EVIDENCE SUMMARY

RESEARCH QUESTION: Among close contacts of COVID-19 patients, should casirivimab-imdevimab be used as post-exposure prophylaxis?

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RECOMMENDATIONS

Recommendations	Certainty of Evidence	Strength of Recommendation
We suggest against the use of casirivimab-imdevimab as post-exposure prophylaxis against COVID-19.	Low	Weak

Consensus Issues

1. The panel decided that more evidence should be available in order to recommend the intervention due to in vitro evidence showing decreased activity of Casirivimab+Imdevimab against newer and more predominant SARS-CoV-2 variants (e.g., Omicron and its subvariant),
2. There are still issues with equity especially on its wide availability in the local market and its large cost (₱70,000). As of this writing, the Philippine FDA has only granted Emergency Use Approval.

KEY FINDINGS

Findings from one (1) randomized controlled trial investigating casirivimab + imdevimab cocktail as post-exposure prophylaxis for RT-PCR SARS-CoV-2 negative close contacts of COVID-19 patients showed a significant decrease in symptomatic and asymptomatic COVID-19 infection, and a decrease in duration of infection among those who developed COVID-19. No significant difference was found in terms of serious adverse events between those given casirivimab + imdevimab and placebo. The overall certainty of evidence was rated low due to indirectness of the study population and imprecision in one critical outcome.

WHAT'S NEW IN THIS VERSION?

This version includes new recommendations from other groups. No new clinical trial data have emerged after the previously reported clinical trial [12].

PREVIOUS RECOMMENDATIONS
As of 04 November 2021

We suggest the subcutaneous use of casirivimab + imdevimab as day 4 post-exposure prophylaxis for COVID-19 close contacts*, ages 12 years and above weighing at least 40 kilograms, who are at risk for severe disease or hospitalization**. *(Moderate certainty of evidence; Weak recommendation)*

Consensus Issues:
Despite moderate quality of evidence, the panel decided on a weak recommendation for prophylactic use of casirivimab + imdevimab cocktail given the following factors related to equity: (1) prohibitive cost (₱25,000-30,000), (2) potential problems with accessibility, (3) limited supply, (4) EUA mandate last October 2021 specifically allowing its use for treatment only and (5) issues on applicability.

The recommendation is based on a single multi-center, randomized controlled trial that was done in the United States. There is a very limited window to administer the drug therefore, the poor contact tracing and the delayed release of test results are issues in our setting that compromises the applicability of the results of this study. The vaccination status of the participants as well as the prevalent viral strains during the time of the trial were considerations of the panel. While neither of the two were discussed in the study, the study was implemented from June 2020 to March 2021.

*The definition of close contacts is the same as in the Living COVID CPG guidelines.

**This includes the following people: elderly; BMI >25; those with chronic diseases such as hypertension, diabetes, and chronic kidney disease; those who are not expected to mount an adequate immune response to the vaccine due to immunosuppressive therapy or those in an immunocompromised state.

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 Regeneron or REGEN-COV, 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]. Recent findings from a randomized controlled trial assessing efficacy of casirivimab+imdevimab in COVID-19 positive patients also showed decreased clearance of viral load for patients with Omicron variants [9].

The University of the Philippines – Philippine Genome Center (UP-PGC) has reported detection of Omicron variant in the Philippines in January 2022 [10]. Data from UP-PGH reported by the Department of Health (DOH) shows that Omicron and its subvariants has been the predominant variant detected to date [11].

REVIEW METHODS

A systematic search was done from September 1, 2021 until October 21, 2022 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 were included in this review. No limits were placed on age, COVID-19 severity, and dosing. A total of 67 related articles were found using MEDLINE, CENTRAL, COVID-NMA initiative, Google Scholar, and preprint websites, but no new published and preprint articles met our inclusion criteria.

RESULTS

Evidence from the previous review is from a multicenter randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of casirivimab + imdevimab as post-exposure prophylaxis among healthy, previously uninfected household contacts of patients with RT-PCR confirmed COVID-19 at least 12 years of age (Part A) [12]. Subjects had at least 1 risk factor for severe COVID-19 - elderly, BMI ≥35, chronic kidney disease, diabetes, immunocompromised disease/treatment (approximately 30% of study participants). Randomization occurred in January 28, 2021. Results showed a significant decrease in risk of developing symptomatic COVID-19 infection (RR 0.19, 95% CI 0.10-0.35), 2) risk of developing symptomatic/asymptomatic COVID-19 infection (RR 0.34, 95% CI 0.23-0.48), and 3) number of participants who developed high viral load of 10^4 copies/mL (RR 0.14, 95% CI 0.08-0.26) among those given casirivimab+imdevimab compared to those given placebo. Likewise, the duration of symptomatic infection (MD -2.0 weeks, 95% CI -2.21 to -1.79) was also significantly reduced in the casirivimab + imdevimab group compared to the placebo group [12].

In terms of safety, the same study showed significant reduction in adverse events when casirivimab +imdevimab was used as post-exposure prophylaxis (RR 0.78, 95% CI 0.72-0.85), with headache and injection-site reactions mentioned as most common side effects. However, no significant difference in serious adverse events between the casirivimab + imdevimab group and the placebo group (RR 0.82, 95% CI 0.41-1.66) was noted Cardiac disorders and other infections were reported as serious adverse events, none of which were attributed to the treatment received [12].

The overall certainty of evidence was rated low due to the indirectness of the study population (Omicron and its subvariants have not yet been detected prior to randomization in the study) and imprecision (wide confidence interval) one critical outcome (serious adverse events). Appraisal of study quality showed no serious risk of bias in this study. The risk of bias summary is seen in Appendix 4. The GRADE evidence profile is shown in Appendix 5.

EVIDENCE TO DECISION

On October 1, 2021, the Philippine Food and Drug Administration (FDA) issued authorization granting Roche (Philippines), Inc. the emergency use approval of Casirivimab + Imdevimab [13,14]. The available preparation is 120mg/mL (2.5ml/vial) concentrate for solution for Infusion, which should be stored in a refrigerator at 2-8℃ in the original carton to protect from light with a shelf life of 24 months from production [14]. 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 [15].

The cost of casirivimab+imdevimab for each infusion is US $1,250. A total of US $20,000 will be needed in order to prevent one infection among close contacts of those with COVID-19 (NNT=16), which roughly amounts to ₱1.16 million.

RECOMMENDATIONS FROM OTHER GROUPS

There were no new recommendations from the WHO guidelines since the last update (March 2, 2021) on the use of casirivimab + imdevimab as post-exposure prophylaxis for COVID-19 [16]. The following table shows the updated recommendations from various groups.

Group or Agency	Recommendation
Australian Guidelines [17] (Last update: October 27, 2022)	Conditional recommendation for casirivimab + imdevimab post-exposure prophylaxis for seronegative or polymerase chain reaction-negative close household contacts of individuals with confirmed COVID-19. • Where Omicron is likely to be the dominant circulating variant, use of casirivimab plus imdevimab as post-exposure prophylaxis is unlikely to be effective and should only be used in exceptional circumstances.
COVID-19 Advisory for Ontario [18] (Last update: November 24, 2021)	Recommendation for Casirivimab + imdevimab (1200 mg IV or SC) among unvaccinated individuals who are currently hospital in-patients or residing in congregate settings (e.g., long-term care settings, retirement homes, shelters, correctional facilities) who have had a high-risk exposure to SARS-CoV-2 and who are at high-risk to progress to moderate or severe COVID-19. Determination of using an AmAb for post-exposure prophylaxis should take into account the nature and context of their exposure.
National Institutes of Health (NIH) Guidelines [19] (Last update: September 26, 2022)	Recommendation against the use of casirivimab plus imdevimab for post-exposure prophylaxis (PEP), as the Omicron variant and its subvariants, which are not susceptible to these agents, are currently the dominant SARS-CoV-2 variants circulating in the United States
Infectious Diseases Society of America [20] (Last update: October 18, 2022)	Recommendation for post-exposure casirivimab/imdevimab in persons exposed to COVID-19 who are at high risk of progression to severe COVID-19 only when predominant regional variants are susceptible to the agent. (Conditional recommendation, Low certainty of evidence)

ONGOING STUDIES AND RESEARCH GAPS

There is one (1) recently completed randomized controlled clinical trial awaiting publication of results and one (1) ongoing clinical trial on casirivimab-imdevimab as prophylaxis for COVID-19 (Appendix 6).

REFERENCES

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Appendix 1: Preliminary Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=7/9)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (N=7)					
Benefits	Large (N=4)	Moderate (N=2)	Small	Varies (N=1)			Contacts of COVID-19 patients given casirivimab + imdevimab as post-exposure prophylaxis had significant decrease in the development of symptomatic COVID-19 infection (RR 0.19, 95% CI 0.10-0.35) and in the development of symptomatic/asymptomatic COVID-19 infection (RR 0.34, 95% CI 0.23-0.48) compared to placebo. Among the study participants who developed COVID-19 infection, there was significant decrease in the duration of symptomatic infection (MD -2.0 weeks, 95% CI -2.21, -1.79) and those who had high viral load (RR 0.14, 95% CI 0.08-0.26) in the casirivimab + imdevimab group compared to placebo.
Harms	Large	Moderate	Small (N=4)	Trivial (N=3)			There were significantly less adverse events in the casirivimab + imdevimab group versus control group (RR 0.78, 95% CI 0.72-0.85). There was no significant difference in serious adverse events (RR 0.82, 95% CI 0.41-1.66).
Balance of Benefits and Harms	Favors the use of intervention (N=1)	Probably favors the use of intervention (N=4)	Varies	Probably favors no intervention (N=1)	Does not favor intervention	Varies (N=1)	Casirivimab + imdevimab cocktail was shown to have net potential benefit in terms of preventing the development of COVID-19 infection and reducing the duration of symptoms. There was also net benefit in terms of adverse events compared to the placebo group.

Certainty of Evidence	High	Moderate (N=1)	Low (N=5)	Very low (N=1)			The overall certainty of evidence was rated low due to indirectness of the study population (Omicron and its subvariants have not yet been detected prior to randomization in the study) and imprecision (wide confidence interval) one critical outcome (serious adverse events).
Values	Important uncertainty or variability (N=3)	Possibly important uncertainty or variability (N=4)	Possibly NO important uncertainty or variability	No important uncertainty or variability			Recent preclinical data showed that casirivimab+imdevimab had reduced in-vitro neutralization against Omicron variants, which is the current dominant variant in the Philippines. Recent findings from a randomized controlled trial assessing efficacy of casirivimab+imdevimab in COVID-19 positive patients also showed decreased viral load clearance for patients with Omicron variants.
Resources Required	Don't Know (N=1)	Large cost (N=4)	Moderate Cost (N=1)	Negligible cost or savings (N=1)	Moderate savings	Large savings	The cost of casirivimab+imdevimab for each infusion is USD 1,250. A total of USD 20,000 will be needed in order to prevent one infection among close contacts of those with COVID-19 (NNT=16), which roughly amounts to ₱1.16 million.
Certainty of evidence of required resources	No included studies (N=5)	Very low	Low	Moderate (N=1)	High (N=1)		
Cost effectiveness	No included studies (N=5)	Probably favors the comparator (N=1)	Does not favor either criteria or the comparator	Probably favors the intervention (N=1)	Favors intervention		
Equity	Don't Know (N=1)	Probably Reduced (N=4)	Reduced (N=1)	Probably No impact (N=1)	Increased	Varies	Various treatment guidelines have recommended to limit use of casirivimab + imdevimab as post-exposure prophylaxis for those at high risk of progression to severe COVID-19, those not fully vaccinated, or those with immunocompromised conditions who many not mount adequate immune

							responses despite being fully vaccinated with non-Omicron variants and advised that casirivimab + imdevimab cocktail is NOT a substitute for vaccination. Several updated guidelines have recommended against its use as the current dominant variant is not susceptible to the said drug.
Acceptability	Uncertain (N=2)	No (N=1)	Probably No (N=1)	Yes	Probably yes (N=1)	Varies (N=2)	
Feasibility	Uncertain (N=2)	No (N=1)	Probably No (N=1)	Yes	Probably yes (N=2)	Varies (N=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 SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (REGEN-COV) OR (REGN-COV2) OR (Casirivimab) AND (Prophylaxis OR Prevention)	Oct 17, 2022 4:00 PM	54	1
Central	{"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 SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (REGEN-COV) OR (REGN-COV2) OR (Casirivimab) AND (Prophylaxis OR Prevention)	Oct 19, 2022 11:00 AM	67	1
Google Scholar	“Casirivimab” AND "COVID-19" AND "prevention" AND "randomized controlled trial"	Oct 19, 2022 3:00 PM	67	1
COVID-NMA initiative	REGEN-COV AND prevention REGN-COV2 AND prevention Casirivimab AND prevention	Oct 20, 2022 9:00 AM	4	1
ClinicalTrials.gov	Casirivimab OR REGEN-COV OR REGN-COV2 and prevention AND COVID-19	Oct 20, 2022 1:00 PM	12	1
Chinese Clinical Trial Registry	Casirivimab OR REGEN-COV OR REGN-COV2 and prevention AND COVID-19	Oct 20, 2021 1:30 PM	0	0
EU Clinical Trials Register	Casirivimab OR REGEN-COV OR REGN-COV2 and prevention AND COVID-19	Oct 20, 2022 3:00 PM	9	0
Republic of Korea - Clinical Research Information Service	Casirivimab OR REGEN-COV OR REGN-COV2 and prevention AND COVID-19	Oct 20, 2022 3:30 PM	0	0

Japan Primary Registries Network/ NIPH Clinical Trials Search	Casirivimab OR REGEN-COV OR REGN-COV2 and prevention AND COVID-19	Oct 20, 2022 4:00 PM	4	0
chinaxiv.org	rivimab OR REGEN-COV OR REGN-COV2 prevention AND COVID-19	Oct 20, 2022 8:00 PM	0	0
Medrxiv.org	rivimab OR REGEN-COV OR REGN-COV2 prevention AND COVID-19	Oct 20, 2022 8:30 PM	14	0
Biorxiv.org	rivimab OR REGEN-COV OR REGN-COV2 prevention AND COVID-19	Oct 20, 2022 9:00 PM	48	0
Cochrane	Casirivimab OR REGEN-COV OR REGN-COV2 AND COVID-19 AND Prevention	Oct 20, 2022 9:30 PM		

Appendix 2: Characteristics of Included Studies

Study ID	Patients (n) & Duration of Follow-Up	Interventions	Outcomes	Study Design
Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19 *O'Brien et al. (USA, Romania, Moldova)*	RT-PCR negative close contacts of confirmed COVID-19 patients ages 12 and above (n=1505) Duration of follow-up: Approximately 28 days	EXPERIMENTAL: REGEN-COV MAB Cocktail 1200mg SC (600mg Casirivimab + 600mg Imdevimab) CONTROL: Placebo	PRIMARY: Development of symptomatic, RT-PCR confirmed COVID-19 infection within 28 days SECONDARY: Viral load >10^4 copies, duration of symptomatic RT-PCR confirmed SARS-CoV-2 infection, duration of any RT-PCR confirmed SARS-CoV-2 infection whether symptomatic or asymptomatic, development of any RT-qPCR confirmed SARS-CoV-2 infection whether symptomatic or asymptomatic	Randomized, double-blind, placebo-controlled

Appendix 3: Characteristics of Excluded Studies*

Study ID	Reason for Exclusion
Efficacy and safety of a single dose of casirivimab and imdevimab for the prevention of COVID-19 over an 8-month period: a randomised, double-blind, placebo-controlled trial *Herman et al. (USA, Romania, Moldova)* NCT04452318	Continuation study of O'brien et al. which reports evidence of the same population of the post-exposure prophylaxis study at 2-8 months follow-up period, wherein COVID-19 risk of household transmission is expected to have subsided (study is more of pre-exposure prophylaxis rather than post-exposure)
Repeat Subcutaneous Administration of REGEN-COV® in Adults is Well-Tolerated and Prevents the Occurrence of COVID-19 *Isa et al. (USA)* NCT04519437	Study on pre-exposure prophylaxis rather than post-exposure prophylaxis

*Studies published/posted beginning December 2021

Appendix 4: Study Appraisal

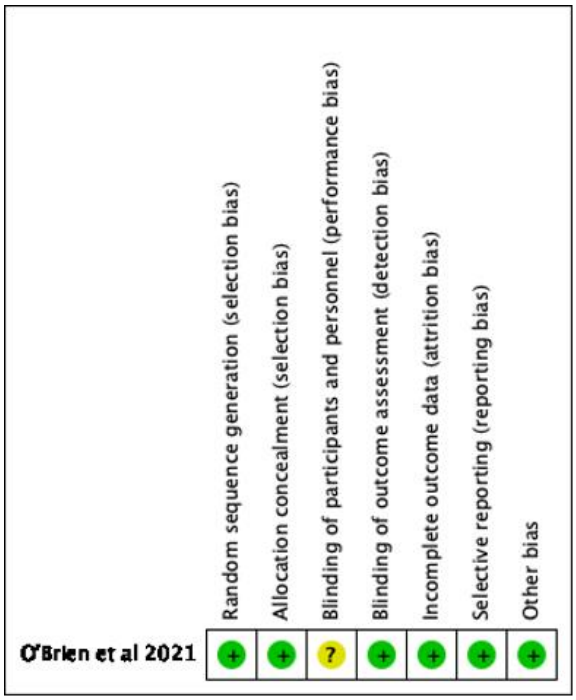

Figure 1. Risk of bias summary table

Appendix 5: GRADE Evidence Profile

Author(s): Patricia C. Orduña, MD
Question: Casirivimab+imdevimab cocktail compared to placebo for post-exposure prophylaxis
Setting: Close contacts of COVID-19 patients
Bibliography: O'Brien M, Forleo-Neto E, Musser B, et al. Subcutaneous REGEN-COV antibody combination for Covid-19 Prevention. NEJM. 2021Aug4. doi:10.1056/NEJMoa2109682.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	casirivimab+imdevimab cocktail	placebo	Relative (95% CI)	Absolute (95% CI)		
Prevention of symptomatic RT-qPCR SARS-CoV-2 infection (follow-up: 28 days)												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	11/753 (1.5%)	59/752 (7.8%)	**RR 0.19** (0.10 to 0.35)	**64 fewer per 1,000** (from 71 fewer to 51 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
Prevention of any RT-PCR confirmed symptomatic or asymptomatic SARS-CoV-2 infection (n=1505) (follow-up: 28 days)												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	36/753 (4.8%)	107/752 (14.2%)	**RR 0.34** (0.23 to 0.48)	**94 fewer per 1,000** (from 110 fewer to 74 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
Prevention of Viral load >10^4 copies/ml (n=1494) (follow-up: 28 days)												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	12/745 (1.6%)	85/749 (11.3%)	**RR 0.14** (0.08 to 0.26)	**98 fewer per 1,000** (from 104 fewer to 84 fewer)	⊕⊕⊕◯ Moderate	IMPORTANT
Duration of symptomatic RT-qPCR–confirmed SARS-CoV-2 infection (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 cocktail	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious[a]	not serious	none	753	752	-	MD **2 weeks lower** (2.21 lower to 1.79 lower)	⊕⊕⊕◯ Moderate	CRITICAL

Adverse events (follow-up: 28 days)

1	randomised trials	not serious	not serious	serious[a]	not serious	none	556/1311 (42.4%)	709/1306 (54.3%)	**RR 0.78** (0.72 to 0.85)	**119 fewer per 1,000** (from 152 fewer to 81 fewer)	⊕⊕⊕◯ Moderate	IMPORTANT

Serious adverse events (follow-up: 28 days)

1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	14/1311 (1.1%)	17/1306 (1.3%)	**RR 0.82** (0.41 to 1.66)	**2 fewer per 1,000** (from 8 fewer to 9 more)	⊕⊕◯◯ Low	CRITICAL

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

Explanations
a. Participants included in this study underwent randomization by January 28, 2021. During this time, omicron and its subvariants were not the dominant variants circulating in the study sites
b. There is a wide confidence interval

Appendix 6: Table of Ongoing Studies

Clinical Trial Identifier/Title	Study Design	Country	Population	Intervention	Outcome	Estimated Date of Completion
NCT04852978 COVID-19 Study to Assess Immunogenicity Safety and Tolerability of Moderna mRNA-1273 Vaccine Administered with Casirivimab+Imdevimab in Healthy Adult Volunteers	Randomized controlled trial	USA	Healthy adults or adults with stable, chronic medical conditions with no COVID-19	Casirivimab+imdevimab, Moderna mRNA-1273 vaccine	Extent of effect of casirivimab+imdevimab administration on vaccine-induced neutralizing antibody responses to SARS-CoV-2 Time interval required between casirivimab+imdevimab administration and Moderna mRNA-1273 vaccine to ensure no meaningful impact on vaccine-induced neutralizing antibody responses to SARS-CoV-2	Aug 30, 2022 (Status: Active, not recruiting)
jRCT2071200117 A phase I study of casirivimab and imdevimab in Japanese adult volunteers	Randomized controlled trial	Japan	Healthy individuals ages 20-89 years old	Single dose IV casirivimab+imdevimab vs single dose IV placebo Single dose SC casirivimab+imdesivimab vs single dose SC placebo	Adverse events, pharmacokinetics of casirivimab and imdevimab, incidence of anti-drug antbodies to casirivimab and imdevimab	Nov 11, 2021 (Completed but no data available)