Anti-SARS-CoV-2 Antibody Products

Last Updated: February 1, 2022

Summary Recommendations

<table>
<thead>
<tr>
<th>Anti-SARS-CoV-2 Monoclonal Antibodies for the Treatment of COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The COVID-19 Treatment Guidelines Panel (the Panel) recommends using a single intravenous infusion of sotrovimab 500 mg, administered as soon as possible and within 10 days of symptom onset, to treat nonhospitalized patients (aged ≥12 years and weighing ≥40 kg) with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by criteria in the Food and Drug Administration (FDA) Emergency Use Authorization (EUA) for the product (AIIa).</td>
</tr>
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<td>• Because the B.1.1.529 (Omicron) variant of concern (VOC) has become the dominant variant in the United States and real-time testing to identify rare, non-Omicron variants is not routinely available, the Panel recommends against using bamlanivimab plus etesevimab or casirivimab plus imdevimab (AIII).</td>
</tr>
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<td>• The strength of the evidence for using anti-SARS-CoV-2 monoclonal antibodies (mAbs) varies depending on the medical conditions and other factors that place patients at risk for progression to severe COVID-19 and/or hospitalization (see Anti-SARS-CoV-2 Monoclonal Antibodies). The ratings for the Panel's recommendations for using anti-SARS-CoV-2 mAbs as treatment are based on the FDA EUA criteria for:</td>
</tr>
<tr>
<td>• High-risk conditions represented in clinical trials (AIIa);</td>
</tr>
<tr>
<td>• Immunocompromising conditions or receipt of immunosuppressive therapy (AIII); and</td>
</tr>
<tr>
<td>• Other medical conditions and factors with limited representation in clinical trials (BIII).</td>
</tr>
<tr>
<td>• When logistical or supply constraints make it impossible to offer available anti-SARS-CoV-2 mAbs or antiviral therapy to all eligible nonhospitalized patients, see Therapeutic Management of Nonhospitalized Adults With COVID-19 for further guidance.</td>
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</tr>
</tbody>
</table>

Anti-SARS-CoV-2 Monoclonal Antibodies as Post-Exposure Prophylaxis for SARS-CoV-2 Infection

• The Panel recommends against the use of bamlanivimab plus etesevimab and casirivimab plus imdevimab for SARS-CoV-2 post-exposure prophylaxis (PEP), as the Omicron VOC, which is not susceptible to these agents, is currently the predominant SARS-CoV-2 variant circulating in the United States (AIII).

Anti-SARS-CoV-2 Monoclonal Antibodies as Pre-Exposure Prophylaxis for SARS-CoV-2 Infection

• The Panel recommends using tixagevimab plus cilgavimab (Evusheld) administered as intramuscular injections as SARS-CoV-2 pre-exposure prophylaxis (PrEP) for adults and adolescents (aged ≥12 years and weighing ≥40 kg) 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 moderately to severely immunocompromised and may have an inadequate immune response to COVID-19 vaccination (BIIa); or
  • Are not able to be fully vaccinated with any available COVID-19 vaccines due to a documented history of severe adverse reaction to a COVID-19 vaccine or any of its components (AIIa).

Tixagevimab plus cilgavimab is not a substitute for COVID-19 vaccination and should not be used in unvaccinated individuals for whom COVID-19 vaccination is recommended and who are anticipated to have an adequate response.

If supplies of tixagevimab plus cilgavimab are limited, priority for use as PrEP should be given to those who are at the highest risk for severe COVID-19 (see Prevention of SARS-CoV-2 Infection).
### Summary Recommendations, continued

#### COVID-19 Convalescent Plasma
- The Panel **recommends against** the use of **COVID-19 convalescent plasma** for the treatment of COVID-19 in hospitalized patients without impaired humoral immunity (AI).
- There is insufficient evidence for the Panel to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19 in:
  - Nonhospitalized patients without impaired humoral immunity; and
  - Hospitalized or nonhospitalized patients with impaired humoral immunity.

#### Anti-SARS-CoV-2 Specific Immunoglobulins
- There is insufficient evidence for the Panel to recommend either for or against the use of anti-SARS-CoV-2 specific immunoglobulins for the treatment of COVID-19.

**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
Anti-SARS-CoV-2 Monoclonal Antibodies

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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 benefit in treating SARS-CoV-2 infection (as discussed below). Some anti-SARS-CoV-2 mAbs have been found to be effective as post-exposure prophylaxis (PEP) after a potential exposure to SARS-CoV-2 in a household setting\(^2\) and during SARS-CoV-2 outbreaks in skilled nursing and assisted living facilities.\(^3\) Other anti-SARS-CoV-2 mAbs have been shown to reduce the risk of infection when used as pre-exposure prophylaxis (PrEP).\(^4\)

### Anti-SARS-CoV-2 Monoclonal Antibodies That Have Received Emergency Use Authorizations From the Food and Drug Administration

Four anti-SARS-CoV-2 mAb products have received Emergency Use Authorizations (EUAs) from the Food and Drug Administration (FDA). Bamlanivimab plus etesevimab, casirivimab plus imdevimab (REGEN-COV), 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 and/or hospitalization. However, the distribution of bamlanivimab plus etesevimab and casirivimab plus imdevimab has been paused because the products have reduced activities against the B.1.1.529 (Omicron) variant of concern (VOC). Sotrovimab is expected to retain efficacy against the Omicron variant.\(^5\) The FDA has issued an EUA for tixagevimab plus cilgavimab (Evusheld), a long-acting anti-SARS-CoV-2 mAb combination. The EUA allows this combination to be used 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 an inadequate immune response to COVID-19 vaccination OR have a documented history of severe adverse reaction to an available 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.

These authorized anti-SARS-CoV-2 mAb products are listed alphabetically as follows:

- **Bamlanivimab plus etesevimab:** These are neutralizing mAbs that bind to different, but overlapping, epitopes in the spike protein RBD of SARS-CoV-2.
  - The broad distribution of bamlanivimab plus etesevimab has been paused in the United States because the Omicron variant has markedly reduced in vitro susceptibility to bamlanivimab and etesevimab, and, therefore, this regimen is not expected to provide clinical benefit for patients with Omicron infection.\(^6\)
- **Casirivimab plus imdevimab:** These are recombinant human mAbs that bind to nonoverlapping epitopes of the spike protein RBD of SARS-CoV-2.
  - The broad distribution of casirivimab plus imdevimab has been paused in the United States because the Omicron variant has markedly reduced in vitro susceptibility to casirivimab and imdevimab, and, 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 variant.\(^8\)

- **Tixagevimab plus cilgavimab:** These are recombinant human anti-SARS-CoV-2 mAbs that bind to nonoverlapping epitopes of the spike protein RBD of SARS-CoV-2. Although available in vitro data suggest that the Omicron variant remains susceptible to this combination, more data are needed to fully assess the activity of this regimen when the Omicron variant is circulating at high frequency.\(^4,9,10\)

The FDA has issued an EUA for tixagevimab plus cilgavimab that allows the combination to be used as SARS-CoV-2 PrEP. Before the pause in distribution of bamlanivimab plus etesevimab and casirivimab plus imdevimab, the FDA had expanded the product EUAs to allow the regimens to be used as PEP for certain individuals who are at high risk of acquiring SARS-CoV-2 infection and, if infected, are at high risk of progressing to serious illness. For more information, see the FDA EUA fact sheets for [bamlanivimab plus etesevimab](https://www.covid19treatmentguidelines.nih.gov/) and [casirivimab plus imdevimab](https://www.covid19treatmentguidelines.nih.gov/) and [Prevention of SARS-CoV-2 Infection](https://www.covid19treatmentguidelines.nih.gov/).

**Anti-SARS-CoV-2 Monoclonal Antibodies for the Treatment of COVID-19**

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. For recommendations and discussion regarding the use of anti-SARS-CoV-2 mAb products as PEP or PrEP, see [Prevention of SARS-CoV-2 Infection](https://www.covid19treatmentguidelines.nih.gov/).

The Omicron VOC has become the dominant SARS-CoV-2 variant in the United States.\(^11\) 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. Sotrovimab retains in vitro activity against the Omicron variant.

**Recommendations**

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using **sotrovimab 500 mg** as a single intravenous (IV) infusion, administered as soon as possible and within 10 days of symptom onset, to treat nonhospitalized patients (aged ≥12 years and weighing ≥40 kg) with mild to moderate COVID-19 who are at high risk of clinical progression (AI\(\text{IIa}\)) (see the EUA criteria for use of the product and the related discussion below).

- Because the Omicron VOC has become the dominant variant in the United States and real-time testing to identify currently rare, non-Omicron variants is not routinely available, the Panel **recommends against** using **bamlanivimab plus etesevimab** or **casirivimab plus imdevimab** (AI\(\text{III}\)).

- 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 (NAAT) and within 10 days of symptom onset.

- 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 EUA criteria for outpatient treatment.

- Anti-SARS-CoV-2 mAbs are not currently authorized for use in patients who are hospitalized with severe COVID-19; however, the products may be available through expanded access programs for patients who either have not developed an antibody response to SARS-CoV-2 infection or are not expected to mount an effective immune response to infection.

- When logistical or supply constraints make it impossible to offer available therapeutics to all
eligible nonhospitalized patients, see Therapeutic Management of Nonhospitalized Adults With COVID-19 for further guidance.

- 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 theoretic 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 sotrovimab plus antiviral therapy in treating COVID-19 is not yet known.

**Rationale**

In randomized placebo-controlled trials in nonhospitalized patients who had 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)\(^8,12,13\). These studies were conducted before the widespread circulation of the Delta and Omicron VOCs. The potential impact of these variants and their susceptibility to different FDA-authorized anti-SARS-CoV-2 mAbs are discussed below.

**Sotrovimab**

Sotrovimab retains in vitro activity against the Omicron variant and is expected to provide clinical benefit in patients with Omicron infection.\(^8\) The data that support the EUA for sotrovimab 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 and/or hospitalization. A total of 583 participants were randomized within 5 days of symptom onset to receive sotrovimab 500 mg IV (n = 291) or placebo (n = 292). 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 3 of 291 participants (1%) in the sotrovimab arm and 21 of 292 participants (7%) in the placebo arm (\(P = 0.002\)), resulting in a 6% absolute reduction and an 85% relative reduction in hospitalizations or death associated with sotrovimab.\(^8,14\)

**Bamlanivimab Plus Etesevimab**

The broad distribution of bamlanivimab plus etesevimab has been paused in the United States because the Omicron variant has markedly reduced in vitro susceptibility to this mAb regimen.\(^6\) 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 and/or hospitalization (see Table 3a).\(^15\)

**Casirivimab Plus Imdevimab**

The broad distribution of casirivimab plus imdevimab has been paused in the United States because the Omicron variant has 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 and/or hospitalization.\(^8\) The FDA also authorized subcutaneous (SQ) injection of the regimen if an IV infusion is not feasible or would delay treatment. SQ administration of casirivimab plus imdevimab requires 4 injections (2.5 mL per injection) at 4 different sites (see the FDA EUA for details).

The recommendation for using the lower dose of casirivimab 600 mg plus imdevimab 600 mg IV is based on data from a Phase 3, double-blind randomized placebo-controlled trial in outpatients with mild to moderate COVID-19. This trial evaluated different doses of casirivimab plus imdevimab administered...
as a single IV infusion. The modified full analysis set included participants aged ≥18 years who had a positive SARS-CoV-2 polymerase chain reaction result at randomization and who had ≥1 risk factors for progression to severe COVID-19. The results demonstrated a 2.2% absolute reduction and a 70% relative reduction in hospitalization or death with receipt of casirivimab 600 mg plus imdevimab 600 mg. The results for the higher dose of casirivimab plus imdevimab are comparable: a 3.3% absolute reduction and a 71% relative reduction in hospitalization or death among the patients who received casirivimab 1,200 mg plus imdevimab 1,200 mg. See Table 3a for additional details from the trial.

The recommendation for administering casirivimab plus imdevimab by SQ injections is based on safety data from the Phase 1 R10933-10987-HV-2093 study (ClinicalTrials.gov Identifier NCT04519437). This double-blind randomized placebo-controlled trial compared casirivimab plus imdevimab administered by SQ injection to placebo in healthy volunteers who did not have SARS-CoV-2 infection. Injection site reactions were observed in 12% of the 729 casirivimab plus imdevimab recipients and in 4% of the 240 placebo recipients. According to the FDA EUA for casirivimab plus imdevimab, there were similar reductions in viral load in the IV and SQ arms in a different trial that evaluated the anti-SARS-CoV-2 combination in symptomatic participants. However, because the safety and efficacy data for casirivimab plus imdevimab administered by SQ injection are limited, this route of administration should only be used when IV infusion is not feasible or would lead to a delay in treatment (BIII).

Criteria for Using Anti-SARS-CoV-2 Monoclonal Antibodies Under the 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.

When logistical or supply constraints make it impossible to offer available therapeutics to all eligible nonhospitalized patients, see Therapeutic Management of Nonhospitalized Adults With COVID-19 for further guidance.

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 and/or hospitalization. The ratings for the recommendations for the use of anti-SARS-CoV-2 mAbs as treatment are based on the FDA EUA criteria for identifying high-risk individuals. These criteria include the following conditions and other factors.

Medical Conditions or Other Factors That Were Represented in Patients in Clinical Trials That Evaluated Anti-SARS-CoV-2 Monoclonal Antibodies

- 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)
Other Conditions or Factors That Had Limited Representation in Patients in Clinical Trials but Are Considered Risk Factors for Progression to Severe COVID-19 by the Centers for Disease Control and Prevention

- An immunocompromising condition or immunosuppressive treatment (AIII). Many experts strongly recommend therapy for patients with these conditions, despite their limited representation in clinical trials.
- Being overweight (BMI 25–30) as the sole risk factor (BIII)
- Chronic kidney disease (BIII)
- Pregnancy (BIII)
- Sickle cell disease (BIII)
- Neurodevelopmental disorders (e.g., cerebral palsy) or other conditions that confer medical complexity (e.g., genetic or metabolic syndromes and severe congenital anomalies) (BIII)
- Medical-related technological dependence (e.g., tracheostomy, gastrostomy, or positive pressure ventilation that is 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 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.8

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 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 because of COVID-19.

The FDA EUAs do permit the use of these 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.21-23

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.24,25
Prior to the spread of the Omicron variant, there were data that 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 with evidence of ongoing viral replication. In a subset analysis of the ACTIV-3 trial, 153 of the 314 participants (49%) were negative for the anti-spike endogenous neutralizing antibody. The subhazard ratio (sHR) comparing bamlanivimab to placebo for sustained recovery (i.e., defined as discharge home and remaining at home for ≥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). Further, 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.

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. 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 standard of care with casirivimab 4,000 mg plus imdevimab 4,000 mg IV or standard of care alone. There was no difference in 28-day all-cause mortality between the casirivimab plus imdevimab arm and the standard of care arm; 944 of 4,839 patients (20%) in the casirivimab plus imdevimab arm died versus 1,026 of 4,946 patients (21%) in the standard of care arm (rate ratio 0.94; 95% CI, 0.86–1.03; P = 0.17). 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. 451 of 1,520 standard of care recipients [30%]; rate ratio 0.80; 95% CI, 0.70–0.91; P = 0.001). 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.

SARS-CoV-2 Variants and Their 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 a number of the authorized anti-SARS-CoV-2 mAbs. The clinical relevance of reduced in vitro susceptibility of select variants to anti-SARS-CoV-2 mAbs is under investigation.

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

• **B.1.1.7 (Alpha):** This variant retains in vitro susceptibility to all the anti-SARS-CoV-2 mAbs that are currently available through FDA EUAs.12,13,30
  
• **B.1.351 (Beta):** This variant has markedly reduced in vitro susceptibility to bamlanivimab and etesevimab. In vitro studies also suggest that the Beta variant has markedly reduced susceptibility to casirivimab, although the combination of casirivimab and imdevimab appears to retain activity against the variant. Sotrovimab also appears to retain activity against the variant.8,13
• **P.1 (Gamma):** This variant has markedly reduced in vitro susceptibility to bamlanivimab and etesevimab.\(^{12,31}\) The Gamma variant also has reduced susceptibility to casirivimab; however, the combination of casirivimab plus imdevimab appears to retain activity against the variant. Sotrovimab also appears to retain activity against the Gamma variant.\(^{8,15}\)

• **B.1.617.2, non-AY.1/AY.2 (Delta):** This VOC retains in vitro susceptibility to all the anti-SARS-CoV-2 mAbs that are currently available through FDA EUAs.\(^{12,13}\)

• **Omicron:** This is the predominant VOC circulating in the United States. This variant, which includes numerous mutations in the spike protein, has markedly reduced in vitro susceptibility to some anti-SARS-CoV-2 mAb products, including bamlanivimab plus etesevimab and casirivimab plus imdevimab.\(^9\) Sotrovimab retains in vitro activity against the Omicron variant.\(^9,10\) In vitro studies have reported a moderate reduction in the susceptibility of Omicron to tixagevimab plus cilgavimab, although this mAb regimen is expected to provide clinical benefit for SARS-CoV-2 PrEP.\(^9,10,32\)

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>In Vitro Susceptibility(^a)</th>
<th>Anticipated Clinical Activity</th>
<th>In Vitro Susceptibility(^a)</th>
<th>Anticipated Clinical Activity</th>
<th>In Vitro Susceptibility(^a)</th>
<th>Anticipated Clinical Activity</th>
<th>In Vitro Susceptibility(^a)</th>
<th>Anticipated Clinical Activity</th>
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</thead>
<tbody>
<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>
<td>Active</td>
<td>No change</td>
<td>Active</td>
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<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(^b)</td>
<td>Active</td>
<td>No change</td>
<td>Active</td>
<td>No change</td>
<td>Active</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(^b)</td>
<td>Active</td>
<td>No change</td>
<td>Active</td>
<td>No change</td>
<td>Active</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>
<td>Active</td>
<td>No change</td>
<td>Active</td>
</tr>
<tr>
<td>Omicron</td>
<td>B.1.1.529</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>
<td>Active</td>
<td>Moderate reduction(^c)</td>
<td>Active</td>
</tr>
</tbody>
</table>

\(^a\) Based on the fold reduction in susceptibility reported in the FDA EUAs.\(^4,8,12,13\)

\(^b\) Marked change for CAS and no change for IMD. The combination of CAS plus IMD appears to retain activity against the variant.

\(^c\) Despite moderately reduced in vitro susceptibility, TIX plus CIL is expected to retain activity against the Omicron variant.

**Key:** BAM = bamlanivimab; CAS = casirivimab; CIL = cilgavimab; CDC = Centers for Disease Control and Prevention; ETE = etesevimab; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; IMD = imdevimab; SOT = sotrovimab; TIX = tixagevimab; VBM = variant being monitored; VOC = variant of concern; WHO = World Health Organization

Ongoing 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 in defining the utility of specific mAbs in the future.
Clinical Trials

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

Monitoring

Sotrovimab should be administered by IV infusion 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 infusion and for at least 1 hour after the infusion 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, dizziness, and pruritus have also been reported.8,13,23

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 pregnant 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 and/or prevention of COVID-19.

Considerations in Children

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

Drug Availability

Bamlanivimab plus etesevimab, casirivimab plus imdevimab, and sotrovimab are available through FDA EUAs. The broad distribution of bamlanivimab plus etesevimab and casirivimab plus imdevimab has been paused in the United States because the Omicron variant has reduced susceptibility to bamlanivimab and etesevimab, and casirivimab and imdevimab.6,7 Efforts should be made to ensure that communities most affected by COVID-19 have equitable access to these anti-SARS-CoV-2 mAbs.

References


Table 3a. Anti-SARS-CoV-2 Monoclonal Antibodies: Selected Clinical Data

Last Updated: December 16, 2021

This table describes only clinical trials that have evaluated anti-SARS-CoV-2 mAbs for the treatment of COVID-19. Please refer to the Prevention of SARS-CoV-2 Infection section for a discussion of clinical trials that have evaluated anti-SARS-CoV-2 mAbs for PEP of SARS-CoV-2 infection.

<table>
<thead>
<tr>
<th>Methods</th>
<th>Results</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLAZE-1</strong>: Double-Blind, Phase 3 RCT of Bamlanivimab 700 mg Plus Etesevimab 1,400 mg in Nonhospitalized Patients With Mild to Moderate COVID-19¹</td>
<td><strong>Participant Characteristics:</strong>&lt;br&gt;• Median age 56 years; 30% ≥65 years; 53% women&lt;br&gt;• 87% White, 27% Hispanic/Latinx, 8% Black/African American&lt;br&gt;• Mean duration of symptoms was 4 days.&lt;br&gt;• 76% had mild COVID-19 and 24% had moderate COVID-19.&lt;br&gt;<strong>Primary Outcomes:</strong>&lt;br&gt;• COVID-19-related hospitalizations or all-cause deaths by Day 29: 4 (0.8%) in BAM plus ETE arm vs. 15 (5.8%) in placebo arm (£ [95% CI] = -5.0 [-8.0, -2.1]; P &lt; 0.001).&lt;br&gt;• All-cause deaths by Day 29: 0 in BAM plus ETE arm vs. 4 (1.6%) in placebo arm.&lt;br&gt;<strong>Interpretation:</strong>&lt;br&gt;• Compared to placebo, BAM plus ETE was associated with 5% absolute reduction and 87% relative reduction in COVID-19-related hospitalizations or all-cause deaths.</td>
<td>&lt;br&gt;<strong>Key Inclusion Criteria:</strong>&lt;br&gt;• Aged ≥12 years&lt;br&gt;• At high risk for severe COVID-19 or hospitalization&lt;br&gt;<strong>Interventions:</strong>&lt;br&gt;• Within 3 days of a positive SARS-CoV-2 test result, single infusion of:&lt;br&gt;• BAM 700 mg plus ETE 1,400 mg (n = 511)&lt;br&gt;• Placebo (n = 258)&lt;br&gt;<strong>Primary Endpoint:</strong>&lt;br&gt;• COVID-19-related hospitalization (defined as ≥24 hours of acute care) or death from any cause by Day 29</td>
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<tr>
<td><strong>BLAZE-1</strong>: Double-Blind, Phase 3 RCT of Bamlanivimab 2,800 mg Plus Etesevimab 2,800 mg in Nonhospitalized Patients With Mild to Moderate COVID-19²</td>
<td><strong>Participant Characteristics:</strong>&lt;br&gt;• Mean age 53.8 years; 31% ≥65 years; 52% women; 48% men&lt;br&gt;• 87% White, 29% Hispanic/Latinx, 8% Black/African American&lt;br&gt;• Median days from symptom onset to infusion was 4 days.&lt;br&gt;• 77% had mild COVID-19.&lt;br&gt;<strong>Primary Outcomes:</strong>&lt;br&gt;• COVID-19-related hospitalizations or all-cause deaths by Day 29: 11 (2.1%) in BAM plus ETE arm vs. 36 (7.0%) in placebo arm; relative risk difference: 70% (P &lt; 0.001).&lt;br&gt;• All-cause deaths by Day 29: 0 in BAM plus ETE arm vs. 10 (1.9%) in placebo arm.&lt;br&gt;<strong>Interpretation:</strong>&lt;br&gt;• Compared to placebo, BAM plus ETE was associated with 4.8% absolute reduction and 70% relative reduction in COVID-19-related hospitalizations or all-cause deaths.</td>
<td>&lt;br&gt;<strong>Key Inclusion Criteria:</strong>&lt;br&gt;• Aged ≥12 years&lt;br&gt;• At high risk for severe COVID-19 or hospitalization&lt;br&gt;<strong>Key Exclusion Criteria:</strong>&lt;br&gt;• SpO₂ ≤93% on room air; or&lt;br&gt;• Respiratory rate ≥30 breaths/min; or&lt;br&gt;• Heart rate ≥125 bpm&lt;br&gt;<strong>Interventions:</strong>&lt;br&gt;• Within 3 days of testing SARS-CoV-2 positive, single infusion of:&lt;br&gt;• BAM 2,800 mg plus ETE 2,800 mg (n = 518)&lt;br&gt;• Placebo (n = 517)</td>
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<tr>
<td>Methods</td>
<td>Results</td>
<td>Interpretation</td>
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<tr>
<td><strong>BLAZE-1</strong>: Double-Blind, Phase 3 RCT of Bamlanivimab 2,800 mg Plus Etesevimab 2,800 mg in Nonhospitalized Patients With Mild to Moderate COVID-19&lt;sup&gt;2&lt;/sup&gt;, continued</td>
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<tr>
<td><strong>Primary Endpoint:</strong>&lt;br&gt;• COVID-19-related hospitalization or death from any cause by Day 29</td>
<td><strong>Secondary Endpoint:</strong>&lt;br&gt;• SARS-CoV-2 VL &gt;5.27 log&lt;sub&gt;10&lt;/sub&gt; copies/mL at Day 7</td>
<td><strong>Secondary Outcome:</strong>&lt;br&gt;• Percentage of patients with SARS-CoV-2 VL &gt;5.27 log&lt;sub&gt;10&lt;/sub&gt; copies/mL at Day 7: 9.8% in BAM plus ETE arm vs. 29.5% in placebo arm (P &lt; 0.001).</td>
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<td><strong>Secondary Endpoint:</strong>&lt;br&gt;• SARS-CoV-2 VL &gt;5.27 log&lt;sub&gt;10&lt;/sub&gt; copies/mL at Day 7</td>
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<tr>
<td><strong>Double-Blind, Phase 3 RCT of Casirivimab Plus Imdevimab in Nonhospitalized Patients With Mild to Moderate COVID-19&lt;sup&gt;3&lt;/sup&gt;</strong></td>
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<td><strong>Key Inclusion Criteria:</strong>&lt;br&gt;• Aged ≥18 years&lt;br&gt;• Laboratory-confirmed SARS-CoV-2 infection&lt;br&gt;• Symptom onset within 7 days of randomization&lt;br&gt;• For patients included in the modified full analysis only:&lt;br&gt;  • ≥1 risk factor for severe COVID-19&lt;br&gt;  • Positive SARS-CoV-2 RT-PCR at baseline</td>
<td><strong>Interventions:</strong>&lt;br&gt;• Single IV infusion of:&lt;br&gt;  • CAS 600 mg plus IMD 600 mg (n = 736) or placebo (n = 748)&lt;br&gt;  • CAS 1,200 mg plus IMD 1,200 mg (n = 1,355) or placebo (n = 1,341)</td>
<td><strong>Participant Characteristics:</strong>&lt;br&gt;• Median age 50 years; 35% Hispanic/Latinx, 5% Black/African American&lt;br&gt;• Median duration of symptoms prior to enrollment was 3 days. &lt;br&gt;<strong>Primary Outcomes:</strong>&lt;br&gt;• COVID-19-related hospitalizations or all-cause deaths through Day 29:&lt;br&gt;  • 7 (1.0%) in CAS 600 mg plus IMD 600 mg arm vs. 24 (3.2%) in placebo arm (P = 0.002).&lt;br&gt;  • 18 (1.3%) in CAS 1,200 mg plus IMD 1,200 mg arm vs. 62 (4.6%) in placebo arm (P &lt; 0.001). &lt;br&gt;<strong>All-Cause Deaths:</strong>&lt;br&gt;• 1 (0.1%) in CAS 600 mg plus IMD 600 mg arm vs. 1 (0.1%) in placebo arm.&lt;br&gt;• 1 (&lt; 0.1%) in CAS 1,200 mg plus IMD 1,200 mg arm vs. 3 (0.2%) in placebo arm.</td>
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## COMET-ICE: Double-Blind, Phase 3 RCT of Sotrovimab in Nonhospitalized Patients With Mild to Moderate COVID-19, Interim Analysis

<table>
<thead>
<tr>
<th>Methods</th>
<th>Results</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key Inclusion Criteria:</strong></td>
<td><strong>Participant Characteristics:</strong></td>
<td><strong>Interpretation:</strong></td>
</tr>
<tr>
<td>• Aged ≥18 years with ≥1 comorbidity or aged ≥55 years</td>
<td>• Median age 53 years; 22% ≥65 years</td>
<td>• Compared to placebo, SOT was associated with 6% absolute reduction and 85% relative risk reduction in all-cause hospitalizations or deaths.</td>
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<td>• Laboratory-confirmed COVID-19</td>
<td>• 63% Hispanic/Latinx, 7% Black/African American</td>
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<td>• Symptom onset ≤5 days before enrollment</td>
<td><strong>Primary Outcome:</strong></td>
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<td>• Hospitalizations or all-cause deaths by Day 29: 3 (1%) in SOT arm vs. 21 (7%) in placebo arm ($P = 0.002$).</td>
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<td><strong>Key Exclusion Criteria:</strong></td>
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<td>• Hospitalized or requiring supplemental oxygen</td>
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<tr>
<td>• Severely immunocompromised</td>
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<tr>
<td><strong>Interventions:</strong></td>
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<td>• SOT 500 mg IV (n = 291)</td>
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<td>• Placebo (n = 292)</td>
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<td><strong>Primary Endpoint:</strong></td>
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<td>• Hospitalization or death from any cause by Day 29</td>
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**Key:** BAM = bamlanivimab; CAS = casirivimab; ETE = etesevimab; IMD = imdevimab; IV = intravenous; mAbs = anti-SARS-CoV-2 monoclonal antibodies; PEP = post-exposure prophylaxis; RCT = randomized controlled trial; RT-PCR = reverse transcription polymerase chain reaction; SOT = sotrovimab; SpO$_2$ = oxygen saturation; VL = viral load

### References


Convalescent Plasma

Last Updated: December 16, 2021

Plasma from donors who have recovered from COVID-19 may contain antibodies to SARS-CoV-2 that could help suppress viral replication.¹ In August 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for convalescent plasma for the treatment of hospitalized patients with COVID-19. On February 4, 2021, the FDA revised the convalescent plasma EUA to limit the authorization to high-titer COVID-19 convalescent plasma and only for the treatment of hospitalized patients with COVID-19 early in their disease course or hospitalized patients who have impaired humoral immunity.² Use of convalescent plasma should be limited to those products that contain high levels of anti-SARS-CoV-2 antibodies (i.e., high-titer products). Products that are not labeled “high titer” should not be used.

Recommendations

• The COVID-19 Treatment Guidelines Panel (the Panel) recommends against the use of COVID-19 convalescent plasma for the treatment of COVID-19 in hospitalized patients without impaired humoral immunity (AI).

• There is insufficient evidence for the Panel to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19 in:
  • Nonhospitalized patients without impaired humoral immunity; and
  • Nonhospitalized or hospitalized patients with impaired humoral immunity.

Rationale

For Hospitalized Patients Without Impaired Humoral Immunity

Clinical data on the use of convalescent plasma for the treatment of COVID-19, including data from several randomized trials and the U.S. Expanded Access Program (EAP) for Convalescent Plasma, are summarized in Table 3b.

The EUA for convalescent plasma for the treatment of hospitalized patients with COVID-19 was issued on the basis of retrospective, indirect evaluations of efficacy generated from the convalescent plasma EAP, which allowed for its use regardless of titer. Several retrospective analyses of the EAP data indicated that patients who received high-titer plasma had a lower relative risk of death than patients who received low-titer plasma.³,⁴ The Panel reviewed the EAP analyses and determined that the data were not sufficient to establish the efficacy or safety of COVID-19 convalescent plasma due to potential confounding, the lack of randomization, and the lack of an untreated control group.

Data from the initial randomized clinical trials evaluating convalescent plasma, which were all underpowered, did not demonstrate the product’s efficacy for the treatment of hospitalized patients with COVID-19.⁵-¹²

Subsequently, results from the 3 largest randomized clinical trials evaluating convalescent plasma in hospitalized patients—RECOVERY,¹³ CONCOR-1,¹⁴ and REMAP-CAP¹⁵—found no evidence of benefit from high-titer convalescent plasma in hospitalized patients with COVID-19. All 3 were open-label trials that were stopped early due to futility.

In the RECOVERY trial, patients were randomized to receive convalescent plasma (n = 5,795) or usual care (n = 5,763). The trial demonstrated no significant difference in the primary endpoint of 28-day
mortality between the convalescent plasma arm and the usual care arm (24% in each arm; risk ratio 1.00; 95% CI, 0.93–1.07). Additionally, there were no differences between the arms in the secondary endpoints of time to hospital discharge and receipt of mechanical ventilation or death.

In the CONCOR-1 trial, patients were randomized to receive convalescent plasma or standard of care. The primary endpoint of intubation or death by Day 30 occurred in 199 of 614 patients (32%) in the convalescent plasma arm and 86 of 307 patients (28%) in the standard of care arm (relative risk 1.16; 95% CI, 0.94–1.43). There were no differences between the arms in secondary endpoints, including time to intubation or death, mortality, or intensive care unit and hospital length of stay. Serious adverse events occurred in 33% of the patients in the convalescent plasma arm and 26% of those in the standard of care arm, including 35 transfusion-related complications reported in the convalescent plasma arm.

The REMAP-CAP trial evaluated convalescent plasma in hospitalized patients. Although noncritically ill patients participated in the study, the reported outcomes are only for those who were critically ill at enrollment (1,084 patients in the convalescent plasma arm and 916 patients in the control arm). There was no difference in the primary endpoint of organ support-free days up to Day 21 between the arms (median of 0 days in the convalescent plasma arm [IQR -1 to 16 days] vs. 3 days in the control arm [IQR -1 to 16 days]). There were also no differences between the arms in secondary endpoints, including in-hospital mortality (401 of 1,075 patients [37.3%] in the convalescent plasma arm died vs. 347 of 904 patients [38.4%] in the control arm). The study showed a potential for harm (90.3% posterior probability) in 126 patients who were randomized to convalescent plasma after >7 days of hospitalization.

Although these trials did not exclude patients with impaired humoral immunity, most of the patients enrolled did not report a history of an immunocompromising condition or receipt of chronic immunosuppressive therapy. Based on the collective results from these studies, the Panel recommends against the use of COVID-19 convalescent plasma for the treatment of COVID-19 in hospitalized patients who do not have impaired humoral immunity (AI).

For Nonhospitalized Patients Without Impaired Humoral Immunity

Current data are insufficient to establish the safety or efficacy of convalescent plasma in nonhospitalized patients with COVID-19. Convalescent plasma is not authorized for nonhospitalized patients with COVID-19 under the EUA.

Data from a double-blind, placebo-controlled, randomized trial of high-titer convalescent plasma in older, nonhospitalized adults with <72 hours of mild COVID-19 symptoms demonstrated benefit in reduced progression of respiratory disease. However, the trial included relatively few participants (80 participants in each arm).

The C3PO study was a single-blind randomized trial that evaluated high-titer convalescent plasma for the treatment of nonhospitalized patients with ≤7 days of mild or moderate COVID-19 symptoms and at least 1 risk factor for severe COVID-19. Trial participants (n = 511) were randomized to receive convalescent plasma or a placebo transfusion. The trial was halted after a second interim analysis indicated a priori futility criteria were reached. There was no difference in the occurrence of the composite primary endpoint of disease progression (i.e., hospital admission, death without hospitalization, or urgent or emergency care within 15 days after randomization) between the patients in the convalescent plasma arm and the placebo arm (30% vs. 32%; risk difference 1.9%; 95% CI, -6.0 to 9.8). There were no differences between the arms in any secondary endpoints, including the worst severity of illness based on an 8-point ordinal scale and hospital-free days after randomization. Five patients in the convalescent plasma arm and 1 patient in the placebo arm died. Infusion-related reactions,
which occurred more often in the convalescent plasma arm, included 3 serious reactions.

Results from additional, adequately powered, well-designed, and well-conducted randomized clinical trials are needed to provide more specific, evidence-based guidance on the role of COVID-19 convalescent plasma in the treatment of nonhospitalized patients with COVID-19.

The FDA has issued EUAs for several anti-SARS-CoV-2 monoclonal antibody products for the treatment of nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progression to severe disease (see Anti-SARS-CoV-2 Monoclonal Antibodies). The Panel recommends using these products for the population specified in the EUAs.

**For Hospitalized or Nonhospitalized Patients With Impaired Humoral Immunity**

People who are immunocompromised are more likely to become severely ill from COVID-19, experience prolonged SARS-CoV-2 infection and shedding, and require hospitalization for breakthrough SARS-CoV-2 infection despite COVID-19 vaccination.\(^{17,18}\) Although some of this vulnerability may be attributed to impaired cellular immune responses, numerous studies indicate that people who are immunosuppressed are at risk of reduced antibody responses to SARS-CoV-2 infection and vaccination.\(^{19-21}\) An analysis from the RECOVERY trial suggests that SARS-CoV-2 seronegative patients are more likely to benefit from convalescent plasma than seropositive patients.\(^{22}\) Therefore, convalescent plasma may be effective in SARS-CoV-2 seronegative patients even though no benefit was observed in the overall population of patients enrolled in the RECOVERY trial.

The REMAP-CAP investigators performed a prespecified subgroup analysis of 126 patients with immunodeficiencies who were critically ill.\(^{15}\) Immunodeficiency was defined as recent chemotherapy or radiation, high-dose or long-term steroid use, or presence of immunocompromising diseases. Although not statistically significant, results of this analysis suggest that, compared to placebo, convalescent plasma offers a potential benefit of improved survival and/or more organ support-free days in this subgroup of immunocompromised patients (OR 1.51; 95% CI, 0.80–2.92).

Severely immunocompromised individuals may experience prolonged SARS-CoV-2 infection with persistent viral replication over several months, as described in the case report of a patient with lymphoma who had received chimeric antigen receptor T cell therapy and who subsequently recovered following repeat transfusions of high-dose convalescent plasma.\(^{23}\) Data from case reports, case series, and a retrospective case-control study also suggest a potential benefit of convalescent plasma in patients with primary and secondary humoral immunodeficiencies, including patients with hematologic malignancy, common variable immune deficiency, or agammaglobulinemia, and those who have received a solid organ transplant.\(^{24-37}\)

Although there is physiologic rationale for the value of convalescent plasma in immunocompromised people and some reports suggesting benefit, there are no definitive data to support the use of convalescent plasma in this patient population. Therefore, there is insufficient evidence for the Panel to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19 in hospitalized or nonhospitalized patients who have impaired humoral immunity. Adequately powered, well-designed, and well-conducted randomized clinical trials are needed to provide more specific, evidence-based guidance on the role of convalescent plasma in the treatment of patients with COVID-19 who have impaired humoral immunity.

**Clinical Data to Date**

Table 3b includes a summary of key studies of convalescent plasma for the treatment of COVID-19.
Considerations in Pregnancy

The safety and efficacy of using COVID-19 convalescent plasma during pregnancy have not been evaluated in clinical trials, and published data on its use in pregnant individuals with COVID-19 are limited to case reports. Pathogen-specific immunoglobulins (Ig) are used clinically during pregnancy to prevent infection from varicella zoster virus and rabies virus and have been used in clinical trials of congenital cytomegalovirus infection. If otherwise indicated, pregnancy is not a reason to withhold convalescent plasma.

Considerations in Children

The safety and efficacy of COVID-19 convalescent plasma have not been systematically evaluated in pediatric patients. Published literature on its use in children is limited to case reports and case series, as well as a systematic review of these reports. A few clinical trials of COVID-19 convalescent plasma in children are ongoing. The use of convalescent plasma may be considered on a case-by-case basis for hospitalized children with impaired immunity who meet the EUA criteria for its use. Convalescent plasma is not authorized by the FDA for use in nonhospitalized patients with COVID-19.

Several anti-SARS-CoV-2 monoclonal antibody products have received EUAs for treatment of nonhospitalized patients aged ≥12 years with mild to moderate COVID-19 who are at high risk of progression to severe disease. Use of these products may be considered on a case-by-case basis for children who meet the EUA criteria (see Anti-SARS-CoV-2 Monoclonal Antibodies).

Adverse Effects

Available data suggest that serious adverse reactions following the administration of COVID-19 convalescent plasma are infrequent and consistent with the risks associated with plasma infusions for other indications. These risks include transfusion-transmitted infections (e.g., HIV, hepatitis B, hepatitis C), allergic reactions, anaphylactic reactions, febrile nonhemolytic reactions, transfusion-related acute lung injury, transfusion-associated circulatory overload, and hemolytic reactions. Hypothermia, metabolic complications, and post-transfusion purpura have also been described.

Additional risks of COVID-19 convalescent plasma transfusion include a theoretical risk of antibody-dependent enhancement of SARS-CoV-2 infection and a theoretical risk of long-term immunosuppression. In the CONCOR-1 trial, higher levels of full transmembrane spike IgG were associated with worse outcomes, suggesting the use of convalescent plasma with nonfunctional anti-SARS-CoV-2 antibodies may be harmful. Subgroup analysis in the REMAP-CAP trial showed potential harm in convalescent plasma transfused >7 days into hospitalization.

When considering convalescent plasma for patients with a history of severe allergic or anaphylactic transfusion reactions, consultation with a transfusion medicine specialist is advised.

Clinical Trials

Randomized clinical trials evaluating convalescent plasma for the treatment of COVID-19 are underway. Please see ClinicalTrials.gov for the latest information.

References


Table 3b. COVID-19 Convalescent Plasma: Selected Clinical Data

Last Updated: December 16, 2021

The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for COVID-19 CP. The studies summarized below are those that have had the greatest impact on the Panel’s recommendations.

Note: The current EUA for COVID-19 CP is limited to the use of high-titer CP. Refer to the revised EUA Letter of Authorization for a list of anti-SARS-CoV-2 antibody tests that can be used to qualify COVID-19 CP as high titer.

<table>
<thead>
<tr>
<th>Methods</th>
<th>Results</th>
<th>Limitations and Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>REMAP-CAP</strong>: Multinational, Open-Label RCT of High-Titer Convalescent Plasma in Hospitalized Patients With Critical COVID-19¹</td>
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<tr>
<td>Key Inclusion Criteria:</td>
<td>Participant Characteristics:</td>
<td>Key Limitations:</td>
</tr>
<tr>
<td>• Admitted to ICU with receipt of respiratory support (HFNC oxygen, NIV, MV, ECMO) and/or vasopressor or inotrope support</td>
<td>• Mean age 61 years; 68% men</td>
<td>• Open-label study</td>
</tr>
<tr>
<td>Key Exclusion Criteria:</td>
<td>• 32% on MV</td>
<td>• Not all patients in CP arm received CP (86% received CP as per protocol and 95% received some CP)</td>
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<tr>
<td>• CP contraindicated</td>
<td>• 29% SARS-CoV-2 antibody negative at baseline</td>
<td>Interpretation:</td>
</tr>
<tr>
<td>• Death imminent</td>
<td>• 94% received corticosteroids, 45% received RDV, 39% received IL-6 inhibitors</td>
<td>• There was no benefit of CP in hospitalized patients with severe COVID-19.</td>
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<tr>
<td>Interventions:</td>
<td>Primary Outcome:</td>
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<tr>
<td>• High-titer CP (550 mL +/- 150 mL) within 48 hours of randomization (n = 1,084)</td>
<td>• No difference in median number of organ support-free days by Day 21: 0 days in CP arm vs. 3 days in usual care arm (OR 0.97; 95% CrI, 0.82–1.14).</td>
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<tr>
<td>• Usual care (n = 916)</td>
<td>Secondary Outcomes:</td>
<td></td>
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<tr>
<td>Primary Endpoint:</td>
<td>• No difference for in-hospital mortality between CP arm (37%) and usual care arm (38%).</td>
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<tr>
<td>• Organ support-free days by Day 21</td>
<td>• No difference in median number of respiratory support-free days: 0 days in CP arm and 2 days in usual care arm.</td>
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<tr>
<td>Key Secondary Endpoints:</td>
<td>• No difference in median ICU LOS: 21 days in CP arm and 17 days in usual care arm.</td>
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<tr>
<td>• Mortality at Day 28 and Day 90</td>
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<tr>
<td>• Progression to respiratory support</td>
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<td>• ICU LOS</td>
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<td>Methods</td>
<td>Results</td>
<td>Limitations and Interpretation</td>
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<tr>
<td><strong>CONCOR-1</strong>: Multinational, Open-Label RCT of Convalescent Plasma for Hospitalized Patients With COVID-19 in Canada, the United States, and Brazil&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td><strong>Key Inclusion Criteria:</strong>&lt;br&gt;• Hospitalized patients receiving supplemental oxygen&lt;br&gt;• Within 12 days of respiratory symptom onset</td>
<td><strong>Participant Characteristics:</strong>&lt;br&gt;• Mean age 68 years; 59% men&lt;br&gt;• 84% receiving systemic corticosteroids at enrollment</td>
<td><strong>Key Limitations:</strong>&lt;br&gt;• Open-label study&lt;br&gt;• Trial stopped after 78% of planned enrollment after meeting prespecified futility criteria for early termination</td>
</tr>
<tr>
<td><strong>Key Exclusion Criteria:</strong>&lt;br&gt;• Imminent or current intubation</td>
<td><strong>Primary Outcome:</strong>&lt;br&gt;• Intubation or death occurred in 32% of patients in CP arm and 28% in SOC arm (relative risk 1.16; 95% CI, 0.94–1.43, <em>P</em> = 0.18).</td>
<td><strong>Interpretation:</strong>&lt;br&gt;• There was no benefit of CP in oxygen-dependent, hospitalized COVID-19 patients within 12 days of symptom onset.</td>
</tr>
<tr>
<td><strong>Interventions:</strong>&lt;br&gt;• 1–2 units CP (approximately 500 mL) from 1–2 donors (n = 625)&lt;br&gt;• SOC (n = 313)</td>
<td><strong>Secondary Outcomes:</strong>&lt;br&gt;• By Day 30, no difference between the CP and SOC arms in:&lt;br&gt;• Time to intubation or death&lt;br&gt;• All-cause mortality (23% in CP arm vs. 21% in SOC arm)&lt;br&gt;• ICU LOS (mean 4.3 days in CP arm vs. 3.7 days in SOC arm)&lt;br&gt;• Need for renal dialysis (1.6% in CP arm vs. 2.0% in SOC arm)&lt;br&gt;• More SAEs reported in CP arm (33% vs. 26% in SOC arm)</td>
<td></td>
</tr>
<tr>
<td><strong>Primary Endpoint:</strong>&lt;br&gt;• Intubation or death at Day 30</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Key Secondary Endpoints:</strong>&lt;br&gt;• Time to intubation or death by Day 30&lt;br&gt;• Mortality at Day 30 and Day 90&lt;br&gt;• ICU LOS by Day 30&lt;br&gt;• Need for renal dialysis by Day 30&lt;br&gt;• SAE by Day 30</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RECOVERY Trial</strong>: Open-Label RCT of High-Titer Convalescent Plasma in Hospitalized Patients in the United Kingdom&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Key Inclusion Criteria:</strong>&lt;br&gt;• Hospitalized patients with clinically suspected or laboratory-confirmed SARS-CoV-2 infection</td>
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<tr>
<td><strong>Key Exclusion Criteria:</strong>&lt;br&gt;• CP contraindicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Interventions:</strong>&lt;br&gt;• 2 units high-titer CP (IgG SARS-CoV-2 spike protein ratio ≥6.0), first unit ASAP after randomization, second unit ≥12 hours later the next day (n = 5,795)&lt;br&gt;• Usual care (n = 5,763)</td>
<td><strong>Participant Characteristics:</strong>&lt;br&gt;• Mean age 63.5 years; 64% men&lt;br&gt;• 5% on MV&lt;br&gt;• 92% received corticosteroids</td>
<td></td>
</tr>
<tr>
<td><strong>Primary Endpoint:</strong>&lt;br&gt;• All-cause mortality at Day 28</td>
<td><strong>Primary Outcomes:</strong>&lt;br&gt;• No difference between the arms in:&lt;br&gt;• Mortality (24% in each arm).&lt;br&gt;• Mortality in patients without detectable SARS-CoV-2 antibodies (32% in CP arm and 34% in SOC arm).</td>
<td></td>
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<tr>
<td></td>
<td><strong>Secondary Outcomes:</strong>&lt;br&gt;• No difference between the arms in:</td>
<td></td>
</tr>
</tbody>
</table>
### Methods

**RECOVERY Trial**: Open-Label RCT of High-Titer Convalescent Plasma in Hospitalized Patients in the United Kingdom³, continued

<table>
<thead>
<tr>
<th>Key Secondary Endpoints:</th>
<th>Results</th>
<th>Limitations and Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Time to hospital discharge by Day 28</td>
<td>• Proportion of patients discharged (66% in CP arm and 67% in SOC arm).</td>
<td></td>
</tr>
<tr>
<td>• Among patients not receiving MV, receipt of MV or death by Day 28</td>
<td>• Proportion of patients who progressed to MV or death (28% in CP arm and 29% in SOC arm).</td>
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</tr>
</tbody>
</table>

**PLACID Trial**: Open-Label RCT of Convalescent Plasma in Hospitalized Adults With Severe COVID-19 in India⁴

<table>
<thead>
<tr>
<th>Key Inclusion Criteria:</th>
<th>Participant Characteristics:</th>
<th>Key Limitations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hospitalized patients with moderate, laboratory-confirmed SARS-CoV-2 infection</td>
<td>• Median age 52 years; 76% men</td>
<td>• Open-label study</td>
</tr>
<tr>
<td>• PaO₂/FiO₂ 200–300 mm Hg or respiratory rate &gt;24 breaths/min with SpO₂ ≤93% on room air</td>
<td>• Higher prevalence of DM in CP arm (48%) than SOC arm (38%)</td>
<td>• SARS-CoV-2 antibody testing not used to select CP; many participants may have received low-titer CP</td>
</tr>
</tbody>
</table>

**PlasmAr Study**: Double-Blind RCT of Convalescent Plasma in Hospitalized Adults in Argentina⁵

<table>
<thead>
<tr>
<th>Key Inclusion Criteria:</th>
<th>Participant Characteristics:</th>
<th>Key Limitations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• PCR-confirmed, severe COVID-19</td>
<td>• Median age 62 years; 68% men</td>
<td>• Small sample size</td>
</tr>
<tr>
<td>• Critical illness</td>
<td>• 65% with coexisting condition</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions:</th>
<th>Primary Outcomes:</th>
<th>Interpretation:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 2 doses of 200 mL of CP transfused 24 hours apart (n = 235)</td>
<td>• No difference in proportion of patients who progressed to severe disease or death between CP arm (19%) and SOC arm (18%) (risk ratio 1.04; 95% CI, 0.71–1.54).</td>
<td>• CP use did not reduce progression to severe disease or death in hospitalized patients with moderate COVID-19.</td>
</tr>
<tr>
<td>• SOC (n = 229)</td>
<td>• Among patients without detectable SARS-CoV-2 neutralizing antibody titers at baseline (n = 70), no difference in proportion of patients who progressed to severe disease or death in CP arm and SOC arm (30% vs. 25%; risk ratio 1.2; 95% CI, 0.6–2.6).</td>
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</table>

<table>
<thead>
<tr>
<th>Primary Endpoint:</th>
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</thead>
<tbody>
<tr>
<td>• Progression to severe disease (defined as PaO₂/FiO₂ &lt;100 mm Hg) or death within 28 days</td>
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</tr>
</tbody>
</table>

### Key Exclusion Criteria:

- Critical illness

### Interventions:

- 2 doses of 200 mL of CP transfused 24 hours apart (n = 235)
- SOC (n = 229)

### Primary Endpoint:

- Progression to severe disease (defined as PaO₂/FiO₂ <100 mm Hg) or death within 28 days

### Participant Characteristics:

- Median age 52 years; 76% men
- Higher prevalence of DM in CP arm (48%) than SOC arm (38%)

### Primary Outcomes:

- No significant difference between the arms in clinical status at 30 days (OR 0.83; 95% CI, 0.52–1.35; P = 0.46).
- 30-day mortality 11% in both arms.

### Key Limitations:

- Open-label study
- SARS-CoV-2 antibody testing not used to select CP; many participants may have received low-titer CP

### Interpretation:

- There was no benefit of CP in hospitalized patients with severe COVID-19.
### Multicenter, Double-Blind RCT of Convalescent Plasma in Hospitalized Adults With Severe COVID-19 in the United States and Brazil

**Methods**

- **Key Inclusion Criteria:**
  - Severe COVID-19 pneumonia
  - $\text{SpO}_2 \leq 94\%$ on room air or requirement of supplemental oxygen, MV, or ECMO

- **Key Exclusion Criteria:**
  - >5 days on MV or ECMO
  - Severe multiorgan failure

- **Interventions:**
  - Single dose of CP with SARS-CoV-2 spike-RBD IgG titer $\geq 1:400$ (n = 150)
  - Non-SARS-CoV-2 plasma (control) (n = 73)

- **Primary Endpoint:**
  - Clinical status on Day 28 (ordinal score)

- **Secondary Endpoints:**
  - In-hospital and 28-day mortality
  - Time to clinical improvement
  - Time to discontinuation of supplemental oxygen
  - Time to hospital discharge

**Participant Characteristics:**

- Median age 61 years; 66% men
- 57% required supplemental oxygen at baseline: 25% high-flow oxygen or NIV and 13% MV or ECMO
- 81% received corticosteroids

**Results**

- No difference in Day 28 clinical status between the arms (OR 1.5; 95% CI, 0.83–2.68; $P = 0.18$).

**Secondary Outcomes:**

- In-hospital mortality lower in CP arm than control arm (13% vs. 25%; OR 0.44; 95% CI, 0.22–0.91; $P = 0.034$). The difference was no longer significant after adjustment for age, sex, and duration of symptoms.

- No difference between CP arm and control arm in median time to:
  - Clinical improvement (5 vs. 7 days).
  - Discontinuation of supplemental oxygen (6 vs. 7 days).
  - Hospital discharge (9 vs. 8 days).

**Limitations and Interpretation**

- Small sample size
- Control arm intervention was blood plasma without SARS-CoV-2 antibodies, therefore not possible to identify potential harm due to plasma infusion

### Double-Blind RCT of Early High-Titer Convalescent Plasma Therapy to Prevent Severe COVID-19 in Nonhospitalized Older Adults in Argentina

**Methods**

- **Key Inclusion Criteria:**
  - Nonhospitalized
  - Aged $\geq 75$ years or aged 65–74 years with $\geq 1$ coexisting condition
  - Mild COVID-19 with symptoms for <72 hours

- **Key Exclusion Criteria:**
  - Severe respiratory disease

- **Interventions:**
  - 250 mL of CP with IgG against SARS-CoV-2 spike protein $>1:1,000$ (n = 80)
  - Placebo (n = 80)

**Participant Characteristics:**

- Mean age 77 years; 38% men
- Most with comorbidities

**Results**

- 16% of patients in CP arm and 31% in placebo arm experienced severe respiratory disease by Day 15 (relative risk 0.52; 95% CI, 0.29–0.94; $P = 0.03$).

**Limitations and Interpretation**

- Small sample size
- Early termination because COVID-19 cases decreased

- This trial demonstrated a benefit of CP in older adult outpatients with <72 hours of mild COVID-19 symptoms.
### Methods

| Double-Blind RCT of Early High-Titer Convalescent Plasma Therapy to Prevent Severe COVID-19 in Nonhospitalized Older Adults in Argentina<sup>7</sup>, continued |
|---|---|---|
| **Primary Endpoint:** | | |
| Severe respiratory disease, defined as respiratory rate $\geq 30$ breaths/min and/or SpO$_2$ <93% on room air by Day 15 | | |

<p>| <strong>C3PO: Multicenter, Single-Blind RCT of High-Titer Convalescent Plasma in the United States&lt;sup&gt;8&lt;/sup&gt;</strong> |
|---|---|---|
| <strong>Key Inclusion Criteria:</strong> | <strong>Participant Characteristics:</strong> | <strong>Key Limitations:</strong> |
| ED patient with $\leq 7$ days of symptoms | Median age 54 years; 46% men | Imbalance of patients requiring hospital admission during the index visit included in the primary analysis |
| PCR-confirmed SARS-CoV-2 infection | More patients with immunosuppression in CP arm (33 [13%]) than in placebo arm (17 [7%]) | Slightly more patients with multiple risk factors, including immunosuppression, in CP arm |
| Aged $\geq 50$ years or aged $\geq 18$ years with $\geq 1$ risk factor for disease progression | More patients with $\geq 3$ risk factors in CP arm (141 [55%]) than in placebo arm (123 [48%]) | |
| <strong>Key Exclusion Criteria:</strong> | | |
| Need for supplemental oxygen | | |
| <strong>Interventions:</strong> | <strong>Primary Outcomes:</strong> | |
| 250 mL high-titer CP (median titer 1:641) (n = 257) | There was no difference between the arms in the number of patients with disease progression: 77 (30%) in CP arm vs. 81 (32%) in placebo arm (risk difference 1.9%; 95% CrI, -6.0% to 9.8%). | |
| Placebo (n = 254) | 25 patients (19 in CP arm and 6 in placebo arm) required hospitalization during the index visit. In a post hoc analysis that excluded these patients, disease progression occurred in 24% of patients in CP arm vs. 30% in placebo arm (risk difference 5.8% [-1.9% to 13.6%]). | |
| <strong>Primary Endpoint:</strong> | <strong>Secondary Outcomes:</strong> | <strong>Interpretation:</strong> |
| Disease progression, defined as hospital admission, death, or seeking emergency or urgent care within 15 days of randomization | 5 patients (1.9%) in CP arm and 1 patient (0.4%) in placebo arm died. | In outpatients with COVID-19 at high risk of severe disease, use of high-titer CP within 1 week of symptom onset did not prevent disease progression. |
| <strong>Key Secondary Endpoints:</strong> | No difference in scores for illness severity or mean number of hospital-free days between the CP and placebo arms. | |
| Severity of illness (ordinal score) | | |
| All-cause mortality within 30 days | | |
| Hospital-free days over 30 days | | |</p>
<table>
<thead>
<tr>
<th>Methods</th>
<th>Results</th>
<th>Limitations and Interpretation</th>
</tr>
</thead>
</table>
| **Retrospective Evaluation of Convalescent Plasma Antibody Levels and the Risk of Death From COVID-19 in the United States**<sup>9</sup> | **Participant Characteristics:**  
- 31% aged ≥70 years; 61% men; 48% White, 37% Hispanic/Latinx  
- 61% in ICU; 33% on MV  
- 51% received corticosteroids and 31% received RDV | **Key Limitation:**  
- Lack of untreated control arm  
**Interpretation:**  
- The study data are not sufficient to establish the efficacy or safety of COVID-19 CP. |
| **Key Inclusion Criteria:**  
- Severe or life-threatening COVID-19  
- Patients for whom samples of transfused CP were available for retrospective analysis of antibody titer | **Primary Outcomes:**  
- Mortality at 30 days after transfusion was 22% in high-titer CP arm, 27% in medium-titer CP arm, and 30% in low-titer CP arm.  
- Patients in high-titer CP arm had a lower risk of death than those in low-titer CP arm (relative risk 0.75; 95% CI, 0.61–0.93).  
- Mortality was lower among patients who were not receiving MV before CP transfusion (relative risk 0.66; 95% CI, 0.48–0.91).  
- Among the patients who were on MV before the CP transfusion, there was no difference in mortality between the high-titer and low-titer arms (relative risk 1.02; 95% CI, 0.78–1.32). | |
| **Intervention:**  
- High-titer CP (n = 515), medium-titer CP (n = 2,006), or low-titer CP (n = 561), characterized retrospectively | **Primary Endpoint:**  
- Mortality at 30 days after CP transfusion | |

**Key:** ASAP = as soon as possible; CP = convalescent plasma; DM = diabetes; ECMO = extracorporeal membrane oxygenation; EUA = Emergency Use Authorization; HFNC = high-flow nasal cannula; ICU = intensive care unit; Ig = immunoglobulin; IL = interleukin; LOS = length of stay; MV = mechanical ventilation; NIV = noninvasive ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; PaO<sub>2</sub>/FiO<sub>2</sub> = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PCR = polymerase chain reaction; RBD = receptor binding domain; RCT = randomized controlled trial; RDV = remdesivir; SAE = serious adverse event; SOC = standard of care; SpO<sub>2</sub> = oxygen saturation

**References**


3. RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled,


Immunoglobulins: SARS-CoV-2 Specific

Last Updated: July 17, 2020

Recommendation

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel to recommend either for or against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins for the treatment of COVID-19.

Rationale

Currently, there are no clinical data on the use of SARS-CoV-2 immunoglobulins. Trials evaluating SARS-CoV-2 immunoglobulins are in development but not yet active and enrolling participants.

Proposed Mechanism of Action and Rationale for Use in Patients with COVID-19

Concentrated antibody preparations derived from pooled plasma collected from individuals who have recovered from COVID-19 can be manufactured as SARS-CoV-2 immunoglobulin, which could potentially suppress the virus and modify the inflammatory response. The use of virus-specific immunoglobulins for other viral infections (e.g., cytomegalovirus [CMV] immunoglobulin for the prevention of post-transplant CMV infection and varicella zoster immunoglobulin for postexposure prophylaxis of varicella in individuals at high-risk) has proven to be safe and effective; however, there are currently no clinical data on the use of such products for COVID-19. Potential risks may include transfusion reactions. Theoretical risks may include antibody-dependent enhancement of infection.

Clinical Data

There are no clinical data on the use of SARS-CoV-2 immunoglobulins for the treatment of COVID-19. Similarly, there are no clinical data on use of specific immunoglobulin or hyperimmunoglobulin products in patients with severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS).

Considerations in Pregnancy

Pathogen-specific immunoglobulins are used clinically during pregnancy to prevent varicella zoster virus (VZV) and rabies and have also been used in clinical trials of therapies for congenital CMV infection.

Considerations in Children

Hyperimmunoglobulin has been used to treat several viral infections in children, including VZV, respiratory syncytial virus, and CMV; efficacy data on their use for other respiratory viruses is limited.
Table 3c. Characteristics of SARS-CoV-2 Antibody-Based Products

Last Updated: February 1, 2022

- The information in this table is based on data from investigational trials evaluating these products for the treatment or prevention of COVID-19. The table includes dose recommendations from the FDA EUAs for patients who meet specified criteria.
- There are limited or no data on dose modifications for patients with organ failure or those who require extracorporeal devices. Please refer to product labels, when available.
- There are currently not enough data to determine whether certain medications can be safely coadministered with therapies for the treatment or prevention of COVID-19. When using concomitant medications with similar toxicity profiles, consider performing additional safety monitoring.
- The potential additive, antagonistic, or synergistic effects and the safety of using combination therapies for the treatment or prevention of COVID-19 are unknown. Clinicians are encouraged to report AEs to the [FDA Medwatch program](https://www.fda.gov/medwatch).
- For drug interaction information, please refer to product labels and visit the [Liverpool COVID-19 Drug Interactions website](https://liverpool-covid19-drug-interactions.sjo.fme.nl/).

<table>
<thead>
<tr>
<th>Dosing Regimens</th>
<th>Adverse Events</th>
<th>Monitoring Parameters</th>
<th>Drug-Drug Interaction Potential</th>
<th>Comments and Links to Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bamlanivimab Plus Etesevimab (Anti-SARS-CoV-2 Monoclonal Antibodies)</strong>&lt;br&gt;Authorized for the treatment or PEP of COVID-19 under FDA EUA.</td>
<td><strong>Nausea</strong></td>
<td><strong>Only for administration in health care settings by qualified health care providers who have immediate access to emergency medical services and medications to treat severe infusion reactions.</strong></td>
<td><strong>Drug-drug interactions are unlikely between BAM plus ETE and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers.</strong></td>
<td><strong>Availability:</strong>&lt;br&gt;• Distribution of BAM plus ETE has paused because the B.1.1.529 (Omicron) VOC has markedly reduced in vitro susceptibility to BAM plus ETE, and this regimen is not expected to provide clinical benefit.&lt;br&gt;• <a href="https://www.covid19treatmentguidelines.nih.gov/">HHS Public Health Emergency updates on the distribution of BAM plus ETE</a> are available.&lt;br&gt;• A list of clinical trials is available: <a href="https://clinicaltrials.gov/">Bamlanivimab Plus Etesevimab</a></td>
</tr>
<tr>
<td>Dose Recommended in EUA for Treatment and PEP of COVID-19 in Adults and Pediatric Patients Weighing ≥40 kg:</td>
<td><strong>Dizziness</strong></td>
<td><strong>Monitor patient during the IV infusion and for ≥1 hour after the infusion is completed.</strong></td>
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<tr>
<td>• BAM 700 mg plus ETE 1,400 mg as a single IV infusion</td>
<td><strong>Pruritis</strong></td>
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<tr>
<td>Doses Recommended in EUA for Treatment and PEP of COVID-19 in Neonates, Infants, Children, and Adolescents Weighing &lt;40 kg:</td>
<td><strong>Hypersensitivity, including anaphylaxis and infusion-related reactions</strong></td>
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<tr>
<td>• 1–12 kg: BAM 12 mg/kg plus ETE 24 mg/kg as a single IV infusion</td>
<td><strong>These AEs were observed in multiple trials in which participants received either the authorized doses of BAM and ETE or higher doses of each drug.</strong></td>
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<tr>
<td></td>
<td></td>
<td><strong>Availability:</strong>&lt;br&gt;• Distribution of BAM plus ETE has paused because the B.1.1.529 (Omicron) VOC has markedly reduced in vitro susceptibility to BAM plus ETE, and this regimen is not expected to provide clinical benefit.&lt;br&gt;• <a href="https://www.covid19treatmentguidelines.nih.gov/">HHS Public Health Emergency updates on the distribution of BAM plus ETE</a> are available.&lt;br&gt;• A list of clinical trials is available: <a href="https://clinicaltrials.gov/">Bamlanivimab Plus Etesevimab</a></td>
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<tr>
<td>Dosing Regimens</td>
<td>Adverse Events</td>
<td>Monitoring Parameters</td>
<td>Drug-Drug Interaction Potential</td>
<td>Comments and Links to Clinical Trials</td>
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<tr>
<td><strong>Bamlanivimab Plus Etesevimab (Anti-SARS-CoV-2 Monoclonal Antibodies), continued</strong></td>
<td><strong>&gt;12 kg to 20 kg:</strong> BAM 175 mg plus ETE 350 mg as a single IV infusion</td>
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<tr>
<td></td>
<td><strong>&gt;20 kg to &lt;40 kg:</strong> BAM 350 mg plus ETE 700 mg as a single IV infusion</td>
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<tr>
<td><strong>Casirivimab Plus Imdevimab (Anti-SARS-CoV-2 Monoclonal Antibodies)</strong></td>
<td>Authorized for the treatment or PEP of COVID-19 under FDA EUA.</td>
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</tr>
<tr>
<td>Dose Recommended in EUA for Treatment and PEP of COVID-19 in Adults and Pediatric Patients Aged ≥12 Years and Weighing ≥40 kg:</td>
<td>• CAS 600 mg plus IMD 600 mg as a single IV infusion over 1 hour.</td>
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<tr>
<td></td>
<td>• IV infusion is the preferred route of administration. However, when IV infusion is not feasible or would delay treatment, CAS 600 mg plus IMD 600 mg can be administered as 4 SQ injections (2.5 mL per injection) at 4 different sites. See the FDA EUA for detailed information.</td>
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<tr>
<td>Dose Recommended in EUA for PEP for Individuals With Ongoing Exposure to SARS-CoV-2:</td>
<td>• After initial dose, repeat dosing of CAS 300 mg plus IMD 300 mg by SQ injections or IV infusion every 4 weeks for duration of ongoing exposure.</td>
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<tr>
<td></td>
<td>• Hypersensitivity, including anaphylaxis and infusion-related reactions</td>
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<tr>
<td></td>
<td>• These AEs were observed in multiple trials in which participants received CAS 600 mg plus IMD 600 mg or higher doses of each drug.</td>
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<tr>
<td></td>
<td>• Injection site reactions, including ecchymosis and erythema, in clinical trial participants who received CAS plus IMD administered by SQ injections.</td>
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<tr>
<td></td>
<td>• Only for administration in health care settings by qualified health care providers who have immediate access to emergency medical services and medications to treat severe infusion reactions.</td>
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<tr>
<td></td>
<td>• Monitor patient during the IV infusion or SQ injections and for ≥1 hour after the infusion or injections are completed.</td>
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</tr>
<tr>
<td></td>
<td>• Drug-drug interactions are unlikely between CAS plus IMD and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers.</td>
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<tr>
<td></td>
<td>• Distribution of CAS plus IMD has paused because the Omicron VOC has markedly reduced in vitro susceptibility to CAS plus IMD, and this regimen is not expected to provide clinical benefit.</td>
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<tr>
<td></td>
<td>• HHS Public Health Emergency updates on the distribution of CAS plus IMD are available.</td>
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<tr>
<td></td>
<td>• A list of clinical trials is available: Casirivimab Plus Imdevimab</td>
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<tr>
<td>Dosing Regimens</td>
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</tbody>
</table>
| **Sotrovimab (Anti-SARS-CoV-2 Monoclonal Antibody)**  
Authorized for the treatment of COVID-19 under FDA EUA.  
Dose Recommended in EUA for Treatment of COVID-19 in Adults and Pediatric Patients Aged ≥12 Years and Weighing ≥40 kg:  
• SOT 500 mg administered by IV infusion over 30 minutes | • Rash  
• Diarrhea  
• Hypersensitivity, including anaphylaxis and infusion-related reactions | • Only for administration in health care settings by qualified health care providers who have immediate access to emergency medical services and medications to treat severe infusion reactions.  
• Monitor patient during the IV infusion and for ≥1 hour after the infusion is completed. | • Drug-drug interactions are unlikely between SOT and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers. | Availability:  
• Under the FDA EUA, SOT is available for the treatment of high-risk outpatients with mild to moderate COVID-19.¹ See Anti-SARS-CoV-2 Monoclonal Antibodies for a list of high-risk conditions.  
• A list of clinical trials is available: Sotrovimab |
| **Tixagevimab Plus Cilgavimab (Evusheld) (Anti-SARS-CoV-2 Monoclonal Antibody)**  
Authorized for PrEP of COVID-19 under FDA EUA.  
Dose Recommended in EUA for PrEP of COVID-19 in Adults and Pediatric Patients Aged ≥12 Years and Weighing ≥40 kg:  
• TIX 150 mg plus CIL 150 mg administered as 2 consecutive 1.5 mL IM injections; dose may be repeated every 6 months | • Hypersensitivity, including anaphylaxis and injection-related reactions  
• In 1 clinical trial, cardiac events reported in participants with cardiac risk factors (0.6% in TIX plus CIL arm vs. 0.2% in placebo arm) | • Use with caution in individuals with thrombocytopenia or any coagulation disorder.  
• Monitor and observe individual for ≥1 hour after injection. | • If a person has received a COVID-19 vaccine, TIX plus CIL should be administered ≥2 weeks after vaccination.  
• Drug-drug interactions are unlikely between TIX plus CIL and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers. | Availability:  
• Under the FDA EUA, TIX plus CIL for PrEP of COVID-19 is available for certain patients at high risk of infection. See Prevention of SARS-CoV-2 Infection for more information.  
• A list of clinical trials is available: Tixagevimab Plus Cilgavimab |

¹ See Anti-SARS-CoV-2 Monoclonal Antibodies for a list of high-risk conditions.
### COVID-19 Convalescent Plasma

**Authorized for the treatment of COVID-19 under FDA EUA.**

#### Dose Recommended in EUA for Treatment of COVID-19:
- Per the EUA, consider starting clinical dosing with 1 high-titer COVID-19 CP unit (about 200 mL), with administration of additional CP units based on the prescribing provider’s medical judgment and the patient’s clinical response.

#### Adverse Events
- TRALI
- TACO
- Allergic reactions
- Anaphylactic reactions
- Febrile nonhemolytic reactions
- Hemolytic reactions
- Hypothermia
- Metabolic complications
- Transfusion-transmitted infections
- Thrombotic events
- Theoretical risk of antibody-mediated enhancement of infection and suppressed long-term immunity

#### Monitoring Parameters
- Before administering CP to patients with a history of severe allergic or anaphylactic transfusion reactions, the Panel recommends consulting a transfusion medicine specialist who is associated with the hospital blood bank.
- Monitor for transfusion-related reactions.
- Monitor patient’s vital signs at baseline and during and after transfusion.

#### Drug-Drug Interaction Potential
- Drug products **should not be added** to the IV infusion line for the blood product.

#### Comments and Links to Clinical Trials
- The decision to use COVID-19 CP for the treatment of COVID-19 in patients aged <18 years should be based on an individualized assessment of risk and benefit.¹
- In patients with impaired cardiac function and heart failure, it may be necessary to reduce the CP volume or decrease the transfusion rate.

#### Availability:
- A list of clinical trials is available: [COVID-19 Convalescent Plasma](https://clinicaltrials.gov/ct2/search resultados.)

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### SARS-CoV-2-Specific Immunoglobulin

**Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.**

#### Dose in Clinical Trials for Treatment of COVID-19:
- Dose varies by clinical trial

#### Adverse Events
- TRALI
- TACO
- Allergic reactions
- Antibody-mediated enhancement of infection
- RBC alloimmunization
- Transfusion-transmitted infections

#### Monitoring Parameters
- Monitor for transfusion-related reactions.
- Monitor patient’s vital signs at baseline and during and after transfusion.

#### Drug-Drug Interaction Potential
- Drug products **should not be added** to the IV infusion line for the blood product.

#### Comments and Links to Clinical Trials
- A list of clinical trials is available: [SARS-CoV-2 Immunoglobulin](https://clinicaltrials.gov/ct2/search).

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**Key:** AE = adverse event; BAM = bamlanivimab; CAS = casirivimab; CIL = cilgavimab; CP = convalescent plasma; CYP = cytochrome P450; ETE = etesevimab; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; HHS = U.S. Department of Health and Human Services; IM = intramuscular; IMD = imdevimab; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PEP = post-exposure prophylaxis; PrEP = pre-exposure prophylaxis; RBC = red blood cell; SOT = sotrovimab; SQ = subcutaneous; TACO = transfusion-associated circulatory overload; TIX = tixagevimab; TRALI = transfusion-related acute lung injury; VOC = variant of concern

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**COVID-19 Treatment Guidelines**

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References


