



Monoclonal Antibodies for COVID-19: The Clinical Evidence

Monoclonal antibodies are laboratory-produced proteins that act as substitute antibodies to restore, enhance, or mimic the immune system's attack on cells. Given the novel nature of SARS-CoV-2, the virus that causes COVID-19, the science is evolving rapidly. This information sheet provides the latest clinical evidence available.

CLINICAL TRIALS AND FDA EMERGENCY USE AUTHORIZATIONS (EUA)

The U.S. Food and Drug Administration (FDA) has granted emergency use authorizations (EUAs) for the following monoclonal antibodies to treat *outpatients* with mild to moderate COVID-19 and who are at high risk of developing severe symptoms. These treatments include:

- **REGEN-COV™ (casirivimab and imdevimab)¹**
- **Bamlanivimab and etesevimab²**
- **Sotrovimab³**

Note: On June 25, the Assistant Secretary for Preparedness and Response (ASPR) paused all distribution of bamlanivimab and etesevimab together on a national basis until further notice.⁴ The distribution was paused due to combined frequency of the SARS-CoV-2 Gamma variant (P.1; first identified in Brazil) and the Beta variant (B.1.351; first identified in South Africa) that now exceed 11% and are trending upward throughout the United States.⁵ Results from in vitro assays that are used to assess the susceptibility of viral variants to particular monoclonal antibodies suggest that bamlanivimab and etesevimab administered together are not active against either the P.1 or B.1.351 variants. In addition, the FDA recommends that healthcare providers nationwide use alternative authorized monoclonal antibody therapies.

The FDA also granted an EUA for the following monoclonal antibody for the treatment of COVID-19 in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO):

- **Actemra® (tocilizumab)⁶**



The NIH COVID-19 Treatment Guidelines Panel recommends (AIIa) using either REGEN-COV (casirivimab and imdevimab) or sotrovimab to treat outpatients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by the Emergency Use Authorization. Furthermore, the Panel recommends against the use of bamlanivimab plus etesevimab (AIII) at this time, due to the increasing prevalence of circulating variants in the U.S. These include the P.1 (Gamma) and B.1.351 (Beta) variants of concern, which have reduced susceptibility to both bamlanivimab and etesevimab.⁷

The Panel also recommends (BIIa) the use of tocilizumab in the inpatient setting for certain patients, as defined by the EUA.⁸

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



Monoclonal Antibodies for COVID-19: The Clinical Evidence

REGEN-COV (Casirivimab and Imdevimab)¹:

Reduced Hospitalization and Death

“COVID-19-related hospitalization or all-cause death through Day 29 [...], events occurred in 7 (1.0%) subjects treated with 600 mg of casirivimab and 600 mg of imdevimab compared to 24 (3%) subjects concurrently randomized to placebo, demonstrating **a 70% reduction in COVID-19-related hospitalization or all-cause death compared to placebo** (p=0.0024).”⁹

— FDA-authorized Fact Sheet for Healthcare Providers (June 3, 2021): Phase 3 data from an ongoing COV-2067 trial; data from 4,567 randomized subjects.

Subcutaneous Injection

“[The] safety findings with subcutaneous administration in the casirivimab and imdevimab arm were similar to the safety findings observed with intravenous administration in COV-2067.”⁹

— FDA-authorized Fact Sheet for Healthcare Providers (June 3, 2021): Analysis from HV-2093 trial; data from 969 randomized healthy volunteer adult subjects.



Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variant Substitutions: REGEN-COV Casirivimab and Imdevimab Together⁹

Lineage with Spike Protein Substitution	Key Substitutions Tested	Fold Reduction in Susceptibility
B.1.1.7 (UK origin)	N501Y ^a	no change ^d
B.1.351 (South Africa origin)	K417N, E484K, N501Y ^b	no change ^d
P.1 (Brazil origin)	K417T + E484K ^c	no change ^d
B.1.427/B.1.429 (California origin)	L452R	no change ^d
B.1.526 (New York origin) ^e	E484K	no change ^d
B.1.617.1/B.1.617.3 (India origin)	L452R + E484Q	no change ^d
B.1.617.2 (India origin)	L452R + K478T	no change ^d

- Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: del69-70, del145, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H.
- Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: D80Y, D215Y, del241-243, K417N, E484K, N501Y, D614G, A701V.
- Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F.
- No change: ≤ 2 -fold reduction in susceptibility.
- Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).



Monoclonal Antibodies for COVID-19: The Clinical Evidence

Bamlanivimab and Etesevimab²:

Reduced Viral Load, Hospitalization, and Death

“[...] COVID-19 related hospitalization [...] or death [...] occurred in 15 subjects treated with placebo (6%) as compared to 4 events in subjects treated with bamlanivimab 700 mg and etesevimab 1,400 mg together (0.8%), an 87% [relative] reduction. There were 4 deaths in subjects treated with placebo and no deaths in subjects treated with bamlanivimab 700 mg and etesevimab 1,400 mg together [...]”¹⁰

“The median time to sustained symptom resolution [...] was 8 days for subjects treated with bamlanivimab 700 mg and etesevimab 1,400 mg together as compared with 10 days for subjects treated with placebo [...]”¹⁰

— FDA-authorized Fact Sheet for Healthcare Providers (May 14, 2021): Phase 3 data from an ongoing BLAZE-1 (bamlanivimab 700 mg and etesevimab 1,400 mg) trial; Bamlanivimab and etesevimab at the authorized doses of 700 mg and 1,400 mg have been administered together to approximately 800 subjects in clinical trials to participants at high risk for progression to severe COVID-19 disease.

Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variant Substitutions: Bamlanivimab and Etesevimab Together (1:2 Molar Ratio)¹⁰

Lineage with Spike Protein Substitution	Key Substitutions Tested ^a	Fold Reduction in Susceptibility
B.1.1.7 (UK origin)	N501Y ^a	no change ^b
B.1.351 (South Africa origin)	K417N + E484K + N501Y	215 ^c
P.1 (Brazil origin)	K417N + E484K + N501Y	>46 ^c
B.1.427/B.1.429 (California origin)	L452R	9 ^d
B.1.526 (New York origin) ^e	E484K	31

a. For variants with more than one substitution of concern, only the substitution(s) with the greatest impact on activity is (are) listed. For B.1.351, P.1 and B.1.427/B.1.429, spike variants reflective of the consensus sequence for the lineage were tested.

b. No change: <5-fold reduction in susceptibility.

c. Bamlanivimab and etesevimab together are unlikely to be active against variants from this lineage. No activity observed at the highest concentration tested for the P.1 variant.

d. Etesevimab retains activity against this variant.

e. Isolates of the B.1.526 lineage harbor several spike protein amino acid substitutions, and not all isolates contain the E484K substitution (as of February 2021). This assay was conducted using pseudotyped VLPs with the E484K substitution only.



Monoclonal Antibodies for COVID-19: The Clinical Evidence

Sotrovimab³:

Reduced Progression of COVID-19 at Day 29

“[P]rogression of COVID-19 at Day 29, was reduced by 85% (adjusted relative risk reduction) in recipients of sotrovimab versus placebo (p = 0.002).”¹¹

— FDA-authorized Fact Sheet for Healthcare Providers (May 26, 2021): Phase 1/2/3 data from an ongoing Phase 1/2/3 COMET-ICE trial; data from 583 randomized subjects.

Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variant Substitutions: Sotrovimab¹¹

Lineage with Spike Protein Substitution	Key Substitutions Tested ^a	Fold Reduction in Susceptibility (Pseudotyped VLP)
B.1.1.7 (UK origin)	N501Y	no change ^b
B.1.351 (South Africa origin)	K417T + E484K + N501Y	no change ^b
P.1 (Brazil origin)	K417T + E484K + N501Y	no change ^b
B.1.427/B.1.429 (California origin)	L452R	no change ^b
B.1.526 (New York origin) ^e	E484K	no change ^b
B.1.617 (India origin)	L452R + E484Q	no change ^b

- a. For variants with more than one substitution of concern, only the one(s) with the greatest impact on activity is (are) listed.
- b. No change: <5-fold reduction in susceptibility.
- c. Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).





Monoclonal Antibodies for COVID-19: The Clinical Evidence

Actemra (Tocilizumab)⁶:

Improved Survival in Hospitalized Patients, Reduced Median Time to Hospital Discharge

In the RECOVERY study, “[t]he median time to hospital discharge was 19 days in the ACTEMRA + usual care arm and >28 days in the usual care arm [...]. Among patients not requiring invasive mechanical ventilation at baseline, the proportion of patients who required mechanical ventilation or died by Day 28 was 35% (619/1754) in the ACTEMRA + usual care arm and 42% (754/1800) in the usual care alone arm [...]”¹²

In the EMPACTA study, “[t]he median time to hospital discharge [...] through Day 28 was 6.0 days in the ACTEMRA arm and 7.5 days in the placebo arm [...]. Mortality at Day 28 was 10.4% in the ACTEMRA arm versus 8.6% in the placebo arm [...]”¹²

In the COVACTA study, “[t]here were no statistically significant differences observed in the distributions of clinical status on the 7-category ordinal scale at Day 28 when comparing the ACTEMRA arm to the placebo arm. The median time to hospital discharge [...] was 20 days in the ACTEMRA arm and 28 days in the placebo arm [...]. Mortality at Day 28 was 19.7% in the ACTEMRA arm versus 19.4% in the placebo arm [...]”¹²

In the REMDACTA study, “[t]here were no statistically significant differences observed between treatment arms with respect to time to hospital discharge [...] through Day 28 [...] or time to mechanical ventilation or death through Day 28 [...]”

Mortality at Day 28 was 18.1% in the ACTEMRA + RDV arm versus 19.5% in the placebo + RDV arm [...]”¹²

— FDA-authorized Fact Sheet for Healthcare Providers (June 24, 2021): Data from one randomized, controlled, open-label, platform trial [Randomised Evaluation of COVID-19 Therapy (RECOVERY)] – 4,116 randomized patients, and 3 randomized, double-blind, placebo-controlled trials (EMPACTA – 389 randomized patients, COVACTA – 452 randomized patients, and REMDACTA – 649 randomized patients).





Monoclonal Antibodies for COVID-19: The Clinical Evidence

For more information, visit
CombatCOVID.hhs.gov

English: 1-877-332-6585 • Spanish: 1-877-366-0310



COMBATCOVID

References

1. Office of the Commissioner. (2021, June 3). REGEN-COV (Casirivimab and Imdevimab) Emergency Use Authorization Letter of Authorization (LOA). U.S. Food and Drug Administration. <https://www.fda.gov/media/145610/download>
2. Office of the Commissioner. (2021, February 25). Bamlanivimab and Etesevimab Emergency Use Authorization Letter of Authorization (LOA). U.S. Food and Drug Administration. <https://www.fda.gov/media/145801/download>
3. Office of the Commissioner. (2021, May 25). Sotrovimab Emergency Use Authorization Letter of Authorization (LOA). U.S. Food and Drug Administration. <https://www.fda.gov/media/149532/download>
4. Public Health and Medical Emergency Support for a Nation Prepared. (2021, June 25). Pause in the Distribution of bamlanivimab/etesevimab. <https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Bamlanivimab-etesevimab/Pages/bamlanivimab-etesevimab-distribution-pause.aspx>
5. Centers for Disease Control and Prevention. (2021, June 29). Variant Proportions in the U.S. <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html>
6. Office of the Commissioner. (2021, June 24). Tocilizumab Emergency Use Authorization Letter of Authorization (LOA). U.S. Food and Drug Administration. <https://www.fda.gov/media/150319/download>
7. Statement on Anti-SARS-CoV-2 Monoclonal Antibodies EUA. (2021, July 8). COVID-19 Treatment Guidelines. <https://www.covid19treatmentguidelines.nih.gov/statement-on-anti-sars-cov-2-monoclonal-antibodies-eua/>
8. NIH COVID-19 Treatment Guidelines. (2021, May 24). Therapeutic Management of Adults With COVID-19. <https://www.covid19treatmentguidelines.nih.gov/therapies/immunomodulators/interleukin-6-inhibitors/>
9. Fact Sheet for Healthcare Providers Emergency Use Authorization (EUA) of REGEN-COV (casirivimab and imdevimab). (revised June 3, 2021). <https://www.fda.gov/media/145611/download>
10. Fact Sheet for Healthcare Providers Emergency Use Authorization (EUA) of bamlanivimab and etesevimab. (revised May 14, 2021). <https://www.fda.gov/media/145802/download>
11. Fact Sheet for Healthcare Providers Emergency Use Authorization (EUA) of sotrovimab. (May 26, 2021). <https://www.fda.gov/media/149534/download>
12. Fact Sheet for Healthcare Providers Emergency Use Authorization (EUA) of ACTEMRA® (tocilizumab) for Coronavirus Disease 2019 (COVID-19). (June 24, 2021) <https://www.fda.gov/media/150321/download>

