Neutralizing Antibodies for Treatment

Section last reviewed and updated 3/3/2022

Last literature search conducted 1/31/2022

Resources*:*

- **CDC**: SARS-CoV-2 variants
- **FDA**: Qualifications for SARS-CoV-2 exposure

Recommendation 1: Among ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease, the IDSA guideline panel suggests bamlanivimab/etesevimab, casirivimab/imdevimab, or sotrovimab rather than no neutralizing antibody treatment. (Conditional recommendation, Moderate certainty of evidence)

Remarks:

- Dosing for casirivimab/imdevimab is casirivimab 600 mg and imdevimab 600 mg IV. Subcutaneous injection is a reasonable alternative in patients for whom it cannot be given intravenously.
- Dosing for sotrovimab is sotrovimab 500 IV once.
- Dosing for bamlanivimab/etesevimab is bamlanivimab 700 mg and etesevimab 1400 mg IV.
- Patients with mild to moderate COVID-19 who are at high risk of progression to severe disease admitted to the hospital for reasons other than COVID-19 may also receive bamlanivimab/etesevimab, casirivimab/imdevimab, or sotrovimab.
- Local variant susceptibility should be considered in the choice of the most appropriate neutralizing antibody therapy. Local availability of different monoclonal antibody combinations may be affected by predominance of local variants.
- There are limited data on efficacy of bamlanivimab/etesevimab, casirivimab/imdevimab, or sotrovimab in high-risk patients under 18 years of age.

Recommendation 2 (NEW): In ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease, the IDSA guideline panel recommends bebtelovimab only in the context of a clinical trial. (Knowledge gap)

Recommendation 3: Among hospitalized patients with severe COVID-19, the IDSA guideline panel recommends against bamlanivimab monotherapy. (Strong recommendation, Moderate certainty of evidence)

Figure 1. Risk factors for the progression to severe COVID-19 or hospitalization per FDA EUA [1,2,3,a]

The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example ≥65 years of age)
- Obesity or being overweight (for example, adults with BMI >25 kg/m^2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate to severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID-19])

a. These criteria refer to Recommendations 1-3

References

1. U.S. Food and Drug Administration. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of Bamlanivimab and Etesevimab. Available at: https://www.fda.gov/media/145808/download. Accessed 13 June 2021.

2. U.S. Food and Drug Administration. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of Casirivimab and Imdevimab. Available at: https://www.fda.gov/media/143894/download. Accessed 13 June 2021.
3. U.S. Food and Drug Administration. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of Sotrovimab. Available at: https://www.fda.gov/media/149535/download. Accessed 13 June 2021.

Why are neutralizing antibodies considered for treatment?

Neutralizing antibodies directed at the receptor-binding domain of SARS-CoV-2 spike protein have been evaluated as therapeutic agents for COVID-19. In animal models there is evidence that antibody therapy may more rapidly reduce viral load in the upper and lower airways of infected animals resulting in reduced viral-induced pathology [1, 2]. Additionally, antibody mediated enhancement of disease has not been detected in animal models [2] but this potential phenomenon should be closely monitored in the future studies.

Potential advantages of neutralizing antibodies include the ability to standardize the amount of neutralizing activity and the possibility of conferring protection more rapidly than with vaccine-induced immune responses (which generally take several weeks).

Antibody treatments have been and continue to be evaluated in both hospitalized and ambulatory patients. For outpatients, logistical challenges exist since the infrastructure for administration of IV infusions does not exist in most ambulatory care settings. There may also be concerns about spread of contagion when administering IV infusions in clinics. However, these challenges are being addressed in a number of outpatient infusion centers and availability of subcutaneous, or intramuscular administration options.

Summary of the evidence

Our search identified six publications of five RCTs reporting on treatment with neutralizing antibodies (bamlanivimab, combination of casirivimab/imdevimab, combination of bamlanivimab/etesevimab, or sotrovimab) for patients with COVID-19 [3-8] (**Tables 1-3**). Due to clinical heterogeneity of the outcome measures across studies, meta-analyses combining the different neutralizing antibodies were not considered appropriate.

One RCT, stopped early for futility, reported on hospitalized patients with COVID-19 randomized to treatment with either a single infusion of bamlanivimab (7000 mg) or placebo (ACTIV-3/TICO) [4]. One phase II/III RCT reported on non-hospitalized patients (adults as well as children aged 12 and up) considered at high risk for progression to severe disease who were within three days of their first positive test for SARS-CoV-2 who were randomized to a single

infusion of bamlanivimab 2800 mg/etesevimab 2800 mg or placebo [5]. One phase II RCT reported on non-hospitalized patients with recently diagnosed mild or moderate COVID-19 randomized to treatment with either a single infusion of neutralizing antibody bamlanivimab in one of three doses (700 mg, 2800 mg, or 7000 mg) or placebo [3].

One phase III RCT assessed a single infusion of either 1200 mg or 2400 mg of casirivimab/imdevimab in non-hospitalized participants with mild to moderate COVID-19 [7]. In the original phase of this trial, participants without risk factors for severe disease were included; however, 1,040 participants were removed after randomization and not analyzed as they had no risk factors for severe disease. In the amended phase of this investigation all participants were considered at high risk for severe disease. Another phase III RCT also reported on non-hospitalized participants with mild to moderate COVID-19 who were at risk for severe disease [6]. Participants in this study received a single infusion of sotrovimab 500 mg. Unlike previous studies, this study did exclude participants with immunocompromising conditions.

Additional clinical data was obtained from the PYAH/BLAZE-4 trials from the manufacturer's fact sheet supporting the EUA for bebtelovimab. Treatment arms 9 through 11 compared bebtelovimab alone to placebo in patients at low risk for COVID-19. Although an additional arm included patients at high risk for progression to severe COVID-19, bebtelovimab was not studied against placebo but rather against combination neutralizing antibodies making effectiveness estimates unavailable against usual care in this population [9].

Benefits

Bamlanivimab/etesevimab

*[**NOTE:** On January 24, 2022, FDA limited EUA for bamlanivimab/etesevimab to patients likely to have been infected with or exposed to a variant that is susceptible to this treatment.]* [10]

In ambulatory persons at high risk for severe COVID-19, bamlanivimab/etesevimab demonstrated an absolute mortality reduction of 1.9% (95% CI includes a minimum of 0.7% reduction in mortality) as no deaths were seen by day 29 in the 518 persons treated with bamlanivimab/etesevimab compared to 10 deaths in the 517 persons who received placebo. However, due to the small number of events (10, of which nine were believed to the result of COVID-19), the certainty of evidence was low due to imprecision. Bamlanivimab/etesevimab demonstrated a lower relative risk of COVID-19 related hospitalizations (defined as ≥24 hours of acute care) through day 29 compared to no bamlanivimab/etesevimab (risk ratio [RR]: 0.30; 95% confidence interval [CI]: 0.16, 0.59; low certainty of evidence [CoE]). Ambulatory persons who received bamlanivimab/etesevimab had a lower relative risk of persistently high viral load at day seven compared to no bamlanivimab/etesevimab (RR: 0.34; 95% CI: 0.25-0.46; low CoE).

Casirivimab/imdevimab

*[**NOTE:** On January 24, 2022, FDA limited EUA for casirivimab/imdevimab to patients likely to have been infected with or exposed to a variant that is susceptible to this treatment.] [10]*

Concerns were raised by the panel whether bias could have been introduced by excluding 1040 persons post-randomization (2400-mg dose group) due to lack of risk factors for severe disease. Therefore, the panel used the amended phase (1200-mg dose) full data set to inform the effect estimates as no exclusions were reported. Sensitivity analyses were carried out to test the robustness of this approach by either adding the 2400-mg to the 1200-mg dose data set or by formally pooling both effect estimates using fixed effects model; these sensitivity analyses resulted in little to no relevant differences in the findings. In addition, the amended phase lower dose (1200 mg) results also served as confirmation that the latest EUA recommended dosing appears to be equally effective as the previously authorized higher dose.

Among ambulatory persons with at least one risk factor for severe disease, there was no difference in 29-day mortality in persons treated with casirivimab/imdevimab compared to no casirivimab/imdevimab 1200 mg (RR: 1.02; 95% CI: 0.06, 16.20; low CoE). However, there was a lower relative risk of hospitalization in persons treated with casirivimab/imdevimab 1200 mg (RR: 0.27; CI: 0.11, 0.65; moderate CoE).

Sotrovimab

Among ambulatory persons with at least one risk factor for severe disease, sotrovimab demonstrated a lower relative risk of mortality compared to no sotrovimab (RR: 0.33; 95% CI: 0.01-8.19, low CoE). The low certainty of evidence was due to imprecision as there were no mortality events in those who received sotrovimab and one death in the placebo arm. Among ambulatory persons, sotrovimab use was associated with a lower relative risk of hospitalization, compared to no sotrovimab (RR: 0.14; 95% CI: 0.04-0.48; moderate CoE). Persons receiving sotrovimab had a lower progression to severe or critical disease compared to no sotrovimab (RR: 0.11; 95% CI: 0.02, 0.45; moderate CoE).

Bamlanivimab monotherapy

*[**NOTE**: On April 16, 2021, FDA revoked EUA for monoclonal antibody bamlanivimab.]* [11]

Among ambulatory persons, bamlanivimab demonstrated a lower relative risk of hospitalization, including visits to the emergency room, compared to no bamlanivimab (RR: 0.26; 95% CI: 0.09, 0.75; very low CoE). The very low certainty of evidence was due to indirectness, as the treatment may not have been provided to enough persons at risk of developing severe disease to be representative of the general population, and imprecision, due to few events recorded. Bamlanivimab may increase viral clearance at three days (MD: -0.49;

95% CI: -0.87, -0.11; low CoE); however, there may not be a meaningful difference at 11 days as measured by change from baseline SARS-CoV-2 viral load (MD: -0.22; 0.95: -0.60, 0.15; low CoE).

Among patients hospitalized for COVID-19, treatment with bamlanivimab compared to placebo failed to show or exclude a beneficial effect on mortality (HR: 2.00; 95% CI: 0.67, 5.99; moderate CoE). Clinical improvement, as defined as a decrease in a pulmonary ordinal scale, may not be meaningfully different among patients hospitalized for COVID-19 who received treatment with bamlanivimab or placebo (OR: 0.85; 0.56, 1.29; moderate CoE).

Bebtelovimab monotherapy

Among ambulatory persons, the limited data available for bebtelovimab. failed to show or to exclude a beneficial effect on hospitalizations (RR: 1.02; 95% CI: 0.15, 7.16; very low CoE). The very low certainty was due to extremely serious imprecision as only 2 events occurred in each study arm, making the estimate uninformative. No deaths were reported, likely due to a combination of the low-risk population and small sample size. The panel did not consider additional outcomes such as persistently high viral load by day 7 (no significant difference) or time to sustained symptom resolution (6 vs. 8 days in placebo), as the clinical relevance of those outcomes remained uncertain and judged as not critical for decision making.

Harms

Bamlanivimab/etesevimab

Persons receiving bamlanivimab/etesevimab experienced more serious adverse events. However, this may not be meaningfully different from those receiving placebo (RR: 1.40; 95% CI: 0.45, 4.37; moderate CoE).

Casirivimab/imdevimab

Serious adverse events were less frequent among persons receiving casirivimab/imdevimab compared to those receiving placebo (RR: 0.34; 95% CI: 0.24, 0.48; moderate CoE).

Sotrovimab

Persons who received sotrovimab were less likely to experience serious adverse events compared to those receiving placebo (RR: 0.27; 95% CI: 0.12-0.63; moderate CoE).

Bamlanivimab monotherapy

Serious adverse events among ambulatory persons receiving bamlanivimab monotherapy may not be meaningfully different from those receiving placebo (RR: 0.15; 95%

CI: 0.01, 3.78; low CoE). Persons receiving bamlanivimab did experience more infusion-related adverse events, including pruritus, flushing, rash, and facial swelling (RR: 1.62; 95% CI: 0.34, 7.70; low CoE).

Similarly, serious adverse events at five and 28 days among patients hospitalized for COVID-19 receiving bamlanivimab may not be meaningfully different from those receiving placebo (RR: 1.85; 95% CI: 0.34, 9.97; moderate CoE and RR: 0.93, 95% CI: 0.27, 3.14; moderate CoE, respectively). Similarly, infusion-related adverse events may not be meaningfully different between patients hospitalized for COVID-19 receiving bamlanivimab or placebo (OR: 1.64, 95% CI: 0.79, 3.44; moderate CoE).

Bebtelovimab monotherapy

Three serious adverse events were reported for bebtelovimab compared to zero in the control group, but due to the small sample size this estimate remains uncertain (RR: 3.41; 95% CI 0.17, 67.50; very low CoE).

Other considerations

Neutralizing antibodies for ambulatory persons

The panel agreed that the overall certainty of evidence for the treatment with bamlanivimab/etesevimab, casirivimab/imdevimab, and sotrovimab in ambulatory persons with COVID-19 at high risk for progression to severe disease (at least one risk factor) was moderate due to mostly low number of events (fragility of results). The results were driven by the number of avoided hospitalizations, as the number of deaths that occurred were too sparse to show a clear trend. Neutralizing antibodies were well tolerated, and serious adverse events were comparable or lower than placebo. The panel noted increased feasibility with the option of providing treatment with casirivimab/imdevimab through subcutaneous injections [12, 13].

Casirivimab/imdevimab has been evaluated for the treatment of COVID-19 at doses of 1200 mg, 2400 mg, and 8000 mg. Across all treatment doses, there was a flat dose-response relationship for viral load and clinical outcomes. As part of the FDA Emergency Use Authorization, the use of casirivimab/imdevimab as an IV infusion is strongly recommended, however the subcutaneous route is authorized as an alternate route when IV infusion is not feasible and would result in a delay in treatment. Clinical outcomes of patients receiving casirivimab/imdevimab via the subcutaneous route for the treatment of COVID-19 have not been reported in available trials. A pre-print manuscript [13] evaluated early casirivimab/imdevimab 1200 mg versus placebo in asymptomatic outpatients with COVID-19 and demonstrated less hospitalizations in those receiving casirivimab/imdevimab compared to those receiving placebo, 0/100 versus 3/104, respectively (RR: 0.15; 95%CI: 0.01-2.84). Peak

pharmacokinetic levels in those receiving subcutaneous casirivimab 600 mg/imdevimab 600 mg appear approximately 75% lower than after IV infusion [14].

Bamlanivimab monotherapy

The panel agreed that the overall certainty of evidence for treatment with bamlanivimab for ambulatory persons with COVID-19 is very low due to concerns with indirectness and imprecision.

The panel agreed that the overall certainty of evidence for treatment with bamlanivimab for patients hospitalized for COVID-19 is moderate due to concerns with fragility in the estimate from the small number of events reported. The guideline panel made a strong recommendation against treatment with bamlanivimab for patients hospitalized for COVID-19. The panel was moderately certain that any relevant benefit (reduction in mortality or clinical improvement) could be excluded.

Bebtelovimab monotherapy

The panel agreed that due to the extremely limited clinical data for bebtelovimab the certainty of evidence was very low, making any estimate of beneficial or harmful effect uninformative.

SARS-CoV-2 variants and neutralizing monoclonal antibodies

The emergence and circulation of new SARS-CoV-2 genetic variants has been reported from the United States and other counties. *In vitro* neutralizing assays using pseudotyped virus-based and authentic SARS Cov2 assays showed that some of the variants had reduced susceptibility to neutralizing antibodies, either individually or in combination. There is limited data from clinical studies.

Bamlanivimab alone and the combination of bamlanivimab and etesevimab together had activity against pseudovirus expressing del69-70 + N501Y found in the B.1.1.7 variant (alpha). Pseudovirus expressing spike protein from the B.1.351 lineage (beta) or substitutions K417N + E484K + N501Y found in this lineage had reduced susceptibility to bamlanivimab and etesevimab together of >45-fold, and pseudovirus expressing K417T + E484K + N501Y found in the P.1 lineage (gamma) had reduced susceptibility to bamlanivimab and etesevimab together of >511-fold. Pseudovirus expressing spike protein from the B.1.427/B.1.429 lineages (epsilon), or the L452R substitution found in this lineage, had reduced susceptibility to bamlanivimab and etesevimab together of 7.7-fold or 7.4-fold, respectively [15]. *In vitro* neutralization studies showed that bamlanivimab lost activity against the delta variant, but etesevimab retained activity [16]. Pseudotyped virus like particles expressing the spike protein from the B.1.1.529/BA.1 lineage (Omicron; South Africa origin) show reduced susceptibility to

bamlanivimab alone (>1,465-fold), etesevimab alone (>616-fold), and bamlanivimab and etesevimab together (>2,938-fold) [15].

Casirivimab and imdevimab individually and together had neutralization activity against pseudovirus expressing all spike protein substitutions found in the B.1.1.7 lineage (alpha) and against pseudovirus expressing only N501Y found in B.1.1.7 (alpha) and other circulating lineages. Casirivimab and imdevimab together had neutralization activity against pseudovirus expressing all spike protein substitutions, or individual substitutions K417N, E484K or N501Y, found in the B.1.1351 lineage (beta), and against K417T+E484K, found in the P.1 lineage (gamma), although casirivimab alone, but not imdevimab, had reduced activity against pseudovirus expressing K417N or E484K, as indicated above. The E484K substitution is also found in the B.1.526 (iota) lineage. Casirivimab and imdevimab, individually and together, retained neutralization activity against the L452R substitution found in the B.1.427/B.1.429 lineages (epsilon) [14]. In *in vitro* neutralization studies, casirivimab and imdevimab remained active against the delta variant [16]. Casirivimab and imdevimab, individually (>1732-fold and >754-fold, respectively) and together (>1013-fold), demonstrated reduced neutralization activity against pseudotyped virus like particle with the full spike protein sequence of the B.1.1.529/BA.1 (Omicron; South Africa origin) lineage [14].

Pseudotype virus-like particle neutralization assays indicate that sotrovimab retains activity against the B.1.1.7, B.1.315, P.1, B.1.427/B.1.429, B1.526 & B.1.617 variant spike proteins. . Pseudotyped virus like particle assays show that sotrovimab neutralizes the omicron BA.2 lineage with a 16-fold reduction in activity relative to wild-type [17]. There is limited nucleotide sequencing data available from COMET ICE to comment on the clinical impact of variants on therapeutic response [17].

The clinical data obtained from studies of bebtelovimab did not include the currently prevalent omicron variant. In vitro data of bebtelovimab in pseudotyped virus-like particle neutralization assays showed that it retains activity (<5-fold reduction) against the Alpha (B.1.1.7, UK origin), Beta (B.1. 351, South Africa origin), Gamma (P.1, Brazil origin), Delta (B.1. 617. 2, India origin), Epsilon (B.1. 427/B.1. 429, California origin), Iota (B.1. 526, New York origin), Kappa (B.1.617.1, India origin), Lambda (C.37, Peru origin), Omicron (B. 1.1. 529/BA.1, South Africa origin) and Omicron BA2 variant lineages. The Mu (B.1. 621, Columbia origin) variant showed a reduction in susceptibility to bebtelovimab of 5.3-fold [9]. In authentic SARS CoV-2 assays, bebtelovimab retained activity (<5-fold reduction) against Alpha (B.1.1.7), Beta (B.1.351), Delta (B.1.617.2/AY.3), and Omicron (B.1.1.529/BA.1) lineages.

We have limited data on how *in vitro* neutralization activity of monoclonal antibodies against pseudotyped virus-like particles expressing spike protein substitutions or even *in vitro* neutralization activity against authentic SARS-CoV-2 variants correlates with clinical efficacy. Genotypic and phenotypic testing for variants and their correlation with patient

important outcomes is being studied in clinical trials evaluating neutralizing antibodies. We still need further studies and surveillance data to understand the implications of SARS-CoV-2 variants on clinical efficacy of COVID-19 therapies.

Conclusions and research needs for this recommendation

The guideline panel suggests using bamlanivimab/etesevimab, casirivimab/imdevimab, or sotrovimab in mild to moderate COVID-19 ambulatory persons at high risk for developing severe disease as the expected benefits likely outweigh any potential harms when given in patients infected with susceptible variants (**Tables 1-3**). However, due to the limited available evidence for bebtelovimab, the guideline panel recommends bebtelovimab only in the context of a clinical trial, ideally including currently circulating predominant variants.

The guideline panel recommends against use of bamlanivimab for patients hospitalized for COVID-19 (**Table 6**).

The guideline panel recognized the need for continued research and accrual of evidence, particularly trials on patient important outcomes (hospitalizations progressing to need for ventilation, or death), existing and new neutralizing antibodies, and outcomes with variants of concern.

Table 1. GRADE evidence profile, Recommendation 1

Question: Bamlanivimab/etesevimab compared to no bamlanivimab/etesevimab for ambulatory persons with mild to moderate COVID-19 at high risk for progression to severe disease

Last updated 3/2/2021; last reviewed 9/19/2021

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bamlanivimab/ etesevimab	no bamlanivimab/ etesevimab	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 29 days)												
1 [1]	randomized trials	not serious	not serious	not serious [a]	serious [b]	none	0/518 (0.0%)	10/517 (1.9%)	**RR 0.05** (0.00 to 0.80) [c]	**19 fewer per 1,000** (from 31 fewer to 7 fewer) [d]	⨁⨁⨁◯ MODERATE	CRITICAL
Hospitalization (>24 hours of acute care) with COVID-19 (follow up: 29 days)												
1 [1]	randomized trials	not serious	not serious	not serious [a,e]	serious [b]	none	11/518 (2.1%)	36/517 (7.0%)	**RR 0.30** (0.16 to 0.59)	**49 fewer per 1,000** (from 58 fewer to 29 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Persistently high viral load at day 7 (follow up: 7 days; assessed with: RT-PCR)												
1 [1]	randomized trials	not serious	not serious	serious [a,f]	serious [b]	none	50/508 (9.8%)	145/499 (29.1%)	**RR 0.34** (0.25 to 0.46)	**192 fewer per 1,000** (from 218 fewer to 157 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events												
1 [1]	randomized trials	not serious	not serious	not serious [a]	serious [b]	none	7/518 (1.4%)	5/517 (1.0%)	**RR 1.40** (0.45 to 4.37)	**4 more per 1,000** (from 5 fewer to 33 more)	⨁⨁⨁◯ MODERATE	CRITICAL

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

NB: Certainty ratings may be derived from evidence that includes pre-print articles, which have not been peer reviewed or published.

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Estimate reflects the use of a higher dose than treatment dose approved by the FDA.
b. Fragility present, low number of events.
c. RR estimated by using continuity correction of 0.5.
d. As the RR 95% CI is wide due to sparse data, absolute risk difference recalculated independently and not based on RR.
e. Hospital admission is an intermediary outcome for morbidity, ICU admission, and need for ventilation. Not rated down.
f. Measure of viral clearance is a surrogate outcome for hospital admission, need for intensive care, intubation and death.
g. Disclaimer: Provisional evidence rating based on preliminary evidence from non-peer reviewed publication.

Reference

1. Dougan M, Nirula A, Azizad M, et al. Bamlanivimab plus Etesevimab in Mild or Moderate Covid-19. N Engl J Med **2021**; 385: 1382-92.

Table 2. GRADE evidence profile, Recommendation 1

Question: Casirivimab/imdevimab compared to no casirivimab/imdevimab for ambulatory persons with mild to moderate COVID-19 at high risk of progression to severe disease

Last updated 6/16/2021; last reviewed 9/19/2021

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	casirivimab/ imdevimab	no casirivimab/ imdevimab	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (1200 mg) (follow up: 29 days)												
1 [1]	randomized trials	not serious [a]	not serious	not serious	very serious [b,c]	none	1/736 (0.1%)	1/748 (0.1%)	**RR 1.02** (0.06 to 16.20)	**0 fewer per 1,000** (from 4 fewer to 4 more) [d]	⨁⨁◯◯ LOW	CRITICAL
COVID-19 related hospitalizations (1200 mg) (follow up: 29 days)												
1 [1]	randomized trials	not serious [a]	not serious	not serious [e]	serious [b]	none	6/736 (0.8%)	23/748 (3.1%)	**RR 0.27** (0.11 to 0.65)	**22 fewer per 1,000** (from 27 fewer to 11 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Serious adverse events (all doses) (follow up: 29 days)												
1 [1]	randomized trials	not serious [a]	not serious	not serious	serious [b]	none	50/3688 (1.4%)	74/1843 (4.0%)	**RR 0.34** (0.24 to 0.48)	**27 fewer per 1,000** (from 31 fewer to 21 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

NB: Certainty ratings may be derived from evidence that includes pre-print articles, which have not been peer reviewed or published.

CI: Confidence interval; **RR:** Risk ratio

Explanations

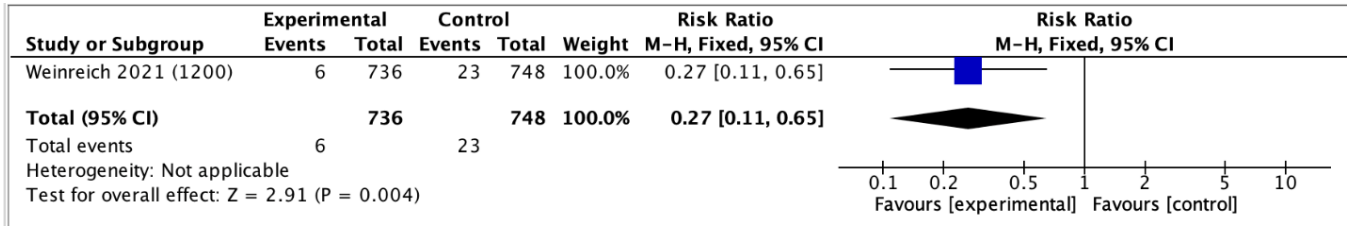
a. Differential post randomization event exclusions (1040 participants) in the original phase (participants without risk factors) is unknown. Publication did not provide an intention to treat analysis. Not rated down for risk of bias as the data in this evidence profile is limited to the amended phase 1,200 mg dose only and not the entire data set (1,200 mg is the currently recommended dose). However, sensitivity analysis of the entire data set showed similar results: for hospitalizations 23/2091 vs 59/1341; RR 0.25 (95% CI 0.16, 0.4); deaths: 2/2091 vs 3/1341; RR 0.43 (95% CI 0.08, 2.3).

b. Small number of events; fragility present.
c. 95% CI cannot exclude no difference or increased mortality.
d. As the RR 95% CI is wide due to sparse data, absolute risk difference recalculated independently and not based on RR.
e. COVID-19 related hospitalizations is a surrogate for ICU admission, mechanical ventilation and death. Not rated down.
f. Disclaimer: Provisional evidence rating based on preliminary evidence from non-peer reviewed publication.

Reference

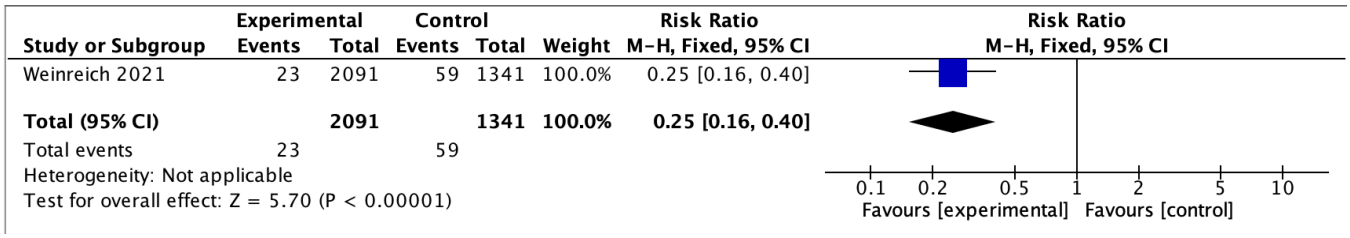
1. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. N Engl J Med **2021**; 384(3): 238-51.

Figure 2a. Forest plot for the outcome of hospitalizations for casirivimab/imdevimab vs. no casirivimab/etesevimab (data for 1200-mg dose only) [1]



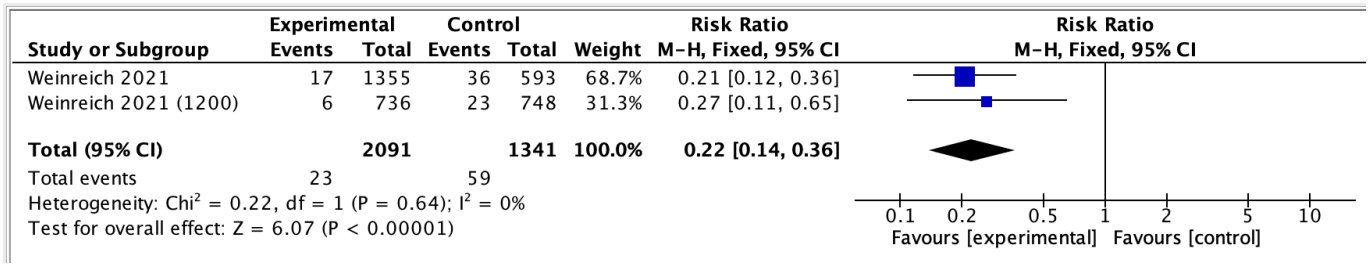
1. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. N Engl J Med **2021**; 384(3): 238-51.

Figure 2b. Forest plot for the outcome of hospitalizations for casirivimab/imdevimab vs. no casirivimab/etesevimab (combining data for 2400-mg dose and 1200-mg dose) [1]



1. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. N Engl J Med **2021**; 384(3): 238-51.

Figure 2c. Forest plot for the outcome of hospitalizations for casirivimab/imdevimab vs. no casirivimab/etesevimab (pooling data for 2400-mg dose and 1200-mg dose) [1]



1. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. N Engl J Med **2021**; 384(3): 238-51.

Table 3. GRADE evidence profile, Recommendation 1

Question: Sotrovimab compared to no sotrovimab for ambulatory persons with mild to moderate COVID-19 at high risk for progression to severe disease

Last updated 6/16/2021; last reviewed 9/19/2021

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	sotrovimab	no sotrovimab	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 29 days)												
1 [1]	randomized trials	not serious	not serious	not serious	very serious [a]	none	0/291 (0.0%)	1/292 (0.3%)	**RR 0.33** (0.01 to 8.18) [b]	**3 fewer per 1,000** (from 10 fewer to 3 more) [c]	⨁⨁◯◯ LOW	CRITICAL
Hospitalization (>24 hours for any cause) (follow up: 29 days)												
1 [1]	randomized trials	not serious	not serious	not serious [d]	serious [a]	none	3/291 (1.0%)	21/292 (7.2%)	**RR 0.14** (0.04 to 0.48)	**62 fewer per 1,000** (from 69 fewer to 37 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Progression to severe or critical disease (follow up: 29 days)												
1 [1]	randomized trials	not serious	not serious	not serious [d]	serious [a]	none	2/291 (0.7%)	19/292 (6.5%)	**RR 0.11** (0.02 to 0.45)	**58 fewer per 1,000** (from 64 fewer to 36 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Serious adverse events (follow up: 29 days)												
1 [1]	randomized trials	not serious	not serious	not serious	serious [a]	none	7/430 (1.6%)	26/438 (5.9%)	**RR 0.27** (0.12 to 0.63)	**43 fewer per 1,000** (from 52 fewer to 22 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

NB: Certainty ratings may be derived from evidence that includes pre-print articles, which have not been peer reviewed or published.

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Small number of events; fragility present
b. RR estimated by using continuity correction of 0.5.
c. As the RR 95% CI is wide due to sparse data, absolute risk difference recalculated independently and not based on RR.
d. COVID-19 related hospitalizations is a surrogate for ICU admission, mechanical ventilation and death. Not rated down for indirectness.

Disclaimer: Provisional evidence rating based on preliminary evidence from non-peer reviewed publication.

Reference

1. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early Covid-19 Treatment With SARS-CoV-2 Neutralizing Antibody Sotrovimab. medRxiv **2021**: Available at: https://www.medrxiv.org/content/10.1101/2021.05.27.21257096v1 [Preprint 28 May 2021].

Table 4. GRADE evidence profile, Recommendation 2

Question: Bebtelovimab compared to no bebtelovimab for ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease

New evidence profile developed 3/3/2022

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bebtelovimab	no bebtelovimab	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: 29 days)												
1 [1]	randomized trials	not serious	not serious	not serious	extremely serious [a]	none	0/125 (0.0%)	0/128 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
Hospitalization (> 24 hours for any cause) (follow-up: 29 days)												
1 [1]	randomized trials	not serious	not serious	not serious [b]	extremely serious [a]	none	2/125 (1.6%)	2/128 (1.6%)	**RR 1.02** (0.15 to 7.16)	**0 fewer per 1,000** (from 13 fewer to 96 more)	⨁◯◯◯ VERY LOW	CRITICAL
Progression to severe or critical disease - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Serious adverse events (follow-up: 29 days)												
1 [1]	randomized trials	not serious	not serious	not serious	extremely serious [a]	none	3/243 (1.2%)	0/138 (0.0%)	**RR 3.41** (0.17 to 67.50)	**12 more per 1,000** (from 26 fewer to 2 fewer) [c]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Small number of events; fragility present; this resulted in non-informative estimates rated down three times for imprecision.
   i. Piggott T, Morgan RL, Cuello-Garcia CA, et al. Grading of Recommendations Assessment, Development, and Evaluations (GRADE) notes: extremely serious, GRADE's terminology for rating down by three levels. J Clin Epidemiol **2020**; 120: 116-20.

b. COVID-19 related hospitalizations is a surrogate for ICU admission, mechanical ventilation and death. The patients studied were at average risk (not high risk) for severe disease. Not rated down for indirectness.

c. Absolute effect calculated not using RR due to zero events on control group

Reference

1. U.S. Food and Drug Administration. Fact Sheet for Healthcare Providers: Emergency Use Authorization for Bebtelovimab. Available at: https://www.fda.gov/media/156152/download. Accessed 2 March 2022.

Table 5. GRADE evidence profile

Question: Bamlanivimab compared to no bamlanivimab for non-hospitalized persons with COVID-19

Last updated 1/29/2021; last reviewed 9/19/2021

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bamlanivimab	no bamlanivimab	Relative (95% CI)	Absolute (95% CI)		
Hospitalization (including ED visits) with COVID-19 (follow up: 29 days)												
1 [1]	randomized trials	not serious	not serious	serious [a]	very serious [b]	none	5/309 (1.6%)	9/143 (6.3%)	**RR 0.26** (0.09 to 0.75)	**47 fewer per 1,000** (from 57 fewer to 16 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Viral clearance (follow up: 3 days; assessed with: change from baseline in SARS-CoV-2 viral load)												
1 [1]	randomized trials	not serious	not serious	serious [a,c]	serious [b]	none	309	143	-	MD **0.49 lower** (0.87 lower to 0.11 lower)	⨁⨁◯◯ LOW	IMPORTANT
Viral clearance (follow up: 11 days; assessed with: change from baseline in SARS-CoV-2 viral load)												
1 [1]	randomized trials	not serious	not serious	serious [a,c]	serious [d]	none	309	143	-	MD **0.22 lower** (0.6 lower to 0.15 higher)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events (upper abdominal pain)												
1 [1]	randomized trials	not serious	not serious	not serious	very serious [d]	none	0/309 (0.0%)	1/143 (0.7%)	**RR 0.15** (0.01 to 3.78)	**6 fewer per 1,000** (from 7 fewer to 19 more)	⨁⨁◯◯ LOW	CRITICAL
Infusion-related adverse events												
1 [1]	randomized trials	not serious	not serious	not serious	very serious [d]	none	7/309 (2.3%)	2/143 (1.4%)	**RR 1.62** (0.34 to 7.70)	**9 more per 1,000** (from 9 fewer to 94 more)	⨁⨁◯◯ LOW	CRITICAL

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

NB: Certainty ratings may be derived from evidence that includes pre-print articles, which have not been peer reviewed or published.

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Uncertain that the treatment was provided in enough participants at risk of developing severe disease to be representative of the general population.
b. The 95% CI may not include a meaningful difference. Few events reported suggests fragility of the estimate.
c. Measure of viral clearance is a surrogate outcome for hospital admission, need for intensive care, intubation and death.
d. The 95% CI includes values that suggest either an increase or decrease in harm. Few events reported suggests fragility of the estimate.

Reference

1. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. N Engl J Med **2021**; 384(3): 229-37.

Table 6. GRADE evidence profile, Recommendation 3
Question: Bamlanivimab monotherapy compared to no bamlanivimab monotherapy for patients hospitalized for COVID-19
Last updated 1/29/2021; last reviewed 9/19/2021

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bamlanivimab	no bamlanivimab	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1 [1]	randomized trials	not serious	not serious	not serious	serious [a]	none	9/163 (5.5%)	5/151 (3.3%)	**HR 2.00** (0.67 to 5.99)	**32 more per 1,000** (from 11 fewer to 150 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Clinical improvement at day 5 (assessed with: pulmonary ordinal outcome [scale 1-7; 1 = least severe])												
1 [1]	randomized trials	not serious	not serious	not serious	serious [a]	none	161	150	**OR 0.85** (0.56 to 1.29) [b]	-	⨁⨁⨁◯ MODERATE	CRITICAL
Serious adverse events (follow up: 5 days)												
1 [1]	randomized trials	not serious	not serious	not serious	serious [a]	none	4/163 (2.5%)	2/151 (1.3%)	**RR 1.85** (0.34 to 9.97)	**11 more per 1,000** (from 9 fewer to 119 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Serious adverse events (follow up: 28 days)												
1 [1]	randomized trials	not serious	not serious	not serious	serious [a]	none	5/163 (3.1%)	5/151 (3.3%)	**RR 0.93** (0.27 to 3.14)	**2 fewer per 1,000** (from 24 fewer to 71 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Infusion-related adverse events												
1 [1]	randomized trials	not serious	not serious	not serious	serious [a]	none	23/163 (14.1%)	21/151 (13.9%)	**OR 1.64** (0.79 to 3.44) [c]	**70 more per 1,000** (from 26 fewer to 218 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

NB: Certainty ratings may be derived from evidence that includes pre-print articles, which have not been peer reviewed or published.

CI: Confidence interval; **HR**: Hazard Ratio; **OR**: Odds ratio; **RR**: Risk ratio

Explanations

a. The 95% CI includes the potential for both appreciable benefit as well as the potential for harm. Few events reported do not meet the optimal information size and suggest fragility of the estimate
b. Study-provided odds ratio adjusted for baseline ordinal category and trial pharmacy.
c. Study-provided odds ratio adjusted for the trial pharmacy.

Reference

1. ACTIV-3/TICO LY-CoV555 Study Group, Grund B, Barkauskas CE, et al. A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19. N Engl J Med **2021**; 384: 905-14.

References

1. Jones BE, Brown-Augsburger PL, Corbett KS, et al. LY-CoV555, a rapidly isolated potent neutralizing antibody, provides protection in a non-human primate model of SARS-CoV-2 infection. bioRxiv **2020**: Available at: https://doi.org/10.1101/2020.09.30.318972 [Preprint 9 October 2020].
2. Baum A, Ajithdoss D, Copin R, et al. REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters. Science **2020**; 370(6520): 1110-5.
3. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. N Engl J Med **2021**; 384(3): 229-37.
4. ACTIV-3/TICO LY-CoV555 Study Group, Grund B, Barkauskas CE, et al. A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19. N Engl J Med **2021**; 384: 905-14.
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6. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early Covid-19 Treatment With SARS-CoV-2 Neutralizing Antibody Sotrovimab. N Engl J Med **2021**; 385: 1941-50.
7. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. N Engl J Med **2021**; 384(3): 238-51.
8. Regeneron Pharmaceuticals, Inc. Phase 3 Trial Shows Regen-CoV™ (Casirivimab with Imdevimab) Antibody Cocktail Reduced Hospitalization or Death by 70% in Non-Hospitalized COVID-19 Patients. Available at: https://investor.regeneron.com/news-releases/news-release-details/phase-3-trial-shows-regen-covtm-casirivimab-imdevimab-antibody. Accessed 9 April 2021.
9. U.S. Food and Drug Administration. Fact Sheet for Healthcare Providers: Emergency Use Authorization for Bebtelovimab. Available at: https://www.fda.gov/media/156152/download. Accessed 2 March 2022.
10. U.S. Food and Drug Administration. Coronavirus (COVID-19) Update: FDA Limits Use of Certain Monoclonal Antibodies to Treat COVID-19 Due to the Omicron Variant. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-limits-use-certain-monoclonal-antibodies-treat-covid-19-due-omicron. Accessed 3 March 2022.
11. U.S. Food and Drug Administration. Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Monoclonal Antibody Bamlanivimab. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-

fda-revokes-emergency-use-authorization-monoclonal-antibody-bamlanivimab. Accessed 13 June 2021.

12. O'Brien MP, Forleo-Neto E, Musser BJ, et al. Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. N Engl J Med **2021**; 385: 1184-95.

13. O'Brien MP, Forleo-Neto E, Sarkar N, et al. Subcutaneous REGEN-COV Antibody Combination in Early SARS-CoV-2 Infection. medRxiv **2021**: Available at: https://doi.org/10.1101/2021.06.14.21258569 [Preprint 14 June 2021].

14. U.S. Food and Drug Administration. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of Regen-CoV™ (casirivimab with imdevimab). Available at: https://www.fda.gov/media/145611/download. Accessed 2 March 2022.

15. U.S. Food and Drug Administration. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of Bamlanivimab and Etesevimab. Available at: https://www.fda.gov/media/145802/download. Accessed 3 March 2022.

16. Planas D, Veyer D, Baidaliuk A, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. Nature **2021**; 596(7871): 276-80.

17. GlaxoSmithKline LLC, U.S. Food and Drug Administration. Fact Sheet for Healthcare Providers: Emergency Use Authorization (EUA) of Sotrovimab. Available at: https://www.fda.gov/media/149534/download. Accessed 2 March 2022.

Supplementary Materials

Study characteristics

- **Table s1.** Should ambulatory and hospitalized patients with COVID-19 receive neutralizing antibodies vs. no neutralizing antibodies?

Forest plots

- **Figure s1a.** Outcome of hospitalizations for casirivimab/imdevimab vs. no casirivimab/etesevimab (data for 1200-mg dose only)
- **Figure s1b.** Outcome of hospitalizations for casirivimab/imdevimab vs. no casirivimab/etesevimab (combining data for 2400-mg dose and 1200-mg dose)
- **Figure s1c.** Outcome of hospitalizations for casirivimab/imdevimab vs. no casirivimab/etesevimab (pooling data for 2400-mg dose and 1200-mg dose)

Risk of bias

- **Table s2.** Randomized controlled studies (bamlanivimab/etesevimab vs. no bamlanivimab/etesevimab; casirivimab/imdevimab vs. no casirivimab/imdevimab; bamlanivimab monotherapy vs. no bamlanivimab monotherapy)

Table s1. Should ambulatory and hospitalized patients with COVID-19 receive neutralizing antibodies [a,b,c] vs. no neutralizing antibodies?

a. Bamlanivimab/etesevimab
b. Casirivimab/imdevimab
c. Bamlanivimab monotherapy

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
ACTIV-3/TICO LY-CoV555 Study Group /2021 [1]	USA (23) Denmark (7) Singapore (1)	RCT	163/151	44	Median (IQR): 61 (49-71)	Hospitalized patients within 12 of illness onset. Included patients with no oxygen requirements and on supplemental oxygen (including noninvasive ventilation). Excluded patients on invasive ventilation or ECMO.	LY-CoV555 (bamlanivimab) 7000 mg once, by intravenous infusion over 1 hour	Placebo plus standard of care	Remdesivir (95%), glucocorticoids (49%), heparinoids (51%)	Pulmonary status at day 5 Sustained recovery Mortality Hospital discharge Adverse events	US Operation Warp Speed National Institute of Allergy and Infectious Diseases Leidos Biomedical Research for the INSIGHT Network National Heart, Lung, and Blood Institute Research Triangle Institute for the PETAL Network US Department of Veterans Affairs

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
											Grants from governments of Denmark, Australia, United Kingdom
Chen/ 2021 [2]	US (41 centers)	RCT	452 (309/143)	N/A	Study population who received bamlanivimab: Median (range): 45 years (18-86 years) Study population who received placebo: Median (range): 46 years (18-77 years)	All the patients had positive results on testing for SARS-CoV-2 and presented with one or more mild or moderate symptoms	LY-CoV55 intravenously once at a dose of one of following: 700 mg, 2800 mg, 7000 mg	(1) Placebo	N/A	Change from baseline in the viral load at day 11 Change from baseline in the viral load at days 3, 7 Hospitalization at day 29 Adverse events	Eli Lilly
Dougan/ 2021 [3]	US (131 centers)	RCT	1035 (518/517)	52%	Mean (SD): 53.8 years (16.8)	Adult patients with mild to moderate COVID-19 (diagnosed with positive antigen or RT-PCR)	Bamlanivimab 2800 mg/Etesevimab 2800 mg x one dose infused over 1 hour	Placebo	None	Mortality Acute care hospitalization ≥ 24 hours Proportion of patients with persistently high viral load	Eli Lilly

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
										at day 7 (PHVL) SAEs	
Gupta/ 2021 [4]	37 study sites in 4 countries (US, Canada, Brazil, Spain)	RCT	583 (291/292)	54	Median 53 years (18-96)	Mild-moderate COVID-19 infection (symptomatic, but no dyspnea at rest, respiratory distress, or supplemental oxygen) and at high risk of progression (age ≥ 55 or at least 1 of following risk factors: diabetes, obesity, chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, moderate-severe asthma)	Sotrovimab 500mg IV infused over 1 hour	Placebo	None	Day 29 all-cause mortality Hospitalization Emergency room visits Patient-reported outcomes Viral load Progression to supplemental oxygen Adverse events	Vir Biotechnology GlaxoSmithKline
Weinreich/ 2021 [6]	US (27 centers)	RCT	4519 (2676/1843)	51%	Median (IQR): -2.4 g: 50 (39:60) - 1.2 g 48.5 (37:57.5)	Adult, non-hospitalized patients with a positive SARS-CoV-2 result no more than 72 hours before randomization and symptoms onset less than 7 days	REGN-COV2 - 2.4 g x 1 dose - 1.2 g x 1 dose	Placebo	N/A	Mortality At least one COVID-19 related medically attended visit through day 29 (included telemedicine,	Regeneron Pharmaceuticals and Biomedical and Advanced Research and Development Authority of the

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
					Concurrent placebo: 50 (37:58)	before randomization				in-person visits, urgent care/ER visits, and hospitalizations). Adverse events	Department of Health and Human Services
Weinreich/ 2020	US (27 centers)	RCT	275 (182/93)	51%	Median (IQR): 44 (35-52)	Adult, non-hospitalized patients with a positive SARS-CoV-2 result no more than 72 hours before randomization and symptoms onset less than 7 days before randomization	REGN-COV2 - 8.0 g (high dose) x 1 dose, - 2.4 g (low dose) x 1 dose	Placebo	N/A	Change from baseline in the viral load at day 7 At least one COVID-19 related medically attended visit through day 29 (included telemedicine, in-person visits, urgent care/ER visits, and hospitalizations). Adverse events	Regeneron Pharmaceuticals and Biomedical and Advanced Research and Development Authority of the Department of Health and Human Services

Figure s1a. Forest plot for the outcome of hospitalizations for casirivimab/imdevimab vs. no casirivimab/etesevimab (data for 1200-mg dose only)

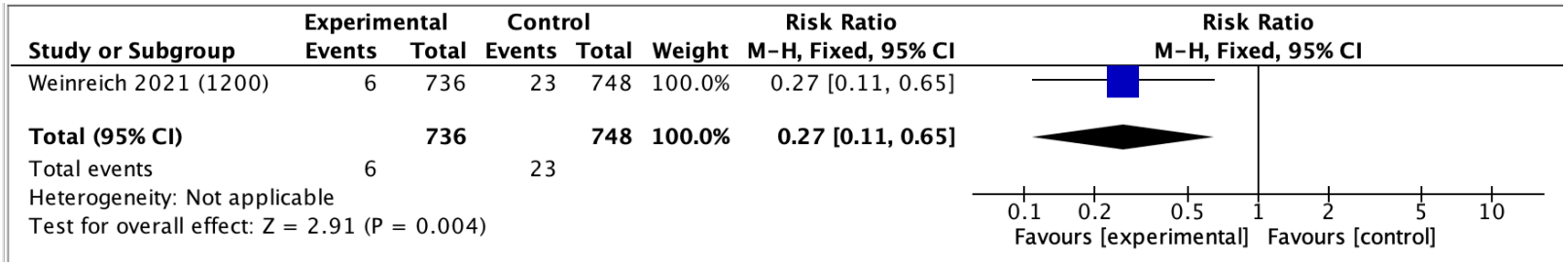

Figure s1b. Forest plot for the outcome of hospitalizations for casirivimab/imdevimab vs. no casirivimab/etesevimab (combining data for 2400-mg dose and 1200-mg dose)

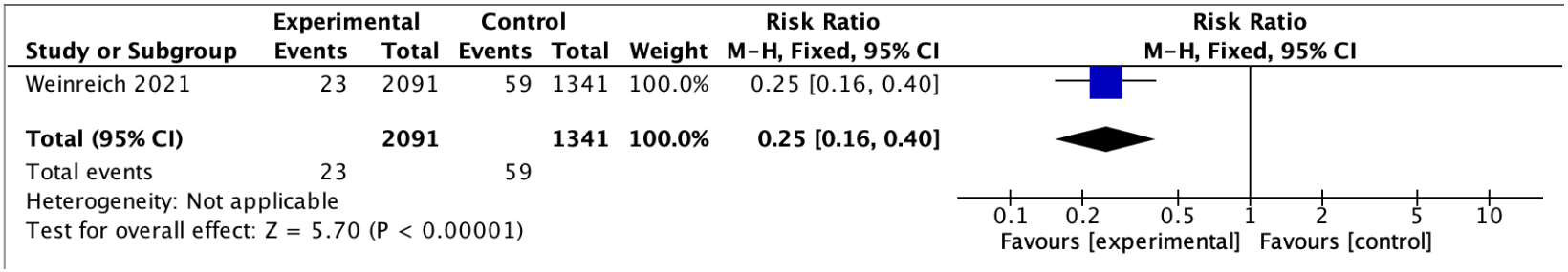

Figure s1c. Forest plot for the outcome of hospitalizations for casirivimab/imdevimab vs. no casirivimab/etesevimab (pooling data for 2400-mg dose and 1200-mg dose)

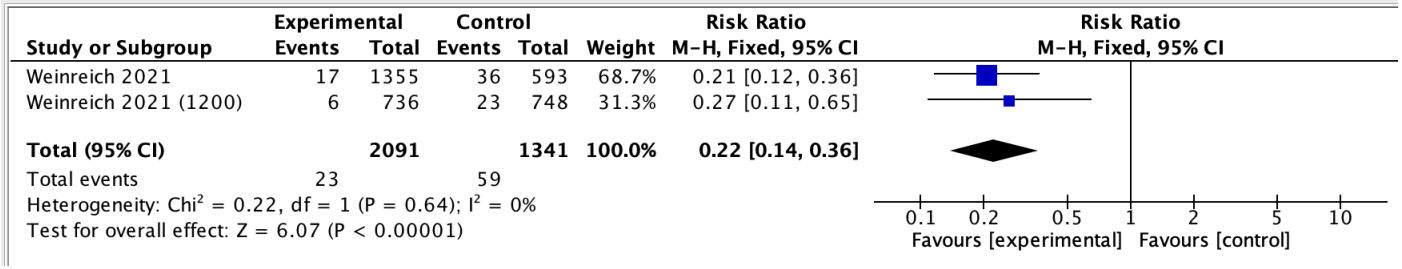

Table s2. Risk of bias for randomized controlled studies (bamlanivimab/etesevimab vs. no bamlanivimab/etesevimab; casirivimab/imdevimab vs. no casirivimab/imdevimab; bamlanivimab monotherapy vs. no bamlanivimab monotherapy)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
ACTIV-3/TICO LY-CoV555 Study Group 2021 [1]							
Chen 2021 [2]							
Dougan 2021 [3]							
Gupta 2021 [4]							
Regeneron Pharmaceuticals, Inc. 2021 [5]							
Weinreich 2021 [6]							

Low	High	Unclear

References for Supplementary Materials

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3. Dougan M, Nirula A, Azizad M, et al. Bamlanivimab plus Etesevimab in Mild or Moderate Covid-19. N Engl J Med **2021**; 385: 1382-92.
4. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early Covid-19 Treatment With SARS-CoV-2 Neutralizing Antibody Sotrovimab. N Engl J Med **2021**; 385: 1941-50.
5. Regeneron Pharmaceuticals, Inc. Phase 3 Trial Shows Regen-CoV™ (Casirivimab with Imdevimab) Antibody Cocktail Reduced Hospitalization or Death by 70% in Non-Hospitalized COVID-19 Patients. Available at: https://investor.regeneron.com/news-releases/news-release-details/phase-3-trial-shows-regen-covtm-casirivimab-imdevimab-antibody. Accessed 9 April 2021.
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