Summary Recommendations

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

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using 1 of the following anti-SARS-CoV-2 monoclonal antibody (mAb) products (listed alphabetically) to treat nonhospitalized patients 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 Authorizations (EUAs) for the products:
  - Bamlanivimab 700 mg plus etesevimab 1,400 mg administered as an intravenous (IV) infusion; or
  - Casirivimab 600 mg plus imdevimab 600 mg administered as an IV infusion or as subcutaneous (SQ) injections; or
  - Sotrovimab 500 mg administered as an IV infusion.

- When using casirivimab plus imdevimab, the Panel recommends:
  - Casirivimab 600 mg plus imdevimab 600 mg administered as an IV infusion (AIIa).
  - If an IV infusion is not feasible or would cause a delay in treatment, casirivimab 600 mg plus imdevimab 600 mg can be administered as 4 SQ injections (2.5 mL per injection) (BIII).

- 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 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:
  - High-risk conditions represented in clinical trials (AII); and
  - Other medical conditions and factors with limited representation in clinical trials (BIII) except for immunocompromising conditions or receipt of immunosuppressive therapy, for which the rating is AIII.

- When using anti-SARS-CoV-2 mAbs, treatment should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 antigen test or nucleic acid amplification test (NAAT) and within 10 days of symptom onset.

- The use of 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 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, they may be available through expanded access programs for patients who either have not developed an antibody response or are not expected to mount an effective immune response to SARS-CoV-2 infection.

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

- The Panel recommends using 1 of the following anti-SARS-CoV-2 mAb combinations as post-exposure prophylaxis (PEP) for people who are at high risk of progressing to severe COVID-19 if infected with SARS-CoV-2 and who have the vaccination status AND exposure history outlined in the Prevention of SARS-CoV-2 Infection section:
  - Bamlanivimab 700 mg plus etesevimab 1,400 mg administered as an IV infusion; or
  - Casirivimab 600 mg plus imdevimab 600 mg administered as SQ injections (AI) or as an IV infusion (BIII).

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

Last Updated: December 16, 2021

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 a clinical benefit in treating SARS-CoV-2 infection (as discussed below). Some anti-SARS-CoV-2 mAbs have been found to be effective in preventing SARS-CoV-2 infection in household contacts of infected patients2 and during SARS-CoV-2 outbreaks in skilled nursing and assisted living facilities.3

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

Currently, 3 anti-SARS-CoV-2 mAb products have received Emergency Use Authorizations (EUAs) from the Food and Drug Administration (FDA) 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. The issuance of an EUA does not constitute FDA approval. These products are:

• **Bamlanivimab plus etesevimab**: These are neutralizing mAbs that bind to different, but overlapping, epitopes in the spike protein RBD of SARS-CoV-2.
  
  • The distribution of bamlanivimab plus etesevimab was paused in the United States because both the Gamma (P.1) and Beta (B.1.351) variants have reduced susceptibility to bamlanivimab and etesevimab.4 However, distribution of the agents has been reinstated in states with low rates of these and other variants that have reduced susceptibility to bamlanivimab and etesevimab. Please refer to the FDA webpage [Bamlanivimab and Etesevimab Authorized States, Territories, and U.S. Jurisdictions](https://www.fda.gov) for the latest information on bamlanivimab plus etesevimab distribution.
  
  • Bamlanivimab plus etesevimab is authorized for adults and children of all ages, including infants and neonates. Please see [Special Considerations in Children](https://www.fda.gov) for therapeutic recommendations for children.

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

• **Sotrovimab**: This mAb was originally identified in 2003 from a SARS-CoV survivor. It targets an epitope in the RBD of the spike protein that is conserved between SARS-CoV and SARS-CoV-2.

The FDA has expanded the EUAs for bamlanivimab plus etesevimab and casirivimab plus imdevimab to authorize their use as post-exposure prophylaxis (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. See [Prevention of SARS-CoV-2 Infection](https://www.covid19treatmentguidelines.nih.gov) and the FDA EUA fact sheets for bamlanivimab plus etesevimab and casirivimab plus imdevimab for more information.

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 mAb products as PEP, see [Prevention of SARS-CoV-2 Infection](https://www.covid19treatmentguidelines.nih.gov).
Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using 1 of the following anti-SARS-CoV-2 mAb products (listed alphabetically) to treat nonhospitalized patients with mild to moderate COVID-19 who are at high risk of clinical progression (see the EUA criteria for use of the products and the related discussion below):
  - **Bamlanivimab 700 mg plus etesevimab 1,400 mg** (or weight-based dosing for pediatric patients weighing <40 kg) administered as an intravenous (IV) infusion in regions where the combined frequency of potentially resistant SARS-CoV-2 variants is low (see the FDA webpage Bamlanivimab and Etesevimab Authorized States, Territories, and U.S. Jurisdictions; or
  - **Casirivimab 600 mg plus imdevimab 600 mg** administered as an IV infusion or as subcutaneous (SQ) injections; or
  - **Sotrovimab 500 mg** administered as an IV infusion.

- When using casirivimab plus imdevimab, the Panel recommends:
  - **Casirivimab 600 mg plus imdevimab 600 mg** administered as an IV infusion (AIIa).
  - If an IV infusion is not feasible or would cause a delay in treatment, **casirivimab 600 mg plus imdevimab 600 mg** can be administered as 4 SQ injections (2.5 mL per injection) (BIII).

- When using anti-SARS-CoV-2 mAbs, treatment should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 antigen test or nucleic acid amplification test (NAAT) and within 10 days of symptom onset.

- The use of 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, they 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.

- For guidance on prioritizing the use of anti-SARS-CoV-2 mAbs for the treatment or prevention of SARS-CoV-2 infection when logistical or supply constraints limit their availability, see the Panel’s statement on patient prioritization for outpatient therapies.

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). It is worth noting that these studies were conducted before the widespread circulation of variants of concern (VOC). The potential impact of these variants and their susceptibility to different anti-SARS-CoV-2 mAbs is discussed below.

Bamlanivimab Plus Etesevimab

This anti-SARS-CoV-2 mAb combination has demonstrated a clinical benefit in people with mild to moderate COVID-19 who are at high risk for progression to severe disease and/or hospitalization (see Table 3a). The distribution of bamlanivimab plus etesevimab was paused in the United States because both the Gamma (P.1) and Beta (B.1.351) variants have reduced susceptibility to bamlanivimab and etesevimab. However, distribution of the product has been reinstated across the United States because the combined frequency of the Gamma and Beta variants is <5%. Casirivimab plus imdevimab and sotrovimab are expected to remain active against the Gamma and Beta variants.
The FDA provides a list of states, territories, and U.S. jurisdictions in which bamlanivimab plus etesevimab is currently authorized. The Centers for Disease Control and Prevention (CDC) COVID-19 Data Tracker website has the latest information on variant frequencies by region in the United States.

Casirivimab Plus Imdevimab

On June 3, 2021, the FDA updated the EUA for casirivimab plus imdevimab to reduce the authorized dosage for a single IV infusion from casirivimab 1,200 mg plus imdevimab 1,200 mg to casirivimab 600 mg plus imdevimab 600 mg. The update also authorized SQ injection of these lower doses of casirivimab and imdevimab if an IV infusion is not feasible or would delay treatment. SQ administration 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 the Phase 3 results from the R10933-10987-COV-2067 study (ClinicalTrials.gov Identifier NCT04425629). This double-blind randomized placebo-controlled trial in outpatients with mild to moderate COVID-19 evaluated different doses of casirivimab plus imdevimab. 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 or more 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. These results are comparable to the those observed for IV infusions of casirivimab 1,200 mg plus imdevimab 1,200 mg, which demonstrated a 3.3% absolute reduction and a 71% relative reduction in hospitalization or death among patients who received this higher dose of casirivimab plus imdevimab. See Table 3a for additional details from the trial.

The recommendation for using SQ injections to administer casirivimab plus imdevimab 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, in a separate trial that evaluated casirivimab plus imdevimab in symptomatic participants, there were similar reductions in viral load in the participants in the IV and SQ arms of the trial. 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).

Sotrovimab

The data that support the EUA for sotrovimab are from the Phase 3 COMET-ICE trial (ClinicalTrials.gov Identifier NCT04545060). The COMET-ICE trial 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 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.

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

COVID-19 Treatment Guidelines

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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 agents in patients with the following conditions: sickle cell disease, neurodevelopmental disorders, medical-related technological dependence, asthma, cardiovascular disease, hypertension, and chronic lung disease.

**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 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 (for bamlanivimab plus etesevimab only) (**CIII**)

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) not listed in the 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](https://www.cdc.gov/coronavirus/2019-ncov/特定条件の人々.html). The decision to use anti-SARS-CoV-2 mAbs for a patient should be based on an individualized assessment of risks and benefits.

Some of the Panel’s recommendations for using anti-SARS-CoV-2 mAbs according to the updated EUA criteria are based on preliminary results from the clinical trials that have evaluated these products. The details on the study designs, methods, and follow-up periods for these trials are currently limited. When
Using Anti-SARS-CoV-2 Monoclonal Antibodies in Patients Hospitalized for COVID-19

The FDA EUAs do not authorize the use of anti-SARS-CoV-2 mAbs for 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 agents 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.\(^{15-17}\)

Anti-SARS-CoV-2 mAbs have been evaluated in hospitalized patients with severe COVID-19. A substudy of the ACTIV-3 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.\(^{18,19}\)

There are now data that support the use of casirivimab 4,000 mg plus imdevimab 4,000 mg in hospitalized patients with COVID-19 who are seronegative for the anti-spike protein antibody. 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; \(P = 0.001\)).\(^{20}\) This higher dose of casirivimab plus imdevimab is not available through the current EUA, and currently, casirivimab plus imdevimab 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.\(^{21}\) 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:

- **Alpha (B.1.1.7):** This variant retains in vitro susceptibility to all the anti-SARS-CoV-2 mAbs that
are currently available through EUAs.\textsuperscript{5,6}

- **Beta (B.1.351):** This variant includes the E484K and K417N mutations, which results in markedly reduced in vitro susceptibility to bamlanivimab and etesevimab.\textsuperscript{5} In vitro studies also suggest that the Beta (B.1.351) 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.\textsuperscript{6,7}

- **Gamma (P.1):** This variant includes the E484K and K417T mutations, which results in markedly reduced in vitro susceptibility to bamlanivimab and etesevimab.\textsuperscript{5,22,23} The Gamma (P.1) 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 (P.1) variant.\textsuperscript{6,7}

- **Delta (B.1.617.2, non-AY.1/AY.2):** This is the predominant VOC circulating in the United States. This VOC retains in vitro susceptibility to all the anti-SARS-CoV-2 mAbs that are currently available through FDA EUAs.\textsuperscript{5,6}

- **Omicron (B.1.1.529):** Ongoing studies are evaluating the susceptibility of this VOC to the anti-SARS-CoV-2 mAbs. This variant, which includes numerous mutations in the spike protein, is predicted to have markedly reduced susceptibility to some anti-SARS-CoV-2 mAb products, including bamlanivimab plus etesevimab and casirivimab plus imdevimab. Sotrovimab appears to retain activity against this variant.\textsuperscript{24}

### 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>SOT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anti-anticipated clinical activity</td>
<td>In Vitro Susceptibility\textsuperscript{a}</td>
<td>Anti-anticipated clinical activity</td>
<td>In Vitro Susceptibility\textsuperscript{a}</td>
</tr>
<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>
</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\textsuperscript{b}</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\textsuperscript{b}</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>
</tr>
<tr>
<td>Omicron</td>
<td>B.1.1.529</td>
<td>VOC</td>
<td>K417N, N440K, G446S, E484A, Q493R, N501Y</td>
<td>Anticipated marked reduction</td>
<td>Unlikely to be active</td>
<td>Anticipated marked reduction</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Based on the fold reduction in susceptibility reported in the FDA EUAs.\textsuperscript{5-7}

\textsuperscript{b} Marked change for CAS and no change for IMD. The combination of CAS plus IMD appears to retain activity against the variant.

**Key:** BAM = bamlanivimab; CAS = casirivimab; CDC = Centers for Disease Control and Prevention; ETE = etesevimab; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; IMD = imdevimab; SOT = sotrovimab; 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.

COVID-19 Vaccination

For people who have received anti-SARS-CoV-2 mAbs for treatment, CDC recommends that COVID-19 vaccination be deferred until at least 90 days after therapy. For people who have received anti-SARS-CoV-2 mAbs for PEP, vaccination should be deferred until at least 30 days after PEP. These deferrals are precautionary because of the theoretic possibility that anti-SARS-CoV-2 mAb treatment may interfere with vaccine-induced immune responses. For people who develop COVID-19 after vaccination, if there are no logistical or supply constraints limiting the availability of the authorized anti-SARS-CoV-2 mAbs, prior vaccination should not affect decisions regarding the use and timing of anti-SARS-CoV-2 mAb treatment. For guidance on the use of anti-SARS-CoV-2 mAbs when there are logistical or supply constraints, see the Panel’s statement on patient prioritization for outpatient therapies.

Monitoring

The authorized anti-SARS-CoV-2 mAbs should be administered by IV infusion or SQ injections 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 or SQ injections and for at least 1 hour after the infusion or injections are 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 pruritis have also been reported. Injection site reactions, including ecchymosis and erythema, were reported in clinical trial participants who received casirivimab plus imdevimab by SQ administration.

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 in the setting of 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.

Drug Availability

Bamlanivimab plus etesevimab, casirivimab plus imdevimab, and sotrovimab are available through FDA EUAs. The availability of bamlanivimab plus etesevimab was previously restricted in areas with an elevated combined frequency of variants that have markedly reduced in vitro susceptibility to these agents (e.g., the Gamma and Beta variants). The FDA provides updated information on the distribution of bamlanivimab plus etesevimab in the United States. Efforts should be made to ensure that communities most affected by COVID-19 have equitable access to these 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>
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<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-19&lt;sup&gt;1&lt;/sup&gt;</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 (Δ [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>
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</table>

| Key Inclusion Criteria: | • Aged ≥12 years<br>• At high risk for severe COVID-19 or hospitalization | **Interventions:**<br>• Within 3 days of a positive SARS-CoV-2 test result, single infusion of:<br>• BAM 700 mg plus ETE 1,400 mg (n = 511)<br>• Placebo (n = 258) | **Participant Characteristics:**<br>• Median age 56 years; 30% ≥65 years; 53% women<br>• 87% White, 27% Hispanic/Latinx, 8% Black/African American<br>• Mean duration of symptoms was 4 days.<br>• 76% had mild COVID-19 and 24% had moderate COVID-19.<br>**Primary Outcomes:**<br>• 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 (Δ [95% CI] = -5.0 [-8.0, -2.1]; P<0.001).<br>• All-cause deaths by Day 29: 0 in BAM plus ETE arm vs. 4 (1.6%) in placebo arm.<br>**Interpretation:**<br>• 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. | |

| Key Exclusion Criteria: | • SpO<sub>2</sub> ≤93% on room air; or<br>• Respiratory rate ≥30 breaths/min; or<br>• Heart rate ≥125 bpm | **Interventions:**<br>• Within 3 days of testing SARS-CoV-2 positive, single infusion of:<br>• BAM 2,800 mg plus ETE 2,800 mg (n = 518)<br>• Placebo (n = 517) | **Participant Characteristics:**<br>• Mean age 53.8 years; 31% ≥65 years; 52% women; 48% men<br>• 87% White, 29% Hispanic/Latinx, 8% Black/African American<br>• Median days from symptom onset to infusion was 4 days.<br>• 77% had mild COVID-19.<br>**Primary Outcomes:**<br>• 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 < 0.001).<br>• All-cause deaths by Day 29: 0 in BAM plus ETE arm vs. 10 (1.9%) in placebo arm.<br>**Interpretation:**<br>• 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. | |

---

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.
## Methods

**BLAZE-1**: Double-Blind, Phase 3 RCT of Bamlanivimab 2,800 mg Plus Etesevimab 2,800 mg in Nonhospitalized Patients With Mild to Moderate COVID-19¹, continued

<table>
<thead>
<tr>
<th>Primary Endpoint:</th>
<th>Secondary Endpoint:</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID-19-related hospitalization or death from any cause by Day 29</td>
<td>SARS-CoV-2 VL &gt;5.27 log₁₀ copies/mL at Day 7</td>
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</tbody>
</table>

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<thead>
<tr>
<th>Double-Blind, Phase 3 RCT of Casirivimab Plus Imdevimab in Nonhospitalized Patients With Mild to Moderate COVID-19²</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>Key Inclusion Criteria:</th>
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<tbody>
<tr>
<td>Aged ≥18 years</td>
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<tr>
<td>Laboratory-confirmed SARS-CoV-2 infection</td>
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<tr>
<td>Symptom onset within 7 days of randomization</td>
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<tr>
<td>For patients included in the modified full analysis only:</td>
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<tr>
<td>≥1 risk factor for severe COVID-19</td>
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<tr>
<td>Positive SARS-CoV-2 RT-PCR at baseline</td>
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<tr>
<th>Interventions:</th>
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<tbody>
<tr>
<td>Single IV infusion of:</td>
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<tr>
<td>CAS 600 mg plus IMD 600 mg (n = 736) or placebo (n = 748)</td>
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<tr>
<td>CAS 1,200 mg plus IMD 1,200 mg (n = 1,355) or placebo (n = 1,341)</td>
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<table>
<thead>
<tr>
<th>Primary Endpoint:</th>
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<tbody>
<tr>
<td>≥1 COVID-19-related hospitalization or death from any cause through Day 29</td>
</tr>
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## Results

**Primary Endpoint:**
- COVID-19-related hospitalization or death from any cause by Day 29

**Secondary Endpoint:**
- SARS-CoV-2 VL >5.27 log₁₀ copies/mL at Day 7

**Secondary Outcome:**
- Percentage of patients with SARS-CoV-2 VL >5.27 log₁₀ copies/mL at Day 7: 9.8% in BAM plus ETE arm vs. 29.5% in placebo arm (P < 0.001).

## Interpretation

- Compared to placebo, CAS 600 mg plus IMD 600 mg was associated with 2.2% absolute reduction and 70% relative risk reduction in COVID-19-related hospitalizations or all-cause deaths.
- Compared to placebo, CAS 1,200 mg plus IMD 1,200 mg was associated with 3.3% absolute reduction and 71% relative risk reduction in COVID-19-related hospitalizations or all-cause deaths.

## Participant Characteristics:

| Median age 50 years; 35% Hispanic/Latinx, 5% Black/African American |
| Median duration of symptoms prior to enrollment was 3 days |

## Primary Outcomes:

- COVID-19-related hospitalizations or all-cause deaths through Day 29:
  - 7 (1.0%) in CAS 600 mg plus IMD 600 mg arm vs. 24 (3.2%) in placebo arm (P = 0.002).
  - 18 (1.3%) in CAS 1,200 mg plus IMD 1,200 mg arm vs. 62 (4.6%) in placebo arm (P < 0.001).

## All-Cause Deaths:

| 1 (0.1%) in CAS 600 mg plus IMD 600 mg arm vs. 1 (0.1%) in placebo arm. |
| 1 (<0.1%) in CAS 1,200 mg plus IMD 1,200 mg arm vs. 3 (0.2%) in placebo arm. |
## 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>
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</thead>
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<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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<tr>
<td>• Laboratory-confirmed COVID-19</td>
<td>• 63% Hispanic/Latinx, 7% Black/African American</td>
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<tr>
<td>• Symptom onset ≤5 days before enrollment</td>
<td><strong>Primary Outcome:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Key Exclusion Criteria:</strong></td>
<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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<tr>
<td>• Hospitalized or requiring supplemental oxygen</td>
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<tr>
<td>• Severely immunocompromised</td>
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</table>

### Interventions:
- SOT 500 mg IV (n = 291)
- Placebo (n = 292)

### Primary Endpoint:
- Hospitalization or death from any cause by Day 29

### Participant Characteristics:
- Median age 53 years; 22% ≥65 years
- 63% Hispanic/Latinx, 7% Black/African American

### Primary Outcome:
- Hospitalizations or all-cause deaths by Day 29: 3 (1%) in SOT arm vs. 21 (7%) in placebo arm (P = 0.002).

### 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 With 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.³⁴ 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](https://www.covid19treatmentguidelines.nih.gov/) for a list of anti-SARS-CoV-2 antibody tests that can be used to qualify COVID-19 CP as high titer.

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<thead>
<tr>
<th>Methods</th>
<th>Results</th>
<th>Limitations and Interpretation</th>
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<tbody>
<tr>
<td><strong>REMAP-CAP</strong>: Multinational, Open-Label RCT of High-Titer Convalescent Plasma in Hospitalized Patients With Critical COVID-19&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>Participant Characteristics:</strong>&lt;br&gt;• Mean age 61 years; 68% men&lt;br&gt;• 32% on MV&lt;br&gt;• 29% SARS-CoV-2 antibody negative at baseline&lt;br&gt;• 94% received corticosteroids, 45% received RDV, 39% received IL-6 inhibitors</td>
<td><strong>Key Limitations:</strong>&lt;br&gt;• Open-label study&lt;br&gt;• Not all patients in CP arm received CP (86% received CP as per protocol and 95% received some CP)&lt;br&gt;<strong>Interpretation:</strong>&lt;br&gt;• There was no benefit of CP in hospitalized patients with severe COVID-19.</td>
</tr>
<tr>
<td><strong>Key Inclusion Criteria:</strong>&lt;br&gt;• Admitted to ICU with receipt of respiratory support (HFNC oxygen, NIV, MV, ECMO) and/or vasopressor or inotrope support</td>
<td><strong>Primary Outcome:</strong>&lt;br&gt;• 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><strong>Key Exclusion Criteria:</strong>&lt;br&gt;• CP contraindicated&lt;br&gt;• Death imminent</td>
<td><strong>Secondary Outcomes:</strong>&lt;br&gt;• No difference for in-hospital mortality between CP arm (37%) and usual care arm (38%).&lt;br&gt;• No difference in median number of respiratory support-free days: 0 days in CP arm and 2 days in usual care arm.&lt;br&gt;• 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><strong>Interventions:</strong>&lt;br&gt;• High-titer CP (550 mL +/- 150 mL) within 48 hours of randomization (n = 1,084)&lt;br&gt;• Usual care (n = 916)</td>
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<tr>
<td><strong>Primary Endpoint:</strong>&lt;br&gt;• Organ support-free days by Day 21</td>
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<tr>
<td><strong>Key Secondary Endpoints:</strong>&lt;br&gt;• Mortality at Day 28 and Day 90&lt;br&gt;• Progression to respiratory support&lt;br&gt;• ICU LOS</td>
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<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 Brazil⁴</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&lt;br&gt;<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>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>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>
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<tr>
<td><strong>Key Exclusion Criteria:</strong>&lt;br&gt;• Imminent or current intubation</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>
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<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>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>
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<tr>
<td><strong>Primary Endpoint:</strong>&lt;br&gt;• Intubation or death at Day 30</td>
<td><strong>Primary Outcome:</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>
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<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><strong>Secondary Outcomes:</strong>&lt;br&gt;• No difference between the arms in:&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)</td>
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**RECOVERY Trial**: Open-Label RCT of High-Titer Convalescent Plasma in Hospitalized Patients in the United Kingdom³

<p>| <strong>Key Inclusion Criteria:</strong>&lt;br&gt;• Hospitalized patients with clinically suspected or laboratory-confirmed SARS-CoV-2 infection | <strong>Participant Characteristics:</strong>&lt;br&gt;• Mean age 68 years; 59% men&lt;br&gt;• 84% receiving systemic corticosteroids at enrollment | <strong>Key Limitations:</strong>&lt;br&gt;• Open-label study&lt;br&gt;• There was no benefit of CP in oxygen-dependent, hospitalized COVID-19 patients within 12 days of symptom onset. |
| <strong>Key Exclusion Criteria:</strong>&lt;br&gt;• CP contraindicated | <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). | |
| <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) | <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) | |
| <strong>Primary Endpoint:</strong>&lt;br&gt;• All-cause mortality at Day 28 | | |</p>
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</thead>
<tbody>
<tr>
<td><strong>RECOVERY Trial</strong>: Open-Label RCT of High-Titer Convalescent Plasma in Hospitalized Patients in the United Kingdom&lt;br&gt;continued</td>
<td>• Proportion of patients discharged (66% in CP arm and 67% in SOC arm).&lt;br&gt;• Proportion of patients who progressed to MV or death (28% in CP arm and 29% in SOC arm).</td>
<td></td>
</tr>
</tbody>
</table>
Key Secondary Endpoints:<br>• Time to hospital discharge by Day 28<br>• Among patients not receiving MV, receipt of MV or death by Day 28  
| **Key Inclusion Criteria**:<br>• Hospitalized patients with moderate, laboratory-confirmed SARS-CoV-2 infection<br>• PaO$_2$/FiO$_2$ 200–300 mm Hg or respiratory rate >24 breaths/min with SpO$_2$ ≤93% on room air | **Participant Characteristics**:<br>• Median age 52 years; 76% men<br>• Higher prevalence of DM in CP arm (48%) than SOC arm (38%) | **Key Limitations**:<br>• Open-label study<br>• SARS-CoV-2 antibody testing not used to select CP; many participants may have received low-titer CP<br>**Interpretation**:<br>• CP use did not reduce progression to severe disease or death in hospitalized patients with moderate COVID-19. |  
Key Exclusion Criteria:<br>• Critical illness  
**Interventions**:<br>• 2 doses of 200 mL of CP transfused 24 hours apart (n = 235)<br>• SOC (n = 229)  
**Primary Endpoint**:<br>• Progression to severe disease (defined as PaO$_2$/FiO$_2$ <100 mm Hg) or death within 28 days  
**Key Limitations**:<br>• SARS-CoV-2 antibody testing not used to select CP; many participants may have received low-titer CP  
**Interpretation**:<br>• CP use did not reduce progression to severe disease or death in hospitalized patients with moderate COVID-19. |

| **PLACID Trial**: Open-Label RCT of Convalescent Plasma in Hospitalized Adults With Severe COVID-19 in India |  
| **Key Inclusion Criteria**:<br>• Hospitalized patients with severe COVID-19  
| **Key Exclusion Criteria**:<br>• Critical illness  
**Interventions**:<br>• 1 unit CP with SARS-CoV-2 viral spike-RBD IgG titer ≥1:800 (n = 228)<br>• Placebo (n = 106)  
**Primary Endpoint**:<br>• Clinical status at 30 days (ordinal score)  
| **Primary Outcome**:<br>• No significant difference between the arms in clinical status at 30 days (OR 0.83; 95% CI, 0.52–1.35; $P = 0.46$).<br>• 30-day mortality 11% in both arms. | **Key Limitations**:<br>• Small sample size  
**Interpretation**:<br>• There was no benefit of CP in hospitalized patients with severe COVID-19. |  
**PlasmAr Study**: Double-Blind RCT of Convalescent Plasma in Hospitalized Adults in Argentina<br>continued |  
| **Key Inclusion Criteria**:<br>• PCR-confirmed, severe COVID-19  
| **Key Exclusion Criteria**:<br>• Critical illness  
**Interventions**:<br>• 1 unit CP with SARS-CoV-2 viral spike-RBD IgG titer ≥1:800 (n = 228)<br>• Placebo (n = 106)  
**Primary Endpoint**:<br>• Clinical status at 30 days (ordinal score) | **Participant Characteristics**:<br>• Median age 62 years; 68% men<br>• 65% with coexisting condition  
| **Primary Outcome**:<br>• No significant difference between the arms in clinical status at 30 days (OR 0.83; 95% CI, 0.52–1.35; $P = 0.46$).<br>• 30-day mortality 11% in both arms. | **Key Limitations**:<br>• Small sample size  
**Interpretation**:<br>• 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

<table>
<thead>
<tr>
<th>Key Inclusion Criteria:</th>
<th>Participant Characteristics:</th>
<th>Key Limitations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Severe COVID-19 pneumonia</td>
<td>- Median age 61 years; 66% men</td>
<td>- Small sample size</td>
</tr>
<tr>
<td>- (\text{SpO}_2) (\leq 94%) on room air or requirement of supplemental oxygen, MV, or ECMO</td>
<td>- 57% required supplemental oxygen at baseline: 25% high-flow oxygen or NIV and 13% MV or ECMO</td>
<td>- Control arm intervention was blood plasma without SARS-CoV-2 antibodies, therefore not possible to identify potential harm due to plasma infusion</td>
</tr>
<tr>
<td>- &gt;5 days on MV or ECMO</td>
<td>- 81% received corticosteroids</td>
<td>- Early termination because COVID-19 cases decreased</td>
</tr>
<tr>
<td>- Severe multiorgan failure</td>
<td></td>
<td>- Although the difference in clinical status on Day 28 between the arms was not statistically significant, lower 28-day mortality in the CP arm suggests potential benefit of CP in hospitalized patients with severe COVID-19.</td>
</tr>
</tbody>
</table>

**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

**Results:**
- No difference in Day 28 clinical status between the arms \((\text{OR} 1.5; 95\% \text{ CI}, 0.83–2.68; P = 0.18)\).

**Secondary Outcomes:**
- In-hospital mortality lower in CP arm than control arm \((13\% \text{ vs. } 25\%; \text{OR} 0.44; 95\% \text{ CI}, 0.22–0.91; P = 0.034)\). 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).

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

<table>
<thead>
<tr>
<th>Key Inclusion Criteria:</th>
<th>Participant Characteristics:</th>
<th>Key Limitations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Nonhospitalized</td>
<td>- Mean age 77 years; 38% men</td>
<td>- Small sample size</td>
</tr>
<tr>
<td>- Aged (\geq 75) years or aged 65–74 years with (\geq 1) coexisting condition</td>
<td>- Most with comorbidities</td>
<td>- Early termination because COVID-19 cases decreased</td>
</tr>
<tr>
<td>- Mild COVID-19 with symptoms for &lt;72 hours</td>
<td></td>
<td>- This trial demonstrated a benefit of CP in older adult outpatients with &lt;72 hours of mild COVID-19 symptoms.</td>
</tr>
</tbody>
</table>

**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

**Primary Outcome:**
- 16% of patients in CP arm and 31% in placebo arm experienced severe respiratory disease by Day 15 \((\text{relative risk} 0.52; 95\% \text{ CI}, 0.29–0.94; P = 0.03)\).
<table>
<thead>
<tr>
<th><strong>Methods</strong></th>
<th></th>
<th><strong>Results</strong></th>
<th></th>
<th><strong>Limitations and Interpretation</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Double-Blind RCT of Early High-Titer Convalescent Plasma Therapy to Prevent Severe COVID-19 in Nonhospitalized Older Adults in Argentina</strong>&lt;sup&gt;7&lt;/sup&gt;, continued</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary Endpoint:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Severe respiratory disease, defined as respiratory rate ≥30 breaths/min and/or SpO&lt;sub&gt;2&lt;/sub&gt; &lt;93% on room air by Day 15</td>
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<tr>
<td><strong>C3PO: Multicenter, Single-Blind RCT of High-Titer Convalescent Plasma in the United States</strong>&lt;sup&gt;8&lt;/sup&gt;</td>
<td></td>
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</tr>
<tr>
<td><strong>Key Inclusion Criteria:</strong></td>
<td></td>
<td><strong>Participant Characteristics:</strong></td>
<td></td>
<td><strong>Key Limitations:</strong></td>
</tr>
<tr>
<td>• ED patient with ≤7 days of symptoms</td>
<td></td>
<td>• Median age 54 years; 46% men</td>
<td></td>
<td>• Imbalance of patients requiring hospital admission during the index visit included in the primary analysis</td>
</tr>
<tr>
<td>• PCR-confirmed SARS-CoV-2 infection</td>
<td></td>
<td>• More patients with immunosuppression in CP arm (33 [13%]) than in placebo arm (17 [7%])</td>
<td></td>
<td>• Slightly more patients with multiple risk factors, including immunosuppression, in CP arm</td>
</tr>
<tr>
<td>• Aged ≥50 years or aged ≥18 years with ≥1 risk factor for disease progression</td>
<td></td>
<td>• More patients with ≥3 risk factors in CP arm (141 [55%]) than in placebo arm (123 [48%])</td>
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</tr>
<tr>
<td><strong>Key Exclusion Criteria:</strong></td>
<td></td>
<td><strong>Primary Outcomes:</strong></td>
<td></td>
<td></td>
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<tr>
<td>• Need for supplemental oxygen</td>
<td></td>
<td>• 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%).</td>
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<tr>
<td><strong>Interventions:</strong></td>
<td></td>
<td>• 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%]).</td>
<td></td>
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<tr>
<td>• 250 mL high-titer CP (median titer 1:641) (n = 257)</td>
<td></td>
<td><strong>Secondary Outcomes:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Placebo (n = 254)</td>
<td></td>
<td>• 5 patients (1.9%) in CP arm and 1 patient (0.4%) in placebo arm died.</td>
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</tr>
<tr>
<td><strong>Primary Endpoint:</strong></td>
<td></td>
<td>• No difference in scores for illness severity or mean number of hospital-free days between the CP and placebo arms.</td>
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<tr>
<td>• Disease progression, defined as hospital admission, death, or seeking emergency or urgent care within 15 days of randomization</td>
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<td></td>
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</tr>
<tr>
<td><strong>Key Secondary Endpoints:</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Severity of illness (ordinal score)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>• All-cause mortality within 30 days</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>• Hospital-free days over 30 days</td>
<td></td>
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</tbody>
</table>
### Methods

**Retrospective Evaluation of Convalescent Plasma Antibody Levels and the Risk of Death From COVID-19 in the United States**

<table>
<thead>
<tr>
<th>Key Inclusion Criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Severe or life-threatening COVID-19</td>
</tr>
<tr>
<td>• Patients for whom samples of transfused CP were available for retrospective analysis of antibody titer</td>
</tr>
</tbody>
</table>

**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

### Results

<table>
<thead>
<tr>
<th>Participant Characteristics:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 31% aged ≥70 years; 61% men; 48% White, 37% Hispanic/Latinx</td>
</tr>
<tr>
<td>• 61% in ICU; 33% on MV</td>
</tr>
<tr>
<td>• 51% received corticosteroids and 31% received RDV</td>
</tr>
</tbody>
</table>

**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).

### Limitations and Interpretation

**Key Limitation:**

- Lack of untreated control arm

**Interpretation:**

- The study data are not sufficient to establish the efficacy or safety of COVID-19 CP.

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**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\_2/FiO\_2 = 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\_2 = 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: December 16, 2021

- 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.
- For drug interaction information, please refer to product labels and visit the Liverpool COVID-19 Drug Interactions website.
- For the Panel’s recommendations on using the drugs listed in this table, please refer to the Anti-SARS-CoV-2 Monoclonal Antibodies, Therapeutic Management of Nonhospitalized Adults With COVID-19, and Prevention of SARS-CoV-2 Infection sections of the Guidelines.

<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>- Nausea&lt;br&gt;- Dizziness&lt;br&gt;- Pruritis&lt;br&gt;- Hypersensitivity, including anaphylaxis and infusion-related reactions&lt;br&gt;- 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.</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.&lt;br&gt;- Monitor patient during the IV infusion and for ≥1 hour after the infusion is completed.</td>
<td>- Drug-drug interactions are unlikely between BAM plus ETE and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers.</td>
<td>Availability:&lt;br&gt;- Under the FDA EUA, BAM plus ETE is available as treatment for high-risk outpatients with mild to moderate COVID-19 and as PEP for certain high-risk patients.¹ See Anti-SARS-CoV-2 Monoclonal Antibodies and Prevention of SARS-CoV-2 Infection for a list of high-risk conditions and criteria for use of BAM plus ETE.&lt;br&gt;- A list of clinical trials is available: Bamlanivimab Plus Etesevimab&lt;br&gt;</td>
</tr>
</tbody>
</table>

Dose Recommended in EUA for Treatment and PEP of COVID-19 in Adults and Pediatric Patients Weighing ≥40 kg:<br>- BAM 700 mg plus ETE 1,400 mg as a single IV infusion

Doses Recommended in EUA for Treatment and PEP of COVID-19 in Neonates, Infants, Children, and Adolescents Weighing <40 kg:<br>- 1–12 kg: BAM 12 mg/kg plus ETE 24 mg/kg as a single IV infusion

¹ See Anti-SARS-CoV-2 Monoclonal Antibodies and Prevention of SARS-CoV-2 Infection for a list of high-risk conditions and criteria for use of BAM plus ETE.
### Bamlovnivimab Plus Etoslwimab (Anti-SARS-CoV-2 Monoclonal Antibodies), continued

- **>12 kg to 20 kg:** Bamlovnivimab 175 mg plus Etoslwimab 350 mg as a single IV infusion
- **>20 kg to <40 kg:** Bamlovnivimab 350 mg plus Etoslwimab 700 mg as a single IV infusion

### Casirivimab Plus Imdevimab (Anti-SARS-CoV-2 Monoclonal Antibodies)

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

**Dose Recommended in EUA for Treatment and PEP of COVID-19 in Adults and Pediatric Patients Aged ≥12 Years and Weighing ≥40 kg:**
- Casirivimab 600 mg plus Imdevimab 600 mg as a single IV infusion over 1 hour.
- 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.

**Dose Recommended in EUA for PEP for Individuals With Ongoing Exposure to SARS-CoV-2:**
- 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.

### Adverse Events

- Hypersensitivity, including anaphylaxis and infusion-related reactions
- These AEs were observed in multiple trials in which participants received CAS 600 mg plus IMD 600 mg or higher doses of each drug.
- Injection site reactions, including ecchymosis and erythema, in clinical trial participants who received CAS plus IMD administered by SQ injections.

### Monitoring Parameters

- 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 or SQ injections and for ≥1 hour after the infusion or injections are completed.

### Drug-Drug Interaction Potential

- Drug-drug interactions are unlikely between CAS plus IMD and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers.

### Comments and Links to Clinical Trials

- Availability:
  - Under the FDA EUA, CAS plus IMD is available as treatment for high-risk outpatients with mild to moderate COVID-19 and as PEP for certain high-risk individuals. See Anti-SARS-CoV-2 Monoclonal Antibodies and Prevention of SARS-CoV-2 Infection for a list of high-risk conditions and criteria for use of CAS plus IMD.
  - A list of clinical trials is available: Casirivimab Plus Imdevimab
### Sotrovimab (Anti-SARS-CoV-2 Monoclonal Antibody)
*Authorized for the treatment of COVID-19 under FDA EUA.*

<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>Dose Recommended in EUA for Treatment of COVID-19 in Adults and Pediatric Patients Aged ≥12 Years and Weighing ≥40 kg:</strong>&lt;br&gt;• SOT 500 mg administered by IV infusion over 30 minutes</td>
<td>• Rash &lt;br&gt;• Diarrhea &lt;br&gt;• Hypersensitivity, including anaphylaxis and infusion-related reactions</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. &lt;br&gt;• Monitor patient during the IV infusion and for ≥1 hour after the infusion is completed.</td>
<td>• Drug-drug interactions are unlikely between SOT and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers.</td>
<td><strong>Availability:</strong>&lt;br&gt;• Under the FDA EUA, SOT is available for the treatment of high-risk outpatients with mild to moderate COVID-19. See Anti-SARS-CoV-2 Monoclonal Antibodies for a list of high-risk conditions. &lt;br&gt;• A list of clinical trials is available: Sotrovimab</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Dose Recommended in EUA for Treatment of COVID-19:</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>• 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.</td>
<td>• TRALI &lt;br&gt;• TACO &lt;br&gt;• Allergic reactions &lt;br&gt;• Anaphylactic reactions &lt;br&gt;• Febrile nonhemolytic reactions &lt;br&gt;• Hemolytic reactions &lt;br&gt;• Hypothermia &lt;br&gt;• Metabolic complications &lt;br&gt;• Transfusion-transmitted infections&lt;sup&gt;4&lt;/sup&gt; &lt;br&gt;• Thrombotic events &lt;br&gt;• Theoretical risk of antibody-mediated enhancement of infection and suppressed long-term immunity</td>
<td>• 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. &lt;br&gt;• Monitor for transfusion-related reactions. &lt;br&gt;• Monitor patient’s vital signs at baseline and during and after transfusion.</td>
<td>• Drug products should not be added to the IV infusion line for the blood product</td>
<td><strong>Availability:</strong>&lt;br&gt;• The decision to use COVID-19 CP for the treatment of COVID-19 in patients aged &lt;18 years should be based on an individualized assessment of risk and benefit.&lt;sup&gt;5&lt;/sup&gt; &lt;br&gt;• In patients with impaired cardiac function and heart failure, it may be necessary to reduce the CP volume or decrease the transfusion rate. &lt;br&gt;• Under the FDA EUA, high-titer COVID-19 CP is available for hospitalized patients with COVID-19.&lt;sup&gt;6&lt;/sup&gt; See Convalescent Plasma. &lt;br&gt;• A list of clinical trials is available: COVID-19 Convalescent Plasma</td>
</tr>
</tbody>
</table>
Dosing Regimens | Adverse Events | Monitoring Parameters | Drug-Drug Interaction Potential | Comments and Links to Clinical Trials
---|---|---|---|---
### 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.*

<table>
<thead>
<tr>
<th>Dose in Clinical Trials for Treatment of COVID-19:</th>
<th>• Dose varies by clinical trial</th>
<th>• TRALI</th>
<th>• Monitor for transfusion-related reactions.</th>
<th>• Drug products <strong>should not be added</strong> to the IV infusion line for the blood product.</th>
</tr>
</thead>
</table>

**Key:** Key: AE = adverse event; BAM = bamlanivimab; CAS = casirivimab; CP = convalescent plasma; CYP = cytochrome P450; ETE = etesevimab; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; IMD = imdevimab; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PEP = post-exposure prophylaxis; RBC = red blood cell; SOT = sotrovimab; SQ = subcutaneous; TACO = transfusion-associated circulatory overload; TRALI = transfusion-related acute lung injury

### References


### Comments and Links to Clinical Trials

- A list of clinical trials is available: [SARS-CoV-2 Immunoglobulin](https://www.fda.gov/media/145802/download)