Neutralizing Antibodies for Treatment

Section last reviewed and updated 5/23/2022

Last literature search conducted 4/30/2022

Resources*:*

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

Recommendation 1 (UPDATED 5/23/2022): Among ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease, the IDSA guideline panel suggests treatment with anti-SARS-CoV-2 monoclonal antibodies with activity against the predominant regional variants within 7 days of symptom onset rather than no anti-SARS-CoV-2 monoclonal antibodies. (Conditional recommendation, Moderate certainty of evidence)

- **Remarks**:
    - The evolving nature of variants may necessitate recommendations based on clinical data accrued using agents that are no longer effective against the predominant circulating variants, combined with *in vitro* data for newer agents.
    - 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 treatment with anti-SARS-CoV-2 monoclonal antibodies with activity against the predominant regional variant.
    - Although bebtelovimab has shown *in vitro* activity against Omicron sub-variant BA.2, in contrast with previous monoclonal antibodies, clinical safety and efficacy data are sparse with no comparative data in high-risk patients, limiting use to patients who are not candidates for alternative treatments. Patients who place a higher value on greater certainty of benefit may reasonably decline bebtelovimab.

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 Recommendation 1

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, a theoretical adverse effect of neutralizing antibody therapy, has not been detected in animal models or in clinical studies [2].

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).

As the pandemic has progressed, new SARS CoV-2 variants have emerged with reduced neutralizing susceptibility to various anti-SARS-CoV2 monoclonal antibodies in assays performed using infectious (also referred to as authentic) and pseudotyped viruses. For example, the first two authorized monoclonal antibody combinations, bamlanivimab/etesevimab and casirivimab/imdevimab, have been found to be largely inactive against the Omicron BA.1 and BA.2 variants. As a result, the FDA limited use of these products only to geographic regions where susceptible variants are likely, of which there are none remaining in the U.S.

In a meta-analysis published as a preprint, sotrovimab displayed a median 4.0-fold (IQR: 2.6 – 6.9) reduction in activity against Omicron BA.1 in 34 studies, and a median 17-fold (IQR: 13-30) reduction in activity against Omicron BA.2 in 12 studies [3]. In this same meta-analysis, the combination of cilgavimab/tixagevimab displayed a median 86-fold (IQR: 27-151) reduction in activity against Omicron BA.1 in 15 studies, and a median 5.4-fold (IQR: 3.7-6.9) reduction in activity against Omicron BA.2 in six studies. In eight studies assessing activity against Omicron BA.1 and six studies against Omicron BA.2, bebtelovimab displayed no reduction in activity.

As a result of the high proportion of cases in the U.S. arising from Omicron BA.2, the FDA discontinued the authorization of sotrovimab for treating SARS-CoV-2 infections on April 5, 2022. Despite limited clinical efficacy data, bebtelovimab was authorized for outpatient treatment of high-risk patients with COVID-19 primarily based on its *in vitro* activity.

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 [4-9] (**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) [5]. 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 and were randomized to a single infusion of bamlanivimab 2800 mg/etesevimab 2800 mg or placebo [6]. 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 [4].

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 [8]. 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 [7]. 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 from the PYAH/BLAZE-4 trials were obtained 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, precluding estimates of effectiveness against usual care in this population [10].

Benefits

<u>Bamlanivimab/etesevimab</u>

*[**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. At present (5/19/22), nowhere in the US meets this criterion, and the drug is not available.]* [11]

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. At present (5/19/22), nowhere in the US meets this criterion, and the drug is not available]* [11]

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

*[**NOTE**: On April 5, 2022, sotrovimab is no longer authorized to treat COVID-19 in any U.S. region due to increases in the proportion of COVID-19 cases caused by the Omicron BA.2 sub-variant]* [12]

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: 0.20; 95% CI: 0.01, 4.16, low CoE). The moderate certainty of evidence was due to imprecision as there were no mortality events in those who received sotrovimab and two deaths in the placebo arm. Among ambulatory persons, sotrovimab use was associated with a lower relative risk of hospitalization, compared to no sotrovimab (RR: 0.21; 95% CI: 0.09-0.50; moderate CoE). Persons receiving sotrovimab had a lower progression to severe or critical disease compared to no sotrovimab (RR: 0.25; 95% CI: 0.11, 0.57; 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.

Bamlanivimab monotherapy

*[**NOTE**: On April 16, 2021, FDA revoked EUA for monoclonal antibody bamlanivimab.]* [13]

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 (mean difference [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 (hazard ratio [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).

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: 0.35; 95% CI: 0.18, 0.68; 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).

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).

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 [14, 15].

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 manuscript [15] 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 [16].

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.

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.

Conclusions and research needs for this recommendation

The guideline panel suggests treatment with anti-SARS-CoV-2 monoclonal antibodies with activity against the predominant regional variants within 7 days of symptom onset 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**). Although bebtelovimab has shown *in vitro* activity against Omicron sub-variant BA.2, in contrast with previous monoclonal antibodies, clinical safety and

efficacy data are sparse with no comparative data in high-risk patients, limiting its use to patients who are not candidates for alternative treatments.

Currently, no anti-SARS-CoV-2 monoclonal antibodies studied in clinical trials among hospitalized patients with COVID-19 show in vitro activity against predominant regional variants.

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

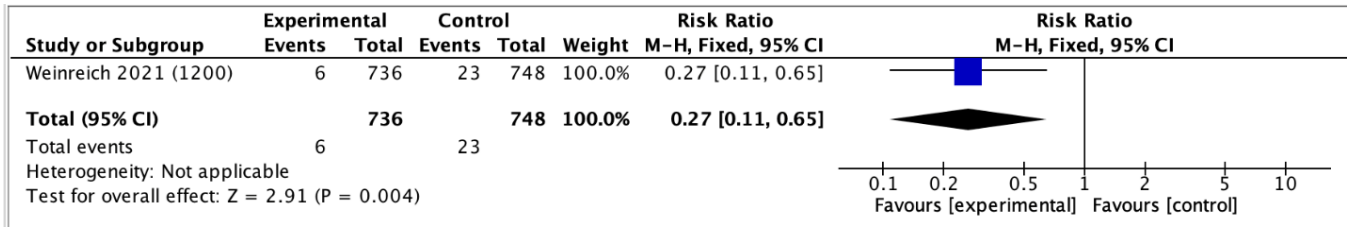
a. Differential post randomization event exclusions (1040 participants) in the original phase (participants without risk factors) is unknown. Publication did not provide an intention to treat analysis. Not rated down for risk of bias as the data in this evidence profile is limited to the amended phase 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.

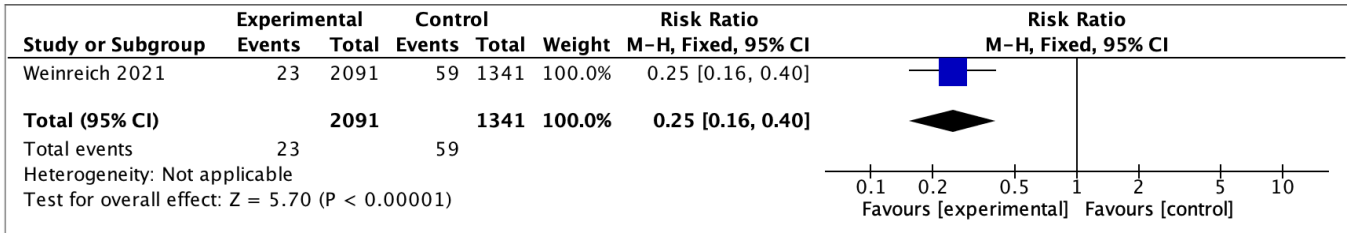
Figure 2a. Forest plot for the outcome of hospitalizations for casirivimab/imdevimab vs. no casirivimab/etesevimab (data for 1200-mg dose only) [1]



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.

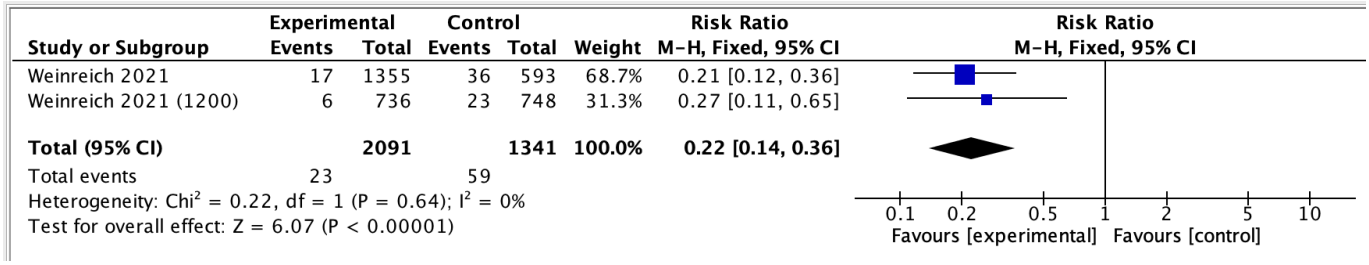
Figure 2b. Forest plot for the outcome of hospitalizations for casirivimab/imdevimab vs. no casirivimab/etesevimab (combining data for 2400-mg dose and 1200-mg dose) [1]



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 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]



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.

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 reviewed and updated 5/17/2022

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	serious [a]	none	0/528 (0.0%)	2/529 (0.4%)	**RR 0.20** (0.01 to 4.16)[b]	**4 fewer per 1,000** (from 9 fewer to 1 more)[c]	⨁⨁⨁◯ MODERATE	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	6/528 (1.1%)	29/529 (5.5%)	**RR 0.21** (0.09 to 0.50)	**43 fewer per 1,000** (from 50 fewer to 27 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	7/528 (1.3%)	28/529 (5.3%)	**RR 0.25** (0.11 to 0.57)	**40 fewer per 1,000** (from 47 fewer to 23 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Serious adverse events (follow-up: 29 days)												
1[1]	randomized trials	not serious	not serious	not serious	serious [a]	none	11/523 (2.1%)	32/526 (6.1%)	**RR 0.35** (0.18 to 0.68)	**40 fewer per 1,000** (from 50 fewer to 19 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. Effect of Sotrovimab on Hospitalization or Death Among High-risk Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial. JAMA **2022**; 327(13): 1236-46.

Table 4. GRADE evidence profile

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

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. Tao K, Tzou PL, Pond SLK, Ioannidis JP, Shafer RW. Susceptibility of SARS-CoV-2 Omicron Variants to Therapeutic Monoclonal Antibodies: Systematic Review and Meta-Analysis. Preprints **2022**: 2022030155. Available at: http://doi.org/10.20944/preprints202203.0155.v1.
4. 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.
5. 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.
6. 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.
7. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Effect of Sotrovimab on Hospitalization or Death Among High-risk Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial. JAMA **2022**; 327(13): 1236-46.
8. 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.
9. 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.
10. 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.
11. 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.

12. U.S. Food and Drug Administration. FDA updates Sotrovimab emergency use authorization. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-sotrovimab-emergency-use-authorization. Accessed 23 May 2022.

13. 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.

14. 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.

15. O'Brien MP, Forleo-Neto E, Sarkar N, et al. Effect of Subcutaneous Casirivimab and Imdevimab Antibody Combination vs Placebo on Development of Symptomatic COVID-19 in Early Asymptomatic SARS-CoV-2 Infection: A Randomized Clinical Trial. JAMA **2021**; 327(5): 432-41.

16. 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.

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/ 2022 [4]	Brazil (6) Canada (1) Peru (1) Spain (3) U.S. (45)	RCT	1057 (528/529)	54.1	Median age: 53 (42-62)	Adults outpatients not on oxygen ,within 5 days of symptom onset, with positive SARS-CoV-2 test, and considered high risk for progression to hospitalization or death	Sotrovimab 500 mg IV administered over one hour	Placebo	Supportive care at discretion of treating provider (4 patients received antivirals, 1 patient monoclonal antibodies)	Proportion of patients with COVID-19 progression through day 29 (hospitalization >24 hours, death) Proportion of patients with all-cause ED visits, hospitalization, or death All-cause mortality Progression to supplemental oxygen or mechanical ventilation Symptom severity and duration measured by a modified	Vir Biotechnology GlaxoSmithKline

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
										FLU-PRO score Adverse events	
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) Concurrent placebo: 50 (37:58)	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 - 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, 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)

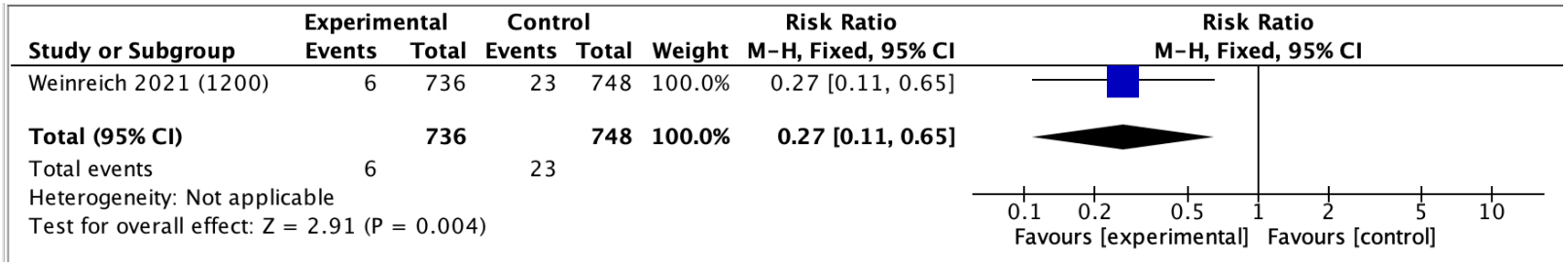


Figure s1b. Forest plot for the outcome of hospitalizations for casirivimab/imdevimab vs. no casirivimab/etesevimab (combining data for 2400-mg dose and 1200-mg dose)

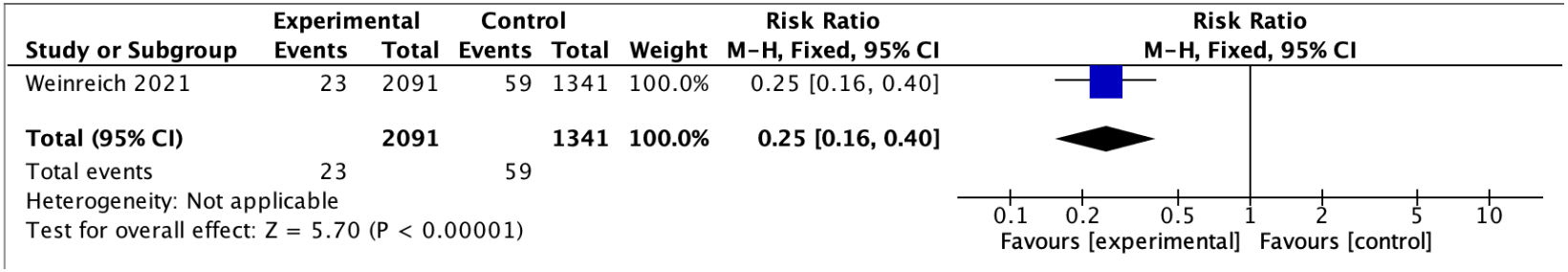


Figure s1c. Forest plot for the outcome of hospitalizations for casirivimab/imdevimab vs. no casirivimab/etesevimab (pooling data for 2400-mg dose and 1200-mg dose)

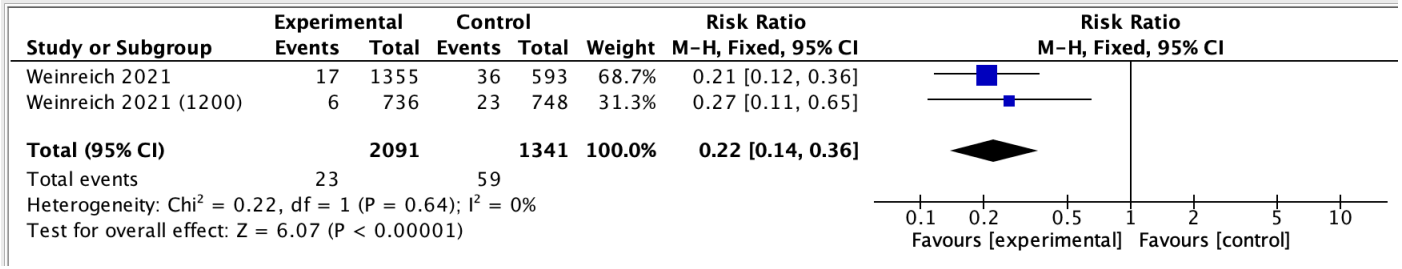


Table s2. Risk of bias for randomized controlled studies (bamlanivimab/etesevimab vs. no bamlanivimab/etesevimab; casirivimab/imdevimab vs. no casirivimab/imdevimab; bamlanivimab monotherapy vs. no bamlanivimab monotherapy)

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 2022 [4]							
Regeneron Pharmaceuticals, Inc. 2021 [5]							
Weinreich 2021 [6]							

Low	High	Unclear

References for Supplementary Materials

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.
2. 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.
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. Effect of Sotrovimab on Hospitalization or Death Among High-risk Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial. JAMA **2022**; 327(13): 1236-46.
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.
6. 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.