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. 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 effectiveness of the different anti-SARS-CoV-2 mAb therapies varies dramatically depending on the circulating variant, and the role of each anti-SARS-CoV-2 mAb in the treatment of COVID-19 remains fluid. The recommendations and discussion below pertain only to the use of the authorized 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 (B.1.1.529) variant of concern (VOC) has become the dominant SARS-CoV-2 variant in the United States. This variant, which includes numerous mutations in the spike protein, has markedly reduced in vitro susceptibility to several anti-SARS-CoV-2 mAbs, especially bamlanivimab plus etesevimab and casirivimab plus imdevimab (REGEN-COV). Sotrovimab is active against the Omicron BA.1 and BA.1.1 subvariants, but it has substantially decreased in vitro activity against the Omicron BA.2 subvariant. Bebtelovimab retains in vitro activity against circulating Omicron subvariants.

**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. These recommendations remain fluid and depend on the prevalence of resistant variants. At this time, the Panel’s anti-SARS-CoV-2 mAb recommendations are for the treatment of nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease.

**Bebtelovimab**

The Panel recommends using bebtelovimab 175 mg intravenous (IV) injection in patients aged ≥12 years as an alternative therapy **ONLY** when 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 Therapeutic Management of Nonhospitalized Adults With COVID-19 for further guidance.

**Bamlanivimab Plus Etesevimab, Casirivimab Plus Imdevimab, and Sotrovimab**

Because the Omicron VOC has become 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**

- 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 during the infusion and observed for at least 1 hour after infusion.

- Treatment with anti-SARS-CoV-2 mAbs should be considered for patients with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 if they otherwise meet the Emergency Use Authorization (EUA) criteria for outpatient treatment.

- The risk for progression to severe COVID-19 in high-risk patients is substantially greater for those who are not vaccinated or those who are vaccinated but not expected to mount an adequate immune response to the vaccine due to an underlying immunocompromising condition. When the available therapies cannot be offered to all eligible patients, 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.

- There are no data 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.

- Severely immunocompromised patients 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 emergence of resistant virus. Additional studies are needed to assess this risk. The role of anti-SARS-CoV-2 mAbs plus antiviral therapy in the treatment of COVID-19 is not yet known.3,4

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

Five anti-SARS-CoV-2 mAb products have received EUAs from the Food and Drug Administration (FDA). Bamlanivimab plus etesevimab, bebtelovimab, casirivimab plus imdevimab, and sotrovimab received EUAs for the treatment of mild to moderate COVID-19 in nonhospitalized patients with laboratory-confirmed SARS-CoV-2 infection who are at high risk for progressing to severe disease or hospitalization. The FDA issued an EUA for tixagevimab plus cilgavimab, a long-acting anti-SARS-CoV-2 mAb combination, as SARS-CoV-2 PrEP for individuals who do not have SARS-CoV-2 infection, who have not been recently exposed to an individual with SARS-CoV-2 infection, AND who are at risk for inadequate immune response to COVID-19 vaccination OR have a documented history of severe adverse reactions to a COVID-19 vaccine or any of its components (see Prevention of SARS-CoV-2 Infection for more information). The issuance of an EUA does not constitute FDA approval.

The authorized anti-SARS-CoV-2 mAb products, listed alphabetically, are:

- **Bamlanivimab plus etesevimab:** These neutralizing mAbs bind to different, but overlapping, epitopes in the spike protein RBD of SARS-CoV-2.
  - The distribution of bamlanivimab plus etesevimab has paused in the United States because the Omicron VOC has markedly reduced in vitro susceptibility to bamlanivimab and etesevimab; therefore, this regimen is not expected to provide clinical benefit for patients with Omicron infection.5

- **Bebtelovimab:** This recombinant neutralizing human mAb binds to the spike protein of SARS-CoV-2. Bebtelovimab retains in vitro activity against all circulating Omicron subvariants, but there are no clinical efficacy data on the treatment of patients at high risk for progression to
severe COVID-19.\(^6\)

- **Casirivimab plus imdevimab:** These recombinant human mAbs bind to nonoverlapping epitopes of the spike protein RBD of SARS-CoV-2.

  - The distribution of casirivimab plus imdevimab has paused in the United States because the Omicron VOC has markedly reduced in vitro susceptibility to casirivimab and imdevimab; therefore, this regimen is not expected to provide clinical benefit for patients with Omicron infection.\(^7\)

- **Sotrovimab:** This mAb was originally identified in 2003 from a survivor of SARS-CoV infection. It targets an epitope in the RBD of the spike protein that is conserved between SARS-CoV and SARS-CoV-2. Sotrovimab retains in vitro activity against the Omicron BA.1 and BA.1.1 subvariants, but it has substantially decreased in vitro activity against Omicron BA.2 and is not expected to provide clinical benefit for patients with Omicron BA.2 infection.\(^8-10\)

  - Because the Omicron BA.2 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 for the treatment of COVID-19.

- **Tixagevimab plus cilgavimab:** These recombinant human anti-SARS-CoV-2 mAbs bind to nonoverlapping epitopes of the spike protein RBD of SARS-CoV-2. The originally authorized dose of tixagevimab 150 mg plus cilgavimab 150 mg has reduced in vitro activity against the Omicron BA.1 and BA.1.1 subvariants. However, the FDA updated the EUA to authorize a dose of tixagevimab 300 mg plus cilgavimab 300 mg, which is expected to maintain activity against these subvariants. Tixagevimab plus cilgavimab has retained in vitro activity against the Omicron BA.2 subvariant.\(^11-13\)

### 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 (see Table A).\(^14\) The clinical relevance of the reduced in vitro susceptibility of select variants to anti-SARS-CoV-2 mAbs is under investigation.

Some key SARS-CoV-2 variants that have been identified are:

- **Alpha (B.1.1.7):** This variant retains in vitro susceptibility to all anti-SARS-CoV-2 mAb products currently available through FDA EUAs.\(^15-17\)

- **Beta (B.1.351):** This variant has markedly reduced in vitro susceptibility to bamlanivimab and etesevimab.\(^15,17\) In vitro studies also suggest that the Beta variant has markedly reduced susceptibility to casirivimab; however, the combination of casirivimab and imdevimab appears to retain activity against the variant.\(^16\) Sotrovimab also appears to retain activity against the variant.\(^8\)

- **Gamma (P.1):** This variant has markedly reduced in vitro susceptibility to bamlanivimab and etesevimab.\(^15,16\) The Gamma variant also has reduced susceptibility to casirivimab; however, the combination of casirivimab plus imdevimab appears to retain activity against the variant.\(^16\) Sotrovimab also appears to retain activity against the Gamma variant.\(^8\)

- **Delta (B.1.617.2, non-AY.1/AY.2):** This VOC retains in vitro susceptibility to all anti-SARS-CoV-2 mAbs currently available through FDA EUAs.\(^15,16\)

- **Omicron (B.1.1.529):** This is currently the predominant VOC circulating in the United States and includes the BA.1, BA.1.1, and BA.2 subvariants. This variant, which includes numerous mutations in the spike protein, has markedly reduced in vitro susceptibility to some anti-SARS-CoV-2 mAb products, as noted below:
• Bamlanivimab plus etesevimab and casirivimab plus imdevimab are not expected to be active against these subvariants.\textsuperscript{12}

• Sotrovimab retains activity against the Omicron BA.1 and BA.1.1 subvariants but has decreased in vitro activity against the Omicron BA.2 subvariant.\textsuperscript{8,12,13}

• Bebtelovimab retains in vitro activity against all circulating Omicron subvariants.\textsuperscript{6,9,19}

• The originally authorized dose of tixagevimab 150 mg plus cilgavimab 150 mg has reduced in vitro activity against the Omicron BA.1 and BA.1.1 subvariants.\textsuperscript{11} However, the FDA updated the EUA to authorize a dose of tixagevimab 300 mg plus cilgavimab 300 mg, which is expected to maintain activity against these subvariants. The duration of protection against the BA.1 and BA.1.1 subvariants remains unclear. Tixagevimab plus cilgavimab has retained in vitro activity against the Omicron BA.2 subvariant.\textsuperscript{11-13,20}

To define the utility of specific mAbs in the future, ongoing \textit{population-based genomic surveillance} of the types and proportions of circulating SARS-CoV-2 variants, as well as studies on the susceptibility of different variants to available anti-SARS-CoV-2 mAbs, will be important.
# Table A. SARS-CoV-2 Variants and Susceptibility to Anti-SARS-CoV-2 Monoclonal Antibodies

<table>
<thead>
<tr>
<th>WHO Label</th>
<th>Pango Lineage</th>
<th>CDC Variant Class</th>
<th>Notable Mutations</th>
<th>BAM Plus ETE</th>
<th>CAS Plus IMD</th>
<th>BEB</th>
<th>SOT</th>
<th>TIX Plus CIL</th>
</tr>
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<tr>
<td>Alpha</td>
<td>B.1.1.7</td>
<td>VBM</td>
<td>N501Y</td>
<td>No change</td>
<td>Active</td>
<td>No change</td>
<td>Active</td>
<td>No change</td>
</tr>
<tr>
<td>Beta</td>
<td>B.1.351</td>
<td>VBM</td>
<td>K417N, E484K, N501Y</td>
<td>Marked reduction</td>
<td>Unlikely to be active</td>
<td>No change</td>
<td>Active</td>
<td>No change</td>
</tr>
<tr>
<td>Gamma</td>
<td>P.1</td>
<td>VBM</td>
<td>K417T, E484K, N501Y</td>
<td>Marked reduction</td>
<td>Unlikely to be active</td>
<td>No change</td>
<td>Active</td>
<td>No change</td>
</tr>
<tr>
<td>Delta</td>
<td>B.1.617.2, non-AY.1/AY.2</td>
<td>VOC</td>
<td>L452R, T478K</td>
<td>No change</td>
<td>Active</td>
<td>No change</td>
<td>Active</td>
<td>No change</td>
</tr>
<tr>
<td>Omicron</td>
<td>B.1.1.529/BA.1</td>
<td>VOC</td>
<td>K417N, N440K, G446S, E484A, Q493R, N501Y</td>
<td>Marked reduction</td>
<td>Unlikely to be active</td>
<td>Marked reduction</td>
<td>Unlikely to be active</td>
<td>No change</td>
</tr>
<tr>
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<td>B.1.1.529/BA.1.1</td>
<td>VOC</td>
<td>R346K, K417N, N440K, G446S, E484A, Q493R, N501Y</td>
<td>Marked reduction</td>
<td>Unlikely to be active</td>
<td>Marked reduction</td>
<td>Unlikely to be active</td>
<td>No change</td>
</tr>
<tr>
<td>Omicron</td>
<td>B.1.1.529/BA.2</td>
<td>VOC</td>
<td>T376A, K417N, N440K, E484A, Q493R, N501Y</td>
<td>Marked reduction</td>
<td>Unlikely to be active</td>
<td>Marked reduction</td>
<td>Unlikely to be active</td>
<td>No change</td>
</tr>
</tbody>
</table>

- α Based on the fold reduction in susceptibility reported in the FDA EUAs.8,11,15,16
- β Marked change for CAS and no change for IMD. The combination of CAS plus IMD appears to retain activity against the variant.
- γ 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.11

The duration of protection against SARS-CoV-2 infection remains unclear.

Key: BAM = bamlanivimab; BEB = bebtelovimab; CAS = casirivimab; CIL = cilgavimab; CDC = Centers for Disease Control and Prevention; ETE = etesevimab; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; IMD = imdevimab; PK/PD = pharmacokinetic/pharmacodynamic; SOT = sotrovimab; TIX = tixagevimab; VBM = variant being monitored; VOC = variant of concern; 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 3a).6,8,15,16 These studies were conducted before the widespread circulation of the Omicron VOC. The potential impact of this variant and its susceptibility to different FDA-authorized anti-SARS-CoV-2 mAbs are discussed below.

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 and BA.2 subvariants.6,9,19 The Panel’s recommendation on 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.6

The multi-armed, Phase 2 BLAZE-4 study included 1 small, placebo-controlled, randomized trial in patients at low risk of disease progression. It also included 1 small randomized controlled trial that compared bebtelovimab alone to an anti-SARS-CoV-2 mAb combination of bamlanivimab, etesevimab, and bebtelovimab in patients at high risk of disease progression (see Table 3a).6 Among low-risk 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 at high risk of progressing to severe COVID-19. In addition, bebtelovimab has mechanisms of action 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 subvariants have markedly reduced in vitro susceptibility to this mAb regimen.5 Prior to the spread of the Omicron variant, the Phase 3 BLAZE-1 trial had demonstrated a clinical benefit of bamlanivimab plus etesevimab in people with mild to moderate COVID-19 who are at high risk for progression to severe disease or hospitalization.21

Casirivimab Plus Imdevimab

The distribution of casirivimab plus imdevimab has paused in the United States because the Omicron VOC and subvariants have markedly reduced in vitro susceptibility to this mAb regimen.7 Prior to the spread of the Omicron variant, the FDA had authorized the use of casirivimab 600 mg plus imdevimab 600 mg administered as a single IV infusion for the treatment of people with
mild to moderate COVID-19 who are at high risk for progression to severe disease or hospitalization. The recommendation for using the dose of casirivimab 600 mg plus imdevimab 600 mg IV is based on data from a Phase 3, double-blind, placebo-controlled, randomized trial demonstrating clinical benefit in outpatients with mild to moderate COVID-19. The FDA also authorized subcutaneous (SUBQ) injection of the regimen if an IV infusion is not feasible or would delay treatment. SUBQ administration of casirivimab plus imdevimab requires 4 injections (2.5 mL per injection) at 4 different sites (see the FDA EUA for details).

**Sotrovimab**

Sotrovimab retains in vitro activity against the Omicron BA.1 and BA.1.1 subvariants of the Omicron VOC, but it has substantially decreased in vitro activity against the Omicron BA.2 subvariant and is not expected to provide clinical benefit for patients with Omicron BA.2 infection. Because the Omicron BA.2 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.

Data that support the sotrovimab EUA are from the Phase 3 COMET-ICE trial, which included outpatients with mild to moderate COVID-19 who were at high risk for progression to severe disease or hospitalization. A total of 1,057 participants were randomized within 5 days of symptom onset to receive sotrovimab 500 mg IV (n = 528) or placebo (n = 529). The primary endpoint was the proportion of participants who were hospitalized for ≥24 hours or who died from any cause by Day 29. Endpoint events occurred in 6 of 528 participants (1%) in the sotrovimab arm and 30 of 529 participants (6%) in the placebo arm, resulting in a 4.53% absolute difference in the risk of hospitalization or death among those who received sotrovimab. The adjusted relative risk of hospitalization or death for those who received sotrovimab was 0.21.

See Table 3a for more information on the clinical trials evaluating the safety and efficacy of anti-SARS-CoV-2 mAbs in patients with COVID-19.

**Criteria for Use of Anti-SARS-CoV-2 Monoclonal Antibodies Under Emergency Use Authorizations**

The FDA EUAs for anti-SARS-CoV-2 mAbs include a list of specific conditions that place patients at high risk for clinical progression. On May 14, 2021, the FDA revised the EUAs to broaden these criteria. Notable changes included lowering the body mass index (BMI) cutoff from ≥35 to >25 and adding other conditions and factors (e.g., pregnancy, race or ethnicity). Other than being aged ≥12 years, there are no longer any age criteria restricting the use of these products in patients with the following conditions: sickle cell disease, neurodevelopmental disorders, medical-related technological dependence, asthma, cardiovascular disease, hypertension, and chronic lung disease.

For guidance when available therapies cannot be offered to all eligible patients, see Prioritization of Anti-SARS-CoV-2 Therapies for the Treatment and Prevention of COVID-19 When There Are Logistical or Supply Constraints.

**Recommendations**

The strength of the evidence for using anti-SARS-CoV-2 mAbs varies depending on the medical conditions and other factors that place patients at high risk for progression to severe COVID-19 or hospitalization. The ratings for the Panel’s recommendations are based on FDA EUA criteria for identifying high-risk individuals.
• For patients with high-risk conditions that have been represented in clinical trials evaluating anti-SARS-CoV-2 mAbs, the Panel recommends the use of anti-SARS-CoV-2 mAbs, with the following ratings:

  • Aged ≥65 years (AIIa)
  • Obesity (BMI >30) (AIIa)
  • Diabetes (AIIa)
  • Cardiovascular disease (including congenital heart disease) or hypertension (AIIa)
  • Chronic lung diseases (e.g., chronic obstructive pulmonary disease, moderate-to-severe asthma, interstitial lung disease, cystic fibrosis, pulmonary hypertension) (AIIa)

• For patients with conditions that have had limited representation in clinical trials but are considered a high risk for progression to severe COVID-19 by the Centers for Disease Control and Prevention (CDC), the Panel recommends the use of anti-SARS-CoV-2 mAbs, with the following ratings:

  • Immunocompromised or receiving immunosuppressive treatment (AIII); many experts strongly recommend therapy for patients with these conditions, despite limited representation in clinical trials
  • Overweight (i.e., BMI 25–30) as a sole risk factor (BIII)
  • Chronic kidney disease (BIII)
  • Pregnancy (BIII)
  • Sickle cell disease (BIII)
  • Neurodevelopmental disorder (e.g., cerebral palsy) or another condition that confers medical complexity (e.g., genetic or metabolic syndromes, severe congenital anomalies) (BIII)
  • Medical-related technological dependence (e.g., tracheostomy, gastrostomy, positive pressure ventilation not related to COVID-19) (BIII)
  • Infants aged <1 year. Although bamlanivimab plus etesevimab is authorized for use in this high-risk group, the Panel recommends against using this mAb regimen (AIII) because it has markedly reduced activity against Omicron, the dominant VOC in the United States.

It is important to note that the likelihood of developing severe COVID-19 increases when a person has multiple high-risk conditions or comorbidities. Medical conditions or other factors (e.g., race or ethnicity) that are not listed in the mAb EUAs may also be associated with high risk for progression to severe COVID-19. The current EUAs state that the use of anti-SARS-CoV-2 mAbs may be considered for patients with high-risk conditions and factors that are not listed in the EUAs. For additional information on medical conditions and other factors that are associated with an increased risk for 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 risks and benefits.

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 use in the following patients:

• Those hospitalized for COVID-19; or
• Those who require oxygen therapy or respiratory support due to COVID-19; or
• 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 do 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 for progressing to severe disease.\(^6,16,27,28\)

Anti-SARS-CoV-2 mAbs have been evaluated in hospitalized patients with severe COVID-19. A substudy of the ACTIV-3/TICO trial randomized patients who were hospitalized for COVID-19 to receive bamlanivimab 7,000 mg or placebo, each in addition to remdesivir. On October 26, 2020, study enrollment was halted after a prespecified interim futility analysis indicated a lack of clinical benefit for bamlanivimab.\(^29,30\)

Prior to the spread of the Omicron VOC, data supported the use of anti-SARS-CoV-2 mAbs in hospitalized patients with COVID-19 who are seronegative for the anti-spike protein antibody and/or have evidence of ongoing viral replication. In a subset analysis of the ACTIV-3 trial, 153 of 314 participants (49%) were negative for the anti-spike endogenous neutralizing antibody. The subhazard ratio (sHR) comparing bamlanivimab to placebo for sustained recovery (defined as discharge home and remaining at home for \(\geq 14\) days through Day 90) was 1.24 among the participants who were seronegative (CI, 0.90–1.70) versus 0.74 among those who were seropositive (CI, 0.54–1.00). Furthermore, the difference for sustained recovery between bamlanivimab and placebo was even greater among the seronegative participants who had high viral loads (sHR 1.89; CI, 1.23–2.91). However, these results are limited due to the trial’s early termination for futility and small sample size.\(^31\)

The ACTIV-3/TICO trial also randomized hospitalized patients with COVID-19 to receive sotrovimab 500 mg IV, an anti-SARS-CoV-2 mAb combination of BRII-196 1,000 mg IV plus BRII-198 1,000 mg IV, or placebo, each in addition to remdesivir. On March 1, 2021, study enrollment was halted after a prespecified interim futility analysis indicated a lack of clinical benefit for sotrovimab or BRII-196 plus BRII-198.\(^32\) A subset analysis did not suggest efficacy for sotrovimab in those with or without endogenous antibodies.

In the RECOVERY study, hospitalized patients with COVID-19 were randomized to receive usual care with casirivimab 4,000 mg plus imdevimab 4,000 mg IV or usual care alone. There was no difference in 28-day all-cause mortality between the casirivimab plus imdevimab arm and the usual care arm; 943 of 4,839 patients (19%) in the casirivimab plus imdevimab arm died versus 1,029 of 4,946 patients (21%) in the usual care arm (rate ratio 0.94; 95% CI, 0.86–1.02; \(P = 0.14\)). However, in the subgroup of patients who were seronegative for the anti-spike protein antibody, there was a significant reduction in 28-day all-cause mortality in the casirivimab plus imdevimab arm (396 of 1,633 casirivimab plus imdevimab recipients [24%] died vs. 452 of 1,520 usual care recipients [30%]; rate ratio 0.79; 95% CI, 0.69–0.91; \(P = 0.0009\)).\(^33\) Under the current EUA, this higher dose of casirivimab plus imdevimab is not available, and the lower dose is only authorized for use in nonhospitalized patients with COVID-19. In addition, rapid serology testing that can identify seronegative individuals in real time is currently not widely available.

Anti-SARS-CoV-2 mAbs 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 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 during the IV injection and for at least 1 hour after the injection is completed.

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.\[^{6,8,16,28}\]

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 3c).

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 (see the EUA criteria for the use of these products above).

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 people when their use is 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

Please see Special Considerations in Children for therapeutic recommendations for children with COVID-19.

Drug Availability

Bebtelovimab is currently being distributed to all regions without restriction. 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.\[^{5,7}\]

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.


