## Summary Recommendations

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

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using one of the following anti-SARS-CoV-2 monoclonal antibody regimens (listed alphabetically and not in order of preference) to treat nonhospitalized patients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by the Emergency Use Authorization (EUA) criteria:
  - Bamlanivimab plus etesevimab; or
  - Casirivimab plus imdevimab; or
  - Sotrovimab

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

- The use of bamlanivimab plus etesevimab is recommended in regions where the combined frequency of potentially resistant variants is low (see the EUA fact sheet). For more information on using bamlanivimab plus etesevimab in nonhospitalized patients with mild to moderate COVID-19, please see The Panel's Statement on Bamlanivimab Plus Etesevimab.

- The strength of the evidence for using anti-SARS-CoV-2 monoclonal antibodies for the treatment of COVID-19 varies depending on the factors that place patients at risk for progression to severe COVID-19 and/or hospitalization (see Anti-SARS-CoV-2 Monoclonal Antibodies for details). The recommendations are based on the following criteria from the Food and Drug Administration EUAs:
  - Patients with high-risk conditions that were represented in clinical trials (AIIa), and
  - Patients with other medical conditions and factors that had limited representation in clinical trials (BIII); however, for patients who have an immunocompromising condition or who are receiving immunosuppressive therapy, the rating is AIII.

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

- The use of anti-SARS-CoV-2 monoclonal antibodies 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 monoclonal antibodies 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 have not developed an antibody response or who are not expected to mount an effective immune response to SARS-CoV-2 infection.

### COVID-19 Convalescent Plasma

- The Panel recommends against the use of low-titer COVID-19 convalescent plasma for the treatment of COVID-19 (AIIb). Low-titer COVID-19 convalescent plasma is no longer authorized through the convalescent plasma EUA.

- For hospitalized patients with COVID-19 who do not have impaired immunity:
  - The Panel recommends against the use of COVID-19 convalescent plasma for the treatment of COVID-19 in mechanically ventilated patients (AII).
  - The Panel recommends against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19 in hospitalized patients who do not require mechanical ventilation, except in a clinical trial (AI).

- For hospitalized patients with COVID-19 who have impaired immunity:
  - There is insufficient evidence for the Panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19.
Summary Recommendations, continued

• For nonhospitalized patients with COVID-19:
  • There is insufficient evidence for the Panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19.

Anti-SARS-CoV-2 Specific Immunoglobulin
• 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

The SARS-CoV-2 genome encodes four 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 two 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. Monoclonal antibodies that target the spike protein have been shown to have a clinical benefit in treating SARS-CoV-2 infection (as discussed below). Preliminary data suggest that monoclonal antibodies may play a role in preventing SARS-CoV-2 infection in household contacts of infected patients and during skilled nursing and assisted living facility outbreaks.

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

Three anti-SARS-CoV-2 monoclonal antibody products currently have 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 monoclonal antibodies that bind to different but overlapping epitopes in the spike protein RBD of SARS-CoV-2.
  - The distribution of bamlanivimab plus etesevimab was paused on June 25, 2021, because of concerns about the reduced susceptibility of both the Gamma (P.1) and Beta (B.1.351) variants of concern (VoC) to bamlanivimab and etesevimab. As of September 2, 2021, the use and distribution of these monoclonal antibodies have been resumed in all U.S. states, territories, and jurisdictions.
- **Casirivimab plus imdevimab**: These are recombinant human monoclonal antibodies that bind to nonoverlapping epitopes of the spike protein RBD of SARS-CoV-2.
- **Sotrovimab**: This monoclonal antibody 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 also updated the EUA for casirivimab plus imdevimab as post-exposure prophylaxis 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 the [FDA EUA Fact Sheet](https://www.covid19treatmentguidelines.nih.gov/) for details.

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using one of the following anti-SARS-CoV-2 monoclonal antibody regimens (listed alphabetically and not in order of preference) to treat nonhospitalized patients with mild to moderate COVID-19 who are at high risk of clinical progression (see below for criteria and discussion):
  - **Bamlanivimab plus etesevimab**; or
  - **Casirivimab plus imdevimab**; or
  - **Sotrovimab 500 mg intravenous (IV) infusion**
• When using casirivimab plus imdevimab, the Panel recommends:
  • **Casirivimab 600 mg plus imdevimab 600 mg IV infusion (AIIa)**
    • If IV infusions are not feasible or would cause a delay in treatment, **casirivimab 600 mg plus imdevimab 600 mg** administered by four subcutaneous (SQ) injections (2.5 mL per injection) can be used as an alternative (BIII).
  • The use of bamlanivimab plus etesevimab is recommended in regions where the combined frequency of potentially resistant variants is low (see the EUA fact sheet). For more information on using bamlanivimab plus etesevimab in nonhospitalized patients with mild to moderate COVID-19, please see The Panel’s Statement on Bamlanivimab Plus Etesevimab.
  • When using monoclonal antibodies, treatment should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 antigen or nucleic acid amplification test (NAAT) and within 10 days of symptom onset.
  • The use of anti-SARS-CoV-2 monoclonal antibodies 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 monoclonal antibodies 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 have not developed an antibody response or who are not expected to mount an effective immune response to SARS-CoV-2 infection.

**Rationale for the Use of Anti-SARS-CoV-2 Monoclonal Antibodies**

In randomized, placebo-controlled trials of nonhospitalized patients who had mild to moderate COVID-19 symptoms and certain risk factors for disease progression, the use of anti-SARS-CoV-2 monoclonal antibody 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 \( \text{VoC} \). The potential impact of these variants on susceptibility to different anti-SARS-CoV-2 monoclonal antibodies is discussed below.

**Casirivimab Plus Imdevimab**

On June 3, 2021, the FDA updated the EUA for casirivimab plus imdevimab. The authorized dosages were reduced from a single IV infusion of casirivimab 1,200 mg plus imdevimab 1,200 mg to casirivimab 600 mg plus imdevimab 600 mg. In addition, these lower doses of casirivimab and imdevimab may now be administered by SQ injection if IV infusions are not feasible or may delay treatment. It should be noted that SQ administration requires four injections (2.5 mL per injection) at four 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 study is a double-blind, placebo-controlled randomized trial in outpatients with mild to moderate COVID-19. 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 one or more risk factors for progression to severe COVID-19. The primary outcome of COVID-19-related hospitalization or death from any cause was reported in 7 of 736 participants (1.0%) in the casirivimab 600 mg plus imdevimab 600 mg IV arm and in 24 of 748 participants (3.2%) in the placebo arm (\( P = 0.0024 \)), demonstrating a 2.2% absolute reduction and a 70% relative reduction in hospitalization or death among the casirivimab plus imdevimab recipients compared to the placebo recipients. These results are comparable to the results observed for IV infusions of casirivimab 1,200 mg plus imdevimab 1,200 mg. The primary outcome of COVID-19-related hospitalization or death from any cause was reported in 18
of 1,355 patients (1.3%) who received casirivimab 1,200 mg plus imdevimab 1,200 mg IV, compared with 62 of 1,341 patients (4.6%) who received placebo ($P < 0.0001$). These findings represent a 3.3% absolute reduction and a 71% relative reduction in hospitalization or death among patients who received this dose of casirivimab plus imdevimab.

The recommendation for using SQ injections is based on safety data from the Phase 1 R10933-10987-HV-2093 study (ClinicalTrials.gov Identifier NCT04519437), a double-blind, placebo-controlled randomized trial that 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 participants and in 4% of the 240 placebo participants. According to the FDA EUA, in a separate trial among symptomatic participants, there were similar reductions in viral load between the IV and SQ arms. 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 infusions are not feasible or would lead to a delay in treatment (BIII).

**Sotrovimab**

The data that support the EUA for sotrovimab come 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 among the sotrovimab recipients compared to the placebo recipients.

**Bamlanivimab Plus Etesevimab**

This antibody combination has been shown to have 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). For more information on the use of bamlanivimab plus etesevimab in nonhospitalized patients with mild to moderate COVID-19, please see The Panel’s Statement on Bamlanivimab Plus Etesevimab.

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

The FDA EUAs for the anti-SARS-CoV-2 monoclonal antibodies originally included a list of specific conditions that placed patients at high risk for clinical progression. On May 14, 2021, the FDA broadened 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). There are no longer any age criteria (other than being aged ≥12 years) for using 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 monoclonal antibodies varies depending on the factors that place patients at high risk for progression to severe COVID-19 and/or hospitalization. The recommendations for treatment are based on the following criteria from the FDA EUAs.
Medical Conditions or Other Factors That Were Represented 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 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)

It is important to note that the likelihood of developing severe COVID-19 increases when a person has multiple high-risk conditions or comorbidities. Other factors (e.g., race or ethnicity) or medical conditions may also place individual patients at high risk for progression to severe COVID-19. The current EUAs state that the use of anti-SARS-CoV-2 monoclonal antibodies may be considered for many of these other patients. For additional information on medical conditions and factors that are associated with increased risks for progression to severe COVID-19, see the CDC webpage Extra Precautions: People With Certain Medical Conditions. Health care providers should consider the benefits and risks of using anti-SARS-CoV-2 monoclonal antibodies for each individual patient.

The Panel’s recommendations for using anti-SARS-CoV-2 monoclonal antibodies according to the updated EUA criteria are based on preliminary results from the clinical trials that evaluated these products. The details on the study designs, methods, and follow-up periods for these trials are currently limited. When peer-reviewed data from the Phase 3 trials become publicly available, the Panel will review the results and update the recommendations if necessary.

See the Considerations in Children section below for additional information on using these products in nonhospitalized children with COVID-19.

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 monoclonal antibodies for the following patients:

- Those hospitalized for COVID-19,
• 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.\textsuperscript{11-13}

Anti-SARS-CoV-2 monoclonal antibodies 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, following a prespecified interim futility analysis, enrollment into this study was stopped due to the lack of a clinical benefit.\textsuperscript{14,15}

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; \textit{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 patients (24\%) died in the casirivimab plus imdevimab arm compared to 451 of 1,520 patients (30\%) in the standard of care arm (rate ratio 0.80; 95\% CI, 0.70–0.91; \textit{P} = 0.001).\textsuperscript{16}

It should be noted that this higher dose of casirivimab plus imdevimab is not available through the current EUA, and at this time, casirivimab plus imdevimab is only authorized for use in nonhospitalized patients with COVID-19. In addition, rapid serology testing that can identify seronegative individuals is currently not widely available.

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

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

In laboratory studies, some CDC SARS-CoV-2 VoC or variants of interest (VoI) that harbor certain mutations have markedly reduced susceptibility to a number of the FDA EUA monoclonal antibody therapies.\textsuperscript{17} However, the impact of these mutations on the patient’s clinical response to anti-SARS-CoV-2 monoclonal antibody combinations varies, as do the proportions of these variants in different geographic regions.

Some of the key variants that have been identified are:

• **Alpha (B.1.1.7) variant:** This VoC retains in vitro susceptibility to all the anti-SARS-CoV-2 monoclonal antibodies that are currently available through EUAs.\textsuperscript{5,6}
• **Beta (B.1.351) variant:** This VoC includes the E484K and K417N mutations, which results in a marked reduction in in vitro susceptibility to bamlanivimab and etesevimab.\textsuperscript{5} In vitro studies also suggest that this variant has markedly reduced susceptibility to casirivimab, although the combination of casirivimab and imdevimab appears to retain activity; sotrovimab appears to retain activity as well.\textsuperscript{6,7}
• **Gamma (P.1) variant:** This VoC includes the E484K and K417T mutations, which results in a marked reduction in in vitro susceptibility to bamlanivimab and etesevimab.\(^5,18,19\) This variant also has reduced susceptibility to casirivimab, although the combination of casirivimab and imdevimab appears to retain activity; sotrovimab appears to retain activity as well.\(^6,7\)

• **Delta (B.1.617.2) variant:** This is the predominant VoC in the United States. The Delta variant contains the L452R mutation, which results in a modest decrease in in vitro susceptibility to the combination of bamlanivimab and etesevimab, although the clinical implications of this finding are not fully known. Sotrovimab and casirivimab plus imdevimab appear to retain activity.\(^6,7,20\)

• **Epsilon (B.1.429/B.1.427) variant:** This VoI (also called 20C/CAL.20C) includes the L452R mutation. There appears to be a modest decrease in in vitro susceptibility to the combination of bamlanivimab and etesevimab, although the clinical implications of this finding are not fully known.\(^5\) Sotrovimab and casirivimab plus imdevimab appear to retain activity.\(^6,7,20\)

• **Iota (B.1.526) variant:** This VoI includes the E484K mutation and is associated with a reduced in vitro susceptibility to the combination of bamlanivimab and etesevimab, although the clinical implications of this finding are not fully known.\(^5\) In vitro studies suggest that the E484K mutation may reduce susceptibility to casirivimab, although the combination of casirivimab and imdevimab appears to retain activity; sotrovimab appears to retain activity as well.\(^6,7,20\)

Table A. SARS-CoV-2 Variants of Concern and Interest 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>Bamlanivimab Plus Etesevimab</th>
<th>Casirivimab Plus Imdevimab</th>
<th>Sotrovimab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha</td>
<td>B.1.1.7</td>
<td>VoC</td>
<td>N501Y</td>
<td>No change</td>
<td>Active</td>
<td>No change</td>
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<tr>
<td>Beta</td>
<td>B.1.351</td>
<td>VoC</td>
<td>K417N, E484K, N501Y</td>
<td>Marked change</td>
<td>Unlikely to be active</td>
<td>No change</td>
</tr>
<tr>
<td>Gamma</td>
<td>P.1</td>
<td>VoC</td>
<td>K417T, E484K, N501Y</td>
<td>Marked change</td>
<td>Unlikely to be active</td>
<td>No change</td>
</tr>
<tr>
<td>Delta</td>
<td>B.1.617.2</td>
<td>VoC</td>
<td>L452R</td>
<td>Modest change(^d)</td>
<td>Likely to be active</td>
<td>No change</td>
</tr>
<tr>
<td>Epsilon</td>
<td>B.1.429 / B.1.427</td>
<td>Vol</td>
<td>L452R</td>
<td>Modest change(^d)</td>
<td>Likely to be active</td>
<td>No change</td>
</tr>
<tr>
<td>Iota</td>
<td>B.1.526</td>
<td>Vol</td>
<td>E484K</td>
<td>Modest change(^d)</td>
<td>Likely to be active</td>
<td>No change</td>
</tr>
</tbody>
</table>

\(^a\) Based on the fold reduction in susceptibility reported in the FDA EUAs.\(^5-7\)

\(^b\) Anticipated clinical activity against the variant, based on in vitro studies.

\(^c\) Marked change for casirivimab and no change for imdevimab. The combination of casirivimab plus imdevimab appears to retain activity.

\(^d\) Modest change for the combination of bamlanivimab and etesevimab, although the clinical implications of this finding are not fully known.

**Key:** CDC = Centers for Disease Control and Prevention; VoC = variant of concern; VoI = variant of interest; 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 monoclonal antibodies, will be important in defining the utility of specific monoclonal antibodies 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 monoclonal antibodies in patients with COVID-19. Health care providers are encouraged to discuss participation in anti-SARS-CoV-2 monoclonal antibody clinical trials with patients who have mild to moderate COVID-19.

**SARS-CoV-2 Vaccination**

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

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

**Monitoring**

These anti-SARS-CoV-2 monoclonal antibodies should be given as either IV infusions 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 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 monoclonal antibodies. Rash, diarrhea, nausea, dizziness, and pruritis have also been reported.

**Drug-Drug Interactions**

Drug-drug interactions are unlikely between the authorized anti-SARS-CoV-2 monoclonal antibodies 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 monoclonal antibodies can be considered in 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 monoclonal antibodies, the authorized anti-SARS-CoV-2 monoclonal antibodies would be expected to cross the placenta. There is no pregnancy-specific data on the use of these monoclonal antibodies; however, other IgG products have been safely used in pregnant people when their use is indicated. Therefore, these products 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...
Considerations in Children

Please see Special Considerations in Children for therapeutic recommendations for children.

Drug Availability

Casirivimab plus imdevimab and sotrovimab are available through FDA EUAs. Updates on the distribution of bamlanivimab plus etesevimab are available from the U.S. Department of Health and Human Services Bamlanivimab/Etesevimab website. Efforts should be made to ensure that the communities that are most affected by COVID-19 have equitable access to these monoclonal antibodies.

References

13. Food and Drug Administration. Frequently asked questions on the emergency use authorization of sotrovimab.


### Study Design

Double-blind, Phase 3 RCT in outpatients with mild to moderate COVID-19 (modified full analysis subset of the Phase 3 trial)  

*This is a preliminary report that has not yet been peer reviewed.*

### Methods

- **Key Inclusion Criteria:**  
  - Onset of COVID-19 symptoms ≤ 7 days before randomization  
  - SARS-CoV-2 PCR positive at baseline  
  - Criteria for the modified full analysis:  
    - Aged ≥ 18 years  
    - ≥ 1 risk factor for severe COVID-19  

- **Interventions:**  
  - Single IV infusion of:  
    - CAS 600 mg plus IMD 600 mg  
    - CAS 1,200 mg plus IMD 1,200 mg  
    - Placebo  

- **Endpoint:**  
  - Proportion of patients with COVID-19-related hospitalization or all-cause death through Day 29

### Results

- **Number of Participants:**  
  - CAS 600 mg plus IMD 600 mg (n = 736) vs. placebo (n = 748)  
  - CAS 1,200 mg plus IMD 1,200 mg (n = 1,355) vs. placebo (n = 1,341)  

- **Participant Characteristics:**  
  - Median age was 50 years.  
  - 35% were Hispanic/Latinx and 5% were Black or African American.  
  - Median duration of symptoms prior to enrollment was 3 days (IQR 2–5 days).  

- **Outcomes:**  
  - COVID-19-related hospitalization or all-cause death through Day 29:  
    - 7 of 736 (1.0%) in CAS 600 mg plus IMD 600 mg arm vs. 24 of 748 (3.2%) in placebo arm (P = 0.0024)  
    - 18 of 1,355 (1.3%) in CAS 1,200 mg plus IMD 1,200 mg arm vs. 62 of 1,341 (4.6%) in placebo arm (P < 0.0001)  
  - All-cause deaths:  
    - 1 of 736 (0.1%) in CAS 600 mg plus IMD 600 mg arm vs. 1 of 748 (0.1%) in placebo arm  
    - 1 of 1,355 (0.07%) in CAS 1,200 mg plus IMD 1,200 mg arm vs. 3 of 1,341 (0.22%) in placebo arm

### Limitations and Interpretation

- **Key Limitations:**  
  - The modified full analysis data is only available as a preprint.

- **Interpretation:**  
  - There was a 2.2% absolute reduction and a 70% relative risk reduction in COVID-19-related hospitalizations or all-cause deaths in patients who received CAS 600 mg plus IMD 600 mg compared to those who received placebo.  
  - There was a 3.3% absolute reduction and a 71% relative risk reduction in COVID-19-related hospitalizations and all-cause deaths in patients who received CAS 1,200 mg plus IMD 1,200 mg compared to those who received placebo.
# Sotrovimab Versus Placebo in Outpatients With COVID-19 (COMET-ICE Trial)³

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Methods</th>
<th>Results</th>
<th>Limitations and Interpretation</th>
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<tbody>
<tr>
<td><strong>Double-blind, Phase 1/2/3 RCT in outpatients with mild to moderate COVID-19</strong>&lt;br/&gt;These data are from the FDA EUA for SOT.</td>
<td><strong>Key Inclusion Criteria:</strong>&lt;br/&gt;• Aged ≥18 years with ≥1 comorbidity, or aged ≥55 years regardless of comorbidities&lt;br/&gt;• Onset of COVID-19 symptoms ≤5 days before enrollment&lt;br/&gt;• Laboratory-confirmed SARS-CoV-2 infection</td>
<td><strong>Number of Participants:</strong>&lt;br/&gt;• SOT (n = 291) and placebo (n = 292)</td>
<td><strong>Key Limitations:</strong>&lt;br/&gt;• Details on the study design, follow-up, and methods are limited.&lt;br/&gt;<strong>Interpretation:</strong>&lt;br/&gt;• There was a 6% absolute reduction and an 85% relative risk reduction in all-cause hospitalizations or deaths in patients who received SOT compared to those who received placebo.</td>
</tr>
<tr>
<td><strong>Participant Characteristics:</strong>&lt;br/&gt;• Median age was 53 years; 22% were aged ≥65 years.&lt;br/&gt;• 63% were Hispanic/Latinx and 7% were Black or African American</td>
<td><strong>Primary Outcome:</strong>&lt;br/&gt;• All-cause hospitalization or death by Day 29: 3 of 291 (1%) in SOT arm vs. 21 of 292 (7%) in placebo arm (P = 0.002)</td>
<td><strong>Other Outcomes:</strong>&lt;br/&gt;• 1% of patients in both arms experienced infusion-related reactions</td>
<td><strong>Interventions:</strong>&lt;br/&gt;• SOT 500 mg IV&lt;br/&gt;• Placebo&lt;br/&gt;<strong>Primary Endpoint:</strong>&lt;br/&gt;• Proportion of patients with hospitalization (i.e., ≥24 hours of acute care) or death from any cause by Day 29</td>
</tr>
</tbody>
</table>
**Study Design**
Double-blind, Phase 3 RCT in outpatients with mild to moderate COVID-19 who were at high risk for progressing to severe COVID-19

**Methods**

**Key Inclusion Criteria:**
- Aged ≥12 years
- Not currently hospitalized
- ≥1 mild or moderate COVID-19 symptom
- ≥1 risk factor for severe COVID-19

**Key Exclusion Criteria:**
- \( \text{SpO}_2 \leq 93\% \) on room air, or
- Respiratory rate ≥30 breaths/min, or
- Heart rate ≥125 bpm

**Interventions:**
- Single IV infusion of:
  - BAM 2,800 mg plus ETE 2,800 mg
  - Placebo
- Administered within 3 days of a positive SARS-CoV-2 virologic test

**Primary Endpoint:**
- Proportion of patients with COVID-19-related hospitalization (i.e., ≥24 hours of acute care) or death by any cause by Day 29

**Secondary Endpoint:**
- Proportion of patients with persistently high VL (SARS-CoV-2 level >5.27 \( \log_{10} \) copies/mL) at Day 7

**Number of Participants:**
- BAM plus ETE (n = 518) and placebo (n = 517)

**Participant Characteristics:**
- Mean age was 53.8 years; 31% were aged ≥65 years.
- 48% were men.
- 87% were White; 8% were Black or African American; and 29% were Hispanic/Latinx.
- Median days from symptom onset to infusion was 4 days.
- 77% had mild COVID-19.

**Primary Outcomes:**
- COVID-19-related hospitalization or death by any cause by Day 29: 11 of 518 (2.1%) in BAM plus ETE arm vs. 36 of 517 (7.0%) in placebo arm; relative risk difference: 70%; \( P < 0.001 \)
- Death from any cause by Day 29: 0 of 518 (0%) in BAM plus ETE arm vs. 10 of 517 (1.9%) in placebo arm

**Secondary Outcome:**
- Proportion of patients with persistently high VLs at Day 7: 9.8% in BAM plus ETE arm vs. 29.5% in placebo arm (\( P < 0.001 \)).

**Limitations and Interpretation**

**Key Limitations:**
- Data are for BAM plus ETE doses that are not currently authorized in the EUA.

**Interpretation:**
- There was a 4.8% absolute reduction and a 70% relative reduction in COVID-19-related hospitalizations or deaths from any cause among the participants who received BAM plus ETE compared to those who received placebo.

**Key:**
- BAM = bamlanivimab; CAS = casirivimab; ETE = etesevimab; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; IMD = imdevimab; IV = intravenous; PCR = polymerase chain reaction; RCT = randomized controlled trial; SOT = sotrovimab; \( \text{SpO}_2 \) = oxygen saturation; VL = viral load
References


Convalescent Plasma

Last Updated: April 21, 2021

Plasma from donors who have recovered from COVID-19 may contain antibodies to SARS-CoV-2 that may help suppress the virus and modify the inflammatory response. The Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for convalescent plasma for the treatment of certain hospitalized patients with COVID-19.

Recommendation

  - Low-titer COVID-19 convalescent plasma is no longer authorized through the convalescent plasma EUA.

For Hospitalized Patients With COVID-19 Who Do Not Have Impaired Immunity

- The Panel recommends against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19 in hospitalized patients who do not require mechanical ventilation, except in a clinical trial (A1).

For Hospitalized Patients With COVID-19 Who Have Impaired Immunity

- There is insufficient evidence for the Panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19.
  - Observational data including data from case reports, case series, and a retrospective case control study suggest a benefit of COVID-19 convalescent plasma in patients with various primary and secondary humoral immunodeficiencies.
  - Several case reports indicate that patients with impaired humoral immunity may experience persistent SARS-CoV-2 viral replication and therefore, may be at risk for developing viral resistance to SARS-CoV-2 antibodies after treatment with COVID-19 convalescent plasma.
  - High-titer convalescent plasma is authorized under the EUA for the treatment of hospitalized patients with COVID-19 and impaired immunity.

For Nonhospitalized Patients With COVID-19

- There is insufficient evidence for the Panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19 in patients who are not hospitalized, except in a clinical trial.
  - Convalescent plasma is not authorized for nonhospitalized patients with COVID-19 under the EUA.
  - 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.
Rationale for Recommendation

On August 23, 2020, the FDA issued an EUA for convalescent plasma for the treatment of hospitalized patients with COVID-19 based on retrospective, indirect evaluations of efficacy generated from a large Expanded Access Program (EAP). The EAP allowed for the use of convalescent plasma regardless of titer. 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.

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 the disease course or hospitalized patients who have impaired humoral immunity.

Use of Convalescent Plasma in Hospitalized Patients With COVID-19 and Without Impaired Humoral Immunity

An updated retrospective analysis of data collected through the EAP indicated that patients who received high-titer plasma had a lower relative risk of death within 30 days after transfusion than patients who received low-titer plasma (relative risk 0.82; 95% CI, 0.67–1.00).20

- Among the patients who were on mechanical ventilation before transfusion, no effect of high-titer plasma versus low-titer plasma was observed (relative risk 1.02; 95% CI, 0.78–1.32).
- Among the patients who were not on mechanical ventilation before transfusion, mortality was lower among patients who received high-titer plasma than among those who received low-titer plasma (relative risk 0.66; 95% CI, 0.48–0.91).20

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is an open-label, randomized controlled platform trial evaluating potential treatments for COVID-19. In the convalescent plasma portion of the trial, 11,558 patients were randomized to receive either convalescent plasma (n = 5,795) or usual care (n = 5,763) before enrollment was stopped due to futility.21

The trial results demonstrated no significant differences in the primary endpoint of 28-day mortality between the convalescent plasma arm (24%) and the usual care arm (24%; risk ratio 1.00; 95% CI, 0.93–1.07). Additionally, the trial did not meet its two secondary endpoints: time to hospital discharge and, for those not on mechanical ventilation at randomization, receipt of invasive mechanical ventilation or death. The proportion of patients discharged within 28 days was similar in the convalescent plasma arm and the usual care arm (66% vs. 67%; rate ratio 0.98; 95% CI, 0.94–1.03). Among those not requiring invasive mechanical ventilation at baseline, the proportion of those progressing to invasive mechanical ventilation or death was also similar in the convalescent plasma arm and the usual care arm (28% vs. 29%; risk ratio 0.99; 95% CI, 0.93–1.05). The 28-day mortality rate ratio was similar in all prespecified patient subgroups, including in those patients without detectable SARS-CoV-2 antibodies at randomization (32% in the convalescent plasma arm vs. 34% in the usual care arm; rate ratio 0.94; 95% CI, 0.84–1.06). Subgroup analyses suggested a slight trend towards benefit of convalescent plasma in certain subgroups (e.g., those with symptom onset ≤7 days, no requirement for supplemental oxygen at baseline, no concomitant use of corticosteroids). See Table 3b for additional details.

Data from several other randomized clinical trials, all of which were underpowered, have not demonstrated the efficacy of convalescent plasma for the treatment of hospitalized patients with COVID-19.22-29 See Table 3b for details.

Additionally, two large, randomized trials evaluating convalescent plasma in hospitalized patients have been paused or have limited enrollment due to futility.
The CONvalescent Plasma for Hospitalized Adults With COVID-19 Respiratory Illness (CONCOR-1) trial, which evaluated convalescent plasma versus usual care, was stopped after an interim analysis of 614 patients met the predefined threshold for futility.\textsuperscript{30}

The Randomised, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP), which evaluated convalescent plasma in hospitalized patients, paused enrollment for patients in intensive care units after a preliminary analysis that included 912 participants indicated that convalescent plasma was unlikely to benefit this patient group.\textsuperscript{31} REMAP-CAP continues to recruit hospitalized patients who do not require intensive care support into the trial’s convalescent plasma evaluation domain.

Results from 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 hospitalized patients with COVID-19 who do not have impaired humoral immunity.

**Use of Convalescent Plasma in Hospitalized Patients With COVID-19 and Impaired Humoral Immunity**

Data from case reports, case series, and a retrospective case-control study suggest a benefit of convalescent plasma in patients with primary and secondary humoral immunodeficiencies, including patients with hematologic malignancy, common variable immune deficiency, and agammaglobulinemia, and those who have received a transplanted solid organ.\textsuperscript{2,13,15,16} Several case reports indicate that patients with impaired humoral immunity may experience persistent SARS-CoV-2 viral replication and, therefore, may be at risk for developing viral resistance to SARS-CoV-2 antibodies after treatment with convalescent plasma.

Results from 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.\textsuperscript{17-19}

**Use of Convalescent Plasma in Nonhospitalized Patients With COVID-19**

Current data are insufficient to establish the safety or efficacy of convalescent plasma in outpatients with COVID-19.

- Data from a double-blind, placebo-controlled randomized trial of high-titer convalescent plasma in elderly outpatients with <72 hours of mild COVID-19 symptoms suggested a potential for benefit.\textsuperscript{32} However, the trial included relatively few participants, and only a small number of clinical events related to COVID-19 occurred. See \textit{Table 3b} for details.
- The Clinical Trial of COVID-19 Convalescent Plasma of Outpatients (C3PO) evaluated convalescent plasma for the treatment of nonhospitalized patients with ≤7 days of mild or moderate COVID-19 symptoms and at least one risk factor for severe COVID-19. The trial was halted after an interim analysis indicated no benefit of convalescent plasma for this group of patients. The trial enrolled 511 of the planned 900 participants before the study was halted.

Convalescent plasma is not authorized for nonhospitalized patients with COVID-19 under the EUA.

**Clinical Data to Date**

\textit{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. Pathogen-specific immunoglobulins 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. Some ongoing clinical trials that are evaluating COVID-19 convalescent plasma include pregnant individuals.

Considerations in Children

The safety and efficacy of COVID-19 convalescent plasma have not been evaluated in pediatric patients outside of evaluations described in single-center reports. Clinical trials of COVID-19 convalescent plasma in children are ongoing. There is insufficient evidence for the Panel to recommend either for or against the use of convalescent plasma for the treatment of COVID-19 in hospitalized children who do not require mechanical ventilation. The Panel recommends against the use of convalescent plasma for the treatment of COVID-19 in mechanically ventilated pediatric patients (AIII). In consultation with a pediatric infectious disease specialist, high-titer convalescent plasma may be considered on a case-by-case basis for children with COVID-19 who meet the EUA criteria.

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.

The Panel recommends consulting a transfusion medicine specialist when considering convalescent plasma for patients with a history of severe allergic or anaphylactic transfusion reactions.

Product Availability

On February 4, 2021, the FDA revised the convalescent plasma EUA to limit the authorization to high-titer COVID-19 convalescent plasma.

- The revised EUA Letter of Authorization provides an expanded list of anti-SARS-CoV-2 antibody tests and corresponding qualifying results that may be used to determine the suitability of donated convalescent plasma.
- Please refer to the FDA’s Recommendations for Investigational COVID-19 Convalescent Plasma webpage for guidance on the transfusion of investigational convalescent plasma while blood establishments develop the necessary operating procedures to manufacture COVID-19 convalescent plasma in accordance with the Conditions of Authorization described in the EUA.

Clinical Trials

Randomized clinical trials that are 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: April 21, 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.

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Methods</th>
<th>Results</th>
<th>Limitations and Interpretation</th>
</tr>
</thead>
</table>
| Convalescent Plasma in Hospitalized Patients With COVID-19 (RECOVERY Trial)
| Open-label, platform RCT evaluating potential treatments, including high-titer CP, in hospitalized patients with COVID-19 in the United Kingdom (n = 11,558)
| This is a preliminary report that has not yet been peer reviewed. |
| **Key Inclusion Criteria:**
| • Clinically suspected or laboratory-confirmed SARS-CoV-2 infection
| • CP available at study site
| **Key Exclusion Criteria:**
| • CP contraindicated (e.g., known allergy to blood components)
| **Interventions:**
| • One 275 mL (+/- 75 mL) unit of CP immediately and another unit the next day (≥12 hours after the first unit)
| • CP was selected by sample to cut-off IgG SARS-CoV-2 spike protein ratio ≥6.0.
| • Usual care
| **Primary Endpoint:**
| • All-cause mortality at Day 28
| **Secondary Endpoints:**
| • Time to hospital discharge
| • Among patients not receiving IMV at randomization, receipt of IMV or death by Day 28
| **Number of Participants:**
| • ITT analysis: CP (n = 5,795) and usual care (n = 5,763)
| **Participant Characteristics:**
| • Mean age was 63.5 years.
| • 63% of patients in the CP arm and 66% in the usual care arm were men.
| • 5% of patients in each arm were on IMV.
| • At baseline, 52% of the patients in the CP arm and 48% in the usual care arm were SARS-CoV-2 antibody seropositive.
| • 93% of the patients in the CP arm and 92% in the usual care arm received corticosteroids.
| **Outcomes:**
| • No difference in 28-day mortality between the CP arm and the usual care arm (24% vs. 24%; rate ratio 1.00; 95% CI, 0.93–1.07).
| • No difference in the proportion of patients discharged within 28 days (66% in CP arm vs. 67% in usual care arm; rate ratio 0.98; 95% CI, 0.94–1.03; P = 0.50).
| • 28-day mortality rate ratio was consistent across prespecified patient subgroups, including subgroups by SARS-CoV-2 antibody presence at randomization. In particular, among patients without detectable SARS-CoV-2 antibodies, there was no evidence of a mortality difference between those who received CP and those who received usual care (32% vs. 34%; rate ratio 0.94; 95% CI, 0.84–1.06).
| • Among those not receiving IMV at baseline, the percentage of patients who progressed to IMV or died was similar in the CP arm and the usual care arm (28% vs. 29%; rate ratio 0.99; 95% CI, 0.93–1.05; P = 0.79).
| • Severe allergic reactions were rare (occurred in 16 patients in the CP arm and 2 in the usual care arm).
| **Limitations:**
| • The study was not blinded.
| • >90% of participants received corticosteroids. There is uncertainty about the effect of CP in hospitalized patients who do not require supplemental oxygen and for whom corticosteroids are not recommended.
| **Interpretation:**
| • The trial did not demonstrate a benefit of CP in hospitalized patients with COVID-19.
## Study Design

<table>
<thead>
<tr>
<th>Convalescent Plasma in Hospitalized Adults With COVID-19 (PLACID Trial)²</th>
<th>Key Inclusion Criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multicenter, open-label, Phase 2 RCT in hospitalized adults with severe COVID-19 in India (n = 464)</td>
<td>• Aged ≥18 years</td>
</tr>
<tr>
<td></td>
<td>• Positive SARS-CoV-2 RT-PCR</td>
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<tr>
<td></td>
<td>• PaO₂/FiO₂ = 200–300 mm Hg or respiratory rate &gt;24 breaths/min with SpO₂ ≤93% on room air</td>
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<tr>
<td></td>
<td>• Critical illness</td>
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<tr>
<td></td>
<td>• 2 doses of 200 mL CP, transfused 24 hours apart</td>
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<tr>
<td></td>
<td>• SOC</td>
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<td></td>
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<tr>
<td></td>
<td>• Composite of progression to severe disease (defined as PaO₂/FiO₂ &lt;100 mm Hg) any time within 28 days of enrollment or all-cause mortality at 28 days</td>
</tr>
</tbody>
</table>

### Methods

**Number of Participants:**
- CP (n = 235) and SOC (n = 229)

**Participant Characteristics:**
- Median age was 52 years.
- 75% of participants in the CP arm and 77% in the SOC arm were men.
- Higher prevalence of diabetes in the CP arm (48%) than in SOC arm (38%).

**Outcomes:**
- No difference between the arms in the primary outcome of progression to severe disease or death (occurred in 18.7% of participants in CP arm and 17.9% in SOC arm).
- A post hoc analysis evaluating outcomes among patients without detectable SARS-CoV-2 neutralizing antibody titers at baseline also revealed no benefit of CP.

### Limitations and Interpretation

**Limitations:**
- The study was not blinded.
- SARS-CoV-2 antibody testing was not used to select donated CP units; therefore, many participants may have received CP units with low titers of SARS-CoV-2 neutralizing antibodies.

**Interpretation:**
- This trial did not demonstrate a benefit of CP in hospitalized patients with severe COVID-19.

## Convalescent Plasma in COVID-19 Severe Pneumonia (PlasmAr Study)³

| Convalescent Plasma in COVID-19 Severe Pneumonia (PlasmAr Study)³ |
|---|---|
| Double-blind, placebo-controlled, multicenter RCT in hospitalized adults with severe COVID-19 in Argentina (n = 333) | Key Inclusion Criteria: |
| | • Aged ≥18 years |
| | • Positive SARS-CoV-2 RT-PCR |
| | • Severe COVID-19 |
| | | Key Exclusion Criteria: |
| | • Critical illness |
| | | Interventions 2:1 Randomization: |
| | • Single dose (median volume |

### Methods

**Number of Participants:**
- CP (n = 228) and placebo (n = 105)

**Participant Characteristics:**
- Median age was 62 years.
- 67.6% of the participants were men.
- 64.9% of the participants had a coexisting condition at trial entry.
- Median time from symptom onset to enrollment was 8 days.
- Of 215 participants tested, 46% had no detectable SARS-CoV-2 antibodies at baseline. Median SARS-CoV-2 antibody titer in both the CP arm and placebo arm was 1:50.

### Limitations

**Limitations:**
- The majority of participants in both arms received concomitant glucocorticoid treatment, potentially masking subtle differences in clinical outcomes between the study arms.
### Convalescent Plasma in COVID-19 Severe Pneumonia (PlasmAr Study)\(^3\), continued

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Methods</th>
<th>Results</th>
<th>Limitations and Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 mL of CP pooled from 2–5 donors. Only plasma units with a SARS-CoV-2 viral spike-RBD IgG titer ≥1:800 were transfused.</td>
<td>Outcomes:</td>
<td>Interpretation:</td>
<td></td>
</tr>
<tr>
<td>• Placebo</td>
<td>• No significant differences between the arms in the distribution of outcomes according to the categories on the 6-point ordinal scale (OR 0.83; 95% CI, 0.52–1.35).</td>
<td>• This trial did not demonstrate a benefit of CP in hospitalized patients with severe COVID-19.</td>
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</tr>
<tr>
<td>Primary Endpoint:</td>
<td>• 30-day mortality was similar in CP arm (11.0%) and placebo arm (11.4%).</td>
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<tr>
<td>• Change in clinical status 30 days after intervention measured using a 6-point ordinal scale</td>
<td>• Infusion-related AEs were more frequent in the CP arm than in the placebo arm (occurred in 4.8% vs. 1.9% of participants).</td>
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</tr>
</tbody>
</table>

### Convalescent Plasma in Adults With Severe COVID-19\(^4\)

<table>
<thead>
<tr>
<th>Key Inclusion Criteria:</th>
<th>Number of Participants:</th>
<th>Limitations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Aged ≥18 years</td>
<td>• CP (n = 150) and normal control plasma (n = 73)</td>
<td>• The intervention in the control group arm was blood plasma without SARS-CoV-2 antibodies. This ensured blinded administration; however, because the trial was not placebo controlled; it is not possible to identify potential harm due to plasma infusion.</td>
</tr>
<tr>
<td>• COVID-19 pneumonia</td>
<td>• Enrollment initiated in New York City in April 2020 and in Brazil in August 2020</td>
<td>• Low sample size and number of events</td>
</tr>
<tr>
<td>• (\text{SpO}_2) ≤94% on room air or requirement for supplemental oxygen, IMV, or ECMO</td>
<td>Participant Characteristics:</td>
<td>• There were imbalances in baseline characteristics between the study arms that may have impacted study outcomes. After adjustment for the imbalances, the</td>
</tr>
<tr>
<td>Key Exclusion Criteria:</td>
<td>• Median age was 61 years.</td>
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<tr>
<td>• &gt;5 days on IMV or ECMO</td>
<td>• 66% of the participants were men.</td>
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<tr>
<td>• Severe multiorgan failure</td>
<td>• Median duration of symptoms prior to randomization was 9 days.</td>
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<tr>
<td>Interventions</td>
<td>• 57% of the participants required supplemental oxygen at baseline, 25% required high-flow oxygen or noninvasive ventilation, and 13% required IMV or ECMO.</td>
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<tr>
<td>2:1 Randomization:</td>
<td>• There were some imbalances between the study arms at baseline. The CP arm included more women; the participants were younger and had slightly longer symptom durations.</td>
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<tr>
<td>• Single dose of SARS-CoV-2 CP (approximately 250 mL). Only units with a SARS-CoV-2 viral spike-RBD IgG titer ≥1:400 were transfused.</td>
<td>• 81% of the participants received corticosteroids.</td>
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</tr>
<tr>
<td>• Non-SARS-CoV-2 plasma (normal control plasma)</td>
<td>Outcomes:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No difference in clinical status on Day 28 was observed between the CP arm and the control arm (OR 1.5 for being in a better category with CP vs. control plasma; 95% CI, 0.83–2.68; (P = 0.18)).</td>
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</tr>
<tr>
<td></td>
<td>• 30-day mortality was similar in CP arm (11.0%) and placebo arm (11.4%).</td>
<td></td>
</tr>
</tbody>
</table>

*This is a preliminary report that has not yet been peer reviewed.*
### Study Design

**Primary Endpoint:**
- Clinical status on Day 28, measured using an ordinal scale (initially with 7 categories, but modified to 6).

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

### Methods

- In-hospital mortality was lower in the CP arm (13%) than in the control arm (25%; HR 0.44; 95% CI, 0.22–0.91; \( P = 0.034 \)). The treatment difference was not significant after adjustment for age, sex, and duration of symptoms at baseline.
- In both arms, mortality at 28 days was the same as in-hospital mortality.
- Time to oxygen discontinuation and time to hospital discharge were similar between the arms.
- 25.5% of patients in the CP arm vs. 36.1% in the control arm experienced SAEs.

### Results

- In-hospital mortality was lower in the CP arm (13%) than in the control arm (25%; HR 0.44; 95% CI, 0.22–0.91; \( P = 0.034 \)). The treatment difference was not significant after adjustment for age, sex, and duration of symptoms at baseline.
- In both arms, mortality at 28 days was the same as in-hospital mortality.
- Time to oxygen discontinuation and time to hospital discharge were similar between the arms.
- 25.5% of patients in the CP arm vs. 36.1% in the control arm experienced SAEs.

### Limitations and Interpretation

- Difference in mortality between the arms was not significant.
- The treatment difference in the primary outcome (clinical status on Day 28) was not statistically significant; mortality was a secondary outcome.
- There were no subgroup analyses for mortality.

**Interpretation:**

- Although the difference between the CP arm and the non-SARS-CoV-2 antibody plasma arm for the primary outcome of clinical status on Day 28 was not statistically significant, the lower 28-day mortality in the CP arm suggests a potential benefit of CP in hospitalized patients with severe COVID-19.
<table>
<thead>
<tr>
<th>Study Design</th>
<th>Methods</th>
<th>Results</th>
<th>Limitations and Interpretation</th>
</tr>
</thead>
</table>
| Early High-Titer Plasma Therapy to Prevent Severe COVID-19 in Older Adults<sup>5</sup> | Double-blind, placebo-controlled RCT in outpatients with mild COVID-19 in Argentina (n = 160) | Key Inclusion Criteria:  
- Aged >75 years or aged 65–74 years with ≥1 coexisting condition  
- Outpatient with <72 hours of mild COVID-19 symptoms  
Key Exclusion Criteria:  
- Severe respiratory disease  
Interventions:  
- Single 250 mL dose of CP with an IgG titer against SARS-CoV-2 spike protein of >1:1000  
- Placebo  
Primary Endpoint:  
- Severe respiratory disease defined as a respiratory rate ≥30 breaths/min and/or SpO<sub>2</sub> <93% on room air by Day 15 | Number of Participants:  
- ITT analysis: CP (n = 80) and placebo (n = 80)  
Participant Characteristics:  
- Mean age was 77 years.  
- Most of the patients had comorbidities.  
Outcomes:  
- 13 of 80 patients (16%) in the CP arm and 25 of 80 (31%) in the placebo arm experienced severe respiratory disease by Day 15 (relative risk 0.52; 95% CI, 0.29–0.94; P = 0.026).  
- 2 participants in the CP arm and 5 in the placebo arm died.  
- No solicited AEs were reported. | Limitations:  
- The trial was terminated early because cases of COVID-19 at the study site decreased.  
- The trial included relatively few participants.  
Interpretation:  
- This trial demonstrated a benefit of CP in elderly outpatients with <72 hours of mild COVID-19 symptoms. |
| Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-Threatening COVID-19<sup>6</sup> | Multicenter, open-label, randomized trial in hospitalized adults with severe or life-threatening COVID-19 in China (n = 103) | Key Inclusion Criteria:  
- Aged ≥18 years  
- Positive SARS-CoV-2 PCR within 72 hours of randomization  
- Met study definition of severe or life-threatening COVID-19 | Number of Participants:  
- CP (n = 52) and SOC (n = 51)  
Participant Characteristics:  
- Median age was 70 years.  
- 58.3% of the participants were men.  
Outcomes:  
- No significant difference in time to clinical improvement between the CP arm and the control arm (HR 1.40; 95% CI, 0.79–2.49; P = 0.26).  
- No significant difference in mortality between the CP arm (16%) and the control arm (24%; P = 0.30). | Limitations:  
- The study was not blinded.  
- The trial was stopped early because of decreasing numbers of cases of COVID-19 at the study site; therefore, the study lacked sufficient power to detect differences in clinical outcomes. |
<table>
<thead>
<tr>
<th>Study Design</th>
<th>Methods</th>
<th>Results</th>
<th>Limitations and Interpretation</th>
</tr>
</thead>
</table>
| Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-Threatening COVID-19<sup>6</sup>, continued | **Key Exclusion Criteria:**  
• Baseline RBD-specific IgG antibody ≥1:64  
• Certain sequelae of severe COVID-19 (e.g., severe septic shock, severe heart failure)  
**Interventions:**  
• Single 4–13 mL/kg dose of CP. Only CP units with a SARS-CoV-2 viral spike-RBD-specific IgG titer of ≥1:640 were transfused.  
• SOC  
**Primary Endpoint:**  
• Time to clinical improvement (patient discharge or a reduction of 2 points on a 6-point disease severity scale; 6 points = death, 1 point = hospital discharge) within 28 days. | • Only 103 of 200 planned participants were randomized to receive treatment.  
• CP was administered late (approximately 1 month) into disease course.  
**Interpretation:**  
• This trial did not demonstrate a benefit of CP in hospitalized patients with severe or life-threatening COVID-19. |

| Early Versus Deferred Anti-SARS-CoV-2 Convalescent Plasma in Hospitalized Patients With COVID-19<sup>7</sup> | **Key Inclusion Criteria:**  
• Aged ≥18 years  
• ≤7 days of COVID-19 symptoms  
• High risk of progression to respiratory failure  
**Key Exclusion Criteria:**  
• PaO<sub>2</sub>/FiO<sub>2</sub> <200 mm Hg  
• Mechanical ventilation  
**Number of Participants:**  
• Immediate CP (n = 28) and deferred CP (n = 30)  
**Participant Characteristics:**  
• Median age was 66 years.  
• 50% of the participants were men.  
• Median interval between symptom onset and randomization was 6 days.  
• 13 of 28 participants (43%) in the deferred CP arm received CP at a median of 3 days after enrollment. | **Limitations:**  
• The study was not blinded.  
• Small sample size.  
**Interpretation:**  
• This trial did not demonstrate a benefit of immediate vs. deferred administration of CP in hospitalized COVID-19 patients with ≤7 days of COVID-19 symptoms. |
### Study Design

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Outcomes:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immediate CP:</strong></td>
<td>• There was no difference between the arms in the percentage of participants who met the primary composite endpoint of death, mechanical ventilation, or &gt;14 days hospitalization (32% in immediate CP arm vs. 33% in deferred CP arm; OR 0.95; 95% CI, 0.32–2.84).</td>
</tr>
<tr>
<td>• Two 400 mL doses of CP with anti-SARS-CoV-2 neutralizing antibody titers ≥1:400, transfused 24 hours apart</td>
<td>• 18% of participants in the immediate CP arm vs. 7% in the deferred CP arm died within 30 days (OR 3.0; 95% CI, 0.5–17.2; P = 0.25).</td>
</tr>
<tr>
<td><strong>Deferred CP:</strong></td>
<td></td>
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<tr>
<td>• CP transfusion only if PaO\textsubscript{2}/FiO\textsubscript{2} &lt;200 mm Hg, or if participant still required hospitalization for COVID-19 symptoms 7 days after enrollment</td>
<td></td>
</tr>
</tbody>
</table>

**Primary Endpoint:**

• Composite of mechanical ventilation, hospitalization >14 days, or in-hospital death

### Limitations and Interpretation

- The study was not blinded.
- Trial halted early by the investigators when the baseline SARS-CoV-2 neutralizing antibody titers of participant plasma and CP were found to be comparable, challenging the potential benefit of CP for the study population. Thus, the study lacked sufficient power to detect differences in clinical outcomes between the study arms.

### Convalescent Plasma for COVID-19 (ConCOVID trial)

- Multicenter, open-label, RCT in hospitalized adults with COVID-19 in the Netherlands (n = 86)
  - This is a preliminary report that has not yet been peer reviewed.

**Key Inclusion Criteria:**

• Aged ≥18 years
• Clinical disease with positive SARS-CoV-2 RT-PCR within 96 hours of enrollment

**Key Exclusion Criteria:**

• Mechanical ventilation for >96 hours

**Interventions:**

• One to two 300 mL doses of CP with anti-SARS-CoV-2 neutralizing antibody titers ≥1:80
• SOC

**Number of Participants:**

• CP (n = 43) and SOC (n = 43)

**Participant Characteristics:**

• Median age was 63 years.
• Most of the participants were men.

**Outcomes:**

• No differences in mortality (P = 0.95), length of hospital stay (P = 0.68), or disease severity at Day 15 (P = 0.58) were observed between the study arms.
<table>
<thead>
<tr>
<th>Study Design</th>
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<th>Results</th>
<th>Limitations and Interpretation</th>
</tr>
</thead>
</table>
| Convalescent Plasma for COVID-19 (ConCOVID trial)², continued | | | • Only 86 of 426 planned participants were randomized to receive CP or SOC.  
Interpretation:  
• This trial did not demonstrate a benefit of COVID-19 CP in hospitalized patients. |
| Primary Endpoint:  
• Day-60 mortality | | | |
| | | | |
| Convalescent Plasma for COVID-19 (ConPlas-19 Study)⁹ | Multicenter, open-label, RCT in hospitalized adults with COVID-19 in Spain (n = 81)  
This is a preliminary report that has not yet been peer reviewed. | Key Inclusion Criteria:  
• Aged ≥18 years  
Key Exclusion Criteria:  
• Receiving IMV, noninvasive ventilation, or high-flow oxygen  
Interventions:  
• Single dose of 250–300 mL of CP plus SOC.  
• All administered units had neutralizing antibodies (VMNT-ID50: all titers >1:80, median titer 1:292, IQR 238–451; pseudovirus neutralizing ID50 assay: median titer 1:327; IQR 168–882)  
• SOC alone  
Primary Endpoint:  
• Proportion of patients in ordinal scale categories 5, 6, or 7 at Day 15. | Number of Participants:  
• CP (n = 38) and SOC (n = 43)  
Participant Characteristics:  
• Mean age was 59 years.  
• At baseline, 49% of the participants were SARS-CoV-2 antibody positive.  
Outcomes:  
• 0 of 38 participants (0%) in the CP arm progressed to ordinal scale categories 5–7 vs. 6 of 43 participants (14.0%) in the SOC arm (P = 0.57, not statistically significant according to the planned analysis; but P = 0.03 using Fisher test as a post hoc sensitivity analysis given small numbers and the by-center heterogenous distribution).  
• 0 of 38 participants (0%) in the CP arm died vs. 4 of 43 (9.3%) in the SOC arm (P = 0.06). | Limitations:  
• The study was not blinded.  
• The trial was stopped early because of decreasing numbers of COVID-19 cases at the study site and, thus, the study lacked sufficient power to detect differences in clinical outcomes.  
• Only 81 of planned 278 participants were enrolled.  
Interpretation:  
• Although the results did not reach statistical significance and only a small number of clinical events related to COVID-19 occurred, these results suggest a potential benefit of CP in hospitalized patients who are not receiving high-flow oxygen, noninvasive ventilation, or invasive ventilation. |
## Clinical and Immunological Benefits of Convalescent Plasma Therapy in Severe COVID-19

**Study Design:** Single-center, open-label, RCT in hospitalized adults with COVID-19 and ARDS in India (n = 80)

*This is a preliminary report that has not yet been peer reviewed.*

**Methods:**

**Key Inclusion Criteria:**
- Evidence of ARDS (defined as \( \text{PaO}_2/\text{FiO}_2 \) 100–300 mm Hg)
- Not on mechanical ventilation

**Key Exclusion Criteria:**
- Mechanical ventilation

**Intervention:**
- 2 consecutive doses of ABO-matched 200 mL CP, 1 day apart
- SOC alone

**Primary Endpoint:**
- All-cause mortality at Day 30

**Results:**

**Number of Participants:**
- CP (n = 40) and SOC (n = 40)

**Participant Characteristics:**
- Mean age was 61 years.
- 71% of the participants were men.
- No difference in mean number of days of hospitalization at enrollment between the CP arm (4.2 days) and the SOC arm (3.9 days).

**Outcomes:**
- 10 of 40 participants (25%) in the CP arm had died by Day 30 vs. 14 of 40 (35%) in the SOC arm.
- Difference in survival between the arms was not statistically significant (HR 0.6731; 95% CI, 0.3010–1.505).

**Limitations and Interpretation:**
- The study was not blinded.
- The study lacked sufficient power to detect differences in clinical outcomes between the study arms.

**Interpretation:**
- This trial did not demonstrate a benefit of CP in hospitalized patients with mild to moderate ARDS who are not receiving mechanical ventilation.

## Convalescent Plasma Therapy Versus Standard Therapy in Patients With Severe COVID-19

**Study Design:** Open-label, RCT in hospitalized adults with COVID-19 in Bahrain (n = 40)

*This is a preliminary report that has not yet been peer reviewed.*

**Methods:**

**Key Inclusion Criteria:**
- Aged \( \geq 21 \) years
- Radiologic evidence of pneumonia
- Requirement for oxygen therapy for COVID-19

**Key Exclusion Criteria:**
- Requirement for IMV, noninvasive ventilation, or high-flow oxygen

**Interventions:**
- Two 200 mL transfusions of CP over 24 hours
- SOC alone

**Primary Endpoint:**
- Requirement for IMV or noninvasive ventilation

**Results:**

**Number of Participants:**
- CP (n = 20) and SOC (n = 20)

**Participant Characteristics:**
- Mean age was 53 years in the CP arm and 51 years in the SOC arm.
- 75% of the participants were men (75%) in the CP arm and 85% in the SOC arm.

**Outcomes:**
- 6 patients in the SOC arm and 4 patients in the CP arm required mechanical ventilation (risk ratio 0.67; 95% CI, 0.22–2.0; \( P = 0.72 \)).
- 2 patients in the SOC arm died vs. 1 in the CP arm.

**Limitations:**
- The study was not blinded.
- The study lacked sufficient power to detect differences in clinical outcomes between the study arms.

**Interpretation:**
- This trial did not demonstrate a benefit of CP in hospitalized patients who are not receiving high-flow oxygen, noninvasive ventilation, or invasive ventilation.
### Study Design

**Convalescent Plasma Therapy Versus Standard Therapy in Patients With Severe COVID-19**

- In patients who require ventilation, duration of ventilation

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**Convalescent Plasma Antibody Levels and the Risk of Death from COVID-19**

**Retrospective, indirect evaluation of a subset of patients from the Mayo Clinic COVID-19 CP EAP (n = 3,082). More than 100,000 patients hospitalized with COVID-19 in the United States received CP through the Mayo Clinic EAP.**

**Key Inclusion Criteria:**
- Aged ≥18 years
- Severe or life-threatening (critical) COVID-19
- Analysis limited to patients for whom samples were available for retrospective analysis of CP titer.

**Intervention:**
- CP transfusion (no titer specified in real time; high, medium, and low titer CP determined retrospectively)

**Primary Endpoint:**
- Mortality 30 days after CP transfusion

**Number of Participants:**
- High-titer CP (n = 515), medium-titer CP (n = 2,006), and low-titer CP (n = 561)

**Participant Characteristics:**
- 61% of the participants were men.
- 48% of the participants were White and 37% were Hispanic/Latino.
- 61% of the participants required ICU-level care prior to infusion.
- 33% of the participants were on mechanical ventilation.
- 51% of the participants received corticosteroids; 31% received RDV.

**Outcomes:**
- The analysis included 3,082 participants who received a single unit of CP. The participants were among 35,322 participants who had received CP through the EAP by July 4, 2020.
- Death within 30 days occurred in 115 of 515 patients (22%) in the high-titer group, 549 of 2,006 patients (27%) in the medium-titer group, and 166 of 561 patients (30%) in the low-titer group.
- Using a relative-risk regression model that assumed all patients who were discharged were alive at Day 30, patients in the high-titer group had a lower relative risk of death within 30 days than patients in the low-titer group (relative risk 0.82; 95% CI, 0.67–1.00).
- Among patients who received mechanical ventilation before transfusion, there was no difference in the risk of death between those who received high-titer CP and those who received low-titer CP (relative risk 1.02; 95% CI, 0.78–1.32).
- Mortality was lower among patients who were not receiving mechanical ventilation before transfusion (relative risk 0.66; 95% CI, 0.48–0.91).

**Limitations:**
- Lack of untreated control arm limits interpretation of the safety and efficacy data; the possibility that differences in outcomes are attributable to harm from low-titer plasma rather than benefit from high-titer plasma cannot be excluded.
- Assays to determine the effective antibody titers remain limited, and the antibody titers of currently available CP from COVID-19 survivors are highly variable.
- Efficacy analysis relied on only a subset of EAP patients who represent a fraction of the patients who received CP through the EAP.
- Post hoc subgroups were selected by combining several subsetting rules that favored subgroups. This approach tends to overestimate the treatment effect.

**Interpretation:**
- Given the lack of an untreated control arm and the limitations listed above, this retrospective analysis is not sufficient to establish the efficacy or safety of CP.
Key: AE = adverse event; ARDS = acute respiratory distress syndrome; ConCOVID Trial = Convalescent-plasma-for-COVID-9; ConPlas-19 Study = Convalescent Plasma for COVID-19; CP = convalescent plasma; EAP = Expanded Access Program; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; ID50 = 50% inhibitory dose; IgG = immunoglobulin G; IMV = invasive mechanical ventilation; ITT = intention to treat; the Panel = the COVID-19 Treatment Guidelines Panel; $\text{PaO}_2/\text{FiO}_2$ = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PCR = polymerase chain reaction; PLACID Trial = Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial; PlasmAr Study = A Randomized Trial of Convalescent Plasma in COVID-19 Severe Pneumonia; RBD = receptor binding domain; RCT = randomized controlled trial; RDV = remdesivir; RECOVERY = Randomised Evaluation of COVID-19 Therapy; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SOC = standard of care; $\text{SpO}_2$ = saturation of oxygen; VMNT = virus microneutralization test

References


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 Under Evaluation for the Treatment of COVID-19

Last Updated: April 21, 2021

- The information in this table is based on data from investigational trials that enrolled people with COVID-19. The table includes dose recommendations from the FDA EUAs for patients with COVID-19 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 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 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 for the drugs listed in this table, please refer to the individual drug sections of the Guidelines and Therapeutic Management of Nonhospitalized Adults With COVID-19.

<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>Casirivimab Plus Imdevimab (Anti-SARS-CoV-2 Monoclonal Antibodies)</td>
<td>Casirivimab 600 mg plus Imdevimab 600 mg IV administered together as a single dose. This is the recommended route of administration.</td>
<td>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 that treat severe infusion reactions.</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>
</tr>
<tr>
<td>Dose Recommended in EUA for Treatment of COVID-19:</td>
<td>These AEs were observed over multiple trials where participants received CAS 600 mg plus IMD 600 mg or higher doses.</td>
<td>• Only for administration in health care settings by qualified health care providers who have immediate access to emergency medical services and medications that treat severe infusion reactions.</td>
<td>• Monitor patient during the IV infusion or SQ injections and for ≥1 hour after the infusion or injections are completed.</td>
<td>Availability:</td>
</tr>
<tr>
<td>- CAS 600 mg plus IMD 600 mg IV administered together as a single dose. This is the recommended route of administration.</td>
<td>- 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 details.</td>
<td>• Hypersensitivity, including anaphylaxis and infusion-related reactions</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>
<td>• CAS plus IMD is available through the FDA EUA for high-risk outpatients with mild to moderate COVID-19. See Anti-SARS-CoV-2 Monoclonal Antibodies for a list of high-risk conditions.</td>
</tr>
<tr>
<td>- 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 details.</td>
<td>- These AEs were observed over multiple trials where participants received CAS 600 mg plus IMD 600 mg or higher doses.</td>
<td>- Only for administration in health care settings by qualified health care providers who have immediate access to emergency medical services and medications that treat severe infusion reactions.</td>
<td>- Monitor patient during the IV infusion or SQ injections and for ≥1 hour after the infusion or injections are completed.</td>
<td>• A list of clinical trials is available: Casirivimab Plus Imdevimab</td>
</tr>
<tr>
<td>- For information regarding the use of CAS plus IMD for PEP, please refer to the revised FDA EUA.</td>
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<td>• For information regarding the use of CAS plus IMD for PEP, please refer to the revised FDA EUA.</td>
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<tr>
<td>Sotrovimab (Anti-SARS-CoV-2 Monoclonal Antibody)</td>
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<tr>
<td><strong>Dose Recommended in EUA:</strong></td>
<td><strong>Adverse Events</strong></td>
<td><strong>Monitoring Parameters</strong></td>
<td><strong>Drug-Drug Interaction Potential</strong></td>
<td><strong>Comments and Links to Clinical Trials</strong></td>
</tr>
</tbody>
</table>
| • SOT 500 mg IV | • Rash | • Only for administration in health care settings by qualified health care providers who have immediate access to emergency medical services and medications that treat severe infusion reactions. | • Drug-drug interactions are unlikely between SOT and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers. | **Availability:**
| | • Diarrhea | • Monitor patient during the IV infusion and for ≥1 hour after the infusion is completed. | | • SOT is available through the FDA EUA for high-risk outpatients with mild to moderate COVID-19. See [Anti-SARS-CoV-2 Monoclonal Antibodies](https://www.covid19treatmentguidelines.nih.gov/) for a list of high-risk conditions. |
| | • Hypersensitivity, including anaphylaxis and infusion-related reactions | | | • A list of clinical trials is available: [Sotrovimab](https://www.covid19treatmentguidelines.nih.gov/) |

<table>
<thead>
<tr>
<th>Bamlnivimab Plus Etesevimab (Anti-SARS-CoV-2 Monoclonal Antibodies)</th>
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</thead>
</table>
| **Dose Recommended in EUA:** | **Adverse Events** | **Monitoring Parameters** | **Drug-Drug Interaction Potential** | **Availability:**
<p>| • BAM 700 mg and ETE 1,400 mg IV administered together as a single dose | • Nausea | • 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. | • Drug-drug interactions are unlikely between BAM plus ETE and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers. | • The distribution of BAM plus ETE has been paused because the Gamma (P.1) and Beta (B.1.351) VoC are circulating in the United States and both have reduced susceptibility to BAM and ETE. Updates on the distribution of BAM plus ETE are available from the <a href="https://www.covid19treatmentguidelines.nih.gov/">U.S. Department of Health and Human Services Bamlanivimab/Etesevimab website</a>. A list of clinical trials is available: <a href="https://www.covid19treatmentguidelines.nih.gov/">Bamlanivimab Plus Etesevimab</a>. |
| | • Dizziness | | | |
| | • Pruritis | | | |
| | • Hypersensitivity, including anaphylaxis and infusion-related reactions | | | |
| | • These AEs were observed over multiple trials where participants received the authorized doses of BAM and ETE or higher doses. | | | |</p>
<table>
<thead>
<tr>
<th>Dosing Regimens</th>
<th>Adverse Events</th>
<th>Monitoring Parameters</th>
<th>Drug-Drug Interaction Potential</th>
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</thead>
<tbody>
<tr>
<td><strong>COVID-19 Convalescent Plasma</strong></td>
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<td><strong>Dose Recommended in EUA:</strong></td>
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<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</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.</td>
<td>• Drug products should not be added to the IV infusion line for the blood product.</td>
<td>• The decision to treat patients aged &lt;18 years with COVID-19 CP should be based on an individualized assessment of risk and benefit.¹</td>
</tr>
<tr>
<td></td>
<td>• TACO</td>
<td>• Monitor for transfusion-related reactions.</td>
<td></td>
<td>• Patients with impaired cardiac function and heart failure may require a smaller volume of CP or a slower transfusion rate.</td>
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<tr>
<td></td>
<td>• Allergic reactions</td>
<td>• Monitor patient's vital signs at baseline and during and after transfusion.</td>
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<td></td>
<td>• Anaphylactic reactions</td>
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<td></td>
<td>• Febrile nonhemolytic reactions</td>
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<td>• Hypothermia</td>
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<td>• Metabolic complications</td>
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<td>• Transfusion-transmitted infections³</td>
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<td>• Thrombotic events</td>
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<td>• Theoretical risk of antibody-mediated enhancement of infection and suppressed long-term immunity</td>
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<td>• RBC alloimmunization</td>
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<td>• Transfusion-transmitted infections³</td>
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<td><strong>SARS-CoV-2-Specific Immunoglobulin</strong></td>
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<td><strong>Dose varies by clinical trial</strong></td>
<td>• TRALI</td>
<td>• Monitor for transfusion-related reactions.</td>
<td>• Drug products should not be added to the IV infusion line for the blood product.</td>
<td>• A list of clinical trials is available: <a href="https://www.covid19treatmentguidelines.nih.gov">SARS-CoV-2 Immunoglobulin</a></td>
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<td>• TACO</td>
<td>• Monitor patient's vital signs at baseline and during and after transfusion.</td>
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<td>• Allergic reactions</td>
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<td>• Antibody-mediated enhancement of infection</td>
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**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; VoC = variants of concern
References


