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, 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 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.

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.

PREVIOUS RECOMMENDATION

There is insufficient evidence to recommend the use of REGN-COV2 (casirivimab/imdevimab) as treatment for COVID-19 infection *(Low quality of evidence)*

Previous Consensus Issues
The study included in this review is only an interim analysis of data from 275 non-severe COVID-19 patients. Complete results from ongoing studies are needed to better determine the effectiveness of regeneron as treatment for COVID-19 infection. The availability and cost of this intervention must also be considered. No mortality and only serious adverse events such as hypertension and hypoxia were reported.

What's new in this version?

This version includes data from one (1) new published randomized controlled trial (RCT) and an updated pre-print on the previously included RCT.

Key Findings

There are two (2) RCTs that evaluated casirivimab + imdevimab cocktail as treatment for patients with COVID-19. A published RCT on casirivimab + imdevimab showed a significant reduction in the combined endpoint of COVID-19 related hospitalization and all-cause mortality at Day 29 and time to resolution of symptoms among non-hospitalized COVID-19 patients. On the other hand, a pre-print RCT showed that there was no significant benefit on all-cause mortality, clinical recovery and need for invasive ventilation when casirivimab + imdevimab was used as treatment for hospitalized patients. There seem to be a possible significant benefit in the above mentioned outcomes among 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 significant difference in adverse events between those given casirivimab + imdevimab and placebo.

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 April 16, 2021 until September 1, 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 and severity and post-hoc subgroup analysis on serologic status were conducted.

Results

A total of 41 related articles were found using MEDLINE, with 1 published article that met our inclusion criteria. The same results were found when searching CENTRAL, COVID-NMA initiative and Google Scholar. One pre-print was found using Medrxiv.org. Both studies evaluated the use of casirivimab + imdevimab as treatment for COVID-19 patients.

The 2 studies included a total of 15,521 COVID-19 confirmed patients.[5,6] The published study included symptomatic or asymptomatic non-hospitalized COVID-19 patients with ≥1 risk factor for severe COVID-19, including 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. These patients were grouped into 3 (≥18 years old, <18 years old, and pregnant at randomization); however, only the results for the first cohort (≥18 years old) were reported and only the outcomes of the seronegative participants could be retrieved. Two different doses were administered to the participants: casirivimab 1200mg + imdevimab 1200mg and casirivimab 600mg + imdevimab 600mg.[5]

The pre-print study is the RECOVERY trial, which included hospitalized COVID-19 patients. Baseline presence of anti-SARS-CoV-2 antibodies (serologic status) was determined for the participants.[6] Outcomes measured included all-cause mortality [5,6], time to symptom resolution [5], clinical recovery (defined as discharged alive from the hospital) [6], need for invasive ventilation [6], and adverse events.[5,6]

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.

Due to the heterogeneity of the populations, the results of the 2 trials are discussed separately. Among non-hospitalized patients, there was a significant reduction in the combined end-point of COVID-19 related hospitalization and all-cause mortality at Day 29 in the experimental group versus the control, regardless of dose Both the casirivimab + imdevimab 2400mg (RR 0.29, 95% CI 0.17-0.48) and the casirivimab + imdevimab 1200mg (RR 0.30, 95% CI 0.13-0.68) were found to significantly reduce COVID-19 related hospitalization or all-cause mortality compared to placebo. Similarly, the time to symptom resolution was also significantly reduced in the casirivimab + imdevimab group compared to placebo, regardless of dose (10 days vs. 14 days, $p<0.0001$).[5]

Among hospitalized patients, there was no significant difference between the casirivimab + imdevimab group versus the control group for all-cause mortality (RR 0.94, 95% CI 0.87-1.02). Likewise, there was no significant difference between the 2 groups for clinical recovery (RR 1.01, 95% CI 0.97-1.07) and need for invasive ventilation (RR 0.96, 95% CI 0.90-1.04). Subgroup analysis by serologic status revealed a significant reduction in all-cause mortality favoring seronegative patients (RR 0.80, 95% CI 0.70-0.91) compared to seropositive patients (RR 1.07, 95% CI 0.94-1.22). Similarly, there was a significantly higher rate of clinical recovery among seronegative patients (RR 1.19, 95% CI 1.08-1.30) compared to seropositive patients (RR 0.94, 95% CI 0.88-1.00) as well as a significant decrease in the use of invasive mechanical ventilation among the seronegative (RR 0.83, 95% CI 0.75-0.92) compared to the seropositive patients (RR 1.10, 95% 0.97-1.24).[6]

Safety

The outcomes for safety were not pooled due to the heterogenous population. Among non-hospitalized patients, serious adverse effects were significantly less in the experimental group versus the control (RR 0.34, 95% CI 0.24-0.48).[5] On the other hand, serious adverse effects were significantly increased in the casirivimab + imdevimab group compared to placebo among hospitalized patients (RR 1.66, 95% CI 1.32-2.10).[6] Common serious adverse effects noted were infusion-related [5,6] and hypersensitivity reactions.[6] There were 5 reports of serious adverse events (SAE) in the hospitalized study participants that the investigators believe to be related to casirivimab + imdevimab, but the specific type of SAE was not reported.[6]

Recommendations from Other Groups

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
Australian Guidelines (updated September 29, 2021)	Conditional recommendation using casirivimab + imdevimab in seronegative patients hospitalized with moderate to critical COVID-19 but not for seropositive patients. [9] Recommends against the use of casirivimab + imdevimab for mild or asymptomatic COVID-19 patients and for seropositive hospitalized patients.[9]
India Covid Guidelines (updated August 16, 2021)	Conditional recommendation using casirivimab + imdevimab in seronegative patients hospitalized with moderate to critical COVID-19 but not for seropositive patients.[10] Recommends against the use of casirivimab + imdevimab for asymptomatic COVID-19 patients.[11]
National Institutes of Health (NIH) Guidelines (updated September 15, 2021)	Recommends the use of casirivimab + imdevimab for non-hospitalized patients at high risk of clinical progression.[12]
World Health Organization (WHO) Guidelines (updated September 24, 2021)	Suggests the use of casirivimab + imdevimab as treatment for patients with severe or critical COVID-19 with seronegative status.[13]
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 four (4) 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] 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

[8] 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

[9] Australian National COVID-19 Clinical Evidence Taskforce. [Internet]. Australian guidelines for the clinical cure of people with COVID-19 v42.0. [cited 2021 Aug 31]. Available from: https://app.magicapp.org/#/guideline/5571

[10] India Covid Guidelines. [Internet]. Casirivimab-Imdevimab (REGEN-COV) for hypoxic patients with moderate, severe or critical COVID-19. [updated 2021 Aug 16; cited 2021 Sept 14]. Available from: https://indiacovidguidelines.org/casirivimab-imdevimab-moderate-to-severe/?preview=true

[11] India Covid Guidelines. [Internet]. Casirivimab-Imdevimab for asymptomatic patients with COVID-19. [updated 2021 Aug 27; cited 2021 Sept 14]. Available from: https://indiacovidguidelines.org/casirivimab-imdevimab-asymptomatic/

[12] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. [Internet]. National Institutes of Health. [cited 2021 Sept 24]. Available from: https://www.covid19treatmentguidelines.nih.gov/.

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

[14] 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 = 10)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (10)					• COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity.
Benefits	Large (4)	Moderate (4)	Small (1)	Uncertain (1)			• Non-hospitalized: significant reduction in all-cause mortality (RR 0.29, 95% CI 0.19-0.46) and time to resolution (10 vs. 14 days) • Hospitalized: significant reduction in all-cause mortality, clinical recovery, and use of invasive ventilation among seronegative patients
Harm	Large (3)	Small (4)	Uncertain (2)	Varies (1)			• Non-hospitalized: less serious adverse effects (RR 0.76, 0.63-0.90) • Hospitalized: increased serious adverse effects (RR 1.66, 1.32-2.10) • Need for more data on possible drug interactions
Certainty of Evidence	High	Moderate (8)	Low (1)	Very low (1)			• Moderate because of serious risk of bias due to issues in attrition, allocation concealment, performance bias, and reporting bias
Balance of effects	Favors drug (7)	Does not favor drug (1)	Uncertain (1)	Varies (1)			• Net potential benefit for non-hospitalized patients only who are at risk for developing severe disease. • For hospitalized patients, the harm of serious adverse effects outweighed the drug's benefit. In particular, benefit was only seen among seronegative hospitalized patients on post-hoc subgroup analysis
Values	Important uncertainty or variability (3)	Possibly important uncertainty or variability (6)	Possibly NO important uncertainty or variability (1)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost (10)	Moderate Cost	Negligible cost	Moderate savings	Large savings	• $1250-6000 (PHP 62,500-300,000) per course (intravenous) • 10/1/21: With EUA from Philippine FDA • Distributor price: PHP 25,0000-30,000 (single dose IV)
Certainty of evidence of required resources	No included studies (2)	Very low	Low (5)	Moderate (2)	High (1)		• Cost is based on news websites (Forbes, PMLive) • Local cost is from personal communication with the distributor

Cost effectiveness	No included studies (6)	Favors the comparison (1)	Does not favor either the intervention or the comparison (1)	Favors the intervention (2)		• None of the included trials assessed cost effectiveness.
Equity	Uncertain (4)	Reduced (2)	Probably no impact	Increased (4)		• The Philippine FDA approved the emergency use authorization (EUA) of casirivimab + imdevimab on October 1, 2021. • At time of consensus panel meeting, there are already several private hospitals offering the drug as single intravenous infusion on ER basis. Given its large cost, there will always be issues on accessibility and equity that need to be addressed.
Acceptability	Uncertain (4)	No (1)	Yes (4)	Varies (1)		
Feasibility	Uncertain (3)	No (1)	Yes (5)	Varies (1)		• Feasible to administer to non-hospitalized patients (who are at risk for severe disease) in the emergency room setting under the supervision of licensed physicians. • Emphasis on the need for close monitoring for adverse effects during and after drug administration.

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 (REGEN-COV) OR (REGN-COV2) OR (Casirivimab) Filters: from April 16, 2021 to September 1, 2021	Sep 1, 2021 9:00 AM	41	1
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 April 16, 2021 to September 1, 2021	Sep 1, 2021 9:30 AM	11	1
Google Scholar	REGEN-COV AND COVID AND randomized trial	Sep 1, 2021 10:00 AM	74	2
COVID-NMA initiative	REGEN-COV REGN-COV2 Casirivimab	Sep 1, 2021 11:30 AM	1	1
ClinicalTrials.gov	Casirivimab OR REGEN-COV OR REGN-COV2 and COVID-19	Sep 1, 2021 1:00 PM	8	0
Chinese Clinical Trial Registry	Casirivimab OR REGEN-COV OR REGN-COV2	Sep 1, 2021 1:30 PM	0	0
EU Clinical Trials Register	Casirivimab OR REGEN-COV OR REGN-COV2 and COVID-19	Sep 1, 2021 3:00 PM	2	0
Republic of Korea - Clinical Research Information Service	Casirivimab OR REGEN-COV OR REGN-COV2	Sep 1, 2021 3:30 PM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Casirivimab OR REGEN-COV OR REGN-COV2	Sep 1, 2021 4:00 PM	2	0

CenterWatch	Casirivimab OR REGEN-COV OR REGN-COV2	Sep 1, 2021 4:30 PM	4	0
chinaxiv.org	Casirivimab OR REGEN-COV OR REGN-COV2	Sep 1, 2021 8:00 PM	0	0
Medrxiv.org	Casirivimab OR REGEN-COV OR REGN-COV2	Sep 1, 2021 8:30 PM	2	2
Biorxiv.org	Casirivimab OR REGEN-COV OR REGN-COV2 AND COVID-19	Sep 1, 2021 9:00 PM	48	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: REGEN-COV MAB Cocktail 1200mg (600mg casirivimab + 600mg imdevimab) IV REGEN-COV MAB Cocktail 2400mg (1200mg casirivimab + 1200mg imdevimab) 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: REGEN-COV MAB Cocktail 8000mg (4000mg casirivimab + 4000mg imdevimab) 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

Appendix 4. Study Appraisal

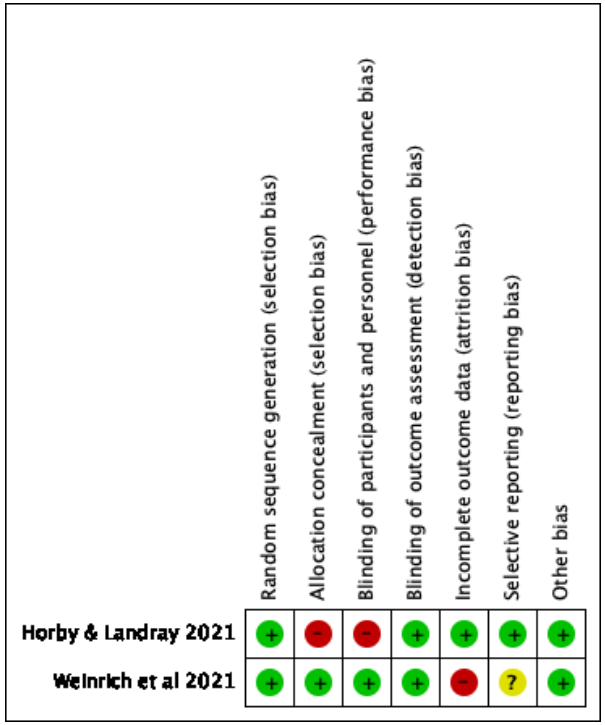

Figure 1. Risk of bias summary table

Appendix 5. GRADE Evidence Profile

Author(s): Isabella S. Ocampo, MD

Question: Casirivimab + Imdevimab compared to Placebo for COVID-19 treatment

Setting: Outpatient and inpatient

Bibliography: 1. Weinrich D, Sivapalasingam S, Norton T et al. REGEN-COV antibody cocktail clinical utcomes study in Covid-19 outpatients. 2021. Preprint. 10.1101/2021.05/19/21257469. 2. 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.

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-19 related hospitalization or all-cause death (1200 mg) (follow-up: 29 days)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	7/736 (1.0%)	24/748 (3.2%)	**RR 0.30** (0.13 to 0.68)	**22 fewer per 1,000** (from 28 fewer to 10 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
At least 1 COVID-19 related hospitalization or all-cause death (2400 mg) (follow-up: 29 days)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	18/1355 (1.3%)	62/1341 (4.6%)	**RR 0.29** (0.17 to 0.48)	**33 fewer per 1,000** (from 38 fewer to 24 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Time to Covid-19 symptoms resolution in non-hospitalized COVID-19 patients (follow-up: 29 days)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	The time to resolution of symptoms was significantly reduced in the REGEN-COV group compared to the placebo group (10 days vs 14 days).				⨁⨁⨁◯ Moderate	CRITICAL
Serious adverse effects in non-hospitalized patients (follow-up: 28 days)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	50/3688 (1.4%)	74/1843 (4.0%)	**RR 0.34** (0.24 to 0.48)	**27 fewer per 1,000** (from 31 fewer to 21 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

All-cause mortality in hospitalized COVID-19 patients (follow-up: 29 days)

1	randomised trials	serious[b]	not serious	not serious	not serious	none	944/4839 (19.5%)	1026/4946 (20.7%)	**RR 0.94** (0.87 to 1.02)	**12 fewer per 1,000** (from 27 fewer to 4 more)	⨁⨁⨁◯ Moderate	CRITICAL

Clinical recovery (discharge from hospital) (follow-up: 28 days)

1	randomised trials	serious[b]	not serious	not serious	not serious	none	3375/4839 (69.7%)	3413/4946 (69.0%)	**RR 1.01** (0.97 to 1.07)	**7 more per 1,000** (from 21 fewer to 48 more)	⨁⨁⨁◯ Moderate	CRITICAL

Use of invasive mechanical ventilation (follow-up: 28 days)

1	randomised trials	serious[b]	not serious	not serious	not serious	none	1089/4556 (23.9%)	1151/4642 (24.8%)	**RR 0.96** (0.90 to 1.04)	**10 fewer per 1,000** (from 25 fewer to 10 more)	⨁⨁⨁◯ Moderate	CRITICAL

Serious adverse effects in hospitalized patients (follow-up: 28 days)

1	randomised trials	serious[b]	not serious	not serious	not serious	none	179/1792 (10.0%)	103/1714 (6.0%)	**RR 1.66** (1.32 to 2.10)	**40 more per 1,000** (from 19 more to 66 more)	⨁⨁⨁◯ Moderate	CRITICAL

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

Explanations

a. There is high risk of bias due to high attrition rate.
b. There is high risk of bias due to unblinded participants.

Appendix 6. 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
NCT04666441 COVID-19 Study Assessing the Virologic Efficacy of REGN10933+REGN10987 Across Different Dose Regimens in Adult Outpatients With SARS-CoV-2 Infection	Randomized controlled trial	USA	COVID-19 positive patients, low risk	Regeneron vs. placebo	Time-weighted average daily change from baseline in viral load	Aug 13, 2021
EudraCT 2021-002612-31 Adaptive, randomized, placebo-controlled trial to evaluate the efficacy of monoclonal antibodies in outpatients with mild	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	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

or moderate COVID-19			the study drug administration			
EudraCT 2021-004035-88 A randomized, open-label, active controlled, parallel group, multicenter phase 3 study to evaluate the efficacy and tolerability of Bamlanivimab and Etesivimab, Casirivimab and Imdevimab, and Sotrovimab versus Standard of Care in patients with mild to moderate COVID-19 disease	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