EVIDENCE SUMMARY

Should monoclonal antibodies be used in the treatment of children with COVID-19 infection?

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Recommendations

1. There is insufficient evidence to recommend the use of casirivimab-imdevimab as treatment of hospitalized children with COVID-19 infection who have ≥1 risk factor for severe COVID-19.

Certainty of Evidence: Very low
Strength of Recommendation: [None]

Consensus Issues
The recommendation is based on two pre-print studies done on hospitalized patients aged 12 years and above. Although there was a significant decrease in the risk for mechanical ventilation use or death for patients given the intervention, most of these studies were conducted on adults and prior to the emergence of the Omicron variant as the dominant variant of concern.

2. There is insufficient evidence to recommend the use of casirivimab-imdevimab as treatment of non-hospitalized children with COVID-19 infection with ≥1 risk factor for severe COVID-19.

Certainty of Evidence: Low
Strength of Recommendation: [None]

Consensus Issues
The recommendation is based on two pre-print studies and a published one on non-hospitalized patients aged 12 years and above who were both symptomatic and asymptomatic for COVID-19. Although there was a significant decrease in the risk for COVID-19 related hospitalization, ER visit or death and ICU admission, most of these studies were conducted on adults and prior to the emergence of the Omicron variant as the dominant variant of concern.

3. There is insufficient evidence to recommend the use of bamlanivimab-etesevimab as treatment of non-hospitalized children with COVID-19 infection with ≥1 risk factor for severe COVID-19.

Certainty of Evidence: Low
Strength of Recommendation: [None]

Consensus Issues
The recommendation is based on two published studies done on non-hospitalized patients aged 12 years and above. Although there was a significant decrease in the risk for COVID-19 related hospitalization and death, most of these studies were conducted on adults and prior to the emergence of the Omicron variant as the dominant variant of concern.

4. There is insufficient evidence to recommend the use of sotrovimab as treatment of non-hospitalized children with COVID-19 infection.

Certainty of Evidence: Low
Strength of Recommendation: [None]

Consensus Issues
The recommendation is based on one published study done on non-hospitalized patients. Although there was a significant decrease in the risk for COVID-19 related hospitalization and use of supplemental oxygen, the study was conducted on adults and prior to the emergence of the Omicron variant as the dominant variant of concern.

5. We suggest against the use of sotrovimab as treatment of hospitalized children with COVID-19 infection.

Certainty of Evidence: Low
Strength of Recommendation: Weak

Consensus Issues
The recommendation is based on one published study done on hospitalized adult patients that showed inconclusive results in terms of reducing risk for use of supplemental oxygen, mechanical ventilation and all-cause mortality. The low certainty of evidence with the inconclusive results were the reasons why the panel voted against the use of this drug.

6. We suggest against the use of amubarvimab-romlusevimab as treatment for children with COVID-19 infection.

Certainty of Evidence: Low
Strength of Recommendation: Weak

Consensus Issues
The recommendation is based on one published study done on hospitalized adult patients that showed inconclusive results in terms of reducing risk for use of supplemental oxygen, mechanical ventilation and all-cause mortality. The low certainty of evidence with the inconclusive results were the reasons why the panel voted against the use of this drug.

7. We suggest against the use of regdanvimab as treatment for children with COVID-19 infection.

Certainty of Evidence: Low
Strength of Recommendation: Weak

Consensus Issues
The recommendation is based on one pre-print study done on hospitalized adult patients that showed inconclusive results in terms of reducing risk for use of supplemental oxygen and requirement for rescue therapy. The low certainty of evidence with the inconclusive results were the reasons why the panel voted against the use of this drug.

Key Findings

Ten randomized controlled trial (RCTs) evaluated the effect of monoclonal antibodies as treatment for patients with COVID-19. Five RCTs studied casirivimab-imdevimab (REGEN-CoV). Two RCTs studied bamlanivimab-etesevimab. Two RCTs studied sotrovimab, of which one RCT studied both sotrovimab and amubarvimab-romlusevimab. One RCT studied regdanvimab. In all of the RCTs, most of the population studied were adults. Three RCTs included children aged 12 years and above. The overall quality of evidence was very low because of indirectness and imprecision.

There was significantly decreased risk of COVID-19 related hospitalization, ER visit, mechanical ventilation, ICU admission or death for patients given intravenous casirivimab-imdevimab. There was significantly decreased risk of COVID-19 related hospitalization and death for non-hospitalized patients given bamlanivimab-etesevimab. There was significantly decreased risk of hospitalization and supplemental oxygen requirement for non-hospitalized COVID-19 patients given sotrovimab.

For the outcomes assessed, there was inconclusive evidence regarding the benefits of 1) subcutaneous casirivimab-imdevimab on asymptomatic COVID-19 patients, 2) sotrovimab on hospitalized COVID-19 patients, and 3) amubarvimab-romlusevimab and regdanvimab on COVID-19 patients.

Monoclonal antibody therapies were generally safe and well-tolerated by patients. However, the current evidence did not show specific results for children with COVID-19. Further studies are recommended to determine the efficacy of monoclonal antibodies as treatment for children with COVID-19.

Introduction

Sotrovimab, regdanvimab, amubarvimab-romlusevimab, bamlanivimab-etesevimab, and casirivimab-imdevimab are monoclonal antibody therapies developed to neutralize SARS-CoV-2 virus. The SARS-CoV-2 virus enters human cells through binding of the surface spike glycoprotein of the virus with human cells [1]. Monoclonal antibodies inhibit the entry of SARS-CoV-2 into human cells by competitively binding with this glycoprotein [1]. These antibodies have same mechanism of action, but they differ based on which epitope or part of the virus they bind with. Casirivimab-imdevimab are examples of antibodies that target the ACE2 receptor binding domain of the virus [2]. With the emergence of new variants such as Delta and Omicron, some binding sites have been found to be more prone to mutations. Hence new drugs such as sotrovimab have been developed. Sotrovimab targets a highly conserved epitope of SARS-Cov-1 and SARS-Cov-2 outside the ACE2 receptor binding domain and is hypothesized to have more efficacy against new variants [3,4]. This review aims to determine the efficacy and safety of anti-SARS-CoV-2 monoclonal antibody therapy on patients with COVID-19 infection.

Review Methods

We conducted a literature search for studies published in December 2019 to January 5, 2022.
The inclusion criteria for choosing studies were: (1) laboratory confirmed COVID-19 infection diagnosed by RT-PCR or antigen test; (2) patients aged 18 years and below; (3) treatment arm was anti-SARS-CoV-2 monoclonal antibody; (4) comparator was either placebo or standard of care; (5) Phase 2 to Phase 3 randomized controlled studies; (6) outcomes studied were mortality, ICU admission, need for mechanical ventilation, length of hospital stay, days to recovery, viral load or cycle threshold, or worsening of symptoms; (7) any severity of COVID-19 infection.

Studies where the intervention arm was composed of a cocktail of drugs including anti-SARS-CoV-2 monoclonal antibody but used only placebo or standard of care as control were excluded.

Databases searched were Pubmed (MEDLINE), Cochrane Central Register of Controlled Trials (CENTRAL), COVID-NMA, Epistemonikos, ChinaXiv, MedRxiv, BioRxiv, and Google Scholar. Registries for ongoing or completed clinical trials were also searched (Clinicaltrials.gov, ISRCTN registry, World Health Organization International Clinical Trials Registry Platform). A combined MeSH and free text search was done using the following terms: COVID-19, coronavirus, SARS-CoV-2, monoclonal antibody, bamlanivimab, etesevimab, casirivimab, imdevimab, sotrovimab, infant, child, children, and adolescents. References of all studies were reviewed to identify other studies. Searches were limited to human studies. Studies of any language or country were included.

Table 1. PICO criteria for monoclonal antibodies and COVID-19.

Population	Children with COVID-19
Intervention/Exposure	Monoclonal antibody therapy
Comparison	Standard of care, no control, placebo
Outcomes	Mortality, ICU admission, need for mechanical ventilation, length of hospital stay, days to recovery, viral load or cycle threshold, worsening of symptoms

After studies were identified, they were appraised using the critical appraisal tool from Dans et al. Painless Evidence-Based Medicine.. The certainty of evidence was evaluated through GRADE. Review Manager version 5.4 was used for meta-analysis of pooled studies. Pooling was planned if multiple studies are found per treatment.

Results

Of the 1516 records identified from the search, ten RCTs with a total of 21,542 participants were included in this review. The following monoclonal antibodies against SARS-CoV-2 were found: REGEN-CoV (casirivimab-imdevimab), bamlanivimab-etesevimab, sotrovimab, amubarvimab-romlusevimab, and regdanvimab. Five RCTs studied casirivimab-imdevimab. Two RCTs studied bamlanivimab-etesevimab. Two RCTs studied sotrovimab, of which one RCT studied both sotrovimab and amubarvimab-romlusevimab. In that RCT, amubarvimab was referred to as BRII-196 and romlusevimab was referred to as BRII-198 [4]. One RCT studied regdanvimab. A new drug, tixagevimab-cilgavimab, has been approved by the US FDA for pre-exposure prophylaxis of COVID-19 but it will not be included in this review. The evidence regarding tixagevimab-cilgavimab has not yet been published or released as preprint. Only three RCTs included adolescents in the participants [1,2,5]. There were no published RCTs that studied treatment on children younger than 12 years old. The characteristics of included studies are reported in Appendix 3. The presentation of the results of the studies did not allow an analysis of the efficacy and safety of the intervention in children. The evidence presented in this review are derived from the Philippine Living COVID-19 clinical practice guidelines for adults. [6]

Casirivimab plus imdevimab (REGEN-CoV)

Hospitalized COVID-19 patients

The studies of Horby et al. and Somersan-Karakaya et al. enrolled hospitalized COVID-19 patients who were given either 1) IV casirivimab-imdevimab or 2) placebo or standard of care [2,7]. Both studies were still preprints. The study of Horby et al., randomized patients to either IV

casirivimab-imdevimab 8 g or standard of care. It included adolescents 12 to 17 but no data were given regarding the number or outcomes of the adolescents included [2]. Outcomes were all-cause mortality, composite outcome of mechanical ventilation or death, and individual outcomes for mechanical ventilation and death. The outcomes from the Horby study were presented according to serologic status (seronegative, seropositive, and overall). The study of Somersan-Karakaya et al. randomized patients to either IV casirivimab-imdevimab (2.4 g or 8 g) or placebo [7]. Outcomes presented were composite outcome for mechanical ventilation or mortality and adverse events.

Horby et al. showed that for seronegative patients, there was decreased risk for mechanical ventilation or death when given 2.4 g casirivimab-imdevimab (RR 0.53, 95% CI 0.35-0.80) [7]. Regardless of serologic status, the intervention was equivalent to placebo for the composite outcome of mechanical ventilation or death for 8 g casirivimab-imdevimab (pooled RR 0.96, 95% CI 0.89-1.03 I^2=0) [2,7]. The overall certainty of evidence was very low due to serious risk of bias, serious indirectness, and serious imprecision. It must be noted that the study was funded by the manufacturing company. No other studies done by independent researchers has been published. The GRADE evidence profile is in Appendix 5.

Safety
There was significantly lower risk of adverse events (RR 0.82, 95% CI 0.68-0.99) and serious adverse events (RR 0.77, 95% CI 0.63-0.94) in hospitalized patients given casirivimab-imdevimab CoV 2.4 g compared to placebo. Serious adverse events are defined as adverse events that cause life threatening events or death, required hospitalization or prolonged existing hospitalization. As to the casirivimab-imdevimab CoV 8 g compared to control, there was no significant difference in adverse events (RR 0.92, 95% CI 0.78-1.12) and serious adverse events (RR 0.86, 95% CI 0.71-1.04) in hospitalized patients. . Nonserious adverse events were not specified. Serious adverse events included allergy, seizure, oxygen desaturation, and transient loss of consciousness. Some patients had hypotension (4% in casirivimab plus imdevimab compared to 2% in standard of care) and thrombotic events (2% in casirivimab plus imdevimab compared to 1% in standard of care).[2,7]

Non-hospitalized asymptomatic COVID-19 patients
The study by O'Brien et al., which was a preprint, involved early asymptomatic COVID-19 patients aged 12 years and above, who were diagnosed using RT-PCR [5]. Patients were given either casirivimab-imdevimab 1.2 g subcutaneously or placebo. Outcomes were proportion of patients that developed COVID-19 symptoms, duration of symptoms, at least one COVID-19-related hospitalization or ER visit, and adverse events. The results were inconclusive for the outcomes of duration of symptoms (mean difference -5.5 days, 95% CI -13.75 to 2.75) and occurrence of at least 1 COVID-19-related hospitalization or ER visit (RR 0.08, 95% CI 0-1.4). There was decreased risk of adverse events (RR 0.7, 95% CI 0.53-0.92), while for serious adverse events the results were inconclusive RR 0.11, 95% CI 0.01-2.06). Nonserious adverse events were not specified. There were no serious adverse events experienced by the casirivimab-imdevimab group. The overall certainty of evidence was low due to serious indirectness and imprecision. This study was funded by the manufacturing company. The GRADE evidence profile is in Appendix 5.

Non-hospitalized COVID-19 patients (regardless if asymptomatic or symptomatic)
Two studies by Weinreich et al. involved adult outpatient COVID-19 patients [8,9]. The Phase 1-2 results of the trial were available as a preprint [8]. The Phase 3 results of the trial have been published [9]. In the Phase 1-2, patients were given intravenous casirivimab-imdevimab (2.4 g or 8 g) or placebo. In the Phase 3 trial, patients were given intravenous casirivimab-imdevimab (1.2 g, 2.4 g, or 8 g) or placebo. Patients in the phase 3 trial had at least 1 risk factor for severe COVID-

19 infection (see Appendix 3). Outcomes were COVID-19 related hospitalization or all cause mortality, time to symptom resolution, proportion of patients with hospitalization, need for mechanical ventilation or ICU admission, and adverse events.

There was significantly decreased risk of COVID-related hospitalization, ER visit or all-cause mortality in patients given 1.2 g casirivimab-imdevimab compared to control (RR 0.27, 95% CI 0.13-0.56). There was inconclusive evidence for the outcome of need for mechanical ventilation (RR 0.51, 95% CI 0.05-5.59) and ICU admission (RR 0.44, 95% CI 0.11-1.68).[9]

There was significantly decreased risk of COVID-related hospitalization, ER visit or all-cause mortality in patients given 2.4 g casirivimab-imdevimab (pooled RR 0.36, 95% CI 0.24-0.54, I^2=0), as well as ICU admission (RR 0.33, 95% CI 0.13-0.83). There was inconclusive evidence for the outcome of need for mechanical ventilation (RR 0.16, 95% CI 0.02-1.37).[8,9]

There was decreased risk of COVID-related hospitalization, ER visit or all-cause mortality in patients given 8 g casirivimab-imdevimab (pooled RR 0.37, 95% CI 0.21-0.62, I^2=0). There was no specific data for the outcomes of need for mechanical ventilation and ICU admission for the 8 g dose. [8,9]

The overall certainty of evidence was low due to serious indirectness and imprecision. The two studies were funded by the manufacturing company. The GRADE evidence profile is in Appendix 5.

Safety
There was decreased risk of serious adverse events in the casirivimab-imdevimab group, regardless of the dose (RR 0.27; 95% CI 0.14-0.54) [6]. The pooled RR for casirivimab-imdevimab 2.4 g and 8 g were 0.35 (95% CI 0.23-0.54 I^2=15) and 0.41 (95% CI 0.25-0.67 I^2=0), respectively [6,8]. Most common adverse events were infusion-related reactions or complications of COVID-19. There were two treatment-emergent adverse events leading to death: one presenting with dyspnea and the other presenting with hypoxia.[8,9]

Bamlanivimab plus etesevimab

The studies of Dougan et al. and Gottlieb et al. compared the efficacy of IV bamlanivimab 2.8 g plus etesevimab 2.8 g compared to placebo on non-hospitalized COVID-19 patients [1,10]. The study by Dougan et al. involved patients aged 12 years and above with risk factor for severe COVID-19, but no results specific for adolescents were provided [1]. The outcomes were COVID-19 related hospitalization or all-cause mortality, time to resolution of symptoms, and adverse events. The study by Gottlieb et al. only involved adult patients with mild to moderate COVID-19 infection [10]. Outcomes were change in viral load, time to recovery, COVID-19 related hospitalization or all-cause mortality, and adverse events.

There was a decreased risk of COVID-19 related hospitalization and deaths (pooled RR 0.28, 95% CI 0.15-0.53 I^2=0). There was no significant difference in adverse events (pooled RR 0.87, 95% CI 0.49-1.57 I^2=75) and serious adverse events (RR 1.4, 95% CI 0.49-4.01 I^2=0) between placebo and treatment. Most common adverse events included nausea, rash/pruritus, and dizziness. The serious adverse events in the Dougan et al. study were not specified. The serious adverse event in the Gottlieb et al. study was a urinary tract infection which was considered unrelated to study drug by the investigators. The overall certainty of evidence was low due to serious indirectness and imprecision. Both studies were funded by the manufacturing company. The GRADE evidence profile is in Appendix 5. [1,10]

Sotrovimab

In the studies of Gupta et al. and Self et al., adult COVID-19 patients were given either IV sotrovimab 500 mg or control [3,4]. The study of Gupta et al. involved non-hospitalized patients with mild to moderate COVID-19 infection but with risk factors [3]. Risk factors included were age ≥55 years old, diabetes, obesity, chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, and moderate to severe asthma. The control was standard of care. The outcomes were hospitalization or all-cause mortality, adverse events, requirement for supplemental oxygen, mechanical ventilation or ICU admission. The study by Self et al. involved hospitalized patients [4]. The control was placebo. The outcomes were time to clinical recovery, all-cause mortality, and composite safety outcome of death, serious adverse events, organ failure, and serious coinfection.

Hospitalized COVID-19 patients
For hospitalized patients, there was inconclusive evidence for the outcomes of need for mechanical ventilation (RR 0.65, 95% CI 0.11-3.86) and all-cause mortality (RR 1.05, 95% CI 0.51-2.18). The intervention was equivalent to placebo for the outcome of need for supplemental oxygen (RR 0.9, 95% CI 0.71-1.15). There was no significant difference between sotrovimab and placebo in the outcomes of composite safety outcome (RR 0.88, 95% CI 0.64-1.2) and incidence of infusion reactions (RR 1.26, 95% CI 0.65-2.45). One patient had anaphylaxis. The overall certainty of evidence was low due to serious indirectness and imprecision. The GRADE evidence profile is in Appendix 5. [4]

Non-hospitalized COVID-19 patients
For non-hospitalized patients, sotrovimab significantly decreased the risk for hospitalization (RR 0.14, 95% CI 0.04-0.48) and need for supplemental oxygen (RR 0.11, 95% CI 0.02-0.45). There was inconclusive evidence for the outcomes of need for mechanical ventilation (RR 0.2, 95% CI 0.01-4.16), ICU admission (RR 0.09, 95% CI 0.01-1.64), and all-cause mortality (RR 0.33, 95% CI 0.01-8.18). There was no significant difference in adverse events (RR 0.87, 95% CI 0.66-1.16). Most common adverse event that occurred was diarrhea. One patient had infusion-related reaction (dyspnea). There was decreased risk of serious adverse events (RR 0.27, 95% CI 0.12-0.63). Serious adverse events were hospitalization for COVID-19-related causes. The overall certainty of evidence was low due to serious indirectness and imprecision. This study was funded by the manufacturing company. The GRADE evidence profile is in Appendix 5. [3]

Amubarvimab plus romlusevimab

In one study, adult COVID-19 patients were given either IV combination of amubarvimab 1 g plus romlusevimab 1 g or placebo. The study involved hospitalized patients. The outcomes were time to clinical recovery, all-cause mortality, and composite safety outcome of death, serious adverse events, organ failure, and serious coinfection. The intervention was equivalent to placebo for the outcome of need for supplemental oxygen (RR 0.9, 95% CI 0.7-1.15). There was inconclusive evidence for the outcomes of need for mechanical ventilation (RR 1.35, 95% CI 0.31 to 5.94) and all-cause mortality (RR 1.17, 95% CI 0.57-2.38). There was no significant difference between treatment and placebo for the composite safety outcome (RR 1.03, 95% CI 0.76-1.39) and incidence of infusion reactions (RR 1.66, 95% CI 0.88-3.12). One patient had anaphylaxis. The overall certainty of evidence was low due to serious indirectness and imprecision. The GRADE evidence profile is in Appendix 5. [4]

Regdanvimab

The study by Eom et al., which was a preprint, involved IV regdanvimab. It enrolled adult patients with mild to moderate COVID-19 infection [11]. Patients were given either 40 mg/kg or 80 mg/kg IV regdanvimab or placebo. We analyzed 40 mg/kg regdanvimab versus placebo, basing from the evidence summary in the Philippine adult living COVID-19 clinical practice guidelines [6]. Outcomes were proportion of patients with clinical recovery at days 7, 14, and 28, requirement for hospitalization, oxygen therapy, mechanical ventilation, ICU admission, rescue therapy (use of other anti-SARS-CoV-2 therapy indicating worsening of symptoms), and all-cause mortality.

The results were inconclusive for the outcomes of hospitalization (RR 0.45; 95% CI 0.14-1.42), need for supplemental oxygen (RR 0.45; 95% CI 0.14-1.42), requirement for rescue therapy (RR 0.48; 95% CI 0.2-1.12), and total adverse events (RR 0.91; 95% CI 0.65-1.29). None of the patients required mechanical ventilation or ICU admission. There was no mortality as well. The most common adverse event was hypertriglyceridemia. One patient had infusion-related reaction, which was fever and dyspnea. The overall certainty of evidence was low due to serious indirectness and imprecision. This study was funded by the manufacturing company. The GRADE evidence profile is in Appendix 5. [11]

There are seven ongoing randomized controlled trials involving children. We plan to include results of these randomized controlled trials once available.

Enrollment of participants in the studies included in this review were done from second half of 2020 until May 2021 [1-5,7-11]. With the emergence of new SARS-CoV-2 variants of concern, the newer variants may be resistant against the currently available anti-SARS-CoV-2 monoclonal antibodies. In November 2021, a new variant of concern, the Omicron variant, was first detected and in January 2022, it has become the dominant variant in the Philippines [12, 13]. In vitro studies showed resistance of the Omicron variant to casirivimab plus imdevimab and bamlanivimab plus etesevimab [14, 15]. Since all studies included in this review were done prior to the detection of the Omicron variant, the results of the studies may not be applicable in the current times.

Other Considerations (Evidence to Decision)

The essential elements of the evidence-to-decision framework are presented in Appendix 7.

Recommendations from Other Groups

Table 2. Summary of Recommendations from Other Groups

Group	Recommendation
Philippine Adult Living COVID-19 CPG Jan. 10, 2022 [6]	For Adults: Bamlanivimab and etesevimab combination was suggested for treatment for mild to moderate, non-hospitalized COVID-19 patients with at least 1 risk factor* for progression to severe disease. *(Low quality of evidence; Weak recommendation)* **Risk factors for severe COVID-19: age ≥65 years, body-mass index ≥35 kg/m2, cardiovascular disease (including hypertension), chronic lung disease (including asthma), chronic metabolic disease (including diabetes), chronic kidney*

	disease (including receipt of dialysis), chronic liver disease, and immunocompromised conditions. Casirivimab plus imdevimab was suggested as treatment for symptomatic, non-hospitalized patients with at least 1 risk factor* for severe COVID-19. (Moderate certainty of evidence; Weak recommendation) **Risk factors: age >50 years, obesity, cardiovascular disease (including hypertension), chronic lung disease (including asthma), chronic metabolic disease (including diabetes), chronic kidney disease (including receipt of dialysis), chronic liver disease, and immunocompromised conditions.* Subcutaneous use of casirivimab + imdevimab was suggested as day 4 post-exposure prophylaxis for COVID-19 close contacts*, ages 12 years and above weighing at least 40 kilograms, who are at risk for severe disease or hospitalization**. *(Moderate certainty of evidence; weak recommendation)* ***This includes the following people: elderly; BMI >25; those with chronic diseases such as hypertension, diabetes, and chronic kidney disease; those who are not expected to mount an adequate immune response to the vaccine due to immunosuppressive therapy or those in an immunocompromised state.*
WHO Dec. 7, 2021 [16]	No specific recommendations for children and adolescents
American Academy of Pediatrics Feb. 13, 2022 [17]	Use of SARS-CoV-2 mAb for all indications remains investigational in children and adolescents. An individual risk/benefit assessment should be performed when considering mAb for a child/adolescent who is at high risk for COVID-19. Sotrovimab and tixagevimab copackaged with cilgavimab (Evusheld) are the only mAb anticipated to have retained neutralizing activity against the SARS-CoV-2 Omicron variant. Only high-risk children ≥12 yo and ≥40 kg would be eligible to receive sotrovimab or tixagevimab and cilgavimab (Evusheld) if they meet the following criteria: (1) Sotrovimab for COVID-19 treatment: Non-hospitalized patient ≥12 yo and ≥40 kg, and Mild to moderate COVID-19, and

	Within 10 days of symptom onset, and High risk for progressing to severe COVID-19 and/or hospitalization (2) Tixagevimab and cilgavimab (Evusheld) for COVID-19 preexposure prophylaxis: ≥12 years of age and ≥40 kg, and No SARS-CoV-2 infection or exposure, and Moderate or severe immunocompromised or vaccination is contraindicated
US NIH Jan 19, 2022 [18]	For children: There is insufficient evidence for the Panel to recommend either for or against the use of anti-SARS-CoV-2 monoclonal antibody products for children with COVID-19 who are not hospitalized but who have risk factors for severe disease. For adults: The Panel recommends against the use of bamlanivimab plus etesevimab and casirivimab plus imdevimab for high risk, non-hospitalized patients with mild to moderate COVID-19 due to reduced activity against Omicron variant. The Panel recommends using sotrovimab to treat non-hospitalized patients with mild to moderate COVID-19 who are at high risk of clinical progression. The Panel recommends using tixagevimab plus cilgavimab as pre-exposure prophylaxis for adults and adolescents (aged ≥12 years and weighing ≥40 kg) for: (1) moderately to severely immunocompromised and; (2) not able to be fully vaccinated due to a history of severe reactions to a COVID-19 vaccine or any of its components.
Australian National COVID-19 Clinical Evidence Taskforce Dec 22, 2021 [19]	Recommendations are not based on evidence but on consensus Consensus recommendations: Consider using, in exceptional circumstances, casirivimab plus imdevimab within 7 days of symptom onset in *children and adolescents aged 12 years and over and weighing at least 40 kg with mild COVID-19* who are at high risk of deterioration. Consider using, in exceptional circumstances, casirivimab plus imdevimab in *seronegative* children and adolescents aged 12 years and over and weighing at least 40 kg with moderate to critical COVID-19 who are at high risk of disease progression.

Research Gaps

There are limited trials studying the efficacy of monoclonal antibodies for treatment of children with COVID-19. Studies that have been published were mostly composed of adult patients. Some studies that included adolescents in their population did not publish the outcomes specific for the adolescents. There are seven (7) ongoing trials studying monoclonal antibodies as treatment specifically for children with COVID-19 (Appendix 6).

References

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Appendix 1. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	((“Child"[Mesh] OR "Child, Preschool"[Mesh] OR "Adolescent"[Mesh] OR "Infant"[Mesh]) OR (children[tiab]) OR (adolescent[tiab])) AND ((“COVID-19"[Mesh]) OR (COVID-19[tiab]) OR (coronavirus[tiab]) OR (SARS-CoV-2[tiab])) AND ((“Antibodies, Monoclonal"[Mesh]) OR (bamlanivimab[tiab]) OR (etesevimab[tiab]) OR (casirivimab[tiab]) OR (imdevimab[tiab]) OR (sotrovimab[tiab]))	Jan. 9, 2022	112	3
CENTRAL	Mesh of COVID-19 AND monoclonal antibody AND child	Jan. 9, 2022	3	1
COVID-NMA Initiative	Treatment name: monoclonal antibodies	Jan. 9, 2022	58	6
Google Scholar	Monoclonal antibody AND COVID-19 AND children AND randomized controlled trial	Jan. 9, 2022	895	0
Epistemonikos	(title:(covid-19) OR abstract:(covid-19)) AND (title:(children) OR abstract:(children)) AND (title:(monoclonal antibody) OR abstract:(monoclonal antibody))	Jan. 9, 2022	9	0
ClinicalTrials.gov	condition:covid-19 age:children intervention:monoclonal antibody	Jan. 9, 2022	17	8
Chinese Clinical Trial Registry	Monoclonal antibody	Jan. 9, 2022	0	0
WHO trials ITCRP	Monoclonal antibody AND COVID-19 Search filter: clinical trials in children	Jan. 9, 2022	2	1
Chinaxiv.org	Monoclonal antibody AND COVID-19 AND children	Jan. 9, 2022	0	0
Medrxiv.org	Children AND COVID-19 AND “monoclonal antibody”	Jan. 9, 2022	357	1
Medrxiv.org	Casirivimab AND children AND COVID-19	Jan. 9, 2022	25	0
Medrxiv.org	Bamlanivimab AND children AND COVID-19	Jan. 9, 2022	30	0
Medrxiv.org	Sotrovimab AND children AND COVID-19	Jan. 9, 2022	8	0
Biorxiv.org	Monoclonal antibody AND COVID-19 AND children	Jan. 9, 2022	0	0

Appendix 2. Characteristics of Included Studies

Casirivimab plus imdevimab (REGEN-CoV)

Author	Study design	Population and Duration of Follow-up	Intervention	Control	Outcomes
Horby et al. Preprint	RCT Open-label, platform design	Age: 12 years and above Confirmed COVID- 19 patients admitted to the hospitals N=11,464 Follow up: 28 days	Casirivimab plus imdevimab 8000mg cocktail IV	Standard of care	PRIMARY: All-cause mortality SECONDARY: Discharge alive from hospital, use of invasive ventilation among patients, serious adverse events
O'Brien et al. Preprint	RCT	Age: 12 years and above Asymptomatic individuals with known exposure to COVID-19, tested positive for COVID- 19 at baseline N = 314 Follow up: 28 days efficacy assessment, 7 month follow up	Casirivimab plus imdevimab 1200mg cocktail SC	Placebo	PRIMARY: Development of COVID-19 symptoms SECONDARY: Duration of COVID-19 symptoms, number of weeks of high viral load, safety
Somersan-Karakaya et al. Preprint	RCT	Age: 18 years and above Hospitalized COVID-19 patients with little to no oxygen support N = 1336 Follow up: 169 days	Casirivimab plus imdevimab 2400mg cocktail IV Casirivimab plus imdevimab 8000mg cocktail IV	Placebo	PRIMARY: Time-weighted average (TWA) daily change from baseline viral load until day 7, progression of disease (need for invasive mechanical ventilation or death) SECONDARY: All-cause mortality, discharge from/readmission to hospital, safety
Weinreich et al. Published	RCT	Age: 18 years and above Ambulatory confirmed COVID-19 patients with ≥1 risk factor for severe COVID-19 Risk factors: >50 yo, obesity, cardiovascular disease (including hypertension), chronic lung disease (including asthma), chronic meta- bolic disease (including diabetes), chronic kidney disease (including receipt of dialysis), chronic liver disease, and an immunocompromised condition (immunosuppression or receipt of immunosuppressants)	Casirivimab plus imdevimab 1200mg cocktail IV Casirivimab plus imdevimab 2400mg cocktail IV Casirivimab plus imdevimab 8000mg cocktail IV	Placebo	PRIMARY: COVID-19 related hospitalization or all-cause death SECONDARY: Time to symptom resolution, adverse events

		N = 4,057 Follow up: 29 days			
Weinreich et al. Preprint	RCT	Age: 18 years and above Non-hospitalized COVID-19 patients N= 799 Follow up: 29 days	Casirivimab plus imdevimab 2400mg cocktail IV Casirivimab plus imdevimab 8000mg cocktail IV	Placebo	PRIMARY: TWA change in viral load from baseline through day 7 SECONDARY: At least 1 COVID-19- related medically- attended visit (MAV), safety

Bamlanivimab plus etesevimab

Author	Study design	Population	Intervention	Control	Outcomes
Gottlieb et al.	RCT	Age: 18 years and above Non-hospitalized confirmed COVID-19 patients with mild to moderate symptoms N=268 Follow up: 29 days	Bamlanivimab 2800 mg + Etesevimab 2800 mg IV	Placebo	PRIMARY: Change in SARS- CoV-2 log viral load at day 11 SECONDARY: Time to viral clearance, time to clinical recovery, COVID-19 related hospitalization or all- cause death, adverse events
Dougan et al.	RCT	Age: 12 years and above Ambulatory confirmed COVID-19 patients with ≥1 risk factor for severe COVID-19 Risk factors: BMI ≥ 85th percentile for age and sex, according to CDC growth charts; sickle cell disease; congenital or acquired heart disease; neurodevelopmental disorders such as cerebral palsy; dependence on a medical-related mechanical device or procedure such as tracheostomy, gastrostomy, or positive- pressure ventilation (not related to Covid-19); asthma, a reactive airway, or another chronic respiratory disease; type 1 or type 2 diabetes mellitus; and an immunocompromised condition or receipt of an immunosuppressive treatment N=1035 Follow up: 29 days	Bamlanivimab 2800 mg + Etesevimab 2800 mg IV	Placebo	PRIMARY: COVID-19 related hospitalization or all-cause death SECONDARY: Time to sustained patient-reported resolution of symptoms, reduction in viral load, time to viral clearance, adverse events

Sotrovimab and Ambuarvimab plus romlusevimab

Author	Study design	Population	Intervention	Control	Outcomes
Gupta et al.	RCT	Age: 18 years and above Mild to moderate High risk, non-hospitalized COVID-19 patients Risk factors: Older age (≥55 years), diabetes, obesity, CKD, CHF, COPD, moderate to severe asthma N=583 Follow up: 168 days	IV Sotrovimab 500 mg	Placebo	Primary: Hospitalization or All cause mortality through day 29 Secondary: Emergency department visit, requirement for supplemental oxygen Safety: Adverse events FF up 72 days
Self et al.	RCT	Adults (≥18 yo) hospitalized COVID-19 patients N=546 Follow up: 90 days	IV single dose Sotrovimab 500 mg Amubarvimab (BRII-196) 1000mg plus Romlusevimab (BRII-198) 1000mg	Placebo	Primary: Time to clinical recovery Secondary: all cause mortality, time to discharge Safety: composite of death, serious adverse events, organ failure, serious coinfection

Regdanvimab

Author	Study design	Population	Intervention	Control	Outcomes
Eom et al. 2021 Preprint	RCT	Age ≥ 18 years, with COVID-19 infection mild to moderate infection N=307 Follow up: 180 days	Regdanvimab at 2 doses (40 mg/kg and 80 mg/kg) as IV infusion, single dose	Matching placebo	Time to conversion to negative RT PCR; Time to clinical recovery ; Proportion of patients with clinical recovery; Proportion of patients requiring hospitalization, oxygen therapy, mechanical ventilation, ICU admission, or rescue therapy; All cause mortality; Proportion of patients with conversion to negative RT PCR

Appendix 3. Detailed Study Appraisal

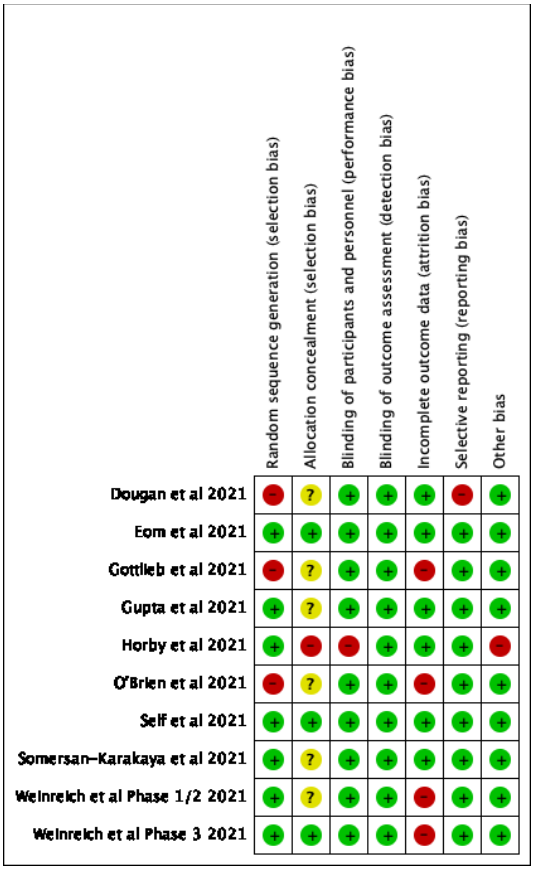

Fig. 1. Risk of bias summary table

Dougan et al. 2021

Appraising Directness	
Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)?	No. Adolescents were included in patients but the outcomes were not reported specifically for adolescents.
Appraising Validity	
1. Were patients randomly assigned to treatment groups?	Yes
2. Was allocation concealed?	It was not indicated.
3. Were baseline characteristics similar at the start of the trial?	No. There were more patients with <96% O2 saturation in the placebo group (90/516 or 20.6%) than treatment group (106/514 or 17.4%).
2. Were patients blinded to treatment assignment?	Yes
3. Were caregivers blinded to treatment assignment?	No
4. Were outcome assessors blinded to treatment assignment?	Yes
5. Were all patients analyzed in the groups to which they were originally randomized?	Yes
6. Was follow-up rate adequate?	Yes
Appraising Results	
1. How large was the effect of treatment?	See GRADE Evidence Profile
2. How precise was the estimate of the treatment effect?	

Eom et al. 2021

Appraising Directness	
Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)?	No. The patient population was only composed of adults.
Appraising Validity	
1. Were patients randomly assigned to treatment groups?	Yes
2. Was allocation concealed?	Yes
3. Were baseline characteristics similar at the start of the trial?	Yes
7. Were patients blinded to treatment assignment?	Yes
8. Were caregivers blinded to treatment assignment?	Yes
9. Were outcome assessors blinded to treatment assignment?	Yes
10. Were all patients analyzed in the groups to which they were originally randomized?	Yes
11. Was follow-up rate adequate?	Yes
Appraising Results	
1. How large was the effect of treatment?	See GRADE Evidence Profile
2. How precise was the estimate of the treatment effect?	

Gottlieb et al. 2021

Appraising Directness	
Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)?	No. The patient population was only composed of adults.
Appraising Validity	
1. Were patients randomly assigned to treatment groups?	Yes
2. Was allocation concealed?	No. It was not mentioned.
3. Were baseline characteristics similar at the start of the trial?	No. Patients $\geq$ 65 years old were greater in placebo (23/156 or 14.7%) than in treatment (13/112 or 11.6%). Patients with BMI $\geq$ 30 but <40 were greater in placebo (63/152 or 41.4%) than in treatment (33/109 or 30.3%). Patients with risk factors for severe COVID-19 were greater in placebo (105/156 or 67.3%) than in treatment (67/112 or 59.8%)
12. Were patients blinded to treatment assignment?	Yes
13. Were caregivers blinded to treatment assignment?	No
14. Were outcome assessors blinded to treatment assignment?	Yes
15. Were all patients analyzed in the groups to which they were originally randomized?	No
16. Was follow-up rate adequate?	Yes
Appraising Results	
1. How large was the effect of treatment?	See GRADE Evidence Profile
2. How precise was the estimate of the treatment effect?	

Gupta et al. 2021

Appraising Directness	
Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)?	No. The patient population was only composed of adults.
Appraising Validity	
1. Were patients randomly assigned to treatment groups?	Yes
2. Was allocation concealed?	No. It was not mentioned.
3. Were baseline characteristics similar at the start of the trial?	Yes
17. Were patients blinded to treatment assignment?	Yes
18. Were caregivers blinded to treatment assignment?	No
19. Were outcome assessors blinded to treatment assignment?	Yes

20. Were all patients analyzed in the groups to which they were originally randomized?	Yes
21. Was follow-up rate adequate?	Yes
Appraising Results	
1. How large was the effect of treatment?	See GRADE Evidence Profile
2. How precise was the estimate of the treatment effect?	

Horby et al. 2021

Appraising Directness	
Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)?	No. Adolescents were included in patients but the outcomes were not reported specifically for adolescents.
Appraising Validity	
1. Were patients randomly assigned to treatment groups?	Yes
2. Was allocation concealed?	No. This trial was open-label.
3. Were baseline characteristics similar at the start of the trial?	Yes
22. Were patients blinded to treatment assignment?	No. This is an open-label, platform trial with factorial design. Interactions between treatment can make it difficult to identify if outcome is due to the casirivimab plus imdevimab or due to other treatments the patients received.
23. Were caregivers blinded to treatment assignment?	No
24. Were outcome assessors blinded to treatment assignment?	Yes
25. Were all patients analyzed in the groups to which they were originally randomized?	Yes
26. Was follow-up rate adequate?	Yes
Appraising Results	
1. How large was the effect of treatment?	See GRADE Evidence Profile
2. How precise was the estimate of the treatment effect?	

O'Brien et al. 2021

Appraising Directness	
Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)?	No. Adolescents were included in patients but the outcomes were not reported specifically for adolescents.
Appraising Validity	
1. Were patients randomly assigned to treatment groups?	Yes
2. Was allocation concealed?	No. It was not mentioned.
3. Were baseline characteristics similar at the start of the trial?	No. There were more patients ≥ 65 years of age (13/106 or 12.5% vs 8/101 or 8%), with diabetes (11/106 or 10.6% vs 5/101 or 5%), and with chronic lung disease (10/106 or 9.6% vs 1/101 or 1%) in the placebo group than in the casirivimab plus imdevimab group.
27. Were patients blinded to treatment assignment?	Yes
28. Were caregivers blinded to treatment assignment?	No
29. Were outcome assessors blinded to treatment assignment?	Yes
30. Were all patients analyzed in the groups to which they were originally randomized?	No
31. Was follow-up rate adequate?	Yes
Appraising Results	
1. How large was the effect of treatment?	See GRADE Evidence Profile
2. How precise was the estimate of the treatment effect?	

Self et al. 2021

Appraising Directness	
Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)?	No. The patient population was only composed of adults.
Appraising Validity	
1. Were patients randomly assigned to treatment groups?	Yes
2. Was allocation concealed?	Yes

3. Were baseline characteristics similar at the start of the trial?	Yes
32. Were patients blinded to treatment assignment?	Yes
33. Were caregivers blinded to treatment assignment?	No
34. Were outcome assessors blinded to treatment assignment?	Yes
35. Were all patients analyzed in the groups to which they were originally randomized?	Yes
36. Was follow-up rate adequate?	Yes
Appraising Results	
1. How large was the effect of treatment?	See GRADE Evidence Profile
2. How precise was the estimate of the treatment effect?	

Somersan-Karakaya et al. 2021

Appraising Directness	
Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)?	No. The patient population was only composed of adults.
Appraising Validity	
1. Were patients randomly assigned to treatment groups?	Yes
2. Was allocation concealed?	No. It was not mentioned.
3. Were baseline characteristics similar at the start of the trial?	Yes
37. Were patients blinded to treatment assignment?	Yes
38. Were caregivers blinded to treatment assignment?	No
39. Were outcome assessors blinded to treatment assignment?	Yes
40. Were all patients analyzed in the groups to which they were originally randomized?	Yes
41. Was follow-up rate adequate?	Yes
Appraising Results	
1. How large was the effect of treatment?	See GRADE Evidence Profile
2. How precise was the estimate of the treatment effect?	

Weinreich et al. 2021 (Phase 1/2)

Appraising Directness	
Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)?	No. The patient population was only composed of adults.
Appraising Validity	
1. Were patients randomly assigned to treatment groups?	Yes
2. Was allocation concealed?	No. It was not mentioned.
3. Were baseline characteristics similar at the start of the trial?	Yes
42. Were patients blinded to treatment assignment?	Yes
43. Were caregivers blinded to treatment assignment?	No
44. Were outcome assessors blinded to treatment assignment?	Yes
45. Were all patients analyzed in the groups to which they were originally randomized?	No
46. Was follow-up rate adequate?	Yes
Appraising Results	
1. How large was the effect of treatment?	See GRADE Evidence Profile
2. How precise was the estimate of the treatment effect?	

Weinreich et al. 2021 (Phase 3)

Appraising Directness

Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)?	No. The patient population was only composed of adults.
Appraising Validity	
1. Were patients randomly assigned to treatment groups?	Yes
2. Was allocation concealed?	Yes
3. Were baseline characteristics similar at the start of the trial?	Yes
47. Were patients blinded to treatment assignment?	Yes
48. Were caregivers blinded to treatment assignment?	No
49. Were outcome assessors blinded to treatment assignment?	Yes
50. Were all patients analyzed in the groups to which they were originally randomized?	No
51. Was follow-up rate adequate?	Yes
Appraising Results	
1. How large was the effect of treatment?	See GRADE Evidence Profile
2. How precise was the estimate of the treatment effect?	

Appendix 4A. GRADE Evidence Profile: Casirivimab-imdevimab (hospitalized)

Author(s): Furqaan I. Lim, MD
Question: Should intravenous casirivimab plus imdevimab (REGEN-CoV) compared to standard of care be used as treatment for COVID-19 in hospitalized children?
Setting:
Bibliography:
Horby PW & Landray MJ. Casirivimab and imdevimab in patients admitted to hospital with COVID- 19 (RECOVERY): a randomized, controlled, open-label, platform trial. 2021. Preprint. 10.1101/2021.6.15.21258542.
Somersan-Karakaya S, Mylonakis E, Menon VP, Wells JC, Ali S, Sivapalasingam S, et al. REGEN- COV for Treatment of Hospitalized Patients with Covid-19. 2021. Preprint. 10.1101/2021.11.05.21265656.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Casirivimab-imdevimab	standard of care	Relative (95% CI)	Absolute (95% CI)		
mechanical ventilation or mortality 2.4g (seronegative patients only)												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	32/406 (7.9%)	58/393 (14.8%)	**RR 0.53** (0.35 to 0.80)	**69 fewer per 1,000** (from 96 fewer to 30 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
adverse events 2.4g												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	149/672 (22.2%)	180/667 (27.0%)	**RR 0.82** (0.68 to 0.99)	**49 fewer per 1,000** (from 86 fewer to 3 fewer)	⨁⨁⨁◯ Moderate	IMPORTANT
serious adverse events 2.4g												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	135/672 (20.1%)	174/667 (26.1%)	**RR 0.77** (0.63 to 0.94)	**60 fewer per 1,000** (from 97 fewer to 16 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
mechanical ventilation or mortality 8g (regardless of serologic status)												
2	randomised trials	serious[b]	not serious	serious[c]	serious[d]	none	1139/4954 (23.0%)	1209/5035 (24.0%)	**RR 0.96** (0.89 to 1.03)	**10 fewer per 1,000** (from 26 fewer to 7 more)	⨁◯◯◯ Very low	CRITICAL
adverse events 8g												
1	randomised trials	not serious	not serious	serious[a]	serious[d]	none	168/668 (25.1%)	180/667 (27.0%)	**RR 0.93** (0.78 to 1.12)	**19 fewer per 1,000** (from 59 fewer to 32 more)	⨁⨁◯◯ Low	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Casirivimab-imdevimab	standard of care	Relative (95% CI)	Absolute (95% CI)		
serious adverse events 8g												
1	randomised trials	not serious	not serious	serious[a]	serious[d]	none	150/668 (22.5%)	174/667 (26.1%)	**RR 0.86** (0.71 to 1.04)	**37 fewer per 1,000** (from 76 fewer to 10 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Population studied were adults only
b. One study had a factorial design.
c. Population studied were adults and adolescents
d. The results include the line of null effect

Appendix 4B. GRADE Evidence Profile: Casirivimab-imdevimab (asymptomatic)

Author(s): Furqaan I. Lim, MD
Question: Should subcutaneous casirivimab plus imdevimab (REGEN-CoV) compared to placebo be used as treatment for COVID-19 in non-hospitalized asymptomatic children?
Setting:
Bibliography:
O'Brien MP, Forleo-Neto E, Sarkar N, Isa F, Hou P, et al. Subcutaneous REGEN-COV Antibody Combination in Early Asymptomatic SARS-CoV-2 Infection: A Randomized Controlled Trial. 2021. Preprint. 10.1101/2021.06.14.21258569.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Casirivimab-imdevimab	placebo	Relative (95% CI)	Absolute (95% CI)		
duration of symptoms												
1	randomised trials	not serious	not serious	serious[b]	serious[c]	none	100	104	-	MD **5.5 lower** (13.75 lower to 2.75 higher)	⨁⨁◯◯ Low	IMPORTANT
at least 1 COVID-related hospitalization or ER visit 1.2g												
1	randomised trials	not serious	not serious	serious[a]	serious[c]	none	0/100 (0.0%)	6/104 (5.8%)	**RR 0.08** (0.00 to 1.40)	**53 fewer per 1,000** (from -- to 23 more)	⨁⨁◯◯ Low	IMPORTANT
adverse events 1.2g												
1	randomised trials	not serious	not serious	serious[b]	not serious	none	52/155 (33.5%)	75/156 (48.1%)	**RR 0.70** (0.53 to 0.92)	**144 fewer per 1,000** (from 226 fewer to 38 fewer)	⨁⨁⨁◯ Moderate	IMPORTANT
serious adverse event 1.2g												
1	randomised trials	not serious	not serious	serious[a]	serious[c]	none	0/155 (0.0%)	4/156 (2.6%)	**RR 0.11** (0.01 to 2.06)	**23 fewer per 1,000** (from 25 fewer to 27 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. The population studied were adults only
b. The population studied were adults and adolescents
c. There is a wide confidence interval

Appendix 4C. GRADE Evidence Profile: Casirivimab-imdevimab (non-hospitalized)

Author(s): Furqaan I. Lim, MD
Question: Should intravenous casirivimab plus imdevimab (REGEN-CoV) compared to placebo be used as treatment for COVID-19 in non-hospitalized children?
Setting:
Bibliography:

Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19. N Engl J Med [Internet]. 2021 Sep 29 [cited 2021 Oct 10]; Available from https://doi.org/10.1056/NEJMoa2108163
Weinrich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGEN-COV Antibody Cocktail in Outpatients with Covid-19. 2021. Preprint. 10.1101/2021.06.09.21257915.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Casirivimab-imdevimab	placebo	Relative (95% CI)	Absolute (95% CI)		
COVID-related hospitalization, ER visit or all cause mortality (1.2 g)												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	9/736 (1.2%)	34/748 (4.5%)	**RR 0.27** (0.13 to 0.56)	**33 fewer per 1,000** (from 40 fewer to 20 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
COVID-related hospitalization, ER visit or all cause mortality (2.4 g)												
2	randomised trials	not serious	not serious	serious[a]	not serious	none	32/1570 (2.0%)	88/1572 (5.6%)	**RR 0.36** (0.24 to 0.54)	**36 fewer per 1,000** (from 43 fewer to 26 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
COVID-related hospitalization, ER visit or all cause mortality (8 g)												
2	randomised trials	not serious	not serious	serious[a]	not serious	none	18/844 (2.1%)	48/824 (5.8%)	**RR 0.37** (0.21 to 0.62)	**37 fewer per 1,000** (from 46 fewer to 22 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
mechanical ventilation (1.2g)												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	1/736 (0.1%)	2/748 (0.3%)	**RR 0.51** (0.05 to 5.59)	**1 fewer per 1,000** (from 3 fewer to 12 more)	⨁⨁◯◯ Low	CRITICAL
mechanical ventilation (2.4g)												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	1/1355 (0.1%)	6/1341 (0.4%)	**RR 0.16** (0.02 to 1.37)	**4 fewer per 1,000** (from 4 fewer to 2 more)	⨁⨁◯◯ Low	CRITICAL
ICU admission (1.2g)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Casirivimab-imdevimab	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	3/736 (0.4%)	7/748 (0.9%)	**RR 0.44** (0.11 to 1.68)	**5 fewer per 1,000** (from 8 fewer to 6 more)	⨁⨁◯◯ Low	CRITICAL
ICU admission (2.4g)												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	6/1355 (0.4%)	18/1341 (1.3%)	**RR 0.33** (0.13 to 0.83)	**9 fewer per 1,000** (from 12 fewer to 2 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
serious adverse events (1.2g)												
1	randomised trials	not serious	not serious	serious[c]	serious[b]	none	9/827 (1.1%)	74/1843 (4.0%)	**RR 0.27** (0.14 to 0.54)	**29 fewer per 1,000** (from 35 fewer to 18 fewer)	⨁⨁◯◯ Low	CRITICAL
serious adverse event (2.4g)												
2	randomised trials	not serious	not serious	serious[a]	not serious	none	28/2107 (1.3%)	80/2105 (3.8%)	**RR 0.35** (0.23 to 0.54)	**25 fewer per 1,000** (from 29 fewer to 17 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
serious adverse event (8g)												
2	randomised trials	not serious	not serious	serious[a]	not serious	none	19/1272 (1.5%)	80/2105 (3.8%)	**RR 0.41** (0.25 to 0.67)	**22 fewer per 1,000** (from 29 fewer to 13 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. The population studied were adults only
b. The results include the line of null effect and has a wide confidence interval
c. The population studied were adults and adolescents

Appendix 4D. GRADE Evidence Profile: Bamlanivimab-etesevimab

Author(s): Furqaan I. Lim, MD
Question: Should Bamlanivimab plus etesevimab compared to placebo be used as treatment for COVID-19 in children?
Setting:
Bibliography:

Dougan M, Nirula, Azizad M et al. Bamlanivimab plus Etesevimab in Mild or Moderate COVID-19. *N Engl J Med.* 2021. [Internet]. Available from: doi:10.1056/NEJMoa2102685.
Gottlieb RL, Nirula A, Chen P, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: A randomized clinical trial. *JAMA – J Am Med Assoc*. [Internet]. 2021;325(7):632-644. Available from: doi:10.1001/jama.2021.0202.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bamlanivimab plus etesevimab	placebo	Relative (95% CI)	Absolute (95% CI)		
Covid-19 related hospitalization and deaths												
2	1andomized trials	not serious	not serious	serious[a]	not serious	none	12/630 (1.9%)	45/673 (6.7%)	**RR 0.28** (0.15 to 0.53)	**48 fewer per 1,000** (from 57 fewer to 31 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Adverse events												
2	1andomized trials	not serious	not serious	serious[a]	serious[b]	none	88/630 (14.0%)	102/673 (15.2%)	**RR 0.87** (0.49 to 1.57)	**20 fewer per 1,000** (from 77 fewer to 86 more)	⨁⨁◯◯ Low	IMPORTANT
Serious adverse events												
2	1andomized trials	not serious	not serious	serious[a]	serious[b]	none	8/630 (1.3%)	6/673 (0.9%)	**RR 1.40** (0.49 to 4.01)	**4 more per 1,000** (from 5 fewer to 27 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. 1 study included adolescents but only composed 1.1% of participants. The other study only involved adults.
b. The results include the line of null effect and has wide confidence interval

Appendix 4E. GRADE Evidence Profile: Sotrovimab (hospitalized)

Author(s): Furqaan I. Lim, MD

Question: Should sotrovimab compared to placebo be used as treatment of COVID-19 in hospitalized children?

Setting:

Bibliography:

Self, WH, Sandkovsky U, Reilly CS, et al. Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and AMUBARVIMAB plus ROMLUSEVIMAB, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial. Lancet Infect Dis. 23 Dec 2021. Available from: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00751-9/fulltext

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	sotrovimab	placebo	Relative (95% CI)	Absolute (95% CI)		
o2 requirement												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	73/182 (40.1%)	79/178 (44.4%)	**RR 0.90** (0.71 to 1.15)	**44 fewer per 1,000** (from 129 fewer to 67 more)	⨁⨁◯◯ Low	IMPORTANT
mechical ventilation												
1	randomised trials	not serious	not serious	serious[a]	serious[c]	none	2/182 (1.1%)	3/178 (1.7%)	**RR 0.65** (0.11 to 3.86)	**6 fewer per 1,000** (from 15 fewer to 48 more)	⨁⨁◯◯ Low	CRITICAL
mortality												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	14/182 (7.7%)	13/178 (7.3%)	**RR 1.05** (0.51 to 2.18)	**4 more per 1,000** (from 36 fewer to 86 more)	⨁⨁◯◯ Low	CRITICAL
composite safety outcome												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	51/182 (28.0%)	57/178 (32.0%)	**RR 0.88** (0.64 to 1.20)	**38 fewer per 1,000** (from 115 fewer to 64 more)	⨁⨁◯◯ Low	CRITICAL
infusion reaction												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	18/182 (9.9%)	14/178 (7.9%)	**RR 1.26** (0.65 to 2.45)	**20 more per 1,000** (from 28 fewer to 114 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Population studied were adults

b. There is serious imprecision because the results include the line of null effect

c. There is serious imprecision because the results include the line of null effect and has wide confidence interval

Appendix 4F. GRADE Evidence Profile: Sotrovimab (non-hospitalized)

Author(s): Furqaan I. Lim, MD

Question: Should sotrovimab compared to placebo be used as treatment for COVID-19 in nonhospitalized children?

Setting:

Bibliography:

Gupta, A, Gozales-Rojas Y, Juarez E, et al. Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab. N Engl J Med. 27 Oct 2021. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2107934

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	sotrovimab	placebo	Relative (95% CI)	Absolute (95% CI)		
hospitalization												
1	randomised trials	not serious	not serious	serious[a]	not serious	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
all cause mortality												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	0/291 (0.0%)	1/292 (0.3%)	**RR 0.33** (0.01 to 8.18)	**2 fewer per 1,000** (from 3 fewer to 25 more)	⨁⨁◯◯ Low	CRITICAL
o2 requirement												
1	randomised trials	not serious	not serious	serious[a]	not serious	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	IMPORTANT
mechanical ventilation												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	0/291 (0.0%)	2/292 (0.7%)	**RR 0.20** (0.01 to 4.16)	**5 fewer per 1,000** (from 7 fewer to 22 more)	⨁⨁◯◯ Low	CRITICAL
ICU admission												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	0/291 (0.0%)	5/292 (1.7%)	**RR 0.09** (0.01 to 1.64)	**16 fewer per 1,000** (from 17 fewer to 11 more)	⨁⨁◯◯ Low	CRITICAL
adverse event												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	sotrovimab	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	73/430 (17.0%)	85/438 (19.4%)	**RR 0.87** (0.66 to 1.16)	**25 fewer per 1,000** (from 66 fewer to 31 more)	⨁⨁◯◯ Low	IMPORTANT
serious adverese event												
1	randomised trials	not serious	not serious	serious[a]	not serious	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

CI: confidence interval; **RR:** risk ratio

Explanations

a. Population studied were adults.
b. The outcome has imprecision because the results include the line of null effect and has a wide confidence interval.

Appendix 4G. GRADE Evidence Profile: Amubarvimab-romlusevimab

Author(s): Furqaan I. Lim, MD
Question: Should amubarvimab plus romlusevimab compared to placebo be used as treatment for covid-19 in hospitalized children?
Setting:
Bibliography:
Self, WH, Sandkovsky U, Reilly CS, et al. Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRII-196 plus BRII-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial. Lancet Infect Dis. 23 Dec 2021. Available from: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00751-9/fulltext

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amubarvimab - romlusevimab	Placebo	Relative (95% CI)	Absolute (95% CI)		
o2 requirement												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	70/176 (39.8%)	79/178 (44.4%)	**RR 0.90** (0.70 to 1.15)	**44 fewer per 1,000** (from 133 fewer to 67 more)	⨁⨁◯◯ Low	IMPORTANT
mechanical ventilation												
1	randomised trials	not serious	not serious	serious[a]	serious[c]	none	4/176 (2.3%)	3/178 (1.7%)	**RR 1.35** (0.31 to 5.94)	**6 more per 1,000** (from 12 fewer to 83 more)	⨁⨁◯◯ Low	CRITICAL
mortality												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	15/176 (8.5%)	13/178 (7.3%)	**RR 1.17** (0.57 to 2.38)	**12 more per 1,000** (from 31 fewer to 101 more)	⨁⨁◯◯ Low	CRITICAL
composite safety outcomes												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	58/176 (33.0%)	57/178 (32.0%)	**RR 1.03** (0.76 to 1.39)	**10 more per 1,000** (from 77 fewer to 125 more)	⨁⨁◯◯ Low	CRITICAL
infusion reaction												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	23/176 (13.1%)	14/178 (7.9%)	**RR 1.66** (0.88 to 3.12)	**52 more per 1,000** (from 9 fewer to 167 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Population studied were adults
b. There is imprecision because results include the line of null effect
c. There is imprecision because results include the line of null effect and have wide confidence interval.

Appendix 4H. GRADE Evidence Profile: Regdanvimab

Author(s): Furqaan I. Lim, MD
Question: Should regdanvimab compared to placebo be used as treatment for COVID-19 in children?
Setting:
Bibliography:
Eom, JS, Ison M, Streinu-Cercel A, et al. Efficacy and safety of CT-P59 plus standard of care: a phase 2/3 randomized, double-blind, placebocontrolled trial in outpatients with mild-to-moderate SARS-CoV-2 infection. 15 March 2021. Preprint. Available from https://www.researchsquare.com/article/rs-296518/v1

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	regdanvimab	placebo	Relative (95% CI)	Absolute (95% CI)		
hospitalization												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	4/101 (4.0%)	9/103 (8.7%)	**RR 0.45** (0.14 to 1.42)	**48 fewer per 1,000** (from 75 fewer to 37 more)	⨁⨁◯◯ Low	IMPORTANT
supplemental oxygen												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	4/101 (4.0%)	9/103 (8.7%)	**RR 0.45** (0.14 to 1.42)	**48 fewer per 1,000** (from 75 fewer to 37 more)	⨁⨁◯◯ Low	CRITICAL
need for rescue therapy												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	7/101 (6.9%)	15/103 (14.6%)	**RR 0.48** (0.20 to 1.12)	**76 fewer per 1,000** (from 117 fewer to 17 more)	⨁⨁◯◯ Low	CRITICAL
total adverse events												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	58/215 (27.0%)	34/110 (30.9%)	**RR 0.87** (0.61 to 1.25)	**40 fewer per 1,000** (from 121 fewer to 77 more)	⨁⨁◯◯ Low	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations

a. Population studied were adults only.
b. The results include the line of null effect and has wide confidence interaval

Appendix 5. Forest Plots

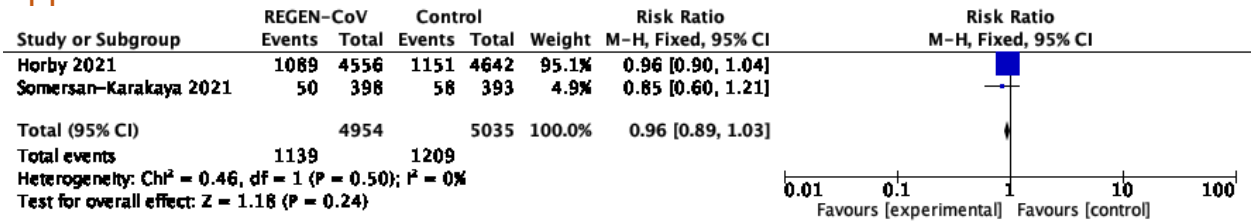

Figure 1. Mechanical ventilation or mortality (Casirivimab-imdevimab 8g), hospitalized patients

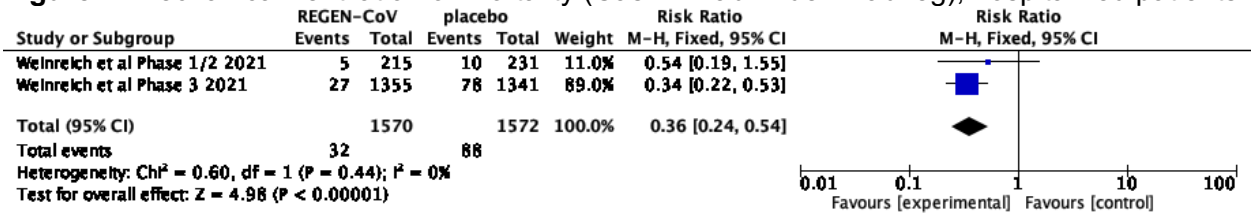

Figure 2. COVID-related hospitalization, ER visit or all-cause mortality (Casirivimab-imdevimab 2.4 g), non-hospitalized patients

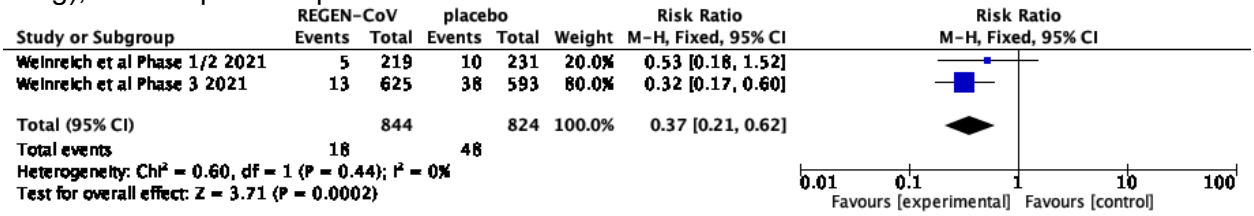

Figure 3. COVID-related hospitalization, ER visit or all-cause mortality (Casirivimab-imdevimab 8 g), non-hospitalized patients

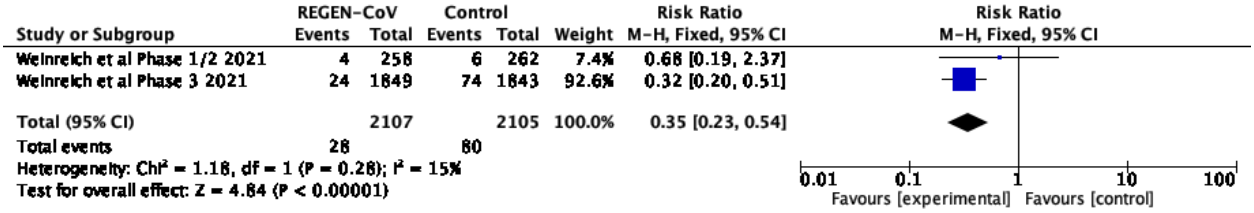

Figure 4. Serious adverse event (Casirivimab-imdevimab 2.4g), non-hospitalized patients

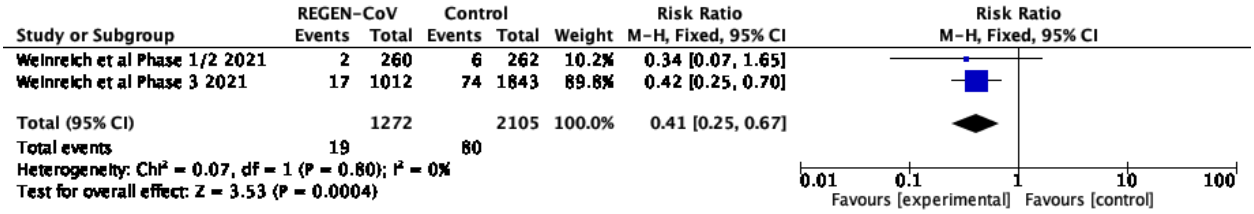

Figure 5. Serious adverse event (Casirivimab-imdevimab 8g), non-hospitalized patients

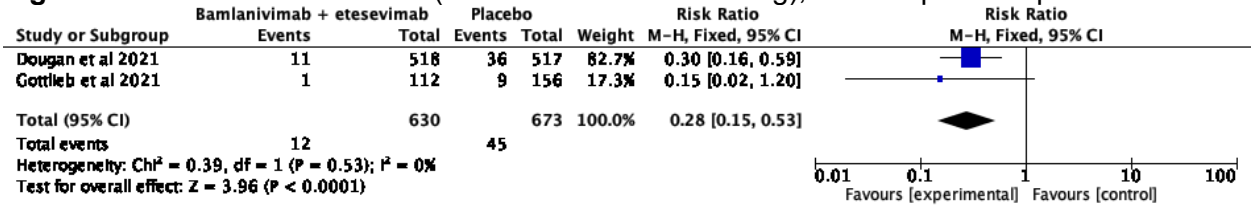

Figure 6. COVID-19 related hospitalization or death (Bamlanivimab-etesevimab)

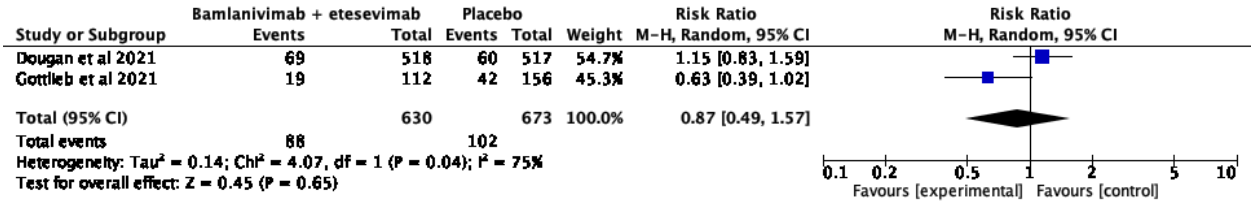

Figure 7. Adverse events (Bamlanivimab-etesevimab)

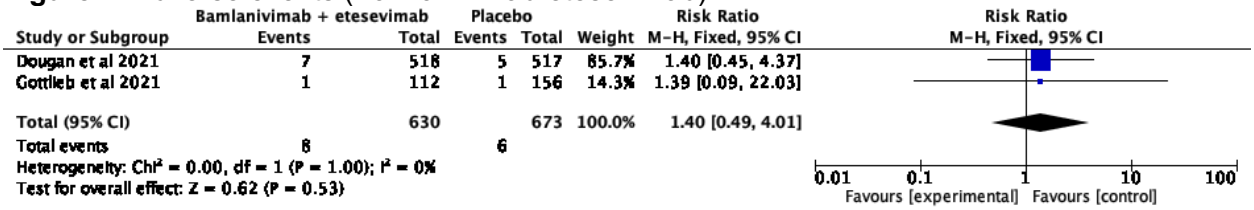

Figure 8. Serious adverse events (Bamlanivimab-etesevimab)

Appendix 6. Characteristics of Ongoing Studies

Study ID and Title	Population	Intervention	Outcomes	Expected Completion Date
NCT05092581 A Phase 1b, Open-Label, Single Dose Study Assessing the Pharmacokinetics, Safety, Tolerability, and Efficacy of Intravenous Anti-Spike(s) SARS-CoV-2Monoclonal Antibodies (Casirivimab+Imdevimab) for the Treatment of Pediatric Patients Hospitalized Due to COVID-19	Children ≤17 years Hospitalized COVID-19 patients	Casirivimab plus Imdevimab Control: not mentioned	Concentrations of casirivimab+imdevimab in serum over time Adverse events	June 2023
NCT04992273 A Phase 2A, Open-Label Study Assessing Pharmacokinetics, Safety, Tolerability, and Immunogenicity of Single-Dose Subcutaneous Anti-Spike(s) SARS-COV-2 Monoclonal Antibodies (Casirivimab and Imdevimab) in High-Risk Pediatric Subjects Under 12 Years of Age	Children ≤12 years Hospitalized COVID-19 patients	Casirivimab plus Imdevimab Control: not mentione	Concentrations of casirivimab+imdevimab in serum over time Adverse events Immunogenicity	Nov 2022
NCT04840459 Use of Monoclonal Antibodies (Bamlanivimab and Casirivimab + Imdevimab) for the Treatment of Mild to Moderate COVID-19 in Non-Hospitalized Setting	Age 12 years and older COVID-19 patients at high risk for progression to severe COVID-19	Bamlanivimab Casirivimab plus Etesevimab Control: not mentioned	Progression to severe COVID-19 and/or hospitalization Rate of Recovery	Jan 31, 2022
NCT04425629 A Master Protocol Assessing the Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Ambulatory Patients With COVID-19	All ages including children COVID-19 patients	Casirivimab plus Imdevimab Control: not mentioned	Adverse events Change in viral load Hospitalization or death Concentration over time COVID-19 related medically-attended visit O2 requirement ICU admission Mechanical ventilation	May 2022
NCT05074433 A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Anti-Spike SARS-CoV-2 Monoclonal Antibodies as Pre-Exposure Prophylaxis to Prevent COVID-19 in Immunocompromised Participants	Age: 12 years and older Immunocompromised seronegative patients	Casirivimab plus Imdevimab Control: Placebo	Incidence of symptomatic COVID-19 infection Adverse events	June 2023

NCT04790786 The UPMC OPtimizing Treatment and Impact of Monocolonal antIbodieS Through Evaluation for COVID-19 Trial	Age: 12 years and older COVID-19 patients	Bamlanivimab Bamlanivimab plus Etesevimab Casirivimab plus Imdevimab Sotrovimab Control: not mentioned	Proportion of alive and non-hospitalized patients Mortality Viral loads Antibody titers Immunogenicity	Dec 2022
NCT04913675 A Phase 3 Randomized, Multi-center, Open Label Study to Assess the Efficacy, Safety, and Tolerability of Monoclonal Antibody VIR-7831 (Sotrovimab) Given Intramuscularly Versus Intravenously for the Treatment of Mild-Moderate Coronavirus Disease 2019 (COVID-19) in High-risk Non-hospitalized Patients	Age: 12 years and older COVID-19 patients with high risk of progression to severe COVID-19	Sotrovimab Control: not mentioned	Progression of COVID-19 Adverse events Change in viral load Serum concentrations	Aug 2022

Appendix 7. Evidence to Decision Framework

Table 1. Summary of initial judgements prior to the panel discussion (N = 9

FACTORS	JUDGEMENT (N = 9)							RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (9)		Varies		Uncertain		
Benefits	Large (3)	Moderate (6)	Small	Trivial	Varies	Uncertain		• IV casirivimab plus imdevimab: decreased risk for MV/death in hospitalized, decreased risk of COVID-19 related hospitalization/death in non-hospitalized • Bamlanivimab plus etesevimab: decreased risk of hospitalization/death • Sotrovimab: decreased risk of hospitalization and oxygen requirement
Harm	Large	Moderate (2)	Small (7)	Trivial	Varies	Uncertain		• No significant difference between interventions and control
Certainty of evidence	High	Moderate		Low (2)		Very low (7)		
Balance of effects	Favors drug (4)	Probably favors drug (5)	Does not favor drug or no drug	Probably favors no drug	Favors no drug	Varies	Uncertain	
Values	Important uncertainty or variability	Possibly important uncertainty or variability (5)		Probably no important uncertainty or variability (4)		No important uncertainty or variability		
Resources required	Uncertain	Varies	Large costs (9)	Moderate costs	Negligible costs or savings	Moderate savings	Large savings	• Casirivimab plus imdevimab: Php 25,551.00 • Bamlanivimab plus etesevimab: $2,100.00 (Php 107,704.00) • Sotrovimab: $2,100.00 (Php 107,04.00) • Amubarvimab plus romlusevimab: no info • Regdanvimab: Php 25,000.00
Certainty of evidence of resources required	No included studies (4)		Very low (1)	Low	Moderate (3)	High (1)		• Only casirivimab plus imdevimab approved by Phil FDA • Other prices from international data
Cost-effectiveness	No included studies (8)	Varies	Favors the comparison	Probably favors the comparison	Does not favor the comparison or the intervention	Probably favors the intervention (1)	Favors the intervention	
Equity	Uncertain (6)	Varies (1)	Reduced (1)	Probably reduced (1)	Probably no impact	Probably increased	Increased	
Acceptability	Uncertain (5)	Varies (2)	No	Probably no	Probably yes (2)	Yes		
Feasibility	Uncertain (4)	Varies (1)	No	Probably no (1)	Probably yes (3)	Yes		• Only casirvimab plus imdevimab with EUA in Philippines for mild to moderate cases aged 12 years and older with risk of progression to severe COVID but not yet oxygen requiring