plus imdevimab:} These recombinant human mAbs bind to nonoverlapping epitopes of the spike protein RBD of SARS-CoV-2.
- \textit{Sotrovimab:} This mAb was originally identified in 2003 from a survivor of SARS-CoV infection. It targets an epitope of the RBD of the spike protein that is conserved between SARS-CoV and SARS-CoV-2.

Sotrovimab retains in vitro neutralization activity against the Omicron BA.1 and BA.1.1 subvariants, but it has substantially decreased in vitro neutralization activity against the Omicron BA.2, BA.4, and BA.5 subvariants and is not expected to provide a clinical benefit at this time.\textsuperscript{5,6,14,22}

\section*{SARS-CoV-2 Variant Susceptibility to Anti-SARS-CoV-2 Monoclonal Antibodies}

In laboratory studies, some SARS-CoV-2 variants that harbor certain mutations have markedly reduced susceptibility to several of the authorized anti-SARS-CoV-2 mAbs.\textsuperscript{23} The clinical relevance of the reduced in vitro susceptibility of select variants to anti-SARS-CoV-2 mAbs is under investigation.

Population-based genomic surveillance of the types and proportions of circulating SARS-CoV-2 variants and studies on the susceptibility of different variants to the available anti-SARS-CoV-2 mAbs will be important in defining the utility of specific anti-SARS-CoV-2 mAbs in the future. See the CDC COVID Data Tracker for regular updates on the data for SARS-CoV-2 variants.
### Table A. SARS-CoV-2 Variants and Susceptibility to Anti-SARS-CoV-2 Monoclonal Antibodies

<table>
<thead>
<tr>
<th>Years of Circulation</th>
<th>WHO Label and Pango Lineage</th>
<th>Notable Mutations</th>
<th>BEB</th>
<th>TIX Plus CIL</th>
<th>BAM Plus ETE</th>
<th>CAS Plus IMD</th>
<th>SOT</th>
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<tbody>
<tr>
<td></td>
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<td>In Vitro Susceptibility</td>
<td>Anticipated Clinical Activity</td>
<td>In Vitro Susceptibility</td>
<td>Anticipated Clinical Activity</td>
<td>In Vitro Susceptibility</td>
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<tr>
<td><strong>Variants Currently or Recently Circulating in the United States</strong></td>
<td></td>
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<tr>
<td>2021–present</td>
<td>Omicron BA.2</td>
<td>T376A, K417N, N440K, E484A, Q493R, N501Y</td>
<td>No change</td>
<td>Active</td>
<td>No change</td>
<td>Active</td>
<td>Marked reduction</td>
</tr>
<tr>
<td>2022–present</td>
<td>Omicron BA.4</td>
<td>BA.2 plus del69/70, L452R, F486V, Q493 reversion</td>
<td>No change</td>
<td>Active</td>
<td>Moderate reduction&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Active&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Marked reduction</td>
</tr>
<tr>
<td>2022–present</td>
<td>Omicron BA.5</td>
<td>BA.2 plus del69/70, L452R, F486V, Q493 reversion</td>
<td>No change</td>
<td>Active</td>
<td>Moderate reduction&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Active&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Marked reduction</td>
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<tr>
<td><strong>Variants That Are Not Currently Circulating in the United States</strong></td>
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<tr>
<td>2020–2021 Alpha B.1.1.7</td>
<td>N501Y</td>
<td>No change</td>
<td>Active</td>
<td>No change</td>
<td>Active</td>
<td>No change</td>
<td>Active</td>
</tr>
<tr>
<td>2020–2021 Beta B.1.351</td>
<td>K417N, E484K, N501Y</td>
<td>No change</td>
<td>Active</td>
<td>No change</td>
<td>Active</td>
<td>Marked reduction</td>
<td>Unlikely to be active</td>
</tr>
<tr>
<td>2020–2021 Gamma P.1</td>
<td>K417T, E484K, N501Y</td>
<td>No change</td>
<td>Active</td>
<td>No change</td>
<td>Active</td>
<td>Marked reduction</td>
<td>Unlikely to be active</td>
</tr>
<tr>
<td>2020–2021 Delta B.1.617.2, non-AY.1/AY.2</td>
<td>L452R, T478K</td>
<td>No change</td>
<td>Active</td>
<td>No change</td>
<td>Active</td>
<td>No change</td>
<td>Active</td>
</tr>
<tr>
<td>2021–2022 Omicron B.1.1.529/BA.1</td>
<td>K417N, N440K, G446S, E484A, Q493R, N501Y</td>
<td>No change</td>
<td>Active</td>
<td>Moderate reduction&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Active&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Marked reduction</td>
<td>Unlikely to be active</td>
</tr>
<tr>
<td>2021–2022 Omicron BA.1.1</td>
<td>BA.1 plus R346K</td>
<td>No change</td>
<td>Active</td>
<td>Moderate reduction&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Active&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Marked reduction</td>
<td>Unlikely to be active</td>
</tr>
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<sup>a</sup> Based on the fold reduction in susceptibility reported in the FDA EUAs.<sup>6,16,24,25</sup>

<sup>b</sup> Despite the moderately reduced in vitro susceptibility of TIX plus CIL, in vitro PK/PD modeling data suggest that the TIX 300 mg plus CIL 300 mg dose will retain activity against the Omicron VOC.<sup>16</sup>

<sup>c</sup> The duration of activity for TIX plus CIL against these subvariants is not well defined. TIX plus CIL should be given in repeat doses every 6 months if ongoing protection is needed.

COVID-19 Treatment Guidelines

Downloaded from [https://www.covid19treatmentguidelines.nih.gov/](https://www.covid19treatmentguidelines.nih.gov/) on 9/15/2022
Marked change for CAS and no change for IMD. The combination of CAS plus IMD appears to retain activity against the variant.

**Key:** BAM = bamlanivimab; BEB = bebtelovimab; CAS = casirivimab; CIL = cilgavimab; ETE = etesevimab; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; IMD = imdevimab; PK/PD = pharmacokinetic/pharmacodynamic; SOT = sotrovimab; TIX = tixagevimab; WHO = World Health Organization

**Clinical Trials**

In placebo-controlled, randomized trials in nonhospitalized patients with mild to moderate COVID-19 symptoms and certain risk factors for disease progression, the use of anti-SARS-CoV-2 mAb products reduced the risk of hospitalization and death (see Table 5a). These studies were conducted before the widespread circulation of the Omicron VOC.

**Bebtelovimab**

Based on in vitro data, bebtelovimab is expected to have activity against a broad range of SARS-CoV-2 variants, including the Omicron VOC and its BA.1, BA.2, BA.4, and BA.5 subvariants. The Panel’s recommendation for bebtelovimab is primarily based on laboratory data showing its potent activity against the Omicron VOC (including the BA.1 and BA.2 subvariants) and other VOCs, as well as on limited clinical trial data from the Phase 2 BLAZE-4 study.

In treatment arms 9 to 11 in the Phase 2 BLAZE-4 trial, patients with COVID-19 who were at low risk of disease progression were randomized to receive a single infusion of bamlanivimab plus etesevimab plus bebtelovimab (n = 127), bebtelovimab alone (n = 125), or placebo (n = 128). Among these individuals, the mean decline in viral load at Day 5 was greater in the 2 bebtelovimab arms than in the placebo arm. The median time to sustained symptom resolution was 6 days in the bebtelovimab alone arm and 8 days in the placebo arm (P = 0.003).

Large randomized controlled trials are needed to fully evaluate the efficacy of bebtelovimab in a high-risk population. Nevertheless, when other therapeutic options are not available, feasible to use, or clinically appropriate, in vitro susceptibility data and the antiviral activity and clinical benefits observed in Phase 2 trials support the use of bebtelovimab for nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe COVID-19. In addition, bebtelovimab has mechanisms of action that are similar to those of other authorized anti-SARS-CoV-2 mAbs that have shown definitive clinical benefits in this population.

**Bamlanivimab Plus Etesevimab**

The distribution of bamlanivimab plus etesevimab has paused in the United States because the Omicron VOC and its subvariants have markedly reduced in vitro susceptibility to this mAb regimen. Prior to the spread of the Omicron VOC, the Phase 3 BLAZE-1 trial had demonstrated a clinical benefit of bamlanivimab plus etesevimab in people with mild to moderate COVID-19 who were at high risk of progressing to severe disease or hospitalization.

**Casirivimab Plus Imdevimab**

The distribution of casirivimab plus imdevimab has paused in the United States because the Omicron VOC and its subvariants have markedly reduced in vitro susceptibility to this mAb regimen. Prior to the spread of the Omicron VOC, the FDA had authorized the use of casirivimab plus imdevimab for the treatment of people with mild to moderate COVID-19 who are at high risk of progressing to severe disease or hospitalization.
Sotrovimab retains in vitro neutralization activity against the BA.1 and BA.1.1 subvariants of the Omicron VOC, but it has substantially decreased in vitro neutralization activity against the Omicron BA.2, BA.4, and BA.5 subvariants. It is not expected to provide a clinical benefit to patients infected with these subvariants. Because the Omicron BA.5 subvariant is now the dominant circulating subvariant in all regions of the United States, distribution of sotrovimab has paused, and the Panel no longer recommends using sotrovimab to treat COVID-19.

See Table 5a for more information on the clinical trials evaluating the safety and efficacy of anti-SARS-CoV-2 mAbs in patients with COVID-19.

Using Anti-SARS-CoV-2 Monoclonal Antibodies in Patients Hospitalized for COVID-19

The anti-SARS-CoV-2 mAbs available through FDA EUAs are not authorized for the treatment of COVID-19 in the following patients:

- Those hospitalized for COVID-19
- Those who require oxygen therapy or respiratory support due to COVID-19
- Those who are on chronic oxygen therapy due to an underlying non-COVID-19-related comorbidity and who require an increase in oxygen flow rate from baseline or respiratory support because of COVID-19

The FDA EUAs permit the use of anti-SARS-CoV-2 mAb products in patients who are hospitalized for a diagnosis other than COVID-19, provided they have mild to moderate COVID-19 and are at high risk of progressing to severe disease. Anti-SARS-CoV-2 mAbs have been evaluated in hospitalized patients with severe COVID-19. In general, anti-SARS-CoV-2 mAbs were not found to provide a clinical benefit in hospitalized patients, although some subanalyses have reported potential benefits. In the RECOVERY trial, casirivimab plus imdevimab demonstrated a potential benefit in individuals who were seronegative for the SARS-CoV-2 anti-spike protein antibody. Patients who received casirivimab 4 g plus imdevimab 4 g had a significant reduction in 28-day all-cause mortality (396 of 1,633 patients [24%]) compared with patients who received usual care (452 of 1,520 patients [30%]; rate ratio 0.79; 95% CI, 0.69–0.91; \( P = 0.0009 \)). A second trial in hospitalized patients with COVID-19 also reported a reduction in mortality among seronegative patients who received casirivimab plus imdevimab. The current EUA does not authorize the use of the higher dose of casirivimab plus imdevimab that was evaluated in these trials. This anti-SARS-CoV-2 mAb combination is also not expected to be efficacious against the Omicron VOC. In addition, rapid serology testing that can identify seronegative individuals in real time is not widely available.

In the ACTIV-3/TICO trial, the use of tixagevimab plus cilgavimab in hospitalized patients with COVID-19 did not improve the proportion of patients who achieved sustained clinical recovery (which was defined as 14 consecutive days at home after hospital discharge). However, the relative risk of mortality decreased by approximately 30% among patients who received this combination. Tixagevimab plus cilgavimab is not currently authorized by the FDA for the treatment of patients hospitalized for COVID-19.

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

**Monitoring**

Bebtelovimab should be administered by IV injection and should only be administered in health care settings by qualified health care providers who have immediate access to emergency medical services and medications that treat severe infusion-related reactions. Patients should be monitored for at least 1 hour after the injection.

**Adverse Effects**

Hypersensitivity, including anaphylaxis and infusion-related reactions, has been reported in patients who received anti-SARS-CoV-2 mAbs. Rash, diarrhea, nausea, vomiting, dizziness, and pruritis have also been reported.\(^6,13,25,28\)

**Drug-Drug Interactions**

Drug-drug interactions are unlikely between the authorized anti-SARS-CoV-2 mAbs and medications that are renally excreted or that are cytochrome P450 substrates, inhibitors, or inducers (see Table 5c).

**Considerations in Pregnancy**

The use of anti-SARS-CoV-2 mAbs can be considered for pregnant people with COVID-19, especially those who have additional risk factors for severe disease.

As immunoglobulin (Ig) G mAbs, the authorized anti-SARS-CoV-2 mAbs would be expected to cross the placenta. There are no pregnancy-specific data on the use of these mAbs; however, other IgG products have been safely used in pregnant people when indicated. Therefore, authorized anti-SARS-CoV-2 mAbs should not be withheld during pregnancy. When possible, pregnant and lactating people should be included in clinical trials that are evaluating the use of anti-SARS-CoV-2 mAbs for the treatment or prevention of COVID-19.

**Considerations in Children**


**Drug Availability**

Bebtelovimab is available for the treatment of COVID-19 and tixagevimab plus cilgavimab is available for SARS-CoV-2 PrEP in all regions of the United States. The broad distribution of bamlanivimab plus etesevimab, casirivimab plus imdevimab, and sotrovimab has paused in the United States because the Omicron VOC has reduced susceptibility to these anti-SARS-CoV-2 mAbs.\(^20,21\)

**References**


27. Food and Drug Administration. Frequently asked questions on the emergency use authorization of bamlanivimab and etesevimab. 2022. Available at: https://www.fda.gov/media/145808/download.


