Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
Funded by the Department of Health

EVIDENCE SUMMARY

Among patients with COVID-19, should casirivimab-imdevimab be used for treatment?

Update by: Isabella S. Ocampo, MD, April P. Padua-Zamora, MD Carol Stephanie C. Tan-Lim, MD, MSc (Clinical Epidemiology), Jemelyn U. Garcia, MD, Leonila F. Dans, MD, MSc, Marissa M. Alejandria, MD, MSc
Initial review by: Anna Antonio L. Faltado Jr. MD, FPCP, FPSEDM, MSc (Cand) and Anna Angelica Macalalad-Josue MD, FPCP, FPSEDM, MSc (Cand.) Howell Henrian G. Bayona, MSc, CSP-PASP

RECOMMENDATIONS

We suggest the use of casirivimab-imdevimab as treatment for symptomatic, 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. (*Low certainty of evidence; Strong recommendation)*

There is insufficient evidence to recommend casirivimab-imdevimab as treatment for asymptomatic COVID-19 patients. *(Low certainty of evidence)*

*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
Addition of 2 new pre-print randomized controlled trials (RCTs) still showed that casirivimab and imdevimab cocktail is beneficial for symptomatic, non-hospitalized COVID-19 patients with at least 1 risk factor for progression to severe disease. Although there was moderate certainty of evidence, the recommendation was weak due to inconclusive evidence on all-cause mortality, large cost, need for emergency room visit for drug administration and close monitoring and equity considerations. At present, the drug is only available in private tertiary hospitals.

The evidence remained inconclusive for hospitalized COVID-19 patients. The previous update included 1 pre-print RCT (RECOVERY trial), which on subgroup analysis showed that casirivimab-imdevimab appeared to have benefit in terms of all-cause mortality, need for mechanical ventilation, and clinical recovery among hospitalized patients who were seronegative at baseline (negative for serum SARS-CoV-2 antibodies). However, addition of 1 (one) new pre-print RCT showed trend towards benefit in clinical recovery only. The panel maintained the previous recommendation against the use of casirivimab-imdevimab cocktail among hospitalized COVID-19 patients because of uncertain balance of effects in this specific subset of patients and both RCTs are still pre-print. As of writing, there are 8 ongoing clinical trials on casirivimab-imdevimab, 2 of which are among hospitalized patients. Results of these trials may further elucidate on the cocktail's effectiveness in the treatment of hospitalized COVID-19 patients.

Lastly, the only available study for asymptomatic, non-hospitalized COVID-19 patients is a small pre-print RCT with low certainty of evidence. The panel deemed that current evidence is still insufficient to make any recommendations for this subset of patients.

PREVIOUS RECOMMENDATIONS

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

We recommend against casirivimab + imdevimab as treatment for hospitalized COVID-19 patients. (*Moderate quality 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.

Previous 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.

What's new in this version?

This version includes data from four (4) new pre-print randomized clinical trials.

Key Findings

Six (6) RCTs evaluated the efficacy of casirivimab-imdevimab cocktail as treatment for patients with COVID-19. Among non-hospitalized patients given casirivimab-imdevimab, there was a significant reduction in combined end-point of need for invasive mechanical ventilation or death, COVID-19-related medically-assisted visits, duration of symptoms, and serious adverse events. However, evidence was largely inconclusive for hospitalized patients and asymptomatic, non-hospitalized patients. There was trend towards benefit in clinical recovery among hospitalized seronegative patients (negative for serum SARS-CoV-2 antibodies at baseline), but not for seropositive patients (positive for serum SARS-CoV-2 antibodies at baseline)**.** There was no benefit in all-cause mortality regardless of hospitalization status.

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]

Review Methods

A systematic search was done from the date of the last search September 1, 2021 until November 26, 2021 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 looked at the COVID-NMA Living Data and searched for ongoing studies in the NIH *clinicaltrials.gov* and various 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. Only randomized controlled trials were included. No limits were placed on age, COVID-19 severity, and dosing. Preplanned subgroup analysis on dosing, severity and serologic status were conducted.

Results

A total of 231 related articles were found using Medline, CENTRAL, COVID-NMA initiative, and Google Scholar, however no new articles met our inclusion criteria. Four pre-prints were found using Medrxiv.org.[7-10] These studies evaluated the use of casirivimab-imdevimab as treatment for COVID-19 patients and were added to the previous 2 studies.[5-6]

The 6 studies included a total of 18,785 COVID-19 confirmed patients.[5-10] One of the pre-prints studied casirivimab-imdevimab as treatment for inpatient adult patients with COVID-19 who required little to no oxygen supplementation. These patients were enrolled in 1 of 4 cohorts: little to no oxygen support (cohort 1 and cohort 1a), high-intensity oxygen (cohort 2), and mechanical ventilation (cohort 3). However, due to low sample size, cohorts 2 and 3 were discontinued. These patients were randomized to receive intravenous (IV) 2400mg casirivimab-imdevimab, IV 8000mg casirivimab-imdevimab or placebo. Standard of care treatments for COVID-19 were permitted.[7]

Another pre-print studied the use of casirivimab-imdevimab as treatment for asymptomatic close contacts of a COVID-19 index case who are at least 12 years of age and tested positive for COVID-19 within 96 hours of exposure. These participants received a subcutaneous (SC) dose of 1200mg casirivimab-imdevimab or placebo.[8]

The 2 other pre-prints are Phase 1/2 trials that included non-hospitalized COVID-19 patients. One of these is a dose-ranging study that included the following interventions: IV 300mg casirivimab-imdevimab, IV 600mg casirivimab-imdevimab, IV 1200mg casirivimab-imdevimab, IV 2400mg casirivimab-imdevimab, SC 600mg casirivimab-imdevimab, and SC 1200mg casirivimab-imdevimab.[9] The second is part of the seamless Phase 1/2/3 trial of the published study.[10]

The overall quality of evidence was rated moderate because of serious risk of bias. 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 4. The GRADE evidence profile is in Appendix 5.

All-cause mortality was not significantly different between the casirivimab-imdevimab group and the placebo group regardless if non-hospitalized (RR 0.33, 95% CI 0.07-1.63) [5] or hospitalized (RR 0.81, 95% CI 0.56-1.17; I^2 = 75%).[6-7]

Among asymptomatic, non-hospitalized patients, there was no difference between the experimental and control groups in reducing the number of COVID-related medically assisted visits (MAVs) (RR 0.08, 95% CI 0.00-1.40). The same study found trend towards benefit in terms of development of symptomatic COVID-19 infection among patients given casirivimab-imdevimab versus placebo (RR 0.69, 95% CI 0.47-1.00).[8]

Among symptomatic non-hospitalized patients, there was a significant reduction in the combined end-point of need for invasive mechanical ventilation or death in the casirivimab-imdevimab group versus the control (RR 0.40, 95% CI 0.32-0.51).[5] Subgroup analysis according to dose showed benefit in the casirivimab-imdevimab 1200mg IV dose group (RR 0.40, 95% CI 0.24-0.66) and the 2400mg IV dose group (RR 0.45, 95% CI 0.33-0.61), but not in the 8000mg IV dose group (RR 0.74, 95% CI 0.48-1.12). 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 0.34, 95% CI 0.26-0.46; I^2 = 7%).[5,10] In one study, there was also a significant decrease in the duration of COVID-19 symptoms (MD -4.00 days, 95% CI -4.24 to -3.76) and in the duration of hospitalization, regardless of dose in the experimental group versus the control group (8.6 days in 2400mg group versus 10 days in control, 7 days in 1200mg group versus 8.4 days in control).[5]

Among hospitalized patients, there was no significant difference between the casirivimab-imdevimab group versus the placebo group in terms of need for invasive ventilation or death (RR 0.85, 95% CI 0.62-1.16; I^2 = 76%).[6-7] Post hoc subgroup analysis by serologic status showed no difference in reducing all-cause mortality among seronegative patients (RR 0.64, 95% CI 0.36-1.15; I^2 = 79%) [6-7] as well as among seropositive patients (RR 1.07, 95% CI 0.94-1.22).[6] There was also no difference in reducing the need for invasive mechanical ventilation or death among seronegative patients (RR 0.70, 95% CI 0.46-1.08; I^2 = 74%) [6-7] and among seropositive patients (RR 1.10, 95% CI 0.97-1.24).[6] However, in one study, the duration of hospitalization among seronegative patients was also shortened by 4 days in the experimental group versus the control group (13 days versus 17 days).[6]

Safety

Overall, there was a significant reduction in the number of serious adverse events (SAEs) in the experimental group versus the control group, regardless of dose (RR 0.52, 95% CI 0.37-0.74; I^2 = 76%) or route of administration (RR 0.51, 95% CI 0.29-0.90; I^2 = 77%). However, based on hospitalization status there is significant reduction in SAEs for the non-hospitalized patients in the experimental group versus the control group (RR 0.35, 95% CI 0.25-0.49; I^2 = 0%) but no significant results for the hospitalized patients (RR 1.15, 95% CI 0.56-2.36; I^2 = 96%). The most common serious adverse events noted were development of COVID-19 pneumonia.[5,7,8] In one study, the investigators noted that the 2 SAEs in the experimental group were miscarriages in the first trimester, both considered unrelated to the study drug or COVID-19. One participant was a primigravida and the other was a patient with significant medical history of abortions.[9] The most common adverse events were infusion-related reactions.[5,7]

Recommendations from Other Groups

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
Australian Guidelines (updated November 26, 2021)	Conditional recommendation using casirivimab plus imdevimab in the following situations: • Within 7 days of symptom onset in adult outpatients and pregnant or breastfeeding women who are outpatients with mild COVID-19 who have one or more risk factors for disease progression • Seronegative adults hospitalized with moderate to critical COVID-19, including pregnant or breastfeeding women Recommends against the use of casirivimab plus imdevimab in the following situations: • For mild or asymptomatic COVID-19 patients and for seropositive hospitalized patients, including seropositive pregnant or breastfeeding women • For seropositive children and adolescents hospitalized with moderate to critical COVID-19 Consensus recommendation to 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 COIVD-19 who are at high risk of deterioration.[9]
Japanese rapid/living recommendations on drug management for COVID-19: Updated guidelines (updated October 22, 2021)	Recommends for the use of casirivimab plus imdevimab administration to patients with mild COVID-19 who do not require oxygen supplementation. No clear recommendation on casirivimab plus imdevimab administration to patients with moderate COVID-19 requiring oxygen supplementation/hospitalization an those with severe COVID-19 requiring mechanical ventilation or intensive care.[10]
India Covid Guidelines (updated October 8, 2021)	Conditional recommendation for the use of casirivimab plus imdevimab in the following situations: • Within 10 days of symptom onset for those with mild COVID-19 with 1 or more risk factors for progression to severe disease [12] • For hospitalized patients requiring oxygen support in the early illness (<7 days of symptoms) with no detectable COVID-19 antibodies [11] Strongly recommend against the use of casirivimab plus imdevimab in the following situations: • For patients with moderate, severe or critical COVID-19 who are seropositive [11]

	• For patients with mild COVID-19 with no risk factors for progression to severe disease [12] • For Asymptomatic patients [13]
National Institutes of Health (NIH) Guidelines (updated October 19, 2021)	Recommends the use of casirivimab plus imdevimab for non-hospitalized patients at high risk of clinical progression.[14]
World Health Organization (WHO) Guidelines (updated September 24, 2021)	Conditional recommendation for the use of casirivimab plus imdevimab as treatment for patients with non-severe COVID-19 who are at highest risk of hospitalization. Conditional recommendation for the use of casirivimab plus imdevimab as treatment for patients with severe or critical COVID-19 with seronegative status.[15]
Infectious Diseases Society of America (updated October 1, 2021)	Suggests the use of casirivimab + imdevimab for non-hospitalized patients with mild to moderate COVID-19 at high risk for progression to severe disease.[14]

Research Gaps

There are currently eight (8) ongoing randomized clinical trials on casirivimab-imdevimab as treatment for COVID-19 (Appendix 6).

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] 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

[6] 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.

[7] 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.

[8] 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.

[9] 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. 2021. Pre-print. 10.1101/2021.11.09/21265912.

[10] 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.

[11] Gosling H. PMLIve.com. US demand for COVID-19 antibody rising fast. [Internet]. 2021. [updated 2021 Aug 31; cited 2021 Sept 3]. Available from: https://www.pmlive.com/pharma_news/us_demand_for_covid-19_antibody_treatments_rising_fast_1376021

[12] Lee B. Forbes.com. Regeneron antibody cocktail for COVID-19 coronavirus gets FDA emergency use authorization. [Internet]. 2020. [updated 2020 Nov 22, cited 2021 Sept 3]. Available from: https://www.forbes.com/sites/brucelee/2020/11/22/regeneron-antibody-cocktail-for-covid-19-coronavirus-gets-fda-emergency-use-authorization/?sh=3310ee75cba8

[13] Australian National COVID-19 Clinical Evidence Taskforce. [Internet]. Australian guidelines for the clinical cure of people with COVID-19 v42.0. [cited 2021 Dec 6]. Available from: https://app.magicapp.org/#/guideline/5571

[14] 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 (September 2021). Acute Medicine & Surgery [Internet]. 2021 Oct 22 [cited 2021 Dec 6]; Available from: doi:10.1002/ams2.706

[15] India Covid Guidelines. [Internet]. Casirivimab-Imdevimab (REGEN-COV) for patients with mild COVID-19. [updated 2021 Oct 8; cited 2021 Dec 6]. Available from: https://indiacovidguidelines.org/casirivimab-and-imdevimab-regn-covtm/

[16] India Covid Guidelines. [Internet]. Casirivimab-Imdevimab (REGEN-COV) for hypoxic patients with moderate, severe or critical COVID-19. [updated 2021 Aug 16; cited 2021 Dec 6]. Available from: https://indiacovidguidelines.org/casirivimab-imdevimab-moderate-to-severe/?preview=true

[17] India Covid Guidelines. [Internet]. Casirivimab-Imdevimab for asymptomatic patients with COVID-19. [updated 2021 Aug 27; cited 2021 Dec 6]. Available from: https://indiacovidguidelines.org/casirivimab-imdevimab-asymptomatic/

[18] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. [Internet]. National Institutes of Health. [cited 2021 Dec 6]. Available from: https://www.covid19treatmentguidelines.nih.gov/.

[19] World Health Organization. [Internet]. Therapeutics and COVID-19 Living Guidelines. [updated 2021 Sept 24; cited 2021 Dec 6]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.2.

[20] Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. [Internet]. Infectious Diseases Society of America 2021; Version 5.2.0. [updated 2021 Sept 21; cited 2021 Sept 24]. Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/.

Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 5)

FACTORS	JUDGEMENT (N = 5)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (5)					
Benefits	Large	Moderate (1)	Small (1)	Uncertain (3)			• Asymptomatic: trend towards benefit in development of symptomatic COVID-19 infection (RR 0.69, 95% I 0.47-1.00); no benefit in reducing COVID-related MAV (RR 0.08, 95% CI 0.00-1.40), • Symptomatic, non-hospitalized: significant reduction in need for invasive mechanical ventilation or death (RR 0.40, 95% CI 0.32-0.51), number of COVID-related MAV (RR 0.34, 95% CI 0.26-0.46), duration of COVID-19 symptoms (MD -4.00 days, 95% CI -4.24, -3.76), duration of hospitalization • Hospitalized: no benefit in need for invasive ventilation or death
Harm	Large	Small (2)	Uncertain (3)				• Non-hospitalized: less serious adverse effects (RR 0.35, 95% CI 0.25-0.49) • Hospitalized: no significant difference in serious adverse effects (RR 1.15, 95% CI 0.56-2.36)
Certainty of Evidence	High	Moderate (1)	Low (4)	Very low			• Serious risk of bias due to issues in attrition, allocation concealment, performance bias, and reporting bias
Balance of effects	Favors drug (3)	Does not favor drug (1)	Uncertain (1)				• Net potential benefit only for symptomatic, non-hospitalized patients who are at risk for developing severe disease.
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability	No important uncertainty or variability			
Resources Required	Uncertain	Large cost (5)	Moderate cost	Negligible cost	Moderate savings	Large savings	• Cost is PHP 28,615 per single dose infusion (2 vials of 300mg casirivimab + 300mg imdevimab/5mL) • Additional cost for ER and doctor's fees may vary across different hospitals
Certainty of evidence of required resources	No included studies (1)	Very low (1)	Low (3)	Moderate	High		• Local cost is from personal communication with the private hospitals
Cost effectiveness	No included studies (4)	Favors the comparison	Does not favor either the intervention or the comparison	Favors the intervention (1)			
Equity	Uncertain (2)	Reduced (2)	Probably no impact (1)	Increased			
Acceptability	Uncertain (4)	No (1)	Yes				

Feasibility	Uncertain (5)	No	Yes		

Additional Comments:

- Specify specific subgroups (eg. severity and site of care)
- Put uncertain on benefits and harms since different subgroups (hospitalized vs non hospitalized have different benefits and harm

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: from September 1, 2021 to November 26, 2021	November 26, 2021 9:30 AM	34	0
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: from September 1, 2021 to November 26, 2021	November 26, 2021 10:30 AM	0	0
Google Scholar	Casirivimab AND imdevimab AND COVID AND randomized trial	November 26, 2021 11:30 AM	191	2
COVID-NMA initiative	REGEN-COV REGN-COV2 Casirivimab	November 26, 2021 2:00 PM	6	0
ClinicalTrials.gov	Casirivimab OR REGEN-COV OR REGN-COV2 and COVID-19	November 27, 2021 1:30 PM	18	0
Chinese Clinical Trial Registry	Casirivimab OR REGEN-COV OR REGN-COV2	November 27, 2021 2:00 PM	0	0
EU Clinical Trials Register	Casirivimab OR REGEN-COV OR REGN-COV2 and COVID-19	November 27, 2021 2:10 PM	2	0
Republic of Korea - Clinical Research Information Service	Casirivimab OR REGEN-COV OR REGN-COV2	November 27, 2021 2:15 PM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Casirivimab OR REGEN-COV OR REGN-COV2	November 27, 2021 2:20 PM	4	0
CenterWatch	Casirivimab OR REGEN-COV OR REGN-COV2	November 27, 2021 2:10 PM	7	0
chinaxiv.org	Casirivimab OR REGEN-COV OR REGN-COV2	November 27, 2021 2:15 PM	0	0
Medrxiv.org	Casirivimab OR REGEN-COV OR REGN-COV2	November 27, 2021 2:20 PM	64	4
Biorxiv.org	Casirivimab OR REGEN-COV OR REGN-COV2 AND COVID-19	November 27, 2021 2:45 PM	60	0

Appendix 3. Characteristics of Included Studies

Study ID	Patients (n) & Duration of Follow-Up	Interventions	Outcomes	Study Design
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); pre-print*	Confirmed COVID-19 patients admitted to the hospitals already participating in the RECOVERY trial (n = 11,464) Duration of follow-up: 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) Duration of follow-up: 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); pre-print*	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); pre-print*	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. Study Appraisal

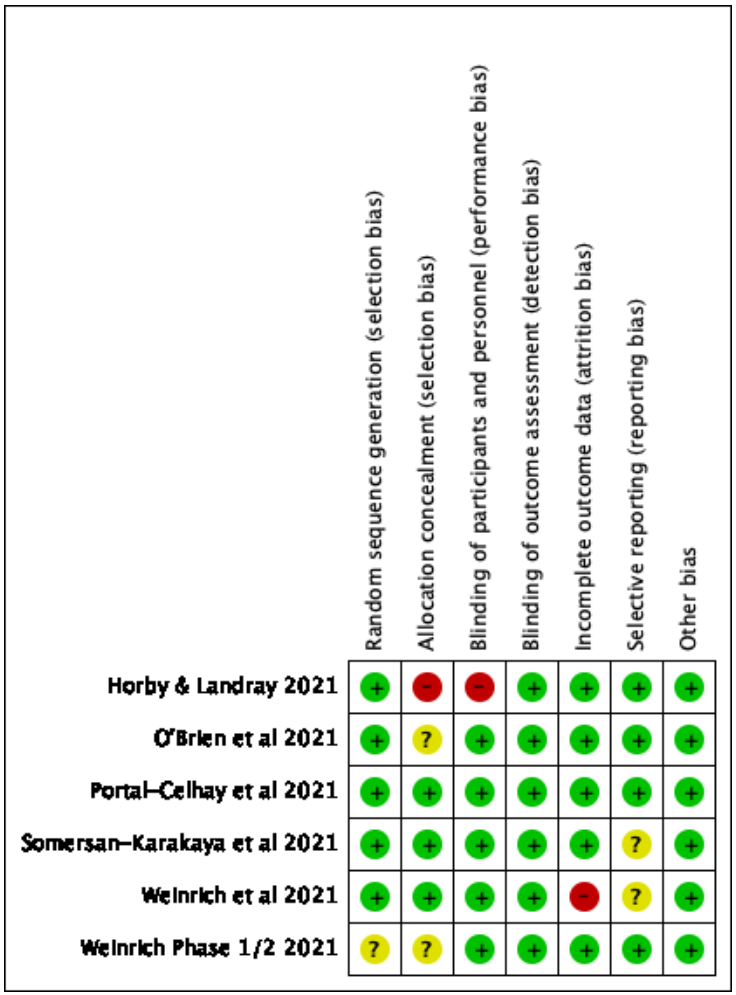

Figure 1. Risk of bias summary table

Appendix 5. GRADE Evidence Profile

Author(s): Isabella S. Ocampo, MD
Question: Casirivimab + Imdevimab compared to Placebo for COVID-19 treatment
Setting: Asymptomatic non-hospitalized
Bibliography: [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)		
At least 1 COVID-related MAV (asymptomatic non-hospitalized) (follow-up: 28 days)												
1	randomized trial	not serious	not serious	not serious	very serious[a,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)	⨁⨁◯◯ LOW	CRITICAL
Duration of COVID-19 symptoms (asymptomatic non-hospitalized) (follow-up: 28)												
1	randomized trial	not serious	not serious	not serious	not serious	none	The duration of symptoms was 4.9 days less in the experimental group versus the control (MD -4.9 days, 95% CI -5.74, -4.06).				⨁⨁⨁⨁ HIGH	CRITICAL
Serious adverse events (asymptomatic non-hospitalized) (follow-up: 28 days)												
1	randomized trial	not serious	not serious	not serious	very serious[a,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)	⨁⨁◯◯ LOW	CRITICAL

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

Explanations

a. Wide confidence intervals
b. Fragility of events

Philippine COVID-19 Living Clinical Practice Guidelines

Author(s): Isabella S. Ocampo, MD
Question: Casirivimab + Imdevimab compared to Placebo for COVID-19 treatment
Setting: Symptomatic, non-hospitalized
Bibliography: [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 non-hospitalized) (follow-up: 29 days)												
1	randomized trial	not serious	not serious	not serious	very serious[a,b]	none	2/2716 (0.1%)	6/2682 (0.2%)	**RR 0.33** (0.07 to 1.63)	**1 fewer per 1,000** (from 2 fewer to 1 more)	⊕⊕◯◯ LOW	CRITICAL
Need for invasive mechanical ventilation or death (outpatient) (follow-up: 29 days)												
1	randomized trial	not serious	not serious	not serious	not serious	none	89/2716 (3.3%)	218/2682 (8.1%)	**RR 0.40** (0.32 to 0.51)	**49 fewer per 1,000** (from 55 fewer to 40 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
At least 1 COVID-related medically-assisted visit (symptomatic non-hospitalized) (follow-up: 29 days)												
2	randomized trials	not serious	not serious	not serious	not serious	none	66/3150 (2.1%)	178/2913 (6.1%)	**RR 0.34** (0.26 to 0.46)	**40 fewer per 1,000** (from 45 fewer to 33 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Duration of hospitalization (outpatient) (follow-up: 29 days)												
1	randomized trial	not serious	not serious	serious	very serious[b,c]	none	Among those hospitalized, the duration of hospitalization was shorter in the experimental group versus the control group regardless of dose (8.6 days in 2400mg group vs 10 days in placebo group; 7 days in 1200mg group vs 8.4 days in placebo group).				⊕◯◯◯ VERY LOW	IMPORTANT
Duration of symptoms in days (symptomatic non-hospitalized) (follow-up: 28 days)												
1	randomized trial	not serious	not serious	not serious	not serious	none	2091	2089	-	mean **4 days lower** (4.24 lower to 3.76 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Serious adverse events (outpatient) (follow-up: 29 days)												
2	randomized trials	not serious	not serious	not serious	not serious	none	56/4361 (1.3%)	84/2261 (3.7%)	**RR 0.35** (0.25 to 0.49)	**25 fewer per 1,000** (from 28 fewer to 19 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

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

Explanations

a. Wide confidence intervals
b. Fragility of events
c. No mentioned confidence intervals

Author(s): Isabella S. Ocampo, MD
Question: Casirivimab + Imdevimab compared to Placebo for COVID-19 treatment
Setting: Hospitalized

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 (inpatient) (follow-up: 28 days)												
2	randomized trials	not serious	serious[b]	not serious	serious[a]	none	1003/5643 (17.8%)	1071/5339 (20.1%)	**RR 0.81** (0.56 to 1.17)	**38 fewer per 1,000** (from 88 fewer to 34 more)	⨁⨁◯◯ LOW	CRITICAL
Need for invasive mechanical ventilation or death (inpatient) (follow-up: 28 days)												
2	randomized trials	not serious	serious[b]	not serious	serious[a]	none	1171/5360 (21.8%)	1209/5035 (24.0%)	**RR 0.85** (0.62 to 1.16)	**36 fewer per 1,000** (from 91 fewer to 38 more)	⨁⨁◯◯ LOW	CRITICAL
Duration of hospitalization (inpatient) (follow-up: 29 days)												
1	randomized trial	serious[c]	not serious	serious[d]	serious[e]	none	Among hospitalized 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
Serious adverse events (inpatient) (follow-up: 29 days)												
2	randomized trials	serious[c]	not serious	not serious	serious[a]	none	460/3132 (14.7%)	277/2381 (11.6%)	**RR 1.15** (0.56 to 2.36)	**17 more per 1,000** (from 51 fewer to 158 more)	⨁⨁◯◯ LOW	CRITICAL

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

Explanations

a. Wide confidence intervals
b. High heterogeneity
c. Open label study
d. Only mentioned for seronegative patients
e. No mentioned confidence intervals

Author(s): Isabella S. Ocampo, MD
Question: Casirivimab + Imdevimab compared to Placebo for COVID-19 treatment
Setting: Seronegative hospitalized
Bibliography: [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 (seronegative hospitalized) (follow-up: 29 days)												
2	randomized trials	not serious	serious[b]	not serious	serious[a]	none	420/1993 (21.1%)	475/1680 (28.3%)	**RR 0.64** (0.36 to 1.15)	**102 fewer per 1,000** (from 181 fewer to 42 more)	⨁⨁◯◯ LOW	CRITICAL
Need for invasive mechanical ventilation or death (seronegative hospitalized) (follow-up: 29 days)												
2	randomized trials	serious[c]	serious[b]	not serious	serious[a]	none	524/1959 (26.7%)	573/1644 (34.9%)	**RR 0.70** (0.46 to 1.08)	**105 fewer per 1,000** (from 188 fewer to 28 more)	⨁◯◯◯ VERY LOW	CRITICAL

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

Explanations

a. Wide confidence intervals
b. High heterogeneity
c. Open label study

Author(s): Isabella S. Ocampo, MD
Question: Casirivimab + Imdevimab compared to Placebo for COVID-19 treatment
Setting: Seropositive hospitalized
Bibliography: [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 (seropositive hospitalized) (follow-up: 29 days)												
1	randomized trial	not serious	not serious	not serious	serious[a]	none	411/2636 (15.6%)	383/2636 (14.5%)	**RR 1.09** (0.95 to 1.26)	**13 more per 1,000** (from 7 fewer to 38 more)	⨁⨁◯◯ MODERATE	CRITICAL
Need for invasive mechanical ventilation or death (seropositive hospitalized) (follow-up: 29 days)												
1	randomized trial	serious[b]	not serious	not serious	serious[a]	none	456/2449 (18.6%)	415/2450 (16.9%)	**RR 1.10** (0.97 to 1.24)	**17 more per 1,000** (from 5 fewer to 41 more)	⨁⨁◯◯ LOW	CRITICAL

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

Explanations

a. Wide confidence intervals
b. Open label study

Appendix 6. Forest Plots

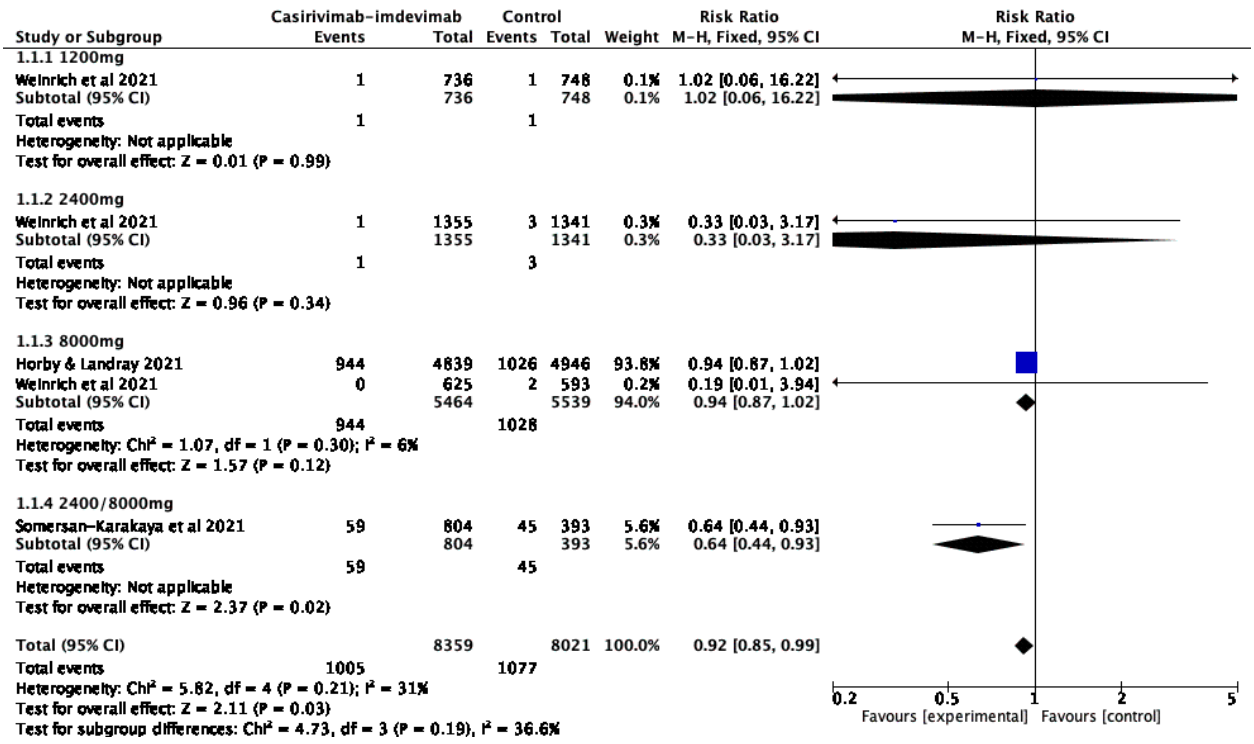

Figure 1. All-cause mortality by dose

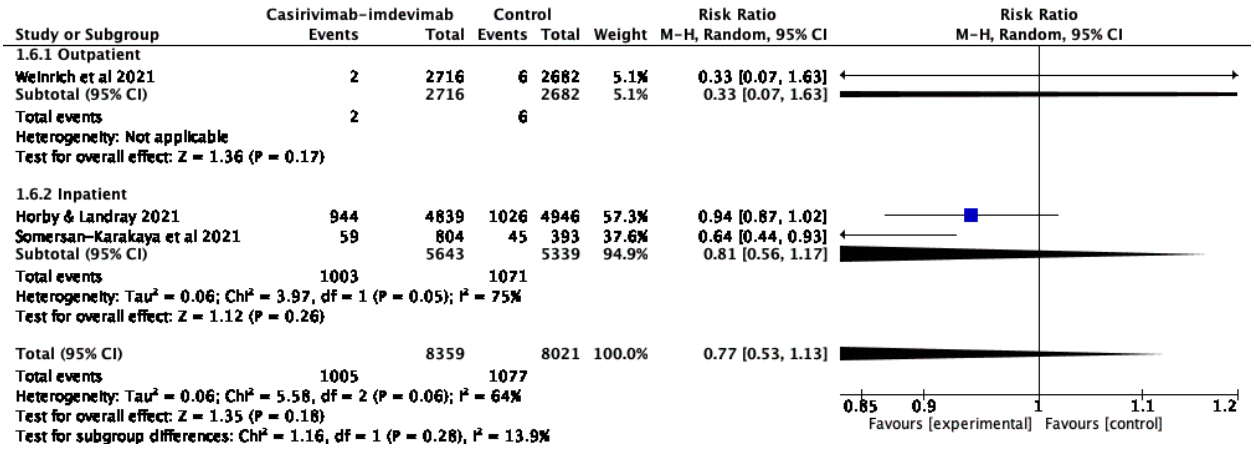

Figure 2. All-cause mortality by hospitalization status

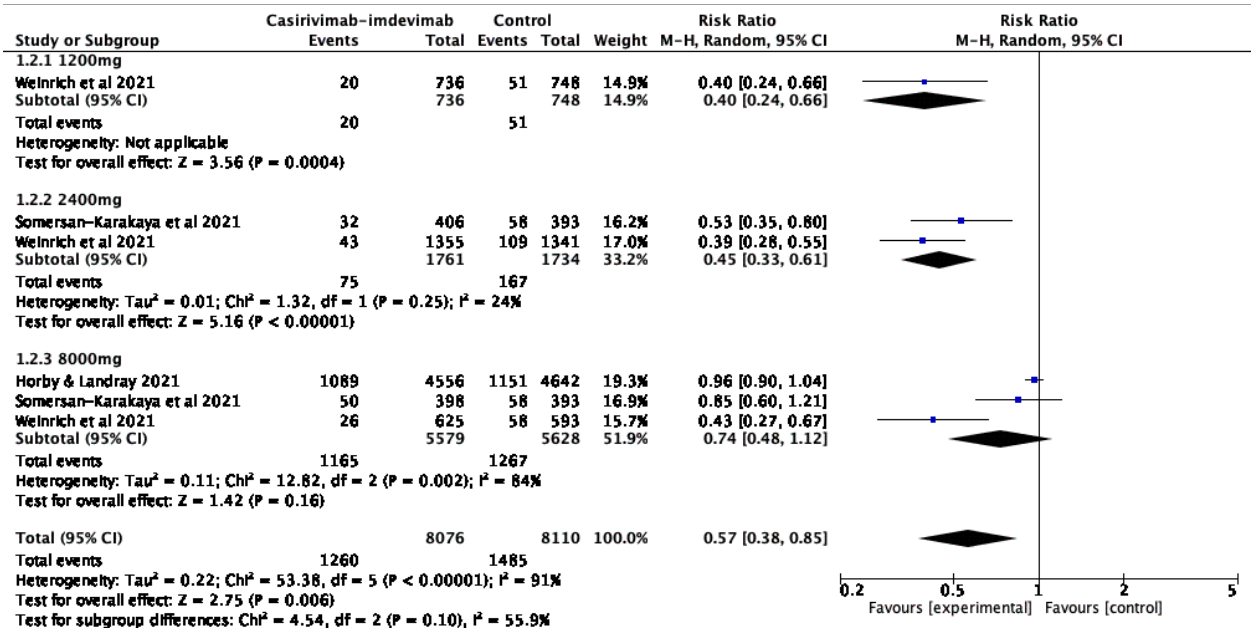

Figure 3. Need for invasive mechanical ventilation or death by dose

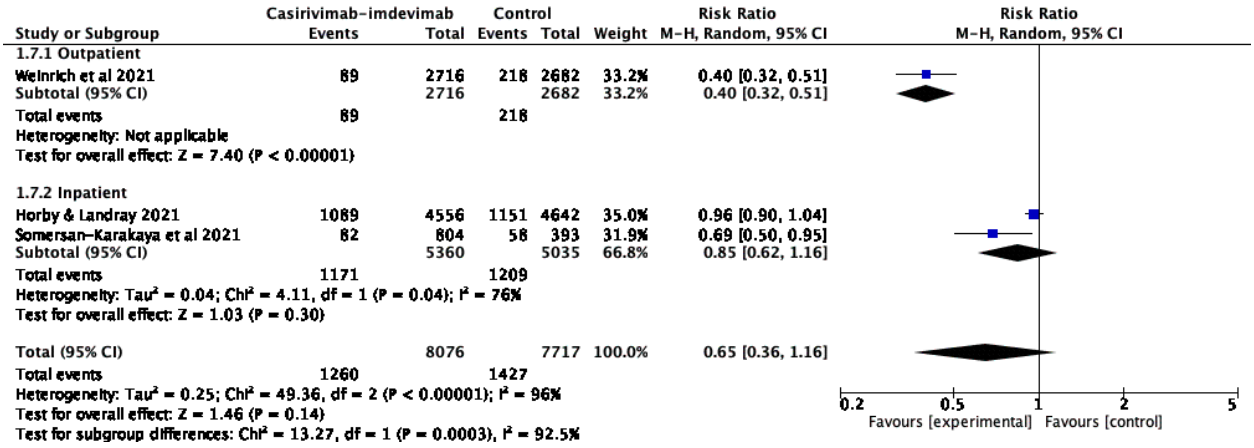

Figure 4. Need for invasive mechanical ventilation or death by hospitalization status

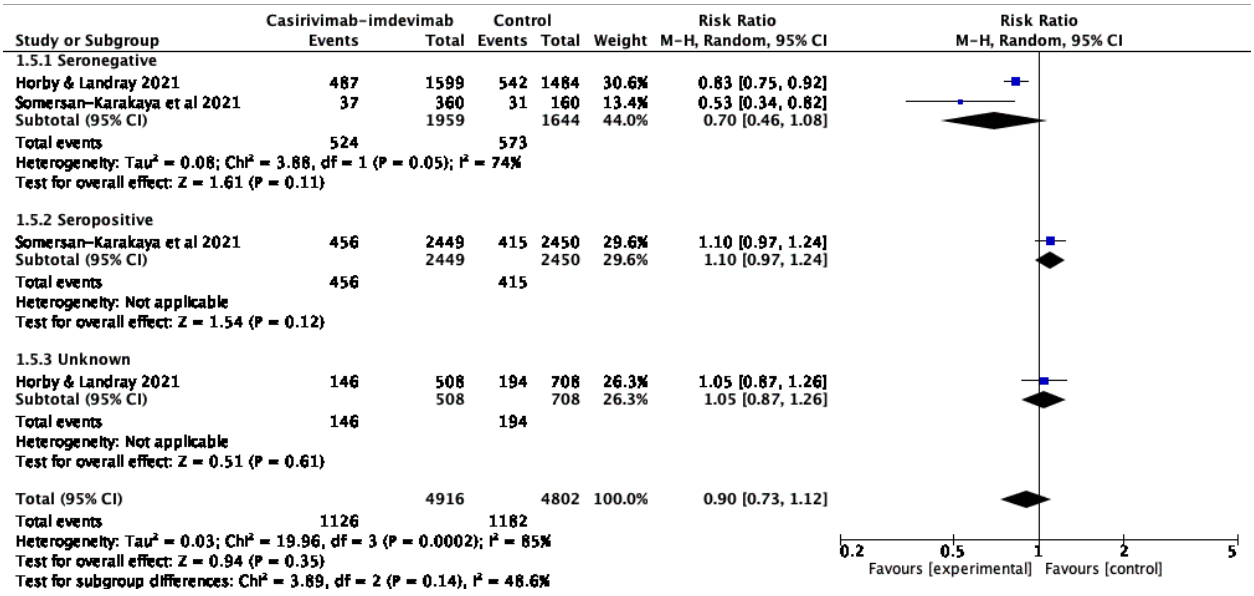

Figure 5. Need for invasive mechanical ventilation by antibody status

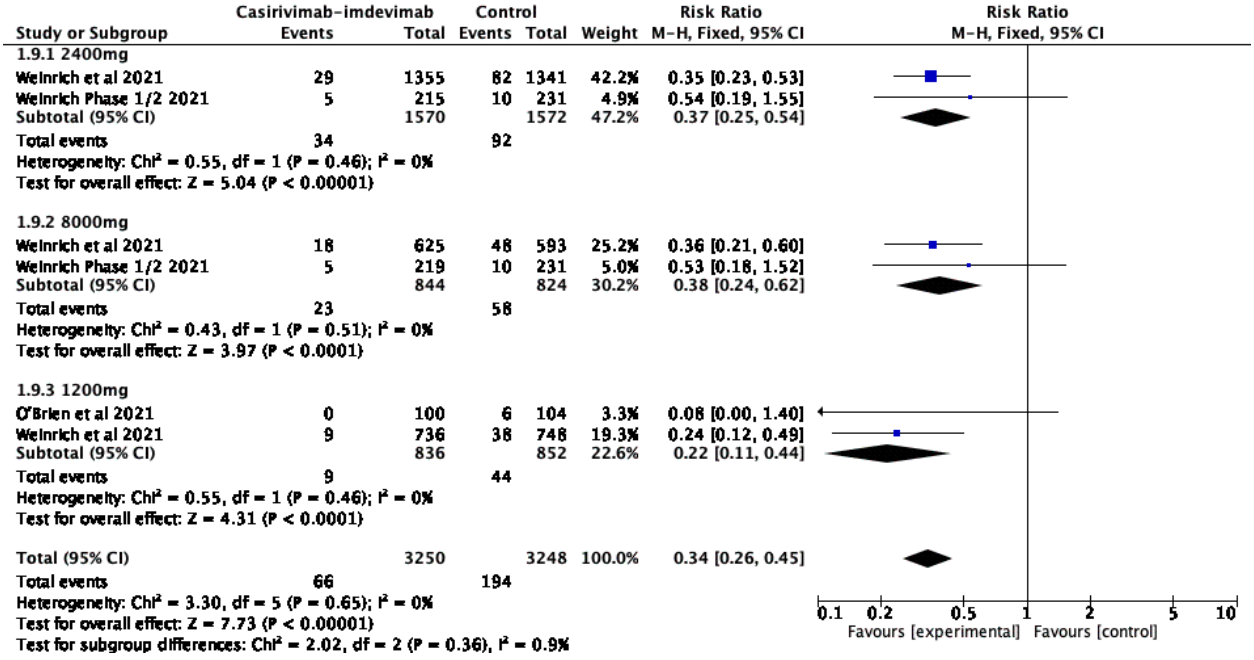

Figure 6. At least 1 COVID-related MAV by dose

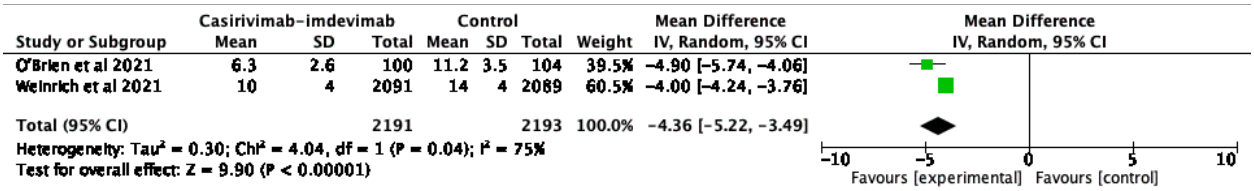

Figure 7. Duration of COVID-19 symptoms in days

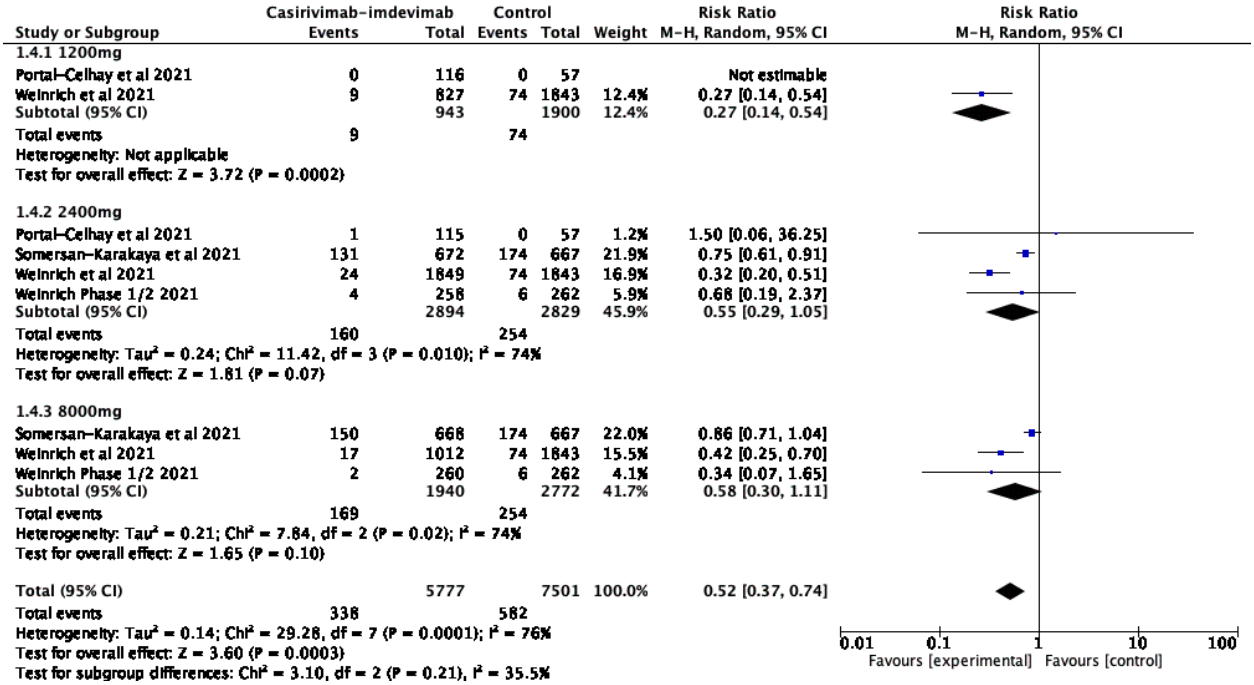

Figure 8. Serious adverse events by dose

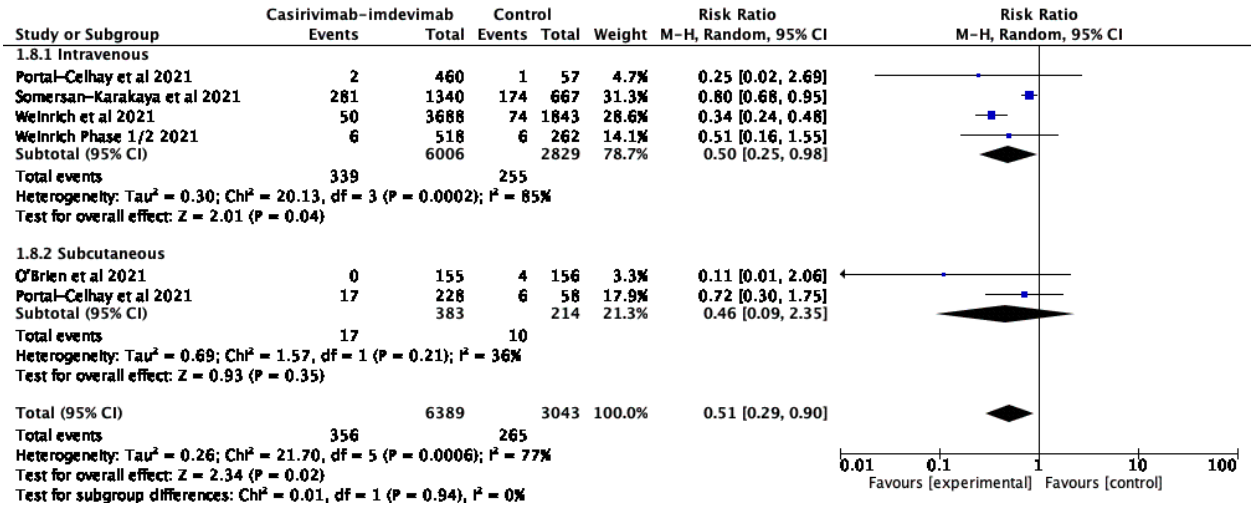

Figure 9. Serious adverse events by route of administration

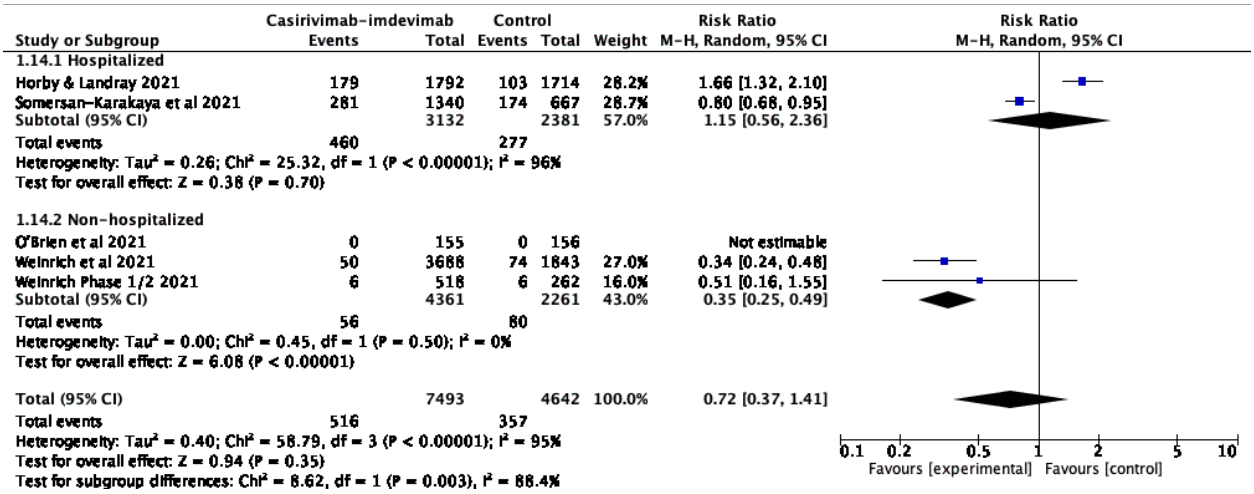

Figure 10. Serious adverse events by hospitalization status

Appendix 7. Table of Ongoing Studies

Clinical Trial Identifier/Title	Study Design	Country	Population	Intervention	Outcome	Estimated Date of Completion
NCT0458410 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	Dec 25, 2023
EudraCT 2021-002612-31 Adaptive, randomized, placebo-controlled trial to evaluate the efficacy of monoclonal antibodies in outpatients with mild or moderate COVID-19	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	Not mentioned
EudraCT 2021-004035-88 A randomized, open-label, active controlled, parallel group, multicenter phase 3 study to evaluate the efficacy and tolerability of	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	Not mentioned

Bamlanivimab and Etesivimab, Casirivimab and Imdevimab, and Sotrovimab versus Standard of Care in patients with mild to moderate COVID-19 disease					period, adverse events	
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 Patients Hospitalized Due to COVID-19	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 casirivmab+imdevimab over time, incidence of neutralizing antibodies to casirivimab+imdevimab over time	June 9, 2023
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, 2022
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	Casrivimab-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	March 31, 2023

					admission, need for new oxygen administration	
NCT04790786 The UPMC Optimizing Treatment and Impact of Monoclonal antIbodies Through Evaluation for COVID-19 Trial (UPMC OPTIMISE-C19)	Randomized controlled trial	USA	COVID-19 positive patients eligible for mAB under FDA EUA	Bamlanivimab vs. Casirivimab-imdevimab vs. Bamlanivimab-etesevimab vs. Sotrovimab vs. placebo	Survival, all-location mortality, all-cause mortality, organ-support free days,	February 2022
NCT05081388 A Phase 1/2/3 Adaptive Sudy 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	November 10, 2022