EVIDENCE SUMMARY

RESEARCH QUESTION: **Among COVID-19 patients, should casirivimab-imdevimab be used for treatment?**

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RECOMMENDATIONS

Recommendations	Certainty of Evidence	Strength of Recommendation
We suggest the use of casirivimab-imdevimab as an alternative to anitivirals* among symptomatic, non-hospitalized COVID-19 adult patients with risk factor for severe disease,** only when the predominant circulating variant is not Omicron SARS-CoV-2. *When other drugs (i.e. molnupiravir and paxlovid [nirmatrelvir-ritonavir]) are contraindicated **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.	Very low	Weak
We recommend against the use of casirivimab-imdevimab as treatment for hospitalized COVID-19 patients.	Very low	Strong
We recommend against the use of casirivimab-imdevimab as treatment for asymptomatic, non-hospitalized patients.	Very low	Strong
We recommend against the use of casirivimab-imdevimab in children with COVID-19.	Very low	Strong

Consensus Issues

The consensus panel suggested the use of casirivimab-imdevimab as an alternative to antivirals (e.g. molnupiravir and paxlovid [nirmatrelvir-ritonavir]) only among symptomatic, non-hospitalized adults with at least one risk factor for severe disease, based on very low certainty of evidence. This is based on the evidence that it had a significant benefit in terms of need for hospitalization and duration of COVID-19 symptoms. The panel however recognizes that all the randomized controlled trials (RCTs) used in the evidence were done at a time before the Omicron SARS-CoV-2 became predominant. Indirect evidence from in-vitro studies showed that casirivimab-imdevimab is ineffective against the Omicron variant, hence the additional caveat about the predominant circulating variant.

The panel also considers that casirivimab-imdevimab is costly and will entail additional costs for its intravenous administration. Additional expenses include emergency room fees and doctor's fees, which may vary across different hospitals. Hence, casirivimab-imdevimab should be reserved for patients in whom

more cost-effective drugs are contraindicated due to allergy or adverse effects, and only when the predominant circulating variant is not Omicron SARS-CoV-2.

On the other hand, the panel strongly recommended against the use of casirivimab-imdevimab among non-hospitalized adults with asymptomatic COVID-19 and hospitalized adults with moderate to severe COVID-19. Current evidence showed that in these subgroup of patients, casirivimab-imdevimab had no benefit in any of the critical outcomes. The panel also considered its ineffectiveness against the Omicron variant, availability of more cost-effective drugs against COVID-19 and its prohibitive cost.

Lastly, the panel strongly recommended against the use of casirivimab-imdevimab in children with COVID-19 due to insufficient evidence that it has benefit in the pediatric population. There was only one RCT including 26 patients with asymptomatic COVID-19 and result was inconclusive in terms of development of COVID-19 symptoms. No other outcomes were reported, including harm.

KEY FINDINGS

- Seven (7) RCTs evaluated the efficacy of casirivimab-imdevimab as treatment for patients with COVID-19.
- Casirivimab-imdevimab did not improve all cause-mortality nor the need for mechanical ventilation.
- Casirivimab-imdevimab significantly reduced viral load clearance, but only among those infected with delta variant, with slower clearance rate for those infected by Omicron variant.
- Among hospitalized patients given casirivimab-imdevimab, there was no significant difference in clinical improvement and/or discharge at day 28.
- Casirivimab-imdevimab showed significant benefit in terms of decreasing the risk of hospitalization, COVID-19 related medically attended visit (MAVs), and duration of symptoms among symptomatic outpatients, but not among asymptomatic outpatients.
- Among seronegative asymptomatic outpatient children, there was likewise no significant benefit when given casirivimab-imdevimab.
- Casirivimab-imdevimab had significantly less reported adverse and serious adverse events compared to those who received placebo/standard of care.
- The overall certainty of evidence was rated very low because of serious risk of bias, indirectness, inconsistency, and imprecision of results.

WHAT'S NEW IN THIS VERSION?

This version includes data from one (1) new pre-print randomized clinical trial and 5 of the previous pre-prints have been published.

PREVIOUS RECOMMENDATIONS
As of 20 December 2021

We suggest casirivimab + imdevimab as treatment for non-hospitalized patients with at least 1 risk factor* for severe COVID-19. *(Moderate certainty of evidence; Weak recommendation)*

We recommend against casirivimab + imdevimab as treatment for hospitalized COVID-19 patients. *(Moderate certainty of evidence; Strong 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.

Consensus Issues
Administration of casirivimab + imdevimab to non-hospitalized COVID-19 patients should be under the supervision of a licensed physician and in a facility capable of monitoring and managing adverse reactions. Patients should be closely monitored during and after drug administration. The recommendation to give casirivimab + imdevimab to non-hospitalized COVID-19 patients who are at risk for severe disease was weak because the evidence was from 1 study only, cost considerations and need for emergency room visit for drug administration and monitoring.

The pre-print study (RECOVERY trial) did not show any benefit in giving casirivimab + imdevimab to hospitalized patients in general but showed benefit only for seronegative patients. However, this subgroup analysis was only post-hoc or exploratory in nature. Hence, the consensus panel recommended against its use among hospitalized COVID-19 patients until further research confirms this finding.

INTRODUCTION

COVID-19 hypoxemia has been theorized to be related to an immune hyperresponsiveness to viral infection. With recent studies showing high viral titers among hospitalized patients with hypoxemia, it is hypothesized that treatments that effectively reduce viral load could prevent complications and death resulting from COVID-19 infection [1,2]. One such treatment that has shown favorable effects from in vitro studies is casirivimab-imdevimab, an antibody cocktail containing two non-competing SARS-CoV-2 neutralizing human IgG1 antibodies (casirivimab [REGN10933] and imdevimab [REGN10987]). By targeting the receptor-binding domain of the SARS-CoV-2 spike protein, viral entry into human cells through the angiotensin-converting enzyme 2 (ACE2) receptor is prevented [3,4].

Casirivimab-imdevimab pharmacokinetic data showed significant susceptibility of pre-Omicron variants [5,6]. However, recent preclinical data showed that casirivimab-imdevimab had reduced in vitro neutralization against Omicron variants [7,8] The Philippine Genome Center has reported detection of Omicron variant in the Philippines in January 2022 [9]. The Department of Health (DOH) shows that Omicron and its subvariants has been the predominant variant detected to date [10].

REVIEW METHODS

A systematic search was done from the date of the last search November 26, 2021 until February 5, 2023 using Medline, CENTRAL, and Google Scholar with a combined MeSH and free text search using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and REGEN-COV or REGN-COV2 or casirivimab. We also searched the COVID-NMA Living Data. Ongoing studies were explored through the NIH clinicaltrials.gov and other trial registries. Preprints were also searched using medrxiv, chinaxiv, and biorxiv. Only randomized controlled trials that compared REGEN-COV against placebo or standard care were included in this review. No limits were placed on age, COVID-19 severity, and dosing. No published or pre-print studies were found specifically for children and adolescents. Preplanned subgroup analysis on dosing, severity, and serologic status were conducted.

RESULTS

Characteristics of included studies

There are 7 randomized controlled trials included with a total of 15,840 COVID-19 confirmed patients [11-16]. Five pre-print articles have since been published in various journals from the last review [12-16]. Recruitment and randomization of these included studies were done between June 10, 2020 (earliest) to May 22, 2021 (latest) [11-16]. Of these, 2 studies examined hospitalized patients [12,13], 4 studies were on outpatients [11,14-16], while 1 study included both outpatient and hospitalized patients [16]. Five studies only included adults 18 years and above [11,13,15-17] while two studies included children ≥12 years of age – one study had 8.28% (n=26) [14] while the other had 0.11% (n=11) [12] of the total included population participants in the 12 to <18 years old age group. Six studies included patients with mild COVID-19 symptoms [11-13,15-17], 2 studies included patients with moderate to severe COVID-19 [12,13], while another study included only asymptomatic COVID-19 confirmed patients [14]. Six studies included patients with risk factors for severe disease [11-16]. One study categorized outcomes of vaccinated vs unvaccinated patients [12], two studies included both vaccinated and unvaccinated patients but did not include these subgroups in their analysis [13,17], while two studies excluded vaccinated patients from the trial [14,15]. The 2 RCTs done by Weinrich et al. had no data on vaccination status [11,16]. Casirivimab-imdevimab was given either subcutaneously [13,14] or intravenously [11-13,15-17] at different doses. Three studies gave high dose intravenous casirivimab-imdevimab at 8,000mg [11-13], 4 studies gave the dose of 2,400mg [10,12,14,15], and 4 studies gave the treatment at 1,200mg [14-17]. One study also included 300mg (IV) and 600mg (IV, SC) [15].

Certainty of evidence

The overall certainty of evidence was rated very low because of serious risk of bias, indirectness, inconsistency, and imprecision of results. The serious risk of bias was due to issues in attrition, allocation concealment, performance bias, and reporting bias. The risk of bias summary is found in Appendix 5. Indirectness is mainly because these studies were done prior to the surge of the Omicron variant, which is the dominant variant to date. The GRADE evidence profile is in Appendix 6.

Effectiveness outcomes

All-cause mortality
Casirivimab-imdevimab was not significantly beneficial over placebo for all-cause mortality (RR 0.81, 95% CI 0.59-1.11, I^2=53%, 5 studies, n=15,402) [12-16], with results showing substantial heterogeneity. A subgroup analysis done showed no significant benefit regardless of hospitalization status (hospitalized or outpatient) and antibody status (seronegative or seropositive) [12,13]. Meanwhile, the subgroup analysis based on dose showed 2,400mg of casirivimab-imdevimab given intravenously is beneficial (RR 0.48, 95% CI 0.29-0.77, 1.16, I^2=0%, 3 studies, n=3,744) in preventing all-cause mortality, while other doses (600mg, 1,200mg and 8,000mg) were not significant.

Need for mechanical ventilation
There was no significant benefit for those given casirivimab-imdevimab in terms of the need for invasive mechanical ventilation (RR 0.56, 95% CI 0.14-2.28, I^2=70.1%, 3 studies n=13,531), with significant heterogeneity [12,14,16]. Subgroup analyses showed inconclusive results regardless of dose and hospitalization status.

Viral load clearance
Pooled analysis of least-squares mean differences in time-weighted average change from baseline (TWACB) in viral load showed benefit for those given casirivimab-imdevimab (MD -0.42 $\log_{10}$ copies/ml, 95% CI -0.43 to -0.40, I^2=100%, 3 RCTs, n=1,473), but heterogeneity was significant. Based on one study [17], viral loads significantly declined 25% faster (95% CI 8-46%) in casirivimab-imdevimab recipients compared to the no study drug arms. Viral clearance rates in Delta variant infections were increased by 58% (95% CI 10-120%) relative to no study drug, while in the Omicron variants, this effect was reduced by nearly three-fold: 20% (95% CI 3-43%).

HOSPITALIZED PATIENTS

Clinical improvement Day 28

There was no significant difference in terms of clinical improvement and/or discharge at day 28 among hospitalized participants (RR 1.04, 95% CI 0.98-1.10, I^2=72%, 2 studies n=11,203). Subgroup analysis based on dose also showed inconclusive results for both 2,400mg and 8,000mg. Meanwhile, casirivimab-imdevimab was observed to be beneficial in terms of clinical improvement/discharge at day 28 among seronegative patients (RR 1.13, 95% CI 1.08-1.19, I^2=15%, 2 studies n=3,673) but is inconclusive among seropositive (RR 3.15, 95% CI 0.32-31.29) or unknown antibody status (RR 0.61, 95% CI 0.19-1.89).

Duration of hospitalization

Among hospitalized patients, one study reported that the median duration of hospitalization was 10 days for both treatment and placebo groups. However, on subgroup analysis, among seronegative patients, the median duration of hospitalization was 4 days shorter in the experimental group versus control (13 days vs 17 days) [12].

OUTPATIENTS

Risk of hospitalization

Outpatients given casirivimab-imdevimab significantly decreased the risk of hospitalization (RR 0.25, 95% CI 0.15-0.39, I^2=0%). A subgroup analysis based on symptomatology showed that the decrease in risk of hospitalization is only among the symptomatic outpatients (RR 0.25, 95% CI 0.16-0.40) and not among the asymptomatic outpatients (RR 0.14, 95% CI 0.01-2.78). Another subgroup analysis based on dose, showed that both intravenous doses of 1,200mg (RR 0.27, 95% CI 0.11-0.65) and 2,400mg (RR 0.29, 95% CI 0.17-0.49) decreases risk of hospitalization, but not among those given 1,200mg SC (RR 0.14, 95% CI 0.01-2.78).

At least one COVID 19-related medically attended visit (MAV)

Among outpatients given casirivimab-imdevimab, there was a significant reduction in the number of COVID-related MAVs defined as consult at the emergency room, urgent care, or hospitalization in the experimental group compared to the placebo group (RR 0.37, 95% CI 0.28-0.50; I^2=0%, 3 studies, n=3,911). Subgroup analysis by presence of symptoms showed that the casirivimab-imdevimab significantly reduced COVID-related MAVs only among those who are symptomatic (RR 0.38, 95% CI 0.28-0.51; I^2=0%, 2 studies, n=3,707) and not among the asymptomatic outpatients (RR 0.08, 95% CI 0-1.40). Another subgroup analysis based on the dose also showed that patients given intravenous 1,200mg (RR 0.40, 95% CI 0.24-0.66) and 2,400mg (RR 0.40, 95% CI 0.28-0.55) significantly decreased at least 1 COVID related MAV but not among those given 8,000mg intravenously (RR 0.52, 95% CI 0.13-2.00) nor those who received the 1,200mg SC (RR 0.17, 95% CI 0.02-1.41). No difference in terms of antibody status was observed.

Duration of COVID-19 symptoms

Casirivimab-imdevimab significantly decreased the duration of COVID-19 symptoms among outpatients (MD -4.00 days, 95% CI -4.24 to -3.76). This decrease in duration of COVID-19 symptoms is significant only among the symptomatic outpatients (MD -4.00 days, 95% CI -4.24 to -3.76) and was inconclusive among the asymptomatic outpatient population (MD -4.20, 95% CI -9.68 to 1.28).

Asymptomatic Outpatients

Development of symptomatic COVID-19

One study looked at the proportion of COVID-19 positive asymptomatic outpatient participants who eventually developed symptoms within 14 days of positive RT-PCR result [14]. For these patients, there was no significant benefit, although there was a trend towards benefit in terms of development of symptomatic COVID-19 infection among patients given low dose subcutaneous casirivimab-imdevimab (1,200mg) versus placebo (RR 0.67, 95% CI 0.44-1.01).

Safety outcomes

Adverse events
For adverse events (AEs), pooled analysis showed lesser reports among patients receiving casirivimab-imdevimab compared to the placebo group (RR 0.78, 95% CI 0.69-0.89; I^2=7%, 6 studies, n=8,072), regardless of route of administration (intravenous or subcutaneous). For the subgroup analysis by dose, lesser adverse events were observed for the treatment group given 600mg (RR 0.16, 95% CI 0.06-0.42) and 2,400mg (RR 0.70, 95% CI 0.59-0.83), but inconclusive for other doses. Subgroup analysis based on hospitalization status showed lesser AEs among those given casirivimab-imdevimab as outpatient, regardless if asymptomatic (RR 0.70, 95% CI 0.53-0.92) or symptomatic (RR 0.62, 95% CI 0.45-0.87), but inconclusive for hospitalized patients (RR 0.88, 95% CI 0.75-1.03). The most common adverse events were infusion-related reactions [11,13-16].

Serious adverse events
Pooled analysis of serious adverse events (SAEs) showed that patients receiving casirivimab-imdevimab had less reported SAEs compared to the placebo group (RR 0.64, 95% CI 0.55-0.75; I^2=84%, 6 studies, n=8,072), with significant heterogeneity. Subgroup analysis show that patients given casirivimab-imdevimab reported less serious adverse events for symptomatic outpatients (RR 0.22, 95% CI 0.14-0.35) and hospitalized patients (RR 0.82, 95% CI 0.69-0.96), but is inconclusive among asymptomatic outpatients (RR 0.11, 95% CI 0.01-2.06). Another subgroup analysis based on doses, showed lesser risk for SAEs with casirivimab-imdevimab for doses of 1,200mg (RR 0.20, 95% CI 0.10-0.42), 2,400mg (RR 0.62, 95% CI 0.52-0.74), and 8,000mg (RR 0.72, 95% CI 0.60-0.86). Subgroup analysis in terms of route of administration, those given casirivimab-imdevimab intravenously have less SAEs (RR 0.65, 95% CI 0.56-0.76) but is inconclusive among those given subcutaneously (RR 0.11, 95% CI 0.01-2.06). In the recent study included, SAE was reported for participant who presented with elevated CPK and in a patient who was admitted for right-sided chest pain and lethargy [17]. The most common serious adverse event in the previously reported trials was the development of COVID-19 pneumonia [11,13,14], while another study reported two miscarriages [15].

CHILDREN AND ADOLESCENTS

Risk of developing symptomatic infection
Only two studies included children and adolescents ≥12 years of age, however, only one study had a subgroup analysis and breakdown of the result per age. Based on one study (n=26) [14], among seronegative children and adolescents (12 to <18 years old), casirivimab-imdevimab had no significant benefit in reducing the risk of developing symptomatic infection compared with the placebo (OR 0.2, 95% CI 0.015-1.642, n=26). No other outcomes specific for children and adolescent age group were available.

RECOMMENDATIONS FROM OTHER GROUPS

Group or Agency	Recommendation	Strength of Recommendation / Certainty of Evidence
Australian Guidelines [22] (Last update: December 20, 2022)	Conditional recommendation using casirivimab plus imdevimab in the following situations: • within 7 days of symptom onset in adults with COVID-19 who do not require oxygen and who have one or more risk factors for disease progression. ○ Where infection with Omicron BA.1, BA.2, BA.4 or BA.5 is confirmed or considered likely, use of casirivimab plus imdevimab should only be considered where other treatments are not suitable or available. • **In seronegative** adults hospitalised with moderate-to-critical COVID-19.	

	○ Where infection with Omicron BA.1, BA.2, BA.4 or BA.5 is confirmed or considered likely, use of casirivimab plus imdevimab should only be considered where other treatments are not suitable or available. • Within 7 days of symptom onset in pregnant or breastfeeding women with COVID-19 who do not require oxygen and have one or more risk factors for disease progression. • In **seronegative** pregnant or breastfeeding women hospitalised with moderate-to-critical COVID-19. Recommends against the use of casirivimab plus imdevimab in the following situations: ○ **In seropositive** adults hospitalised with moderate-to-critical COVID-19. ○ In **seropositive** pregnant or breastfeeding women who are hospitalised with moderate-to-critical COVID-19. ○ in **seropositive** children and adolescents hospitalised with moderate-to-critical COVID-19. ○ in children under 12 years of age without risk factors for deterioration who have **mild or asymptomatic COVID-19** outside of randomised trials with appropriate ethical approval. Consensus recommendation to consider using casirivimab plus imdevimab: ○ within 7 days of symptom onset in **children and adolescents with COVID-19 aged 12 years and over and weighing at least 40 kg who do not require oxygen** and who are at high risk of deterioration in exceptional circumstances in **seronegative** children and adolescents aged 12 years and over and weighing at least 40 kg who require oxygen and who are at high risk of disease progression.	
Japanese rapid/living recommendations on drug management for COVID-19: Updated guidelines [23] (Last update: July 2022)	Suggest casirivimab/imdevimab administration to patients with mild COVID-19 who do not require oxygen No clear recommendation on casirivimab/imdevimab administration to patients with moderate COVID-19 requiring oxygen/hospitalization or patients with severe COVID-19 requiring mechanical ventilation/intensive care	Weak recommendation/low certainty of evidence: GRADE 2C
National Institutes of Health (NIH) Guidelines [24] (Last update: December 28, 2022)	The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of anti-SARS-CoV-2 mAbs for the treatment of COVID-19 **(AIII)** because the dominant Omicron subvariants in the United States are not expected to be susceptible to these products.	AIII
World Health Organization (WHO) Guidelines [25]	Recommend against treatment with casirivimab-imdevimab. ○ Several other therapeutic options exist for patients with COVID-19 across the severity	Strong recommendation against

(Last update: 13 January 2023)	spectrum for patients with non-severe COVID-19 ○ Considered *in vitro* data demonstrating that casirivimab-imdevimab does not neutralize the currently circulating variants of SARS-CoV-2 and their subvariants. ○ Consensus that the meaningful reduction of *in vitro* neutralization activity strongly suggests absence of clinical effectiveness of monoclonal antibodies such as sotrovimab and casirivimab-imdevimab. Consensus regarding the need for clinical trial evidence in order to confirm any clinical effectiveness of new monoclonal antibodies that reliably neutralize the circulating strains *in vitro.*	
Infectious Diseases Society of America [26] (Last update: January 20, 2023)	No new recommendation regarding treatment using casirivimab-imdevimab. Last recommendation: Suggests the use of casirivimab-imdevimab for non-hospitalized patients with mild to moderate COVID-19 at high risk for progression to severe disease	

ONGOING STUDIES AND RESEARCH GAPS

There is one completed randomized controlled clinical trials awaiting publication of results and three ongoing trials on casirivimab-imdevimab as treatment for COVID-19. Two of these include children 12 years and above, while one study includes newborn subjects to elderly subjects. Two trials were terminated due to susceptibility issues of the current dominant variant (Appendix 4).

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

COST

The cost of casirivimab-imdevimab for each infusion is US$1,250-6,000 (₱69,000-₱330,000) per course (intravenous). A cost-effectiveness study was done among ambulatory patients from a US payer's perspective, which showed that casirivimab- imdevimab is cost-effective for patients older than 40 years of age with a baseline risk of hospitalization of ≥2% or for younger patients aged 20 years with a baseline risk of ≥4% at a willingness-to-pay threshold of US$100,000, but not found to be cost-effective for younger patients with lower risks [21]. No local cost-effectiveness studies have been done.

PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

The Philippine Food and Drug Administration (FDA) issued authorization on October 21, 2021 granting Roche (Philippines), Inc. the emergency use approval of casirivimab-imdevimab [18,19]. The available preparation is 120mg/mL (2.5mL/vial) concentrate for solution for Infusion, which should be stored in a refrigerator at 2˚C to 8˚C in the original carton to protect from light with a shelf life of 24 months from production [19]. An amendment on November 17, 2021 shortened this to three months. It is best administered via four subcutaneous injections in one day for post-exposure prophylaxis. Four syringes must be prepared with 25-gauge or 27-gauge needles for subcutaneous injections. The prepared syringes must be administered immediately. If immediate administration is not possible, the prepared syringes must be stored at room temperature up to 25˚C for no more than a total of 4 hours. If refrigerated, the syringes must be allowed to equilibrate to room temperature for approximately 20 minutes prior to administration. The injections must be administered in 4 separate injection sites (thighs, back of the upper arms, abdomen except for 2 inches around the navel and waistline (which should be avoided). Patients must be monitored clinically for at least 1 hour after administration [20].

REFERENCES

[1] Blanco-Melo D, Nilsson-Payant BE, Liu WC, et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell 2020;181(5):1036-1045.e9.

[2] Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. Nature 2020;581:465-9.

[3] Baum A, Fulton BO, Wloga E, et al. Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. Science 2020;369:1014-8.

[4] Hansen J, Baum A, Pascal KE, et al. Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. Science 2020;369:1010-4.

[5] Wang P, Nair MS, Liu L, Iketani S, Luo Y, Guo Y, et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. Nature 2021;593:130-135.

[6] Copin R, Baum A, Wloga E, Pascal KE, Giordano S, Fulton BO, et al. The monoclonal antibody combination REGEN-COV protects against SARS-CoV-2 mutational escape in preclinical and human studies. Cell 2021; 184(15):3949-3961.e11.

[7] Tatham L, Sharp J, Kijak E, Herriott J, Neary M, Box H, et al. Lack of Ronapreve (REGN-CoV; casirivimab and imdevimab) virological efficacy against the SARS-CoV-2 Omicron variant (B.1.1.529) in K18-hACE2 mice. 2022. Preprint. 10.1101/2022.01.23.477397

[8] Wilhelm A, Widera M, Grikscheit K, Toptan T, Schenk B, Pallas C, et al. Limited neutralisation of the SARS-CoV-2 Omicron subvariants BA.1 and BA.2 by convalescent and vaccine serum and monoclonal antibodies. EBioMedicine. 2022;82:104158. 10.1016/j.ebiom.2022.104158

[9] Philippine Genome Center. [Internet]. PGC SARS-CoV-2 Bulletin No. 8: Detection of the first 500 SARS-CoV-2 Omicron Variant in the Philippines [cited 14 Nov 2022]. Available from https://pgc.up.edu.ph/detection-of-the-sars-cov-2-omicron-variant-in-the-philippines/

[10] Department of Health. [Internet]. Latest COVID-19 Biosurveillance Report [cited 20 Nov 2022]. from https://doh.gov.ph/covid19-variants

[11] 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. 2021 Sep 29.

[12] Horby PW & Landray MJ. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomized, controlled, open-label, platform trial. Lancet. 2022; 399: 665-76.

[13] Somersan-Karakaya S, Mylonakis E, Menon VP, Wells JC, Ali S, Sivapalasingam S, et al. Casirivimab and Imdevimab for the treatment of hospitalized patients with COVID-19. The Journal of Infectious Diseases. 2021. 2022 Jul 27 jiac320.

[14] 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. JAMA. 2022;327(5):432-441. doi:10.1001/jama.2021.24939

[15] Portal-Celhay C, Forleo-Neto E, Eagan W, Musser BJ, Davis JD, Turner KC, Norton T, et al. Phase 2 dose-ranging study of the virologic efficacy and safety of the combination COVID-19 antibodies casirivimab and imdevimab in the outpatient setting. JAMA Netw Open. 2022;5(8):e2225411. doi:10.1001/jamanetworkopen.2022.25411

[16] Weinrich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGEN-COV Antibody Cocktail in Outpatients with Covid-19. N Engl J Med 2021; 384:238-251. 10.1056/NEJMoa2035002

[17] Jittamala P, Schilling WH, Watson JA, Luvira V, Siripoon T, Ngamprasertcha T, et al. Clinical antiviral efficacy of remdesivir and casirivimab/imdevimab against the SARS-CoV-2 Delta and Omicron variants. 2022. Preprint. 10.1101/2022.10.17.22281161

[18] FDA.gov.ph. Emergency Use Authorization (EUA) for Casirivimab + Imdevimab (Ronapreve). [Internet]. October 1, 2021. [cited October 27, 2022]. Available from: https://www.fda.gov.ph/wp-content/uploads/2021/10/EUA-Ronapreve-Website.pdf

[19] FDA.gov.ph. Amended Emergency Use Authorization (EUA) for Casirivimab + Imdevimab. [Internet]. November 17, 2021. [cited October 27, 2022]. Available from: https://www.fda.gov.ph/wp-content/uploads/2021/11/Amended-EUA-Casirivimab-plus-Imdevimab-w.pdf

[20] FDA.gov. Reeneron EUA HCP Fact Sheet 09172021. [Internet]. 2021. [updated 2021 September 17; cited October 27, 2022]. Available from: https://www.fda.gov/media/145611/download.

[21] Jovanoski N, Kuznik A, Becker U, Hussein M, Briggs A. Cost-effectiveness of casirivimab/imdevimab in patients with COVID-19 in the ambulatory setting. J Manag Care Spec Pharm. 2022; 28(5): 555-565.

[22] Australian National COVID-19 Clinical Evidence Taskforce. [Internet]. Australian guidelines for the clinical cure of people with COVID-19 v42.0. [updated 2022 Dec 20; cited 2023 Jan 23] Available from: https://app.magicapp.org/#/guideline/L4Q5An/section/L6pBYE

[23] Yamakawa K, Yamamoto R, Terayama T, Hashimoto H, Ishihara T, Ishimaru G, et al., Japanese rapid/living recommendations on drug management for COVID-19: Updated guidelines (July 2022). Acute Medicine & Surgery [Internet]. 2022 Jan-Dec [cited 2022 Oct 27]; Available from: doi:10.1002/ams2.789

[24] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. [Internet]. National Institutes of Health. [updated 2022 Dec 28; cited 2023 Jan 23]. Available from: https://www.covid19treatmentguidelines.nih.gov/.

[25] [19] World Health Organization. [Internet]. Therapeutics and COVID-19 Living Guidelines. [updated 2023 Jan 13; cited 2023 Jan 23]. Available from: https://app.magicapp.org/#/guideline/nBkO1E/rec/jOp0R7

[26] Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, et al. IDSA Guidelines on the Treatment and Management of Patients with COVID-19. [updated 2023 Jan 20; cited 2023 Jan 23]. Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

Appendix 1: Preliminary Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=6/10)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (5)	Varies (1)				• Yes, COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity
Benefits	Large	Moderate (2)	Small (2)	Trivial (1)	Varies (1)	Uncertain	• Asymptomatic: Inconclusive • Outpatient symptomatic: Significantly reduced risk for hospitalization, COVID-19 related MAVs, symptom duration • Hospitalized: No benefit for all-cause mortality, need for mechanical ventilation, clinical improvement/discharge at day 28 • Less effective in terms of viral load clearance against Omicron variants (20%, 95% CI 3-43%) compared to delta variant (58%, 95%CI 10-120%)
Harm	Large (1)	Moderate	Small (4)	Trivial (1)	Varies	Uncertain	• Less risk for AE and SAE compared to placebo
Certainty of Evidence	High	Moderate	Low (1)	Very low (5)			• Overall certainty of evidence is very low • The serious risk of bias was due to issues in attrition, allocation concealment, performance bias, and reporting bias • Inconsistency and imprecision of results • Indirectness of evidence to address current dominant variant
Balance of effects	Favors intervention	Probably favors intervention (6)	Does not favor intervention or no intervention	Probably favors no intervention	Favors no intervention	Varies	• Net potential benefit only for symptomatic, non-hospitalized patients who are at risk for developing severe disease
Values	Important uncertainty or variability	Possibly important uncertainty or variability (5)	Probably no important uncertainty or variability (1)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost (6)	Moderate Cost	Negligible cost or savings	Moderate savings	Large savings	• Cost is $1,250-6,000 (₱69,000-₱330,000) per course (intravenous) • Additional cost for ER, admission, and doctor's fees may vary across different hospitals
Certainty of evidence of required resources	No included studies (1)	Very low (2)	Low	Moderate (1)	High (2)		• Local cost is from personal communication with the private hospitals

Cost effectiveness	No included studies (1)	Favors using the comparison	Probably favors the comparison (2)	Does not favor either the intervention or the comparison (1)	Probably favors the invention (1)	Varies (1)	• Ambulatory patients, US payer's perspective: casirivimab-imdevimab is cost-effective for patients older than 40 years of age with a baseline risk of hospitalization of ≥2% or for younger patients aged 20 years with a baseline risk of ≥4% at a willingness-to-pay threshold of US$100,000, but not found to be cost-effective for younger patients with lower risks. • No local studies.
Equity	Varies (1)	Reduced (2)	Probably reduced (1)	Probably no impact (1)	Probably increased	Increased (1)	
Acceptability	Uncertain	Varies	No	Probably no (4)	Probably yes (2)	Yes	
Feasibility	Uncertain	Varies	No	Probably no (3)	Probably yes (3)	Yes	
Recommendation	For (1)	Against (5)					
Strength	Weak (5)	Strong (1)					

Appendix 2: Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (Casirivimab) Filters: November 27, 2021 to October 22, 2022	October 22, 2022 10:00 AM	195	5
CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2 AND (REGEN-COV) OR (REGN-COV2) OR (Casirivimab) Filters: November 27, 2021 to October 22, 2022	October 22, 2022 11:30 AM	13	4
Google Scholar	Casirivimab AND imdevimab AND COVID AND randomized trial Filters: Published since 2022	October 22, 2022 12:30 PM	144	2
COVID-NMA initiative	REGEN-COV REGN-COV2 Casirivimab	October 22, 2022 2:00 PM	4	0
ClinicalTrials.gov	Casirivimab OR REGEN-COV OR REGN-COV2 and COVID-19	October 22, 2022 3:00 PM	12	0
Chinese Clinical Trial Registry	Casirivimab OR REGEN-COV OR REGN-COV2	October 22, 2022 3:15 PM	0	0
EU Clinical Trials Register	Casirivimab OR REGEN-COV OR REGN-COV2 and COVID-19	October 22, 2022 3:20 PM	2	0
Republic of Korea - Clinical Research Information Service	Casirivimab OR REGEN-COV OR REGN-COV2	October 22, 2022 3:30 PM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Casirivimab OR REGEN-COV OR REGN-COV2	October 22, 2022 3:40 PM	4	0
CenterWatch	Casirivimab OR REGEN-COV OR REGN-COV2	October 22, 2022 4:00 PM	16	0
chinaxiv.org	Casirivimab OR REGEN-COV OR REGN-COV2	October 23, 2022 2:15 PM	0	0
Medrxiv.org	Casirivimab OR REGEN-COV OR REGN-COV2	October 23, 2022 2:20 PM	159	5
Biorxiv.org	Casirivimab OR REGEN-COV OR REGN-COV2 AND COVID-19	October 23, 2022 2:45 PM	114	0

Appendix 3: Characteristics of Included Studies

Study ID	Patients (n) & Duration of Follow-Up	Interventions	Outcomes	Study Design
Clinical antiviral efficacy of remdesivir and casirivimab/imdevimab against the SARS-CoV-2 Delta and Omicron variants *Jittamala et al. (Thailand); pre-print*	SARS-CoV-2 RT-PCR positive previously healthy adults aged 18 and 50 years (n = 163) Duration of follow-up: Approximately 28 days	EXPERIMENTAL: Casirivimab-imdevimab (600mg/600mg) cocktail IV CONTROL: Placebo	PRIMARY: Rate of viral clearance, expressed as a slope coefficient (28), and estimated under a Bayesian hierarchical linear model fitted to the daily log10 viral load measurements between days 0 and 7 (18 measurements per patient). SECONDARY: All cause hospitalization for clinical deterioration (until day 28) Adverse events	Phase 2 open label, randomized, controlled adaptive platform trial
REGEN-COV Antibody Cocktail Clinical Outcomes Study in COVID-19 Outpatients *Weinrich et al. (USA)*	Ambulatory confirmed COVID-19 patients with ≥1 risk factor for severe COVID-19 (n = 4,057) Duration of follow-up: Approximately 29 days	EXPERIMENTAL: Casirivimab-imdevimab 1200mg cocktail IV Casirivimab-imdevimab 2400mg cocktail IV Casirivimab-imdevimab 8000mg cocktail IV CONTROL: Placebo	PRIMARY: COVID-19 related hospitalization or all-cause death SECONDARY: Time to symptom resolution, adverse events	Randomized, double-blind, placebo-controlled

Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomized, controlled, open-label, platform trial *Horby et al., (United Kingdom)*	Confirmed COVID-19 patients admitted to the hospitals already participating in the RECOVERY trial (n = 11,464) <u>Duration of follow-up:</u> 28 days	EXPERIMENTAL: Casirivimab-imdevimab 8000mg cocktail IV CONTROL: Standard of care	PRIMARY: All-cause mortality SECONDARY: Discharge alive from hospital, use of invasive ventilation among patients, serious adverse events	Randomized, open-label, controlled
REGEN-COV for Treatment of Hospitalized Patients with Covid-19 *Somersan-Karakaya et al. (USA); pre-print*	Hospitalized COVID-19 patients with little to no oxygen support (n = 1336) <u>Duration of follow-up:</u> 29 days	EXPERIMENTAL: Casirivimab-imdevimab 2400mg cocktail IV Casirivimab-imdevimab 8000mg cocktail IV CONTROL: 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	Randomized, double-blinded, placebo-controlled trial
Subcutaneous REGEN-COV Antibody Combination in Early Asymptomatic SARS-CoV-2 Infection: A Randomized Clinical Trial *O'Brien et al., (USA);*	Asymptomatic individuals at least 12 years of age with known exposure to COVID-19, tested positive for COVID-19 at baseline (n = 314) <u>Duration of follow-up:</u> 28 days	EXPERIMENTAL: Casirivimab-imdevimab 1200mg cocktail SC CONTROL: Placebo	PRIMARY: Development of COVID-19 symptoms SECONDARY: Duration of COVID-19 symptoms, number of weeks of high viral load, safety	Randomized, double-blind, placebo-controlled trial

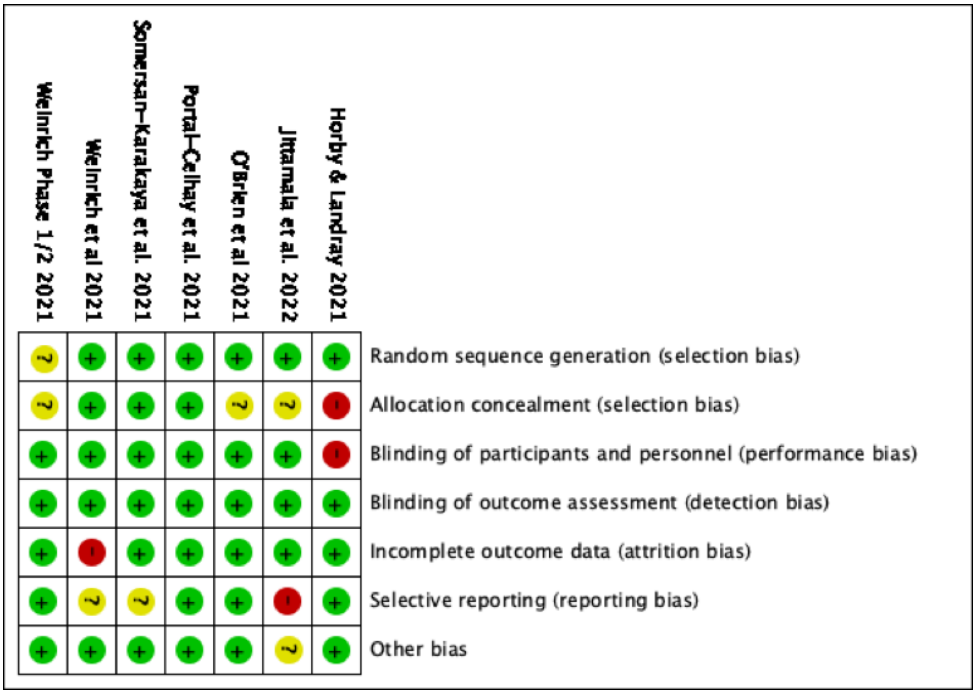
Phase 2 Dose-Ranging Study of the Virologic Efficacy and Safety of the Combination COVID-19 Antibodies Casirivimab and Imdevimab in the Outpatient Setting *Portal-Celhay et al. (USA); pre-print*	Non-hospitalized COVID-19 patients without risk factors for developing severe COVID-19 (n = 815) <u>Duration of follow-up:</u> 4 months	EXPERIMENTAL: Casirivimab-imdevimab 300mg cocktail IV Casirivimab-imdevimab 600mg cocktail IV Casirivimab-imdevimab 1200mg cocktail IV Casirivimab-imdevimab 2400mg cocktail IV Casirivimab-imdevimab 600mg cocktail SC Casirivimab=-imdevimab 1200mg cocktail SC CONTROL: Placebo	PRIMARY: TWA daily change from baseline in viral load from day 1 to 7 SECONDARY: Virologic efficacy, safety and tolerability, REGEN-COV concentrations in serum over time, safety	Randomized, double-blind, placebo-controlled, parallel-group, dose-ranging trial
REGEN-COV Antibody Cocktail in Outpatients with Covid-19 *Weinrich et al., (USA)*	Non-hospitalized COVID-19 patients (n = 799) <u>Duration of follow-up:</u> 29 days	EXPERIMENTAL: Casirivimab-imdevimab 2400mg cocktail IV Casirivimab-imdevimab 8000mg cocktail IV CONTROL: Placebo	PRIMARY: TWA change in viral load from baseline through day 7 SECONDARY: At least 1 COVID-19-related medically-attended visit (MAV), safety	Randomized, double-blind, placebo-controlled trial

Appendix 4: Characteristics of Excluded Studies*

Study ID	Reason for Exclusion
Effectiveness of Casirivimab-Imdevimab and Sotrovimab During a SARS-CoV-2 Delta Variant Surge A Cohort Study and Randomized Comparative Effectiveness Trial *Huang et al. (USA)*	Different comparison (Casirivimab+Imdevimab vs Sotrovimab)
Clinical Study to Evaluate the Possible Efficacy and Safety of Antibodies Combination (casirivimab and imdevimab) versus standard antiviral therapy as antiviral agent against Corona virus 2 infection in hospitalized COVID-19 patients *Hassan, Hegazy & Radwan (Egypt); pre-print*	Different comparison (Casirivimab+Imdevimab vs Remdesivir vs Favipavir)

*Studies published/posted beginning December 2021

Appendix 5: Study Appraisal (Risk of Bias Summary)



Appendix 6: GRADE Evidence Profile

Author(s): Patricia Orduna, MD
Question: Casirivimab+imdevimab compared to placebo for treatment of covid-19
Setting: Asymptomatic, outpatient
Bibliography: O'brien et al. (2021)

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)		
Development of COVID-19 symptoms (follow-up: 28 days)												
1	randomised trials	not serious	not serious	very serious[a]	serious[b]	none	29/156 (18.6%)	44/158 (27.8 %)	**RR 0.67** (0.44 to 1.01)	**92 fewer per 1,000** (from 156 fewer to 3 more)	⨁◯◯◯ Very low	CRITICAL
At least 1 COVID-related MAV (follow-up: 28 days)												
1	randomised trials	not serious	not serious	very serious[a]	serious[b]	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)	⨁◯◯◯ Very low	CRITICAL
Duration of COVID-19 symptoms (follow-up: 28 days)												
1	randomised trials	not serious	not serious	very serious[a]	serious[b]	none	100	104	-	MD **4.2 days lower** (9.68 lower to 1.28 higher)	⨁◯◯◯ Very low	IMPORTANT
Adverse events (follow-up: 28 days)												
1	randomised trials	not serious	not serious	very serious[a]	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)	⨁⨁◯◯ Low	CRITICAL
Serious adverse events (follow-up: 28 days)												
1	randomised trials	not serious	not serious	very serious[a]	serious[b]	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)	⨁◯◯◯ Very low	

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

Explanations

a. Study conducted prior to the emergence of the current predominant variant (Omicron)
b. Wide confidence intervals

Author(s): Patricia Orduña, MD
Question: Casirivimab-imdevimab compared to placebo for treatment of COVID-19
Setting: Symptomatic, outpatient
Bibliography: Weinreich et al. 2021; Portal-Celhay et al. 2022; Weinrich et al. 2021 (Phase 1/2)

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)		
All-cause mortality (symptomatic outpatient) (follow-up: 28 days)												
2	randomised trials	not serious	not serious	very serious[a]	serious[b]	none	2/2521 (0.1%)	3/1418 (0.2%)	**RR 0.43** (0.07 to 2.56)	**1 fewer per 1,000** (from 2 fewer to 3 more)	⨁◯◯◯ Very low	CRITICAL
Hospitalization (symptomatic, outpatient) (follow-up: 28 days)												
1	randomised trials	not serious	not serious	very serious[a]	not serious	none	23/2091 (1.1%)	59/1341 (4.4%)	**RR 0.25** (0.15 to 0.39)	**33 fewer per 1,000** (from 37 fewer to 27 fewer)	⨁⨁◯◯ Low	CRITICAL
Need for invasive mechanical ventilation (symptomatic outpatient) (follow-up: 28 days)												
1	randomised trials	not serious	not serious	very serious[a]	serious[b]	none	2/2091 (0.1%)	6/1341 (0.4%)	**RR 0.21** (0.04 to 1.06)	**4 fewer per 1,000** (from 4 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL
At least 1 COVID-related medically-assisted visit (symptomatic outpatient) (follow-up: 29 days)												
1	randomised trials	not serious	not serious	very serious[a]	not serious	none	69/2273 (3.0%)	115/1434 (8.0%)	**RR 0.40** (0.29 to 0.56)	**48 fewer per 1,000** (from 57 fewer to 35 fewer)	⨁⨁◯◯ Low	CRITICAL
Duration of symptoms in days (symptomatic, outpatient) (follow-up: 28 days)												
1	randomised trials	not serious	not serious	very serious[a]	not serious	none	2091	2089	-	mean **4 days lower** (4.24 lower to 3.76 lower)	⨁⨁◯◯ Low	CRITICAL
Adverse event (symptomatic outpatient) (follow-up: 28 days)												
3	randomised trials	not serious	not serious	very serious[a]	not serious	none	108/3540 (3.1%)	59/2051 (2.9%)	**RR 0.62** (0.45 to 0.87)	**11 fewer per 1,000** (from 16 fewer to 4 fewer)	⨁⨁◯◯ Low	CRITICAL
Serious adverse events (symptomatic, outpatient) (follow-up: 28 days)												

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)		
3	randomised trials	not serious	not serious	very serious[a]	not serious	none	24/3452 (0.7%)	73/2051 (3.6%)	**RR 0.22** (0.14 to 0.35)	**28 fewer per 1,000** (from 31 fewer to 23 fewer)	⨁⨁◯◯ Low	CRITICAL

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

Explanations

a. Study conducted prior to the emergence of the current predominant variant (Omicron)
b. Wide confidence intervals

Author(s): Patricia Orduna
Question: Casirivimab+imdevimab compared to placebo for treatment of covid-19
Setting: Hospitalized
Bibliography: Somersan-Karakaya et al. 2022; Horby et al. 2022

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)		
All-cause mortality (follow-up: 28 days)												
2	randomised trials	not serious	serious[a]	very serious[b]	serious[c]	none	1002/5751 (17.4%)	1074/5398 (19.9%)	**RR 0.82** (0.58 to 1.16)	**36 fewer per 1,000** (from 84 fewer to 32 more)	⨁◯◯◯ Very low	CRITICAL
Need for invasive mechanical ventilation (follow-up: 28 days)												
2	randomised trials	not serious	serious[a]	very serious[b]	serious[c]	none	283/4839 (5.8%)	304/4946 (6.1%)	**RR 0.95** (0.85 to 1.11)	**3 fewer per 1,000** (from 9 fewer to 7 more)	⨁◯◯◯ Very low	CRITICAL
Clinical improvement/discharge at Day 28 (follow-up: 28 days)												
2	randomised trials	not serious	serious[a]	very serious[b]	serious[c]	none	4103/5805 (70.7%)	3750/5398 (69.5%)	**RR 1.03** (0.96 to 1.10)	**21 more per 1,000** (from 28 fewer to 69 more)	⨁◯◯◯ Very low	CRITICAL
Duration of hospitalization (follow-up: 28 days)												
1	randomised trials	serious[d]	not serious	very serious[b]	serious[e]	none	Among hospitalized patients, the median duration of hospitalization was 10 days for both treatment and placebo groups. Among seronegative patients, the median duration of hospitalization was 4 days shorter in the experimental group versus control (13 days vs 17 days)				⨁◯◯◯ Very low	CRITICAL
Adverse events (follow-up: 28 days)												
1	randomised trials	serious[d]	not serious	very serious[b]	not serious	none	317/1340 (23.7%)	180/667 (27.0%)	**RR 0.88** (0.75 to 1.03)	**32 fewer per 1,000** (from 67 fewer to 8 more)	⨁◯◯◯ Very low	CRITICAL
Serious adverse event (follow-up: 28 days)												
1	randomised trials	serious[d]	not serious	very serious[b]	not serious	none	285/1340 (21.3%)	174/667 (26.1%)	**RR 0.82** (0.69 to 0.96)	**47 fewer per 1,000** (from 81 fewer to 10 fewer)	⨁◯◯◯ Very low	CRITICAL

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

Explanations

a. High heterogeneity
b. Study conducted prior to the emergence of the current predominant variant (Omicron)
c. Wide confidence intervals
d. Open label study
e. No mentioned confidence intervals

Author(s): Patricia C. Orduña, MD
Question: Casirivimab+imdevimab compared to placebo for treatment among patients with COVID-19
Setting: Symptomatic
Bibliography: Portal-Celhay et. al. (2022); Weinrich et al. 2021; Jittamala et al. (2022)

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)		
Least-squares mean differences in time-weighted average change from baseline (TWACB) in viral load (follow-up: 7 days)												
4	randomised trials	not serious	serious[a]	serious[b]	not serious	none	743	730	-	MD **0.42 log10 copies/ml lower** (0.43 lower to 0.4 lower)	⨁⨁◯◯ Low	IMPORTANT
Rate of viral load clearance (follow-up: 7 days)												
1	randomised trials	serious[c,d]	serious[e]	not serious	very serious[f,g]	none	Overall, viral loads declined 25% faster (95%CI 8 to 46%) in casirivimab/imdevimab recipients compared to the no study drug arms. Viral clearance rates in Delta variant infections were increased by 58% (95% CI: 10 to 120%) relative to no study drug. In the Omicron variants overall, this effect was reduced by nearly three-fold: 20% (95% CI: 3to 43%)				⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; **MD:** mean difference

Explanations

a. Substantial heterogeniety
b. Study conducted prior to the emergence of the current predominant variant (Omicron)
c. Reporting bias
d. Open label study
e. Heterogeniety of COVID-19 variants
f. p values not provided
g. Viral load least squares mean difference/time-weighted average change from baseline were not provided

Author(s): Patricia Orduna, MD
Question: Casirivimab+imdevimab compared to placebo for treatment of covid-19 in children
Setting: Asymptomatic, outpatient
Bibliography: O'brien et al. (2021)

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)		
Development of COVID-19 symptoms (follow-up: 28 days)												
1	randomised trials	not serious	not serious	very serious[a]	serious[b]	none			**OR 0.20** (0.15 to 1.64)	**0 fewer per 1,000** (from 2 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **OR:** odds ratio

Explanations

a. Study conducted prior to the emergence of the current predominant variant (Omicron)
b. Wide confidence intervals

Appendix 7: Forest Plots

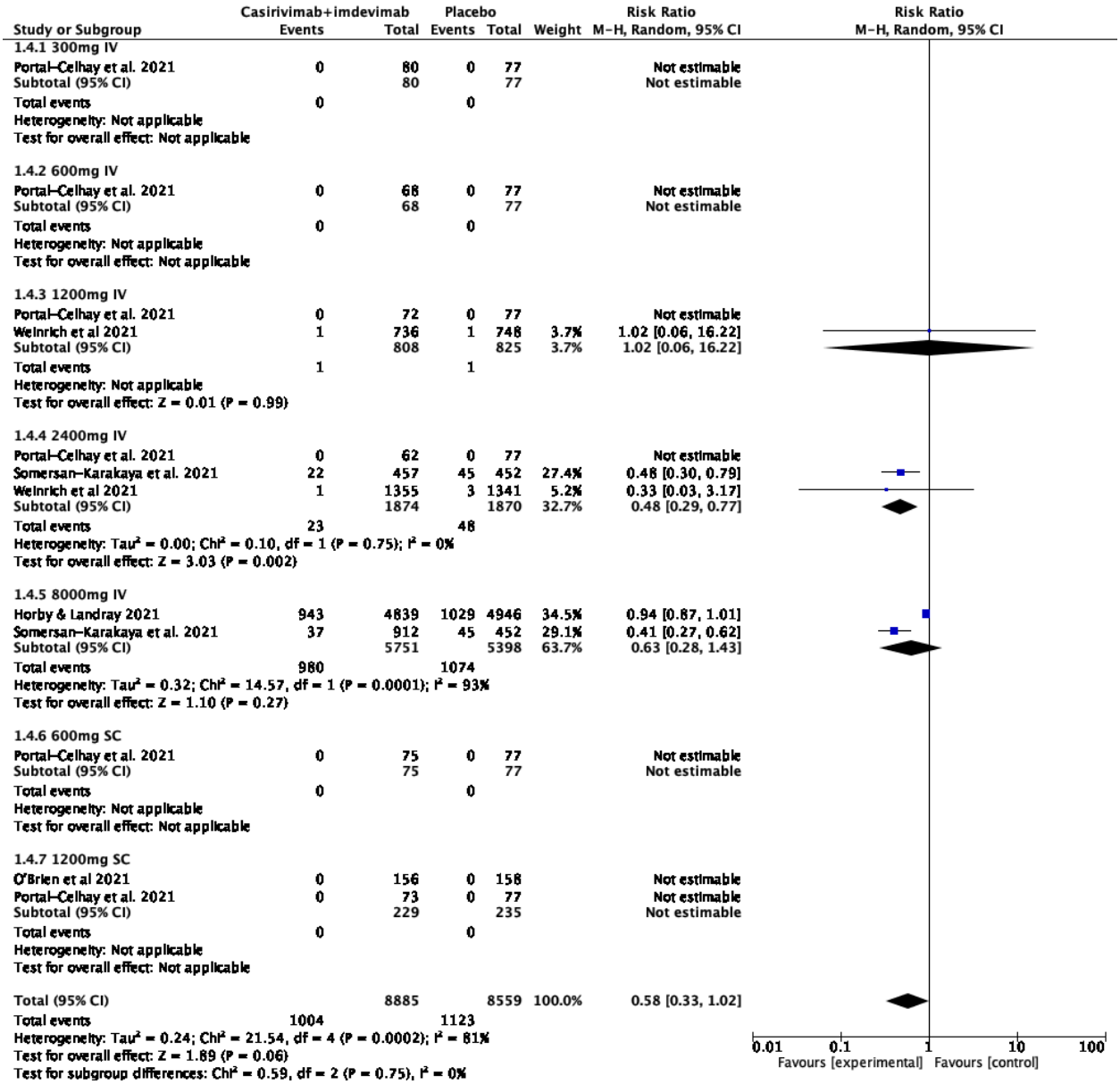


Figure 1. All-cause mortality by dose

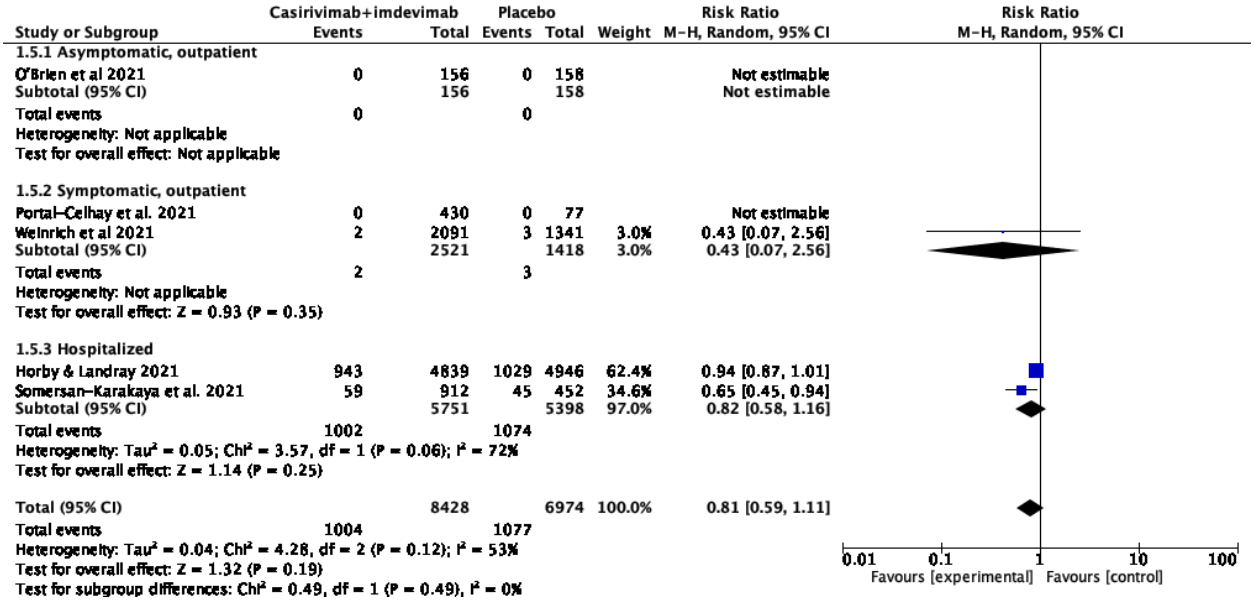


Figure 2. All-cause mortality by hospitalization status

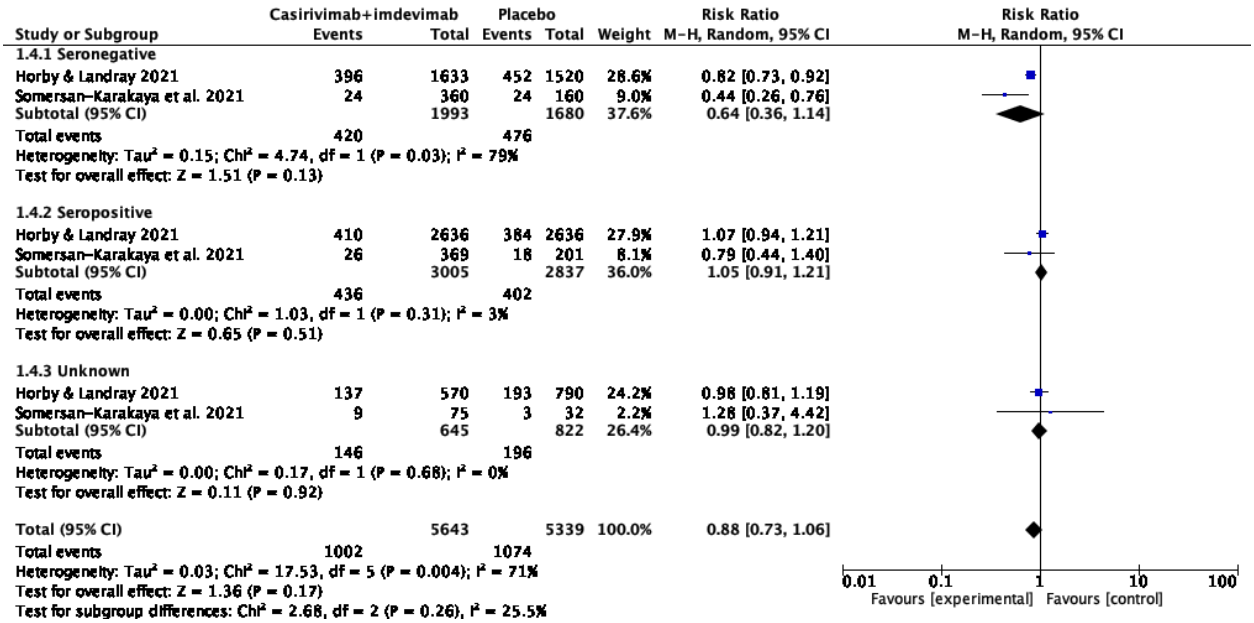


Figure 3. All-cause mortality by antibody status

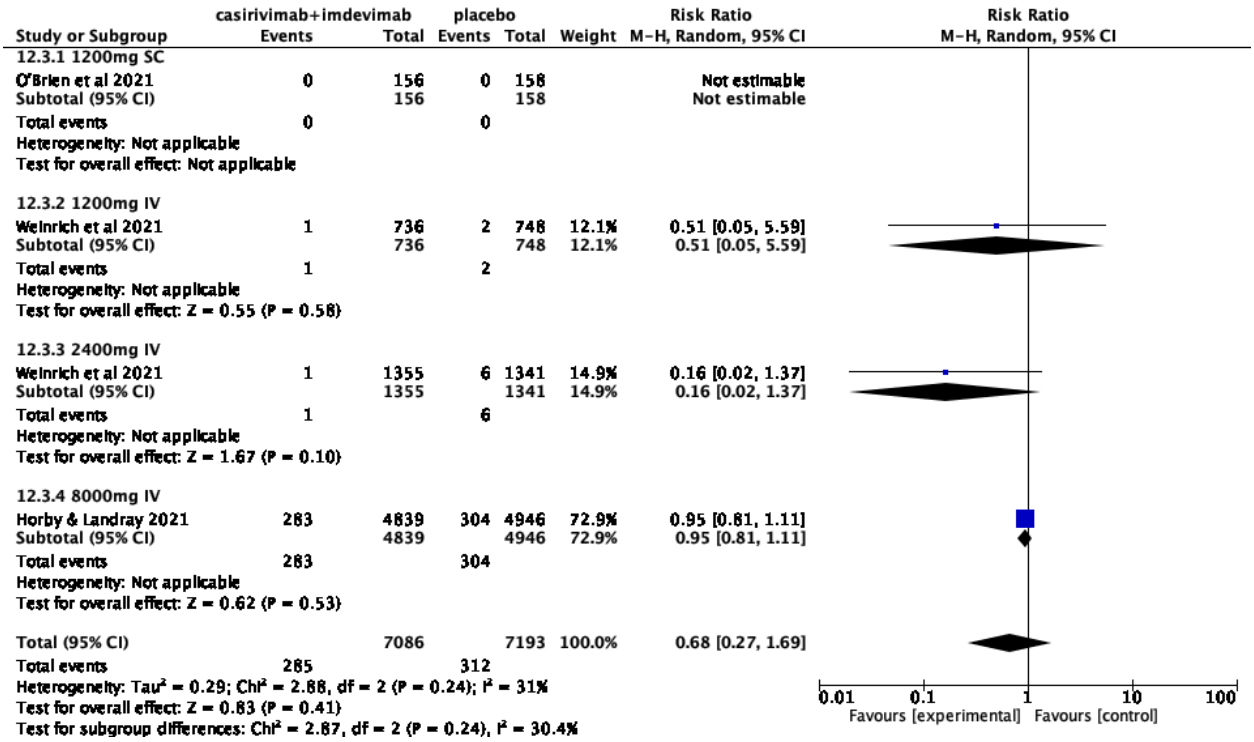


Figure 4. Need for invasive mechanical ventilation by dose

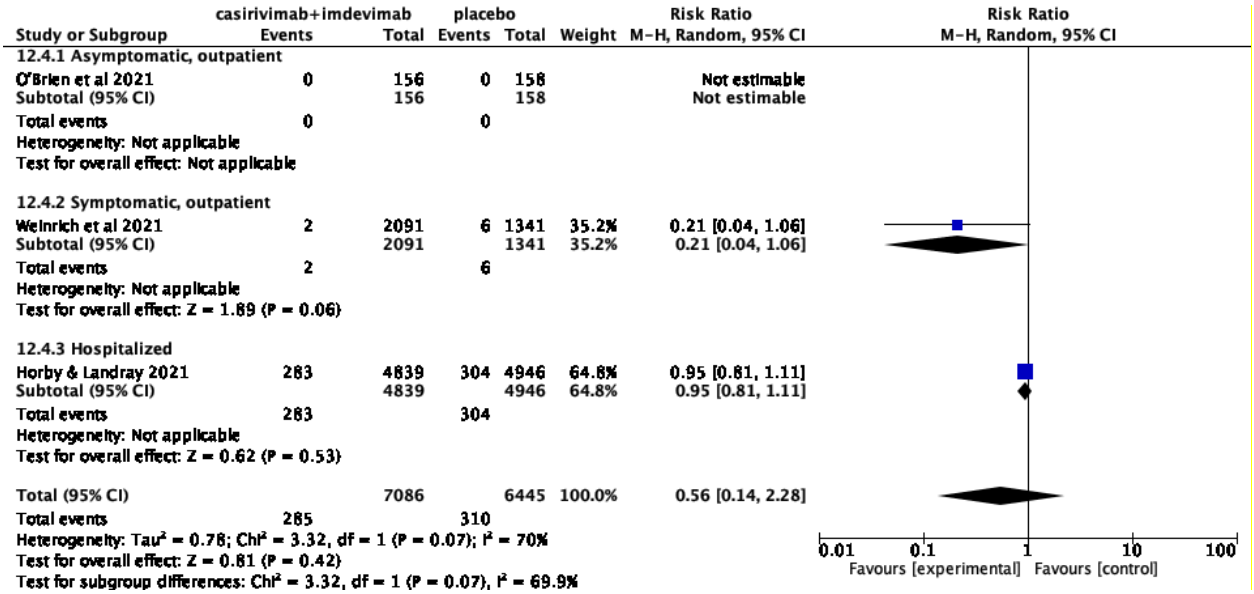


Figure 5. Need for invasive mechanical ventilation by hospitalization status

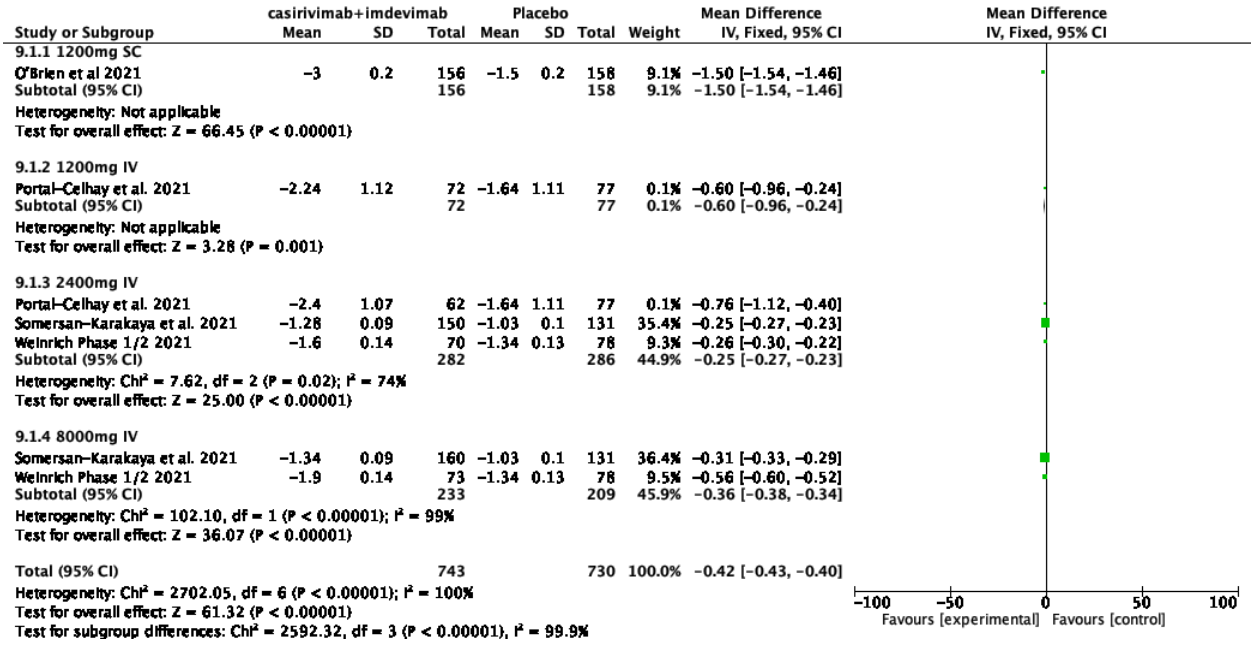


Figure 6. Least-squares mean differences in time-weighted average change from baseline (TWACB) in viral load

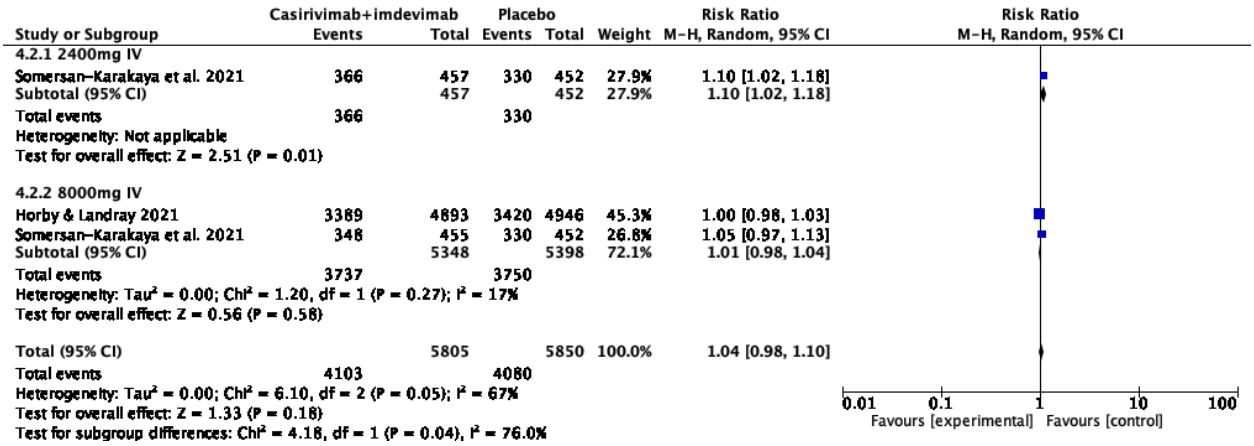


Figure 7. Clinical improvement/discharge from hospital at day 28 by dose

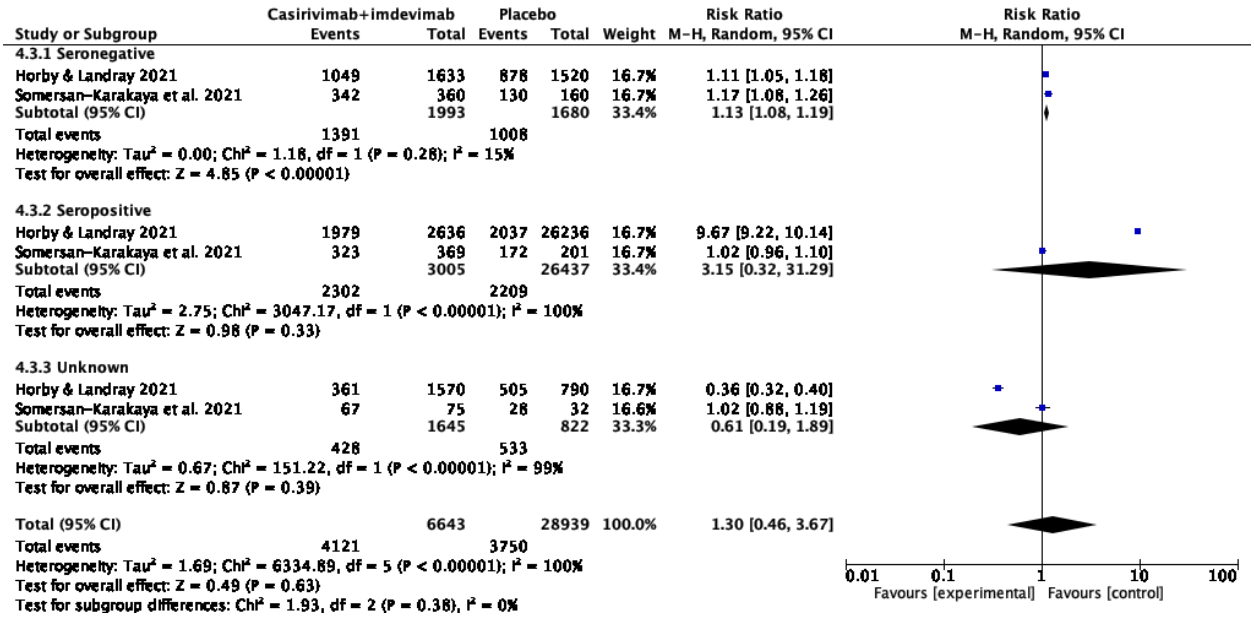


Figure 8. Clinical improvement/discharge from hospital at day 28 by antibody status

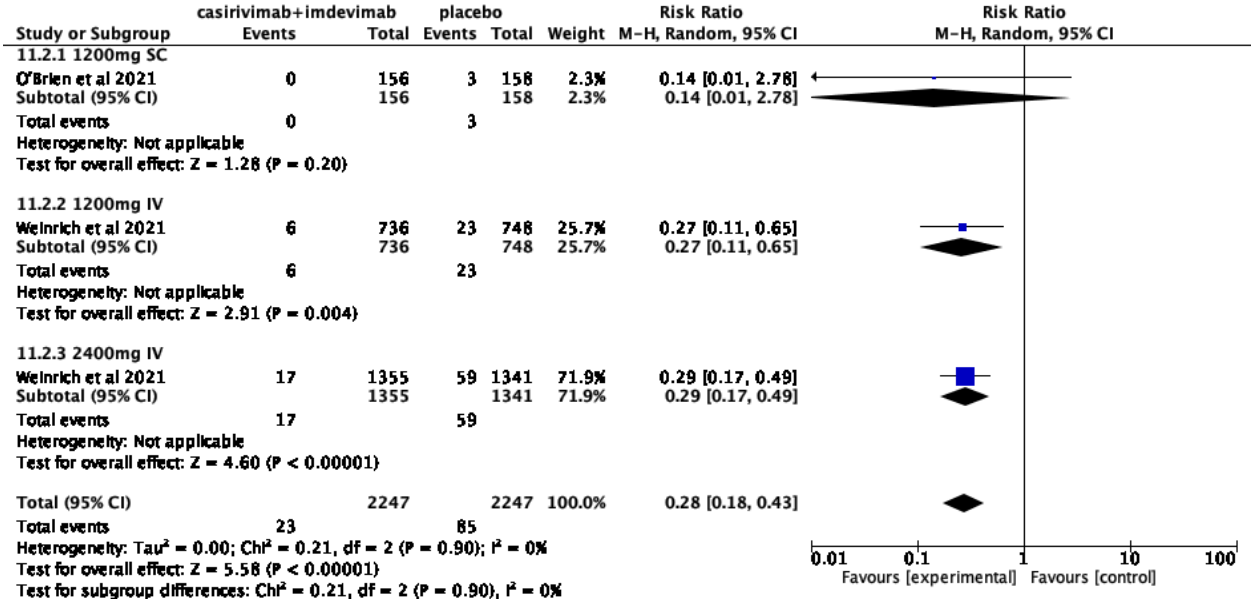


Figure 9. Risk of hospitalization among outpatients by dose

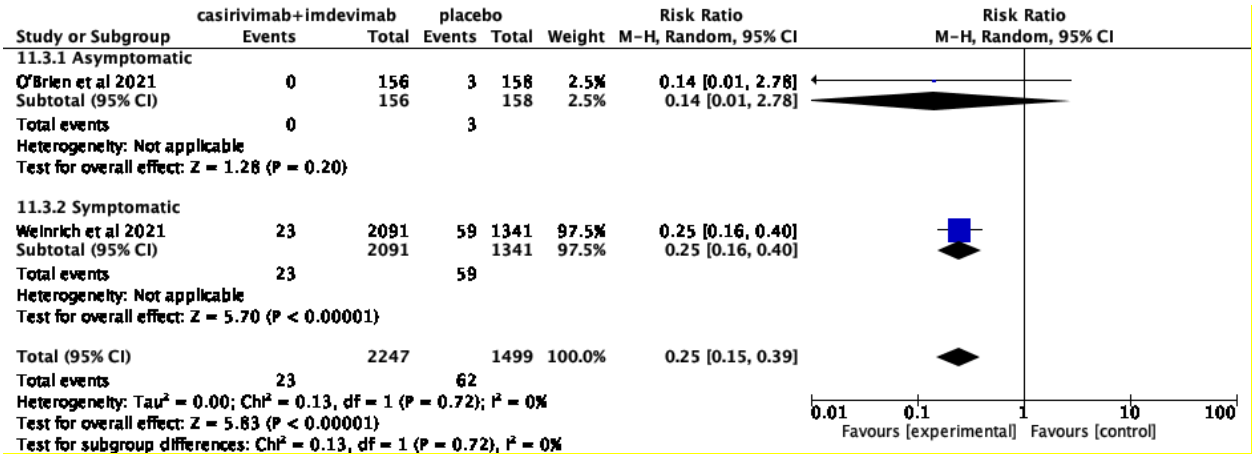


Figure 10. Risk of hospitalization among outpatients by symptom

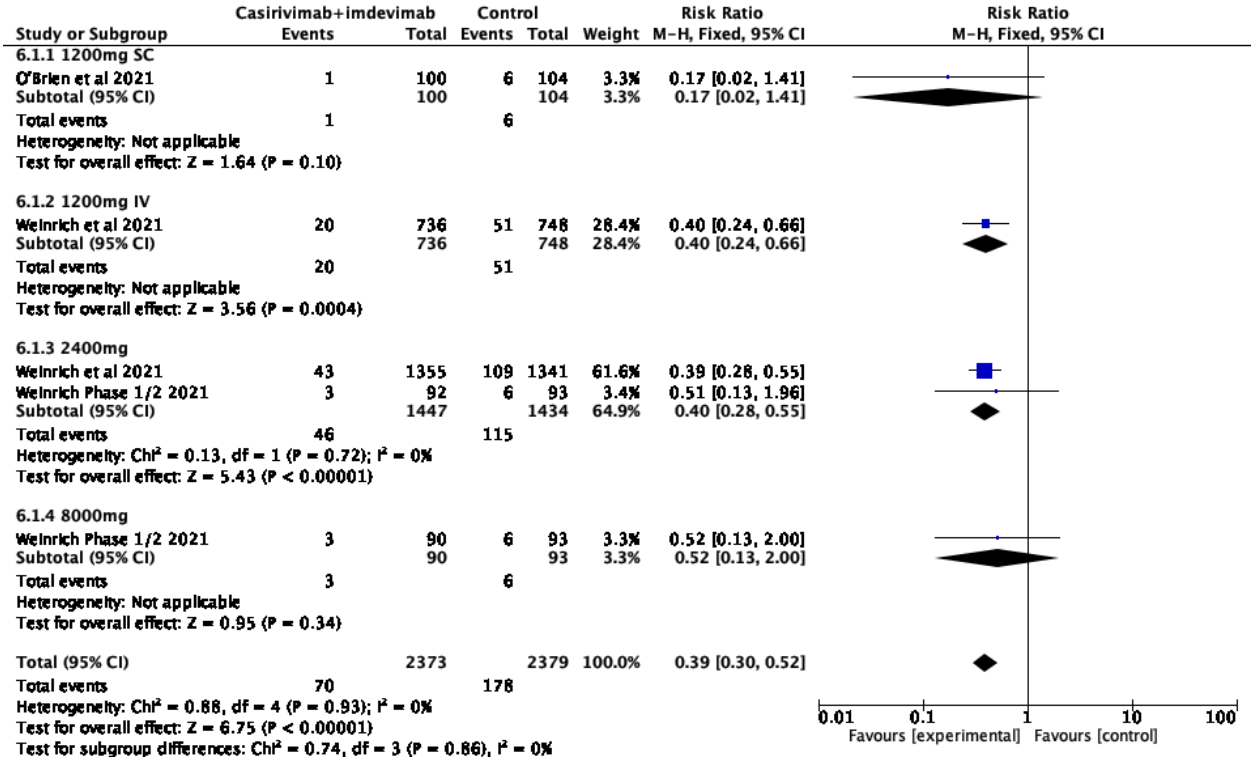


Figure 11. At least 1 COVID-related MAV by dose

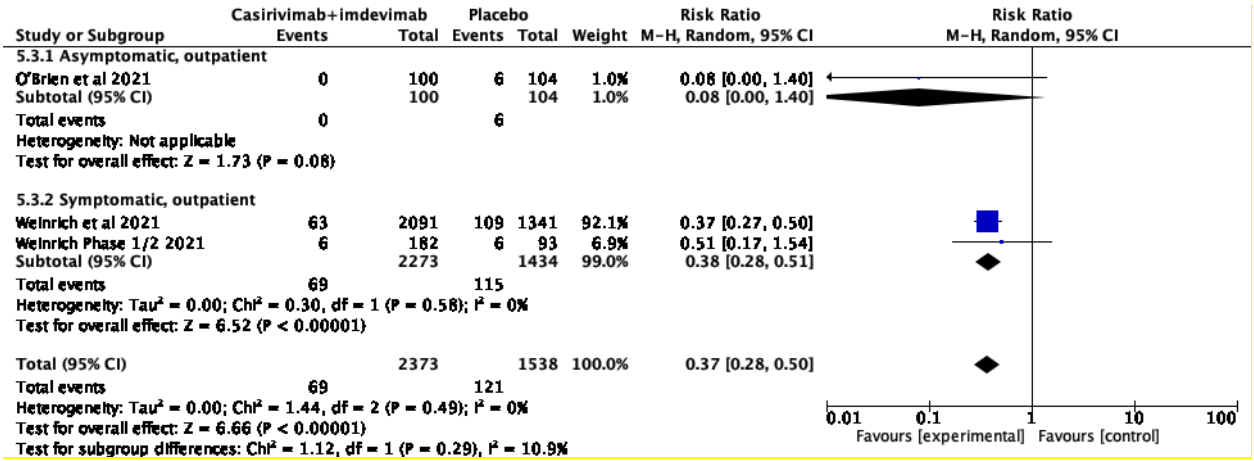


Figure 12. At least 1 COVID-related MAV by symptom

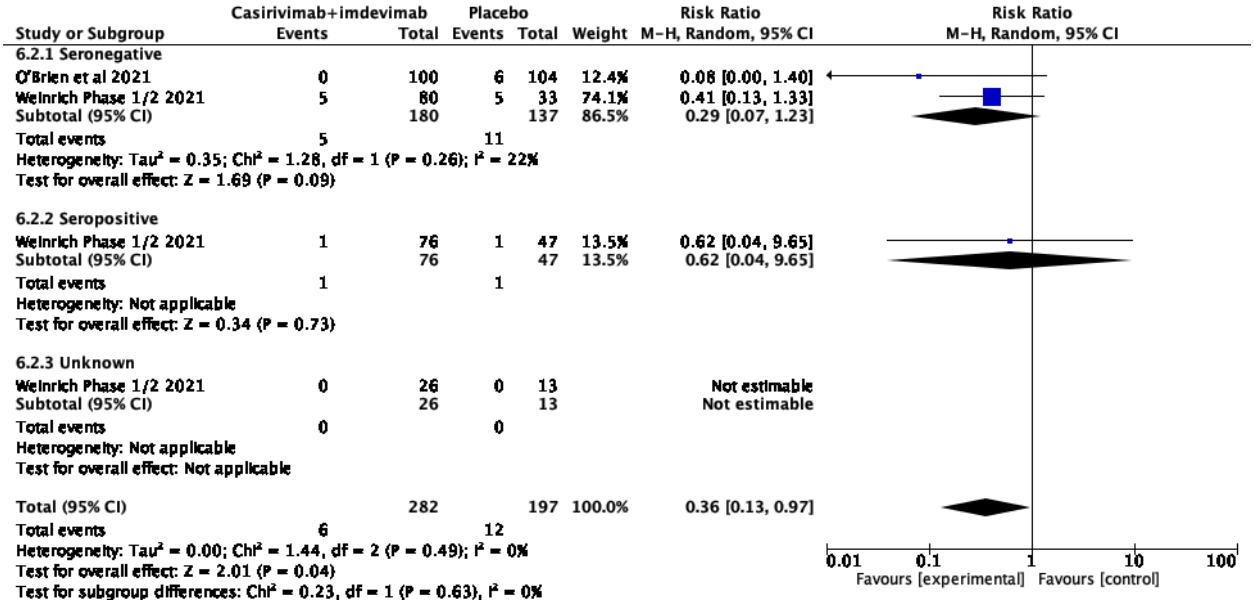


Figure 13. At least 1 COVID-related MAV by antibody status

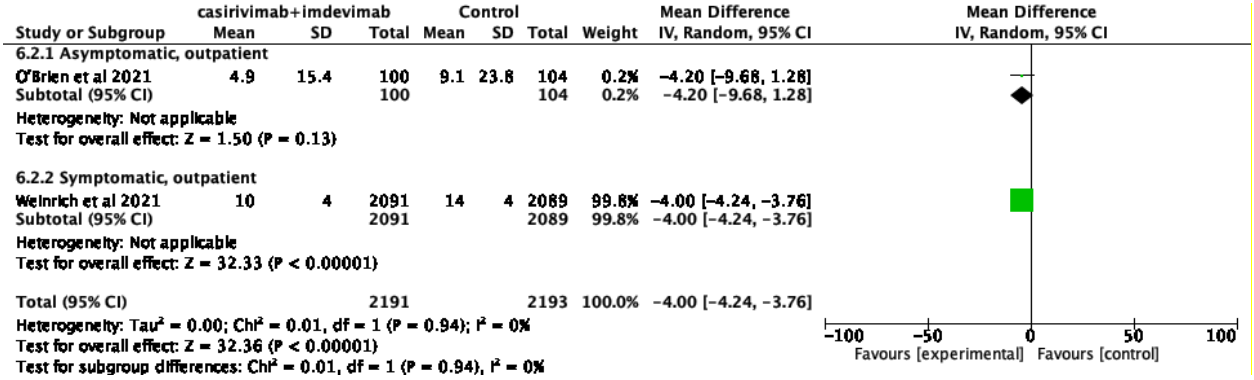


Figure 14. Duration of COVID-19 symptoms in days by symptom

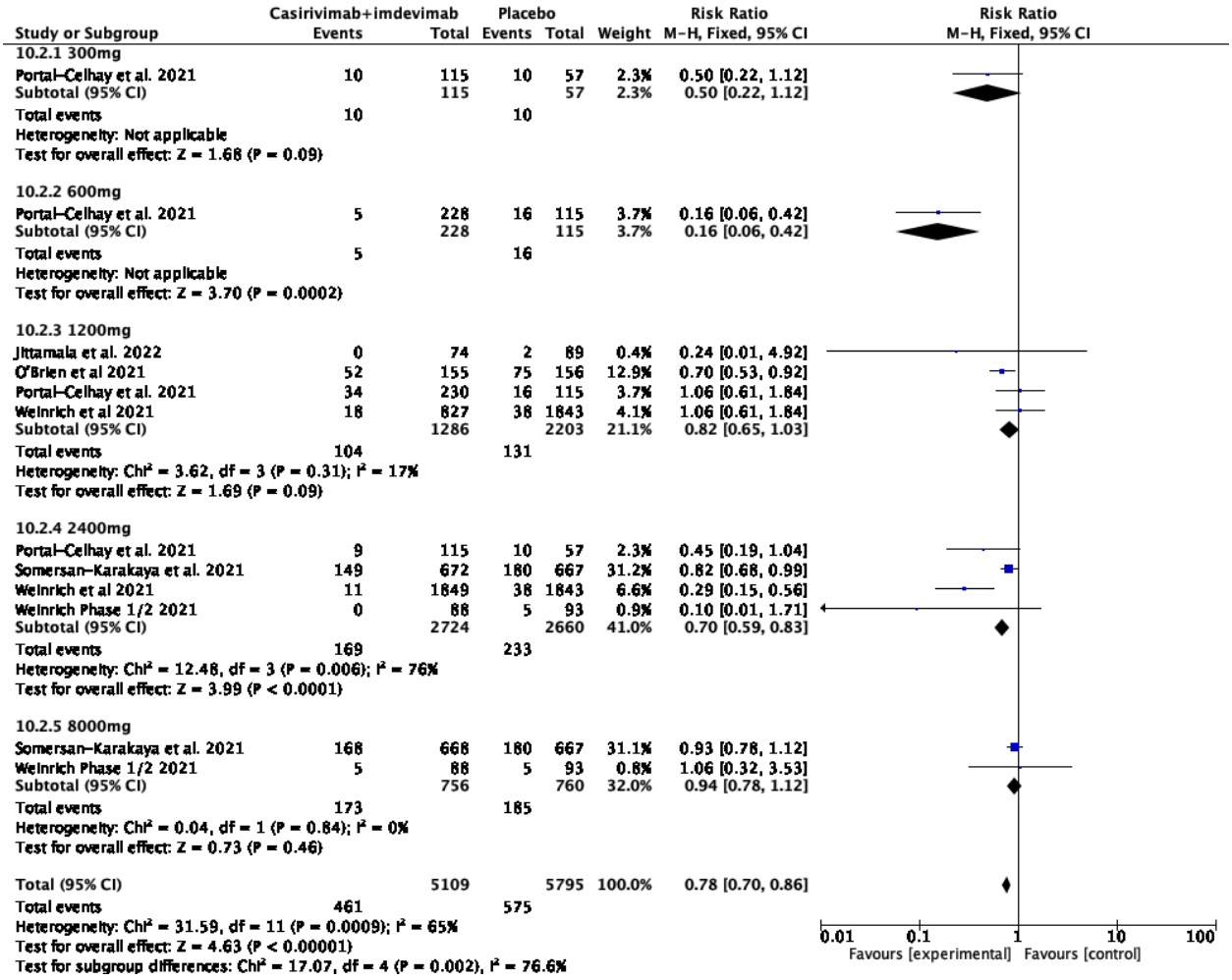


Figure 15. Adverse events by dose

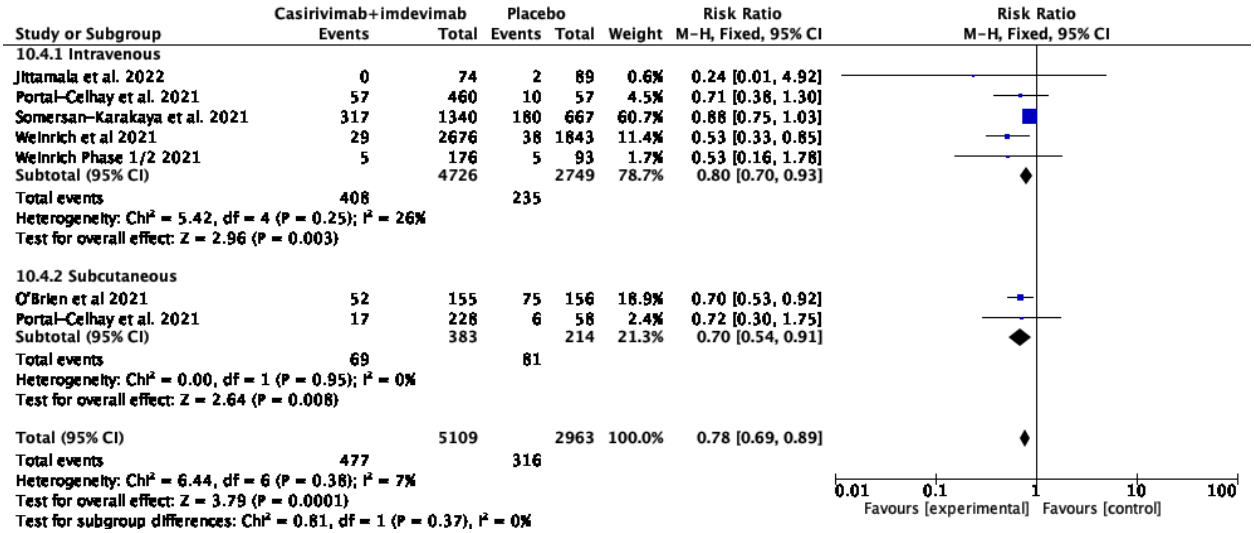


Figure 16. Adverse events by route of administration

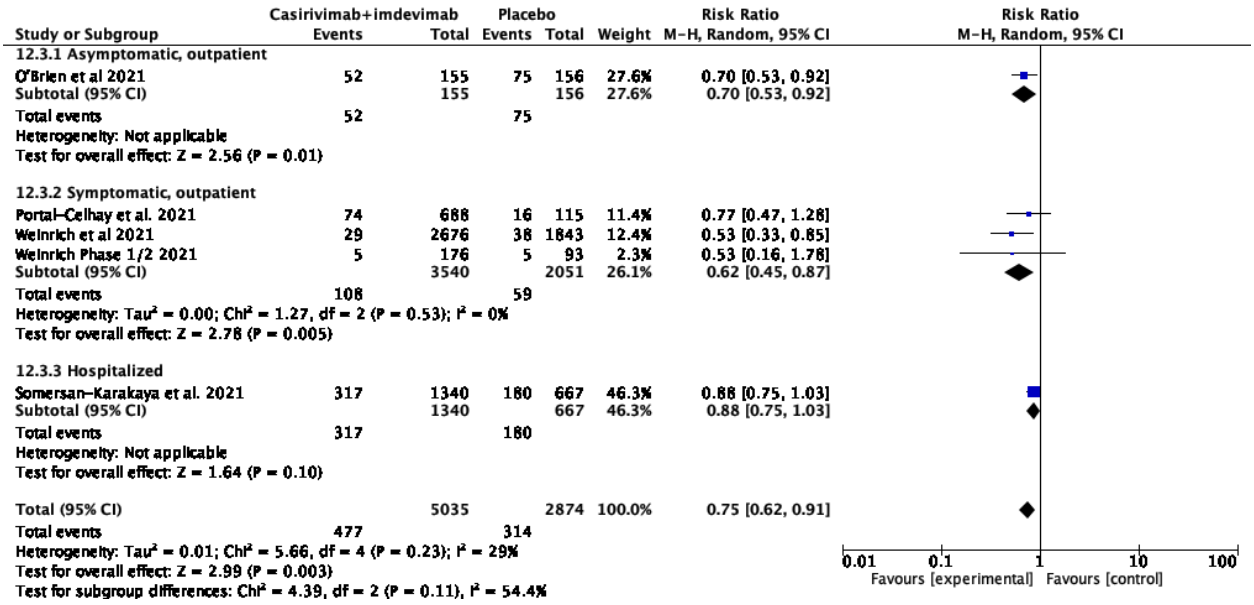


Figure 17. Adverse events by hospitalization status

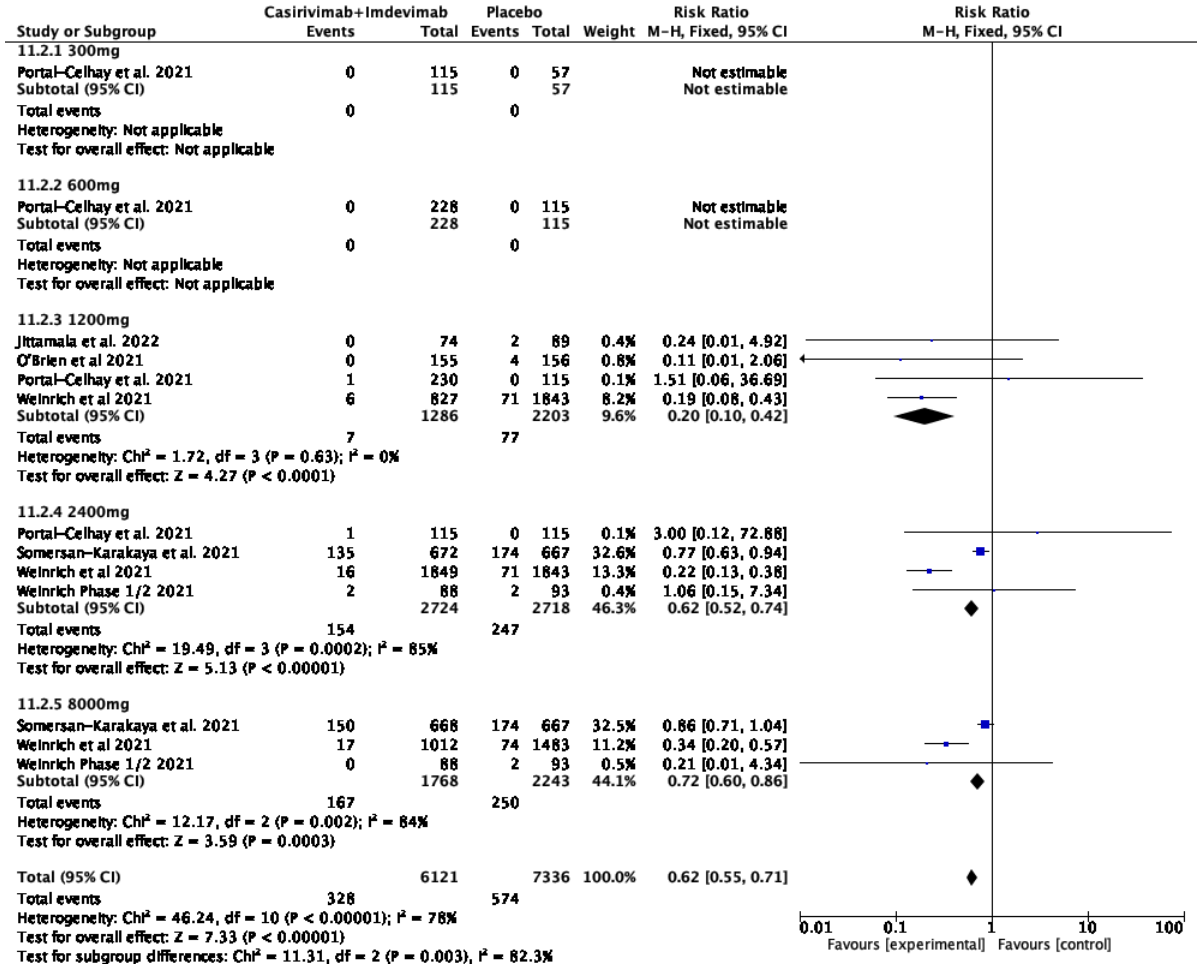


Figure 18. Serious adverse events by dose

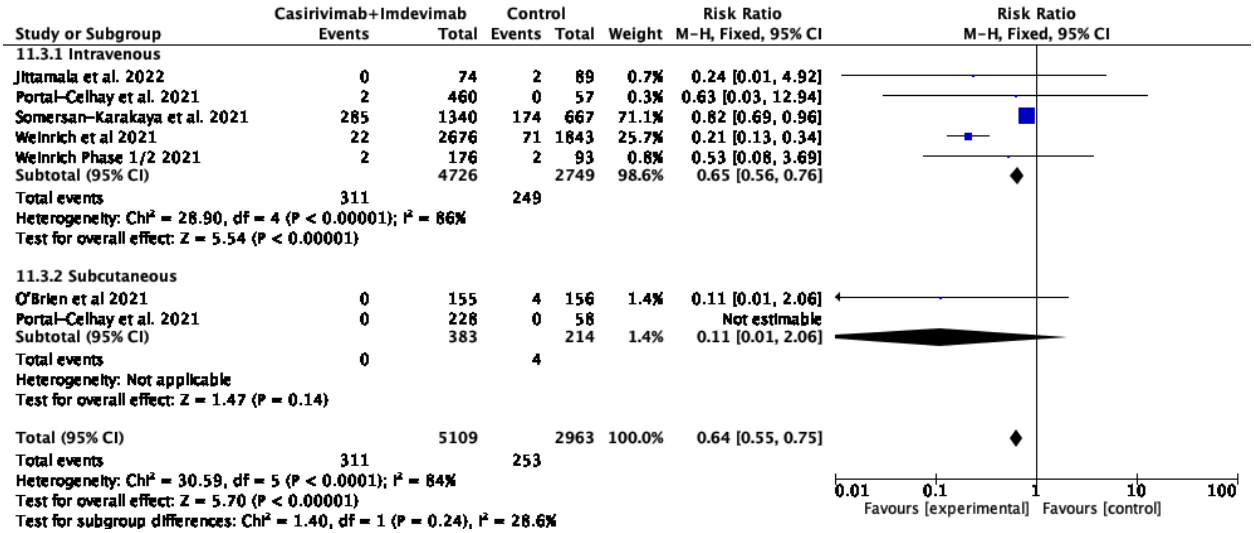


Figure 19. Serious adverse events by route of administration

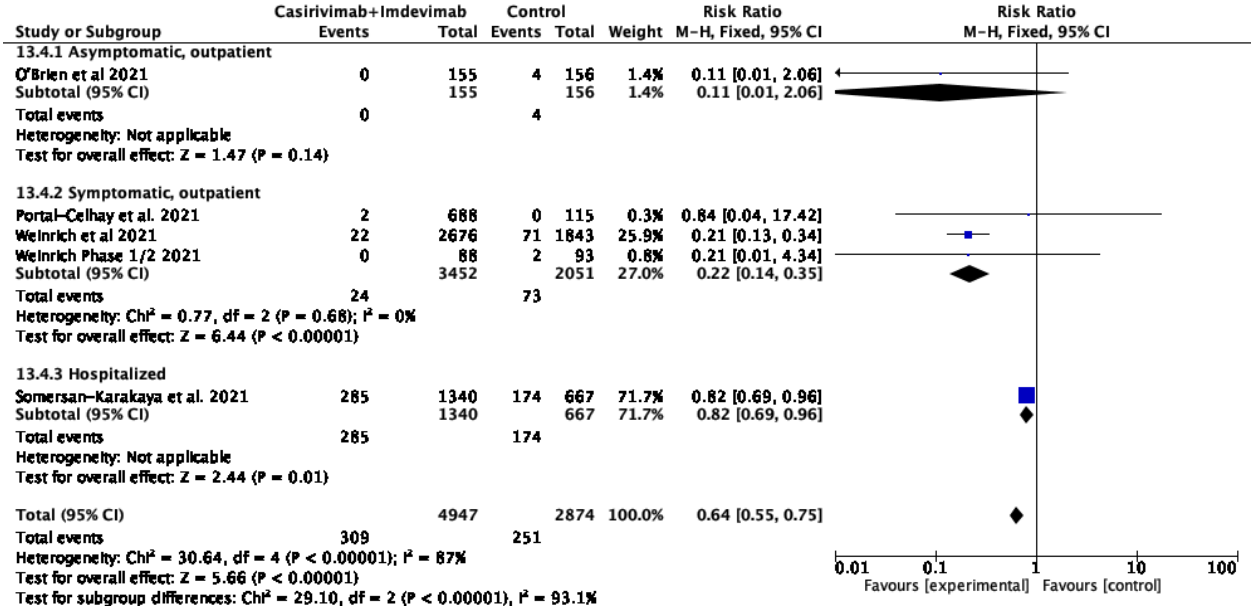


Figure 20. Serious adverse events by hospitalization status

Appendix 8: Table of Ongoing Studies

Clinical Trial Identifier/Title	Study Design	Country	Population	Intervention	Outcome	Estimated Date of Completion
NCT05081388 A Phase 1/2/3 Adaptive Study to Evaluate the Safety, Tolerability, and Efficacy of REGN14256+Imdevimab for the Treatment of COVID-19 Patients Without Risk Factors for Progression to Severe Disease	Randomized controlled trial	USA	Mild to moderate COVID-19 patients without co-morbidities	Casirivimab vs. imdevimab vs. casirivimab + imdevimab vs. placebo	Treatment emergent adverse events, injection-site reactions, hypersensitivity reactions, time-weight average daily change from baseline in viral load, time to COVID-19 symptom resolution	Completed June 30, 2022 No available published/pre-print data
NCT04518410 ACTIV-2: A Study for Outpatients with COVID-19	Randomized control trial	USA	Mild to moderate COVID-19 positive patients	Experimental 1: Bamlanivimab IV Experimental 2: BRII-196/BRII-198 IV Experimental 3: AZD7442 IV Experimental 4: SNG001 inhalation Experimental 5: AZD7442 IM Experimental 6: Camostat PO Experimental 7: BMS 986414 + BMS 986413 SC Experimental 8: SAB-185 IV Experimental 9: Casirivimab + imdevimab IV Control: Placebo IV	Prevention of disease progression	June 22, 2023
EudraCT 2021-004035-88 A randomized, open-label, active controlled, parallel group, multicenter phase 3 study to evaluate the efficacy	Randomized controlled trial	Italy	Mild to moderate COVID-19 positive patients	Bamlanivimab + etesivimab vs. casirivimab + imdevimab vs. sotrovimab vs. standard of care	Disease progression (hospitalization in intensive care unit, oxygen desaturation ≥4% or peripheral oxygen saturation ≤92%) during the 30-day follow-up period, adverse events	Not mentioned (Latest status ongoing)

and tolerability of Bamlanivimab and Etesevimab, Casirivimab and Imdevimab, and Sotrovimab versus Standard of Care in patients with mild to moderate COVID-19 disease						
NCT04840459 Use of Monoclonal Antibodies (Bamlanivimab and Casirivimab+Imdevimab) for the Treatment of Mild to Moderate COVID-19 in Non-Hospitalized Setting	Randomized controlled trial	USA	Non-hospitalized COVID-19 positive patients ages 12 years and older weighing at least 40 kg who are at "high risk" for progressing to severe COVID-19 and/or hospitalization	Bamlanivimab vs. casirivimab-imdevimab vs. placebo	Disease progression (hospitalization), time to symptom resolution	January 31, 2023 (latest status recruiting)
EudraCT 2021-002612-31 NCT05205759 Adaptive, randomized, placebo-controlled trial to evaluate the efficacy of monoclonal antibodies in outpatients with mild or moderate COVID-19 (MANTICO)	Randomized controlled trial	Italy	COVID-19 positive patients ≥94% O2 saturation on room air with onset of COVID-19 symptoms no more than 4 days prior to the study drug administration	Bamlanivimab + etesevimab vs. placebo Casirivimab + imdevimab vs. placebo	COVID-19 disease progression (hospitalization, need for supplemental oxygen therapy at home or death) within 14 days of randomization	*Terminated* (Futility after the onset of the omicron wave)
NCT05092581 A Phase 1b, Open-Label, Single Dose Study Assessing the Pharmacokinetics, Safety, Tolerability and Efficacy of Intravenous Anti-Spike(s) SARS-CoV-2 Monoclonal Antibodies (Casirivimab+Imdevimab) for the Treatment of Pediatric	Randomized controlled trial	USA	Hospitalized children (up to 17 years old) with COVID-19	Casirivimab + imdevimab vs placebo	Concentrations of casirivimab+imdevimab in serum over time, proportion of patients with treatment-emergent SAEs, proportion of patients with infusion-related reactions, proportion of patients with hypersensitivity reactions, incidence of anti-drug antibodies to casirivimab+imdevimab over time, incidence of neutralizing antibodies	*Terminated* (emerging SARS-CoV-2 variants impacting susceptibility to study drug)

Patients Hospitalized Due to COVID-19					to casirivimab+imdevimab over time	
NCT04748588 Canadian Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of Nosocomial Acquired COVID-19 Patients	Randomized controlled trial	Canada	Nosocomially-acquired hospitalized COVID-19 patients	Casirivimab-imdevimab vs. bamlanivimab vs. sotrovimab	Proportion of patients requiring mechanical ventilation or not surviving to hospital discharge, in-hospital death, need for mechanical ventilation, need for new intensive care admission, need for new oxygen administration	*Suspended* (Equipose requirement no longer met)