NCT05074433
IND: 148069
EudraCT: 2021-005222-14

Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ANTI-SPIKE SARS-CoV-2 MONOCLONAL ANTIBODIES AS PRE-EXPOSURE PROPHYLAXIS TO PREVENT COVID-19 IN IMMUNOCOMPROMISED PARTICIPANTS

Compound:	Casirivimab+Imdevimab
Clinical Phase:	3
Protocol Number:	R10933-10987-COV-2176
Protocol Version:	Amendment 2 US
Amendment 2 US Date of Issue:	*See appended electronic signature page*
Amendment 1 (Not Implemented)	N/A
Original Date of Issue	24 September 2021
Medical /Study Director:	[redacted]

Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

[redacted]

AMENDMENT HISTORY

Amendment 2

The primary purpose of this amendment is to close the study. The procedures described in this amendment supersede those of the original protocol and site memorandum.

Description of Change	Brief Rationale	Section(s)
Added a new section with procedures specifying the study closure process, which includes the following: • Participants will be offered the option to receive a supplemental final dose of casirivimab+ imdevimab1200 mg SC • All participants, including those who do not consent to receive the optional final dose, will have a follow-up (end-of-study) telephone visit approximately 3 months from their last dose of investigational drug (casirivimab+imdevimab or placebo) to monitor safety • Participants with suspected COVID-19 may have an optional visit to evaluate signs and symptoms and to receive local and central laboratory testing for SARS-CoV-2 • For participants who are SARS-CoV-2 positive, additional weekly visits can optionally occur until 2 consecutive negative RT-qPCR tests are obtained • Safety collection will be broadened from original protocol to include treatment-emergent AEs considered by the investigator to be unrelated to baseline conditions and unrelated to treatments for baseline conditions. • Participants will be monitored for at least 60 minutes after receiving study drug • Sites will ensure that an additional discussion about the potential risks and benefits to the participant and fetus is discussed as part of re-consent for participants who become pregnant during the study • A modified statistical analysis plan has been summarized for participants who have already enrolled in the study	To provide guidance to US sites regarding study close-out procedures.	Protocol Amendment 2 Procedures Table 2 Schedule of Events for Study Close-Out (Applies to All Enrolled Participants Per Protocol Amendment 2) Section 9.1.2 Footnotes for the Schedule of Events (Protocol Amendment 2)

Site Memorandum

This section describes changes to study conduct that were implemented by a site memorandum issued on 21 October 2021.

Original Protocol	Change / Additional Measures
No Scheduled Safety Labs	Measure absolute neutrophil count, platelet count, hemoglobin, ALT, AST, total bilirubin, and creatinine at the baseline visit as well as study visits days 29, 85 and 169
Monitor for 15 minutes after first dose	Monitor for 60 minutes after administration of study drug
Report treatment emergent adverse events (TEAEs) that are grade ≥3 in severity	Report all clinical and laboratory TEAEs that are not related to the patient's underlying (non-COVID) disease and/or not related to treatments for the underlying conditions

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
CI	Confidence interval
CRF	Case report form (electronic or paper)
CRO	Contract research organization
EC	Ethics Committee
EDC	Electronic data capture
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HSCT	Hematopoietic stem cell transplantation
ICF	Informed consent form
ITT	Intention-to-treat
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IV	Intravenous
IVIG	Intravenous immunoglobulin
mITT	Modified intention-to-treat
NAb	Neutralizing antibody
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NP	Nasopharyngeal
PCSV	Potentially clinically significant value
PK	Pharmacokinetic
Q4W	Every 4 weeks
Q12W	Every 12 weeks
Regeneron	Regeneron Pharmaceuticals, Inc.
RBQM	Risk-Based Quality Monitoring
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SCIG	Subcutaneous immunoglobulin
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CLINICAL STUDY PROTOCOL SYNOPSIS

As of protocol amendment 2 this study will close. Please refer to Protocol Amendment 2 Procedures for further details.

VV-RIM-00181183-1.0 Approved - 25 Jan 2022 GMT-5:00

PROTOCOL AMENDMENT 2 PROCEDURES

Study R10933-10987-COV-2176 will be terminated early by the Sponsor due to evidence surrounding variants of concern and reduced neutralization potency of casirivimab+imdevimab against the Omicron variant. The study is not being terminated due to any safety concerns, nor from any data obtained in this study.

The procedures described in amendment 2 should be implemented immediately at sites that have participants who are currently enrolled in the study.

Optional Dose

The Sponsor believes that casirivimab+imdevimab may continue to serve as an important pre-exposure prophylaxis therapeutic among immunocompromised individuals in regions where Omicron is not the dominant variant or in regions where Omicron prevalence subsides. For this reason, participants will have the option to receive a 1200 mg SC dose of casirivimab+imdevimab as a final study dose. This optional dose may be administered to all participants regardless of treatment assignment at randomization. However, participants will not be eligible to receive this dose if they have already received casirivimab+imdevimab as post-infection treatment.

Participants will be asked to return to the site for an unscheduled visit, during which they will be asked to consent to protocol amendment 2 and receive the final optional dose, if desired. This visit to receive the final optional dose should occur approximately 4 weeks after the most recent dose. Note that consent may be obtained remotely prior to this visit, if available and allowable by the study site.

Procedures in the Event of Suspected COVID-19

Participants with suspected COVID-19 may undergo an optional visit to evaluate symptoms by a study clinician (investigator or designee) and to undergo laboratory testing of SARS-CoV-2, as detailed in the new schedule of events (Table 2). This optional visit should occur as soon as possible (**within 48 hours of symptom onset, if feasible)**. Note that clinician assessment of sign or symptoms may occur remotely. If remote assessment is performed, a confirmatory site visit for laboratory testing of SARS-CoV-2 can optionally occur after a clinician deems that the signs or symptoms are related to COVID-19.

Clinical Evaluation. Signs and symptoms will be evaluated by a clinician (investigator or designee, evaluation may occur remotely) as described below. If the clinician confirms that at least one sign or symptom is potentially related to COVID-19, samples may be collected to perform both **local** and **central** testing for SARS-CoV-2 infection.

Laboratory Testing of SARS-CoV-2. Local testing must be performed by RT-PCR using local sample collection and assay standards. A nasopharyngeal (NP) swab sample is the preferred sample type, but other samples (eg, nasal, oropharyngeal, saliva) adhering to local standards are acceptable. An additional NP swab sample will be collected for the purposes of central RT-qPCR testing. The samples will be collected prior to any administration of post-infection treatment (described below). The qualitative result of the central RT-qPCR will be reported back to the corresponding study site.

SARS-CoV-2 viral genome sequencing will be performed using NP swab samples collected during the study that have been confirmed positive by RT-qPCR at the central laboratory.

Documentation of Clinical Evaluation. For each symptom, the start (onset) date, end date, and severity will be recorded (mild, moderate, severe) in the participant's medical record (source document). It is important to record this information in the source document, to ensure that the temporal dimensions of each sign or symptom are captured.

The following information may subsequently be recorded in EDC as applicable:

- The sign or symptom, with start (onset) calendar date, end calendar date, and severity (mild, moderate, severe)
- Confirmatory local RT-PCR test result and date of sample collection
- Confirmatory central RT-qPCR test result and date of sample collection
- Weekly central RT-qPCR test results and dates of sample collection
- Record of any post-infection treatment with casirivimab+imdevimab administered

Note that any sign or symptom considered by the investigator to be unrelated to baseline conditions and unrelated to treatments for baseline conditions will also be recorded and used for safety evaluation.

Post-Infection Treatment. Participants with confirmed positive SARS-CoV-2 RT-PCR will be eligible for post-infection treatment (as described in Section 6.4.4) at any time prior to receipt of the optional 1200 mg SC dose (eg, during the 4 weeks between receipt of the last protocol-defined dose and the optional 1200 mg SC dose). Once this optional dose has been administered, post-infection treatment will no longer be offered. Likewise, any participant who receives post-infection treatment will not be eligible to receive the optional 1200 mg SC dose.

*Participants with Positive SARS-COV-2 RT-PCR. P*articipants with a positive SARS-CoV-2 RT-PCR may have additional assessments and sample collections, during unscheduled visits every 7 days (±1 day) for central laboratory RT-qPCR analysis until 2 consecutive negative test results are obtained:

- NP swab samples for RT-qPCR
- COVID-19 signs and symptoms evaluated by the investigator or designee
- Information regarding COVID-19-related medically-attended visits (MAVs; defined in Section 9.2.4.3)

End-of-Study Visit

All participants, including those who do not consent to receive the optional final dose, will have a follow-up (end-of-study) telephone visit approximately 85 days (3 months) from their last dose of investigational drug (casirivimab+imdevimab or placebo) to monitor safety. Study assessments for the 3-month follow-up visit will be limited to the collection of targeted adverse events, as detailed in the new schedule of events (Table 2).

Sites will ensure that an additional discussion about the potential risks and benefits to the participant and fetus is discussed as part of re-consent for participants who become pregnant during the study.

Statistical Analysis Plan

At the time that enrollment was paused, 66 participants had been enrolled in the study. Due to the early study closure and the resulting small sample size of enrolled participants, all analyses will be performed descriptively and only numeric comparisons will be performed.

All safety endpoints (including AEs, TEAEs, AESIs, SAEs, and safety laboratory values) will be summarized. Selected efficacy, virology, PK, and/or immunogenicity data may also be analyzed descriptively. Additional details will be provided in the Statistical Analysis Plan (SAP).

No interim analysis will be performed for this study, and no IDMC review meetings will occur.

VV-RIM-00181183-1.0 Approved - 25 Jan 2022 GMT-5:00

1. INTRODUCTION

1.1. SARS-CoV-2 and COVID-19

Severe acute respiratory syndrome coronavirus (SARS-CoV-2) is a betacoronavirus determined to be the pathogen responsible for coronavirus disease 2019 (COVID-19) (WHO, 2020).

The spike (S) protein of SARS-CoV-2 is essential for virus infectivity, and is the main target of the humoral immune response, as demonstrated by serology analysis of recovered COVID-19 patients (Long, 2020). By mediating binding to the host receptor angiotensin-converting enzyme 2 (ACE2), the SARS-CoV-2 S protein facilitates membrane fusion and entry of the virus into susceptible cells (Hoffmann, 2020). The S protein is composed of an S1 subunit, which contains the receptor binding domain (RBD) that binds ACE2, and the S2 subunit, which mediates virus-cell membrane fusion (Walls, 2020).

1.2. Casirivimab+Imdevimab: A Combination of Two Non-Competing Monoclonal Antibodies that Target the SARS-CoV-2 S Protein RBD

Casirivimab and imdevimab are two non-competing recombinant monoclonal antibodies (mAbs), developed by Regeneron Pharmaceuticals, Inc., that bind simultaneously to the RBD and block its interaction with ACE2. As a co-administered combination therapy, casirivimab+imdevimab has demonstrated efficacy as an antiviral agent for the treatment and prevention of COVID-19, across a variety of populations, and is generally well-tolerated with a favorable safety and tolerability profile. In the outpatient treatment setting, casirivimab+imdevimab enhances viral clearance and reduce rates of COVID-19-related hospitalization or all-cause death, and in hospitalized patients was shown to reduce all-cause death (Horby, 2021) (Weinreich, 2021b). When given in a prophylaxis setting to household contacts of SARS-CoV-2-infected individuals, casirivimab+imdevimab reduces asymptomatic and symptomatic infections, produces faster viral clearance, and in those who develop symptoms, leads to shorter symptoms duration (O'Brien, 2021a) (refer to Section 3.3.1 for additional information).

Casirivimab+imdevimab retains neutralization potency against all SARS-CoV-2 variants of concern/interest, including alpha (B.1.1.7; UK), beta (B.1.351; South Africa), delta (B.1.617.2; India) gamma (P.1; Brazil), lambda (C.37; Peru) and mu (B.1621; Colombia), and protects against the selection of drug resistant variants in vitro, in vivo, and in the clinical setting (REGEN-COV™ (casirivimab with imdevimab) [HCP Fact Sheet], 2021) (Copin, 2021).

1.3. Monoclonal Antibody Therapy as Pre-Exposure Prophylaxis in Immunocompromised Individuals

The available evidence indicates that some immunocompromised conditions, such as certain primary or secondary immunodeficiencies, can lead to a reduced production of endogenous antibodies against SARS-CoV-2. Individuals with such conditions may be at a greater risk of becoming infected or experiencing prolonged infection, potentially leading to increased morbidity and mortality, and may also have a significantly impaired protective immune response to COVID-19 vaccination (Agha, 2021) (Babaha, 2020) (Boyarsky, 2021a) (Boyarsky, 2021b) (Deepak, 2021) (Gao, 2020) (Herishanu, 2021) (Lewis, 2020) (Sonani, 2021). These at-risk individuals may benefit from the prophylactic use of exogenous anti-SARS-CoV-2 mAbs given prior to infection

or exposure to the virus (ie, pre-exposure prophylaxis), by providing an increased level of passive immunity to supplement an inadequate endogenous immune response from prior SARS-CoV-2 infection or vaccination.

This is a randomized, double-blind, placebo-controlled, phase 3 study in adults and adolescents to assess the safety and efficacy of casirivimab+imdevimab as prophylaxis against symptomatic COVID-19 in immunocompromised individuals, defined according to the primary and secondary immunodeficiencies outlined in the study eligibility criteria (Section 7.2).

For more information regarding the rationale for the study design and dose selection, refer to Section 3.2. A summary of key efficacy and safety data from the casirivimab+imdevimab clinical development program is provided in Section 3.3. Additional background information on the study drug and the overall development program can be found in the Investigator's Brochure.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to evaluate the effect of casirivimab+imdevimab, compared with placebo, in preventing symptomatic SARS-CoV-2 infection in immunocompromised participants.

2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the safety and tolerability of repeated SC injections of casirivimab+imdevimab in the study population
- To characterize concentrations of casirivimab and imdevimab in serum over time
- To assess the immunogenicity of casirivimab and imdevimab

2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To evaluate additional indicators of casirivimab+imdevimab clinical efficacy and disease prevention compared to placebo
- To evaluate the effect of casirivimab+imdevimab, compared to placebo, in preventing SARS-CoV-2 infection with elevated viral load
- To explore biomarkers predictive and/or indicative of safety and/or efficacy of casirivimab+imdevimab, COVID-19 vaccine response, SARS-CoV-2 infection and immune response, COVID-19 disease progression and clinical outcomes of casirivimab+imdevimab
- To explore the effect of baseline immune response to COVID-19 vaccination on response to casirivimab+imdevimab and clinical outcomes

- To characterize viral variants by sequencing SARS-CoV-2 in participants who become infected post-baseline

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

Pre-exposure prophylaxis with anti-SARS-CoV-2 mAbs (casirivimab+imdevimab) will prevent symptomatic SARS-CoV-2 infection in immunocompromised individuals who have not mounted an effective response to vaccination.

3.2. Rationale

3.2.1. Rationale for Study Design

3.2.1.1. Study Population

In the absence of a universal clinical definition, this study will define an immunocompromised state according to a discrete set of primary and secondary immunodeficiencies used as eligibility criteria. These criteria can be found in Section 7.2.

Immunocompromising Conditions. As described in Section 1, certain immunocompromising conditions can negatively impact the production of endogenous antibodies against SARS-CoV-2, particularly in response to vaccination. This study therefore aims to evaluate the use of anti-SARS-CoV-2 mAb therapies, casirivimab+imdevimab, in immunocompromised individuals age ≥12 years (Section 7.2).

The definition of immunocompromised participants used for study enrollment (provided in Section 7.2.1) are consistent with criteria regarding conditions and treatments associated with moderate to severe immune compromise described at the August 2021 meeting of CDC Vaccine Recommendations of the Advisory Committee on Immunization Practices (ACIP). The criteria provided during this meeting were as follows (ACIP, 2021):

- Active or recent treatment for solid tumor and hematologic malignancies
- Receipt of solid-organ or recent hematopoietic stem cell transplants
- Severe primary immunodeficiency
- Advanced or untreated HIV infection
- Active treatment with high-dose corticosteroids, alkylating agents, antimetabolites, tumor-necrosis (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory
- Chronic medical conditions such as asplenia and chronic renal disease, some patients with these conditions may be associated with varying degrees of immune deficit

The above criteria were presented in the context of identifying individuals that may be considered for a booster COVID-19 vaccine dose. The criteria described in this study (Section 7.2.1) are slightly modified, taking into consideration experience with study populations in the

casirivimab+imdevimab clinical development program, other government, academic, industry publications and presentations, advice from experts in the field, and other clinical trials.

Prior Non-Response to COVID-19 Vaccination. To ensure that the enrolled study population has a demonstrated risk of future SARS-CoV-2 infection despite having been vaccinated, the study will require as a condition of enrollment that participants previously received a full course of COVID-19 vaccination (unless medically ineligible or contraindicated), and demonstrated a non-response to COVID-19 vaccination (ie, a lack of circulating anti-S protein IgG antibodies) (Section 7.2.1).

Non-response will be further evaluated retrospectively and quantitatively via central analysis of baseline samples, and the results of this analysis will be used to define the primary efficacy analysis population (modified intention-to-treat). A quantitative cutoff value will serve as the upper bound for non-response definition in the primary analysis, with a value derived from ongoing clinical trials evaluating immunologic response to COVID-19 booster vaccines (NCT05000216). Additional information regarding the assay and definition of the efficacy analysis population can be found in Section 9.2.8.1 and Section 11.3.1.

As the study will be conducted in an at-risk population, additional treatment with casirivimab+imdevimab will be offered at sites to participants who become infected with SARS-CoV-2 at any point during the study (Section 6.4.4).

Focused Enrollment. The study will be conducted in regions where there is an ongoing COVID-19 outbreak and active community transmission of COVID-19, further ensuring that the scientific aim of evaluating prevention in at-risk individuals can be attained.

3.2.1.2. Double Blind Design

The double-blind design serves to reduce potential bias introduced by knowing the study drug assignment. The comparator arm in this study will be placebo, as no approved or authorized pre-exposure preventative treatments are currently available in the regions where the study is being conducted.

3.2.1.3. Clinical Efficacy

The primary endpoint of this study will evaluate the occurrence of symptomatic, laboratory-confirmed SARS-CoV-2 infection (Section 4.1). This endpoint is similar to the primary endpoint utilized in COVID-19 vaccine trials (Baden, 2021) (Polack, 2020) (Sadoff, 2021) and is thus intended to evaluate efficacy in the pre-exposure prophylaxis setting.

In this study, participants will be asked to promptly report any potential signs or symptoms of COVID-19, so that symptoms can be confirmed clinically prior to any laboratory testing for SARS-CoV-2 infection (Section 6.4.2). However, it is possible that participants may obtain incidental testing outside of the study, either during that course of standard of care for their immunocompromising condition or for other personal reasons. The study will therefore accommodate participants who receive an outside positive test result for SARS-CoV-2 infection, and these participants will receive additional protocol-defined laboratory viral testing (Section 6.4.3). Since these participants may be asymptomatic at the time of laboratory-confirmed infection per protocol, the study will additionally evaluate (as an exploratory endpoint; Section 4.3) the occurrence of confirmed infection regardless of symptoms.

The casirivimab+imdevimab clinical development program includes several controlled phase 3 studies that have shown consistent clinical benefit from treatment across the SARS-CoV-2/COVID-19 disease spectrum, spanning uninfected individuals to those with asymptomatic SARS-CoV-2 infection to non-hospitalized and hospitalized patients with COVID-19. In the outpatient setting, treatment with casirivimab+imdevimab has demonstrated efficacy on clinically-meaningful endpoints, including a reduction in risk in COVID-19-related hospitalization and/or all-cause death through study day 29 (Section 3.3.1). Although study participants will be offered additional casirivimab+imdevimab treatment at sites following laboratory-confirmed SARS-CoV-2 infection (Section 6.4.4), it is nevertheless of interest to evaluate whether prior prophylactic dosing may confer subsequent clinical benefit post-infection. The study will therefore evaluate, as exploratory endpoints, several clinical outcome measures derived from the outpatient treatment setting.

3.2.1.4. Virologic Efficacy

The study will evaluate, in an exploratory manner, endpoints assessing viral load among participants who develop COVID-19 symptoms (Section 4.3). Virologic efficacy has been evaluated in all clinical efficacy studies in the casirivimab+imdevimab program, and has been used as a proximal indicator of pharmacological activity showing that the burden of disease following SARS-CoV-2 infection is correlated with high viral load, and that casirivimab+imdevimab virologic efficacy is consistently associated with clinical efficacy (refer to Section 3.3.1 and references therein).

3.2.2. Rationale for Dose Selection

Three dosing regimens of casirivimab+imdevimab (co-administered casirivimab and imdevimab in a 1:1 ratio) will be evaluated in the current study: 1200 mg SC loading dose + 600 mg SC Q4W x 5 maintenance dose; 300 mg SC Q4W x 6; and 300 mg SC Q12W x 2. For post-exposure prophylaxis, a single 1200 mg SC casirivimab+imdevimab dose demonstrated a statistical and clinically-meaningful benefit in the prevention of SARS-CoV-2 infection (Section 3.3.1). In the chronic prevention setting, 1200 mg SC loading dose + 600 mg SC Q4W maintenance dose is authorized in the United States for post-exposure prophylaxis in individuals at high risk for progressing to severe COVID-19. The maintenance arm (600mg SC Q4W) is anticipated to maintain trough concentration at steady-state ($C_{trough,ss}$) of casirivimab and imdevimab in serum, similar to the day 29 concentration after a single 1200 mg SC dose in study (as observed in COV-2069).

Concentrations of casirivimab+imdevimab combined in serum for a single 1200 mg SC dose are estimated to exceed the concentrations in serum required to achieve 90% neutralizing concentration (IC_{90}) in respiratory tract fluid ($C_{s,target}$) against currently circulating variants of concern/variants of interest (alpha, beta, delta, gamma, kappa, lambda, and mu) as early as 4.8 hours after dosing and through 28 days after dosing, using a conservative estimate of serum to respiratory tract fluid penetration of 1% (Magyarics, 2019) (Shah, 2013) (Wollacott, 2016). For the casirivimab+imdevimab 1200mg SC loading dose + 600mg SC Q4W maintenance dose regimen, population PK estimated median casirivimab+imdevimab combined $C_{trough,ss}$ is ~14x to 35x the $C_{s,target}$ against reference SARS-CoV-2 viruses (Wuhan, D614G) and currently circulating variants of concern/variants of interest. In outpatients with low risk for developing severe COVID-19 (study COV-20145), time-weighted average change from baseline in nasopharyngeal (NP) viral

load from day 1 to day 7 was significantly and comparably reduced relative to placebo across all single IV (300, 600, 1200, and 2400 mg) and SC (600, 1200 mg) doses tested, indicating that all doses were on the plateau of the dose-response curve for NP viral load reduction. As all of these doses were maximally effective in lowering viral load in outpatients with COVID-19, these results warrant evaluation of lower doses in both the treatment and prevention settings.

In addition to the 1200 mg SC loading dose + 600 mg SC Q4W x 5 maintenance dose regimen, two additional dosing regimens will be evaluated to understand whether a lower dose and/or a lower dose with an extended dosing interval will be efficacious in preventing SARS-CoV-2 infection in immunocompromised individuals. For the intermediate dosing regimen of 300 mg SC Q4W x 6, the population PK estimated median casirivimab+imdevimab concentration in serum 12 hours after the first dose exceeds the $C_{s,target}$ against reference SARS-CoV-2 viruses and currently circulating variants of concern/variants of interest, with a predicted $C_{trough,ss}$ 50% of that for the 1200 mg SC loading dose + 60 0mg SC Q4W maintenance dose regimen. Based on the in vitro potency of casirivimab+imdevimab against reference SARS-CoV-2 viruses and currently circulating variants of concern/variants of interest, and the modest reduction in exposure for 300 mg SC Q4W x 6, it is expected that this intermediate dosing regimen will be efficacious in preventing SARS-CoV-2 infection. For the low dose regimen of 300 mg SC Q12W x 2, population PK estimated median casirivimab+imdevimab $C_{trough,ss}$ is ~7% of $C_{trough,ss}$ for the 1200 mg SC loading dose + 600 mg SC Q4W maintenance dose regimen, and is being explored to evaluate efficacy of a more convenient Q12W dose regimen.

As the lower end of the proposed body weight range for adolescent subjects ≥12 years of age (≥40 kg) falls within the range of expected body weights for adults, similar exposures are expected between these 2 populations for each of the dosing regimens.

3.3. Risk-Benefit

The anticipated risks and benefits of casirivimab+imdevimab are informed by pre-clinical and clinical data, including data from phase 3 trials.

For additional information concerning clinical and pre-clinical data, refer to the Investigator's Brochure.

3.3.1. Summary of Efficacy and Safety Profile in Clinical Trials

Clinical trial data are summarized below. Overall, casirivimab+imdevimab has demonstrated efficacy as an anti-viral agent for the treatment and prevention of COVID-19, across a variety of populations, and is generally well-tolerated with an acceptable safety profile.

Intravenous Administration of Casirivimab+Imdevimab in Clinical Trials.

Outpatient Setting. In COV-2067 (R10933-10987-COV-2067), the phase 3 outpatient treatment trial, a single intravenous dose of casirivimab+imdevimab was shown (relative to placebo) to reduce COVID-19-related hospitalizations or all-cause death by 71.3% (2400 mg dose) and 70.4% (1200 mg dose), reduce symptom duration by 4 days (2400 mg and 1200 mg), and reduce viral load over the first 7 days. The incidence of serious adverse events was higher in the placebo group (4.0%) than in either of the active treatment groups (2400 mg, 1.1%; 1200 mg, 1.3%), and grade ≥2 infusion-related reactions were infrequent (≤0.3% in all active treatment groups; 0% in placebo group) (Weinreich, 2021b). Similar virologic efficacy and a similar safety profile were observed

in the phase 1/2 portion of this trial, which evaluated casirivimab+imdevimab at 8000 mg and 2400 mg IV doses (Weinreich, 2021a).

Hospitalized Setting. COV-2066 was a randomized, placebo-controlled study evaluating single dose casirivimab+imdevimab 2400 mg IV and 8000 mg IV in hospitalized patients, with those requiring different baseline oxygen supplementation enrolled into separate cohorts. Among patients who were seronegative at baseline and did not require supplemental oxygen or required low-flow oxygen, the 2400 mg IV and 8000 mg IV doses (when analyzed together) exhibited a significantly greater reduction in viral load through day 7 relative to placebo, and exhibited a nominally significant reduction in the proportion of patients who died or were mechanically ventilated (relative risk reduction of 30.9%; nominal p=0.0212). Similar efficacy outcomes were observed when the 2400 mg and 8000 mg dose groups were analyzed separately, for either of the two cohorts (those who did not require supplemental oxygen and those who required low-flow oxygen at baseline). Both doses of casirivimab+imdevimab were well-tolerated, and safety findings were consistent with results from other studies in the development program. No new or serious safety concerns were observed.

The controlled, open-label, platform study RECOVERY evaluated casirivimab+imdevimab 8000 mg IV in hospitalized patients with varying baseline supplemental oxygen requirements (no oxygen, simple oxygen, non-invasive ventilation, mechanical ventilation). A single dose of casirivimab and imdevimab 8000 mg IV, when given in addition to usual care, reduced the incidence of death through day 28 (compared to usual care alone) by 20% in those who were seronegative for anti-SARS-CoV-2 antibodies at baseline (24% of patients died in the casirivimab+imdevimab group versus 30% in the usual care group). Among seronegative patients, the median duration of hospitalization was 4 days shorter in the casirivimab+imdevimab group (13 days versus 17 days), and the proportion of patients discharged alive by day 28 was greater (64% versus 58%) (Horby, 2021). Among patients who were seropositive at baseline, neither clinical benefit nor evident clinical harm was observed following treatment with casirivimab+imdevimab.

Safety information was collected within 72 hours of randomization to evaluate the effect of casirivimab+imdevimab on select parameters. No clinically meaningful differences were observed between the casirivimab+imdevimab group and the usual care group. There were minor numeric imbalances in specific targeted safety outcomes: the reported frequency of fever (4% versus 3%), sudden hypotension (4% vs. 2%), and thrombotic events (2% vs. 1%) was marginally higher in the casirivimab+imdevimab group versus the usual care group, while the frequency of sudden worsening in respiratory status (21% versus 22%) and clinical hemolysis (1% versus 2%) was marginally lower (Horby, 2021). Upon Sponsor review, these events were considered likely related to COVID 19-and its associated complications.

In COV-2066, enrollment of patients requiring baseline high-intensity oxygen or mechanical ventilation was paused, following early imbalances in safety observed by the study IDMC (refer to the Investigator's Brochure for additional information). These patient populations continued to enroll in RECOVERY, however, and within the larger RECOVERY dataset a similar safety signal was not observed. Instead, among seronegative patients, trends of clinical benefit were observed in subgroups across the different of respiratory support received (Horby, 2021). Subsequent review of complete follow-up data in COV-2066 did not show clear treatment-associated trends for death or mechanical ventilation among these participants, although the sample size was too small to draw definitive conclusions.

Subcutaneous Administration of Casirivimab+Imdevimab in Clinical Trials.

Prophylaxis Setting. In COV-2069 (R10933-10987-COV-2069), the phase 3 prevention trial in those at high risk of infection by a household contact, a single subcutaneous dose of casirivimab+imdevimab (1200 mg) reduced (relative to placebo) symptomatic SARS-CoV-2 infection by 81.4%, and reduced overall SARS-CoV-2 infection by 66.4%. The incidence of serious adverse events was similar between the active treatment group (1%) and placebo group (1%). Injection-site reactions were more common in the treatment group (4%) compared to the placebo group (2%), and were all mild to moderate with injection-site reactions in the study grade 3 or above. The majority of injection site reactions occurred within one day and resolved within two days (O'Brien, 2021c).

Among a sub-group of individuals in COV-2069 who were identified as SARS-CoV-2 positive but asymptomatic during screening, a single subcutaneous dose of casirivimab+imdevimab (1200 mg) reduced (relative to placebo) progression to symptomatic disease by 31.5%, and reduced the duration of symptoms in those that developed symptomatic infections. Injection-site reactions were more common in the treatment group (4%) compared to the placebo group (1%), but no injection-site reactions in the study were grade 3 or above (O'Brien, 2021b).

In COV-2069, efficacy results were similar in adolescents (age 12 to <18) as observed in adults: 0% of subjects in the 1200 mg SC treatment group experienced symptomatic infection, compared with 9.3% of subjects in the placebo group. Safety data in adolescent subjects were also similar to that observed in adults. Injection site reactions were more common in the treatment group (5.9%) compared to the placebo group (1.6%), but none were grade 3 or above in any group.

Adult Volunteers. In HV-2093 (R10933-10987-HV-2093), an adult volunteer study evaluating repeated doses of subcutaneously-administered casirivimab+imdevimab 1200 mg SC (monthly dosing over 6 months), casirivimab+imdevimab was well-tolerated with no unexpected safety findings. The incidence of treatment-emergent AEs was higher in the active treatment group (52.7%) compared to placebo (46.3%). This difference was primarily due to a higher incidence of injection-site reactions in the casirivimab+imdevimab group (34.6%, compared with 15.8% in the placebo group), but none were grade 3 or above in any group. All injection-site reactions were thus mild or moderate in severity and most events resolved without treatment. Although very few participants experienced symptomatic SARS-CoV-2 infection in the study, infection was less common within the active treatment group (0.4%; 3 participants) compared with placebo (5.0%; 12 participants)

3.3.2. Summary of Risks

Identified Risks. As with other protein therapeutics, hypersensitivity reactions, including acute infusion-related reactions (intravenous administration) or injection site reactions (subcutaneous administration), may develop immediately or within a few hours to days after study drug administration. Hypersensitivity reactions, including infusion-related reactions or injection site reactions, have been observed in study participants who received casirivimab+imdevimab during ongoing clinical trials.

Potential Risks. The potential risks of casirivimab+imdevimab are the clinical consequences of immunogenicity and embryo-fetal toxicity.

Protein therapeutics carry the potential risk of an immunogenic response in the form of anti-drug antibody (ADA) and neutralizing antibody (NAb) development following administration, with possible consequences on safety and efficacy. Therefore, blood samples for immunogenicity assessment will be collected during the studies.

Reproductive and developmental toxicology studies have not been conducted, and the effects of casirivimab, imdevimab, or casirivimab+imdevimab combination therapy on the fetus and reproductive organs in males and females are unknown. There is also currently limited clinical experience in the use of casirivimab, imdevimab, or casirivimab+imdevimab combination therapy in females who are pregnant or breastfeeding.

Human IgG1 antibodies are known to cross the placental barrier and are present in breast milk. Casirivimab and imdevimab combination therapy therefore has the potential to be transferred from the mother to the developing fetus or a breastfed child. Given the high affinity and specificity of casirivimab+imdevimab, off-target pharmacological effects are not anticipated in either the mother or the fetus, and no off-target binding of casirivimab or imdevimab was observed in any of the human or monkey tissues evaluated ex vivo in tissue cross-reactivity studies. However, it is unknown whether the potential transfer of casirivimab+imdevimab combination therapy provides any treatment benefit or risk to the developing fetus or a breastfed child.

The combination of casirivimab+imdevimab therapy should be used during pregnancy or breastfeeding only if the potential benefit justifies the potential risk for the mother and the fetus or breastfed child considering all associated health factors. Pregnancy that occurs during this study will be reported and followed, including any complications and pregnancy outcome, as described in Section 10.1.3.

Other Theoretical Risks. Theoretical risks of casirivimab+imdevimab include interference with the participant's endogenous immune response to either SARS-CoV-2 infection or vaccination against COVID-19. This study will enroll individuals with a demonstrated non-response to COVID-19 vaccination (Section 7.2), regardless of prior passive antibody therapy. This theoretical risk is therefore unlikely to apply to the study population.

Antibody-dependent enhancement (ADE) has been observed for some therapeutics targeting exogenous viral proteins. Clinical trials of casirivimab+imdevimab, including analyses of post-treatment follow-up periods in studies COV-2069 and COV-2093. have not identified any evidence of an increase in reinfection corresponding to the waning effect of antibody treatment. To assess any potential ADE, a similar approach as that of COV-2069 and COV-2093 will be adopted in this study: All participants will have follow-up assessments during the drug elimination period (for over five half-lives), and participants will be monitored for any signal of ADE.

3.3.3. Summary

The available clinical and nonclinical data for casirivimab+imdevimab demonstrates anti-viral efficacy with a favorable safety profile. Based on these data, and given the current unmet need for prophylactic therapies to prevent SARS-CoV-2 infection and COVID-19 disease in immunocompromised individuals, it is the opinion of the Sponsor that the overall risk-benefit balance for casirivimab+imdevimab is acceptable to allow evaluation of casirivimab+imdevimab in the study population.

VV-RIM-00181183-1.0 Approved - 25 Jan 2022 GMT-5:00

4. ENDPOINTS

4.1. Primary Endpoint

The primary endpoint is cumulative incidence of symptomatic (broad term), RT-PCR-confirmed SARS-CoV-2 infection cases during the efficacy assessment period (EAP).

Note: definitions of symptomatic SARS-CoV-2 infection and the EAP are provided in Section 6.2.

4.2. Secondary Endpoints

The secondary endpoints are:

- Proportion of participants with grade ≥3 treatment-emergent adverse events (TEAEs), during the EAP and follow-up period
- Proportion of participants with TEAEs leading to study drug discontinuation, during the EAP and follow-up period
- Proportion of participants with treatment-emergent serious adverse events (SAEs) during the EAP and-follow up period
- Incidence of adverse events of special interest (AESIs) during the EAP
- Concentration of each mAb (as applicable to the treatment arm) over time
- Incidence and titer of anti-drug antibodies (ADA), and incidence of neutralizing antibodies (NAb) to each mAb (as applicable to the treatment arm) over time

4.3. Exploratory Endpoints

The exploratory endpoints are:

- Cumulative incidence of symptomatic (broad term), RT-PCR-confirmed SARS-CoV-2 infection cases during the follow-up period
- Cumulative incidence of RT-PCR-confirmed SARS-CoV-2 infection cases (regardless of symptoms) during the EAP
- Proportion of participants with ≥1 moderate COVID-19 symptom (broad term) during the EAP and follow-up period
- Duration of COVID-19 signs and symptoms in weeks (broad term) after diagnosis
- Proportion of participants with COVID-19-related hospitalization, emergency room visit, urgent care center visit or death during the EAP and follow-up period
- Proportion of participants with COVID-19-related hospitalization or death during the EAP and follow-up period
- Proportion of participants requiring supplemental oxygen due to COVID-19 during the EAP and follow-up period
- Proportion of participants admitted to an intensive care unit (ICU) due to COVID-19 during the EAP and follow-up period

- Proportion of participants requiring mechanical ventilation due to COVID-19 during the EAP and follow-up period
- Proportion of symptomatic (broad term) participants with viral load >4 $\log_{10}$ copies/mL in NP swab sample collected at the time of COVID-19 diagnosis
- Maximum SARS-CoV-2 RT-qPCR viral load ($\log_{10}$ copies/mL) in NP swab samples among individuals with ≥1 RT-qPCR positive test that has an onset during the EAP
- Number of weeks of viral load >4 $\log_{10}$copies/mL in NP swab samples among symptomatic (broad term) participants during the EAP
- Viral variant characteristics of SARS-CoV-2 in participants who become infected post-baseline

5. STUDY VARIABLES

A summary of study variables is provided below. A full accounting of variables will be provided in the statistical analysis plan (SAP).

5.1. Demographic and Baseline Characteristics

The variables for baseline characteristics include standard demography (eg, age, race, weight, height), medical history, vaccination history, and medication history.

5.2. Efficacy Variables

Efficacy variables include number of participants with symptomatic RT-qPCR-confirmed SARS-CoV-2 infection and viral load ($\log_{10}$ copies/mL).

5.3. Safety Variables

Safety variables include recordings or measurements for individual participants of targeted TEAEs, vital signs, and laboratory test results.

5.4. Pharmacokinetic Variables

The PK variables are concentrations of casirivimab and imdevimab in serum and time. The sampling time points are specified in Table 1.

5.5. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, and NAb status at nominal sampling time/visit. Serum samples for ADA will be collected at the visits specified in Table 1. Samples positive in the ADA assays will be further characterized for ADA titers and for the presence of NAb.

6. STUDY DESIGN

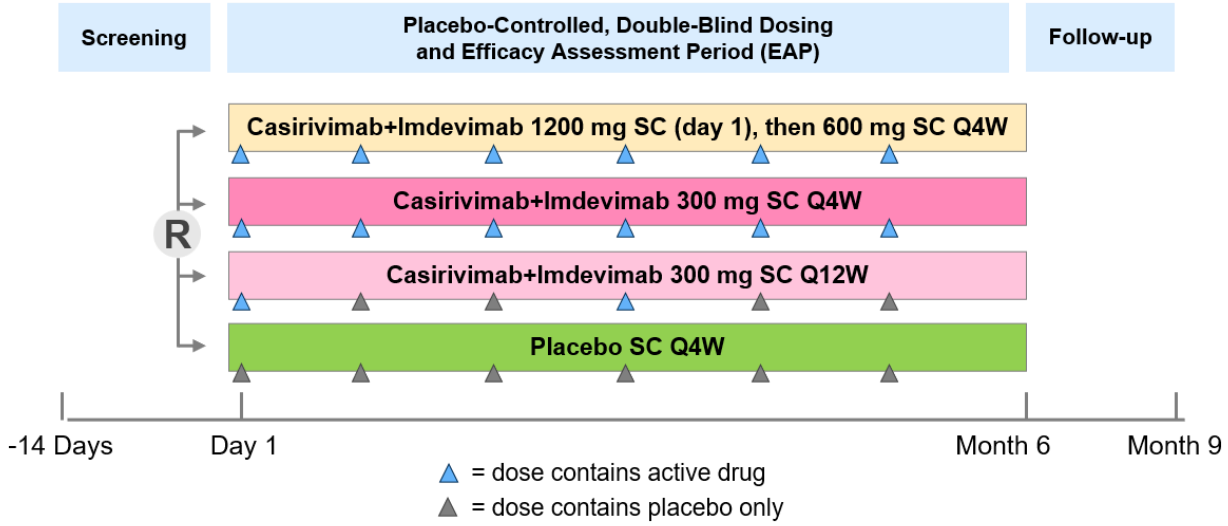
6.1. Study Description and Duration

This is a randomized, double-blind, placebo-controlled, phase 3 study to assess the safety and efficacy of casirivimab+imdevimab as pre-exposure prophylaxis against symptomatic COVID-19 in immunocompromised individuals, defined according to the primary and secondary immunodeficiencies outlined in the study eligibility criteria (Section 7.2).

The study consists of three periods: a screening period of up to 14 days, an efficacy assessment period (EAP) of approximately 6 months (precise definition provided in Section 11.4.3.1), and a 3-month follow-up period. A diagram depicting the study design is provided in Figure 1. The Schedule of Events is provided in Section 9.1.

In addition to the main study, an optional immunology sub-study will be conducted outside of the protocol.

Figure 1: Study Flow Diagram



Casirivimab+imdevimab will be co-administered sequentially. To maintain blinding, additional placebo injections will be administered such that all participants receive the same number of injections and the same dosing frequency.

6.2. Evaluation of Symptomatic SARS-CoV-2 Infection

The primary endpoint of the study will evaluate **symptomatic SARS-CoV-2 infection cases**. The conditions for symptomatic SARS-CoV-2 infection are as follows:

- At least 1 sign or symptom (broad term definition) confirmed by a study clinician (investigator or designee) to be related to COVID-19, **and**
- A positive SARS-CoV-2 RT-PCR result (local or central analysis), **with**

- The sign/symptom onset date and the date of collection for the positive sample occurring within ±7 days of one another

The primary endpoint will analyze symptomatic SARS-CoV-2 infection during the efficacy assessment period (EAP), whose definition is provided in Section 11.4.3.1.

Broad Term COVID-19 signs and symptoms include fever ≥38.0°C as well as 23 sign/symptoms designed to be consistent with the Symptom Evolution of COVID-19 (SE-C19) instrument developed by the Sponsor. Broad term signs and symptoms are listed in Table 3.

6.3. Study Periods

Screening/Baseline

After participants provide informed consent, they will be assessed for study eligibility. Refer to Section 7.2 for detailed eligibility criteria and testing requirements. Screening will include negative test result by RT-PCR. Prior to dosing, a baseline nasopharyngeal swab sample will be collected for retrospective, central laboratory confirmation of SARS-CoV-2 negativity by RT-qPCR.

Participants who are unable to complete screening requirements within the screening period are allowed to be rescreened once, after consultation with the Sponsor.

Treatment and Efficacy Assessment Period (EAP)

On day 1, participants will be randomized to repeated subcutaneously-administered study drug or placebo as described in Section 8.1 and Figure 1. The method of randomization and stratification are described in Section 8.5.

Study visits will occur every 4 weeks during the EAP. During these visits, dosing and collection of study information will occur, including an evaluation of any possible signs or symptoms of COVID-19. Signs and symptoms will be evaluated by a clinician (the investigator or designee) as described in Section 9.2.4.2, and will be used in the evaluation of the symptomatic SARS-COV-2 infection (ie, the primary endpoint).

Following the first dose, participants will be monitored for at least 15 minutes and then released from the study site, if medically appropriate. Dosing will continue for the duration of the EAP, with the last visit in the EAP occurring approximately one month after the final dose.

Blood samples will be collected during select EAP visits, for evaluation of drug concentration, immunogenicity, serum antibody concentration, or for exploratory research.

Follow-up Period

Participants will continue to have visits every 4 weeks during the follow-up period. These visits may occur in person, by phone, or by other means of communication as necessary. These visits will be used to collect safety information and follow up on any COVID-19 signs/symptoms as described in the Schedule of Events. The final study visit will occur (by phone) at 9 months.

6.4. Monitoring and Management of Suspected COVID-19

6.4.1. Monitoring for Suspected COVID-19

Participants will be monitored for suspected COVID-19 symptoms throughout the study. Participants (or their caregivers, when applicable) will be provided with contact information for the clinical study site and will be given written and verbal instructions to call site personnel as soon as possible if the experience any changes in their health status. This could include any symptoms or signs potentially related to COVID-19 or if they observe any new sense of feeling unwell.

6.4.2. Evaluation of Suspected COVID-19

Participants with suspected COVID-19 will undergo an evaluation of symptoms by a study clinician (investigator or designee) as soon as possible (**within 48 hours of symptom onset, if feasible)**. To ensure prompt evaluation, an unscheduled visit is highly preferred, unless a scheduled study visit is the soonest visit available.

Signs and symptoms will be evaluated by a clinician (investigator or designee) as described in Section 9.2.4.2, and will be used for the analysis of symptomatic SARS-CoV-2 infection. If the clinician confirms that at least one sign or symptom is related to COVID-19, samples will be collected to perform both **local** and **central** testing for SARS-CoV-2 infection.

Local testing must be performed by RT-PCR using local sample collection and assay standards. A nasopharyngeal (NP) swab sample is the preferred sample type, but other samples (eg, nasal, oropharyngeal, saliva) adhering to local standards are acceptable. An additional NP swab sample will be collected for the purposes of central RT-qPCR testing.

The samples will be collected prior to any administration of post-infection treatment (described below). The qualitative result of the central RT-qPCR will be reported back to the corresponding study site.

6.4.3. Laboratory-Confirmed SARS-CoV-2 Infection Obtained Outside of the Study

If a site receives notification from a participant that a positive test result for SARS-CoV-2 infection was obtained outside of the study, the test result will be obtained and documented, and the participant will have an unscheduled study visit as soon as feasible. If the outside documented positive test utilized any assay type other than RT-PCR, the participant will have samples collected to perform local RT-PCR and central RT-qPCR testing for SARS-CoV-2 infection. If the outside test utilized RT-PCR, the participant will only require sample collection for central RT-qPCR testing. In all cases, participants will undergo an evaluation of COVID-19 signs and symptoms by the investigator or designee during the unscheduled visit.

Test results outside of the study will qualify as laboratory-confirmed SARS-CoV-2 infection for the purposes of study analyses, but only if an RT-PCR assay was utilized.

6.4.4. Post-Infection Treatment for Participants with Confirmed Positive SARS-CoV-2 RT-PCR

Participants with a confirmed positive SARS-CoV-2 RT-PCR at any time during the study (local, central, or documented outside of the study) should be treated with standard of care per local practices and per the investigator's judgment. In addition, casirivimab+imdevimab may be offered to the participant as post-infection treatment if medically appropriate in the investigator's judgment.

If post-infection treatment with casirivimab+imdevimab is deemed medically appropriate, the treatment should be provided through the most expeditious mechanism available. To this end, casirivimab+imdevimab may be given through mechanisms outside of the study in regions where it is approved or authorized. Where regionally approved or authorized, casirivimab+imdevimab should be administered at the approved or authorized dose.

For participants who are able to receive post-infection care at a study site, casirivimab+imdevimab may also be offered to the participant as part of the study. This mechanism can be used, for example, if casirivimab+imdevimab is not regionally approved or authorized for treatment of SARS-CoV-2 infection, or if treatment cannot be made available in an expeditious manner via the approved or authorized mechanisms.

The following investigational dose levels will be offered as part of the study, and may be provided if medically indicated in the investigator's judgement:

- Not hospitalized due to COVID-19 and does not require supplemental oxygen or an increase in baseline oxygen flow rate due to COVID-19: **1200 mg** (600 mg per mAb), administered either intravenously or subcutaneously
- Hospitalized due to COVID-19 and does not require supplemental oxygen due to COVID-19, or requires low-flow supplemental oxygen due to COVID-19: **2400 mg** (1200 mg per mAb), administered intravenously
- Hospitalized due to COVID-19 and requires either high-intensity supplemental oxygen due to COVID-19 or requires mechanical ventilation due to COVID-19: **8000 mg** (4000 mg per mAb), administered intravenously

If feasible, treatment with casirivimab+imdevimab should be provided within 48 hours after a positive RT-PCR result is obtained.

Administration of post-infection treatment with casirivimab+imdevimab will not require unblinding of the participant's randomization assignment (Section 8.7).

6.4.5. Schedule of Events for Participants with Positive SARS-CoV-2 RT-PCR

Participants with a positive SARS-CoV-2 RT-PCR (from either local or central testing) will discontinue the study drug assigned at randomization and enter the follow-up period. This includes any participant for whom post-infection treatment with casirivimab+imdevimab was offered but was declined by the participant or investigator, or otherwise not received.

All participants with a positive SARS-CoV-2 RT-PCR will have **additional** assessments and sample collections, as noted in the Schedule of Events and summarized below):

- NP swab samples will be collected during unscheduled visits every 7 days (±1 day) for central laboratory RT-qPCR analysis until 2 consecutive negative test results are obtained. During these visits, COVID-19 signs and symptoms will also be evaluated by the investigator or designee.
- Information regarding COVID-19-related medically-attended visits (MAVs; defined in Section 9.2.4.3) will be recorded, and participants will be asked to notify study personnel as soon as possible about such occurrences.

6.4.6. Schedule of Events for Participants with Negative SARS-CoV-2 RT-PCR

Participants with a negative SARS-CoV-2 RT-PCR will continue to follow the Schedule of Events, and will continue to receive the treatment assigned to them at randomization.

6.4.7. Management of Participants with Positive SARS-CoV-2 Infection at Baseline

Participants who are negative for SARS-CoV-2 by local RT-PCR at screening but have a positive baseline (day 1) result for SARS-CoV-2 from the central laboratory RT-qPCR will be discontinued from the treatment assigned to them at randomization. These individuals will be eligible for post-infection treatment with casirivimab+imdevimab as defined in Section 6.4.4. However, these participants will not be considered as having received post-infection treatment for the purposes of study analyses.

Individuals who are positive at baseline will not undergo any protocol-defined assessments related to COVID-19 symptom evaluation or SARS-CoV-2 testing, but will directly enter the follow-up period and continue to be followed for safety according to the Schedule of Events.

6.5. Study Stopping Rules

An independent data monitoring committee (IDMC) will actively monitor interim data to review the ongoing safety of participants and may recommend to halt the study or implement changes in the study conduct as deemed necessary. Refer to Section 6.8.1 additional information regarding the IDMC.

6.6. End of Study Definition

The end of study is defined as the date the last participant completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the participant can no longer be contacted by the study site).

6.7. Planned Interim Analysis

Refer to Section 11.5.

6.8. Study Committees

6.8.1. Independent Data Monitoring Committee

An IDMC will actively review data throughout the study to monitor participant safety and efficacy data. The IDMC can make recommendations about early study closure or changes to the study conduct. The IDMC will also perform planned interim analyses (Section 11.5), and make recommendations based on these analyses. The operation of the IDMC is governed by a charter describing further details, such as procedures (including but not limited to periodic safety monitoring) and requirements for reporting its observations to the Sponsor. The IDMC will conduct periodic data reviews as detailed in the IDMC charter. These data reviews will include all available safety data, including deaths, from all enrolled study participants up to the data cutoff date for the analysis.

6.8.2. Safety Monitoring Team

A safety monitoring team at Regeneron may meet periodically to review blinded safety data as needed. The team may be comprised of the medical directors, a Global Patient Safety representative, a Clinical Pharmacology representative and representatives from Biostatistics and Data Management, as well as representatives from Clinical Operations and Regulatory Affairs. The data to be reviewed include, but are not limited to:

- Serious adverse events (SAEs)
- Grade ≥3 injection-site reactions or grade ≥3 hypersensitivity reactions
- Treatment-emergent adverse events that result in an early study withdrawal
- Selected laboratory tests, as deemed appropriate by the safety monitoring team

VV-RIM-00181183-1.0 Approved - 25 Jan 2022 GMT-5:00

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PARTICIPANTS

7.1. Number of Participants Planned

Approximately 8,752 participants will be enrolled in the study. Additional information on sample size can be found in Section 11.2.

7.2. Study Population

Participants enrolled in this study must have an immunocompromised condition, documented evidence of non-response to COVID-19 vaccination, a negative SARS-CoV-2 RT-PCR test result, and must have completed a full standard-of-care course (defined regionally) of COVID-19 vaccination with documented evidence of non-response, unless medically ineligible or contraindicated.

7.2.1. Inclusion Criteria

A participant must meet the following criteria to be eligible for inclusion in the study:

1. Is ≥12 years of age at randomization

   Note: participants <18 years of age will only be enrolled where permitted by local requirements.

2. Meets ≥1 of the following criteria:

   a. Solid organ transplant (SOT) or hematopoietic stem cell transplant (HSCT) recipients receiving immunosuppressive medication
   b. Active hematologic malignancies
   c. Solid organ malignancies receiving active treatment with T cell or B cell immunosuppressive therapy
   d. Primary immunodeficiency (such as hypogammaglobulinemia, common variable immune deficiency, severe combined immunodeficiency)
   e. HIV and CD4 <200 cells/microliter
   f. Patients with rheumatologic disease, autoimmune disease, or multiple sclerosis receiving immunosuppressive therapy that modulates Th1, Th17, anti-TNF such as infliximab, adalimumab, etanercept, or B cell responses
   g. Currently receiving any of the following immunosuppressant drugs:

      – T cell suppressing agents (eg, ≥5 mg prednisone equivalent/day during >3 weeks
      – Proteasome inhibitors (such as bortezomib, lenalidomide), alemtuzumab, anti-thymocyte globulin, CAR-T therapy, calcineurin inhibitors)
      – Alkylating agents and anthracyclines
      – Antimetabolites and purine analogues, such as mycophenolate, fludarabine, or cladribine
      – B cell targeted therapies, such as rituximab, ocrelizumab, CD19/CD20, and BTK inhibitors
      – mTOR inhibitors

- JAK/STAT pathway inhibitors

3. Has received a full course of standard-of-care COVID-19 vaccination per regional guidance, **or** is deemed medically ineligible or contraindicated to receiving a full course of standard-of-care COVID-19 vaccine
4. Has a documented negative (based on test reference values) serology/antibody response in an anti-SARS-CoV-2 spike (S) protein IgG clinical test (including, but not limited to, RBD-specific tests), **or** ≤50 U/mL on the Elecsys® SARS-CoV-2 S Total Ig test. The test should be performed on a sample collected at least 2 weeks after the final dose of a COVID-19 vaccine and within 3 months prior to randomization

   Note: Lateral flow immunoassay (LFIA) results will not be accepted. Test should be considered acceptable for clinical use by local standards (approved or with EUA issued by the US FDA or by equivalent local health authority).
5. Has SARS-CoV-2-negative RT-PCR from a sample collected ≤72 hours prior to randomization, using local assay and sample collection and assay standards

   Note: Historical record of negative result is acceptable, as long as the sample was collected ≤72 hours prior to randomization. Nasopharyngeal swab sample is highly preferred but other sample types (such as nasal, oropharyngeal [OP], or saliva) adhering to local standards are acceptable.
6. Is willing and able to:
   a. Provide informed consent signed by study participant or legally acceptable representative
   b. Comply with clinic visits and study-related procedures, including providing samples for viral load testing
7. Is judged by the investigator to be in stable health based on medical history, physical examination, vital sign measurements, and laboratory measurements performed at screening and/or other times prior to administration of study drug

7.2.2. Exclusion Criteria

A participant who meets any of the following criteria will be excluded from the study:

1. Has a life expectancy of less than 2 years
2. Weighs <40 kg (only applies to participants ≥12 to <18 years of age)
3. Has any signs or symptoms consistent with COVID-19 (as determined by the investigator)
4. Has a history of SARS-CoV-2 infection within 90 days prior to randomization
5. Planned use of any investigational, authorized, or approved vaccine for COVID-19 within 90 days (or per current CDC recommendations) of the last dose of study drug (CDC, 2021)
6. Prior, current, or planned use of any of the following treatments: COVID-19 convalescent plasma, other monoclonal antibodies against SARS-CoV-2 (eg, bamlanivimab and

etesevimab, sotrovimab), or any COVID-19 treatment (authorized, approved, or investigational)

Note: Prior use is defined as the past 30 days or within 5 half-lives of the investigational product (whichever is longer) from screening.

7. Is planned to begin intravenous immunoglobulin (IVIG) or subcutaneous immunoglobulin (SCIG) therapy, is planned to have a change to existing IVIG or SCIG regimen, or has been on a chronic stable dose of their IVIG or SCIG regimen for less than 90 days prior to screening.
8. Has any known active acute respiratory infection
9. Has no documented laboratory blood chemistry and hematology (including differential) results in the 6 months prior to randomization
10. Has persistent (refractory to treatment for ≥14 days) bacterial or fungal infection
11. Has known allergy or hypersensitivity to components of the study drugs
12. Has been discharged, or is planned to be discharged, to a quarantine center
13. Is a member of the clinical site study team or their immediate family member

7.3. Premature Withdrawal from the Study

A participant has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and/or Sponsor have the right to withdraw a participant from the study if it is no longer in the interest of the participant to continue in the study, or if the participant's continuation in the study places the scientific outcome of the study at risk (eg, if a participant does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of participants should be avoided.

Participants who are withdrawn prematurely from the study will be asked to complete the early termination visit, as described in Section 9.1.1.

Rules for permanent discontinuation of study treatment are discussed in Section 8.3.2.

7.4. Replacement of Participants

Participants will not be replaced.

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

Eligible participants will be randomized in a 1:1:1:1 allocation ratio to:

- Co-administered casirivimab+imdevimab combination therapy, 1200 mg (600 mg per mAb) on day 1, then 600 mg (300 mg per mAb) SC Q4W
- Co-administered casirivimab+imdevimab combination therapy, 300 mg (150 mg per mAb) SC Q4W
- Co-administered casirivimab+imdevimab combination therapy, 300 mg (150 mg per mAb) SC Q12W
- Placebo SC Q4W

In order to maintain blinding, additional placebo injections will be administered such that all participants receive the same number of injections and the same dosing frequency (Q4W).

For study drug administration which requires multiple SC injections, it is recommended to use different quadrants of the abdomen (avoiding navel and waist areas), front and upper outer sides of the thighs, or the back side of the upper outer area of the arm. During the dose administration, each injection must be given in a different anatomical location (eg, 1 injection administered in the right lower quadrant of the abdomen, another in the left lower quadrant of the abdomen, etc). Numbing cream at the sites of injection should not be used as this will interfere with the safety assessment, ie, evaluation of injection site reactions.

Instructions on dose preparation are provided in the pharmacy manual.

8.2. Background Treatment(s)

Participants may self-administer non-prescribed medications and continue other concomitant medications with the exception of those prohibited in Section 8.9.1. Participants will continue current treatments for their baseline conditions.

8.3. Dose Modification and Study Treatment Discontinuation Rules

8.3.1. Dose Modification

Dose modification for an individual participant is not allowed.

8.3.2. Study Drug Discontinuation

Participants who permanently discontinue from study drug should be encouraged to remain in the study. Participants who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 9.1.1.

8.3.2.1. Reasons for Permanent Discontinuation of Study Drug

Study drug dosing will be permanently stopped in the event of:

- Grade ≥3 injection-site reaction or grade ≥3 hypersensitivity reaction determined to be related to study drug

- Serious adverse event or other potentially life-threatening (grade 4) event that is determined to be related to study drug
- Investigator's clinical judgment, in coordination with principal investigator, that it is in the best interest of the participant
- Receipt of a COVID-19 vaccine during the study
- A positive baseline (day 1) result for SARS-CoV-2 from central laboratory RT-qPCR (however, eligible for additional treatment as defined in Section 6.4.7)
- Receipt of post-infection treatment with casirivimab+imdevimab (Section 6.4.4)
- Participant withdrawal of consent
- Unblinding of participant

8.4. Management of Acute Reactions

8.4.1. Acute Injection Reactions

8.4.1.1. Hypersensitivity Reaction (Systemic)

Emergency equipment and medication for the treatment of systemic reactions must be available for immediate use. Hypersensitivities must be reported as AESIs if they meet the severity criteria defined in Section 10.1.3. The corresponding NCI-CTCAE severity scale is provided in Section 10.2.4.

Acute systemic reactions following SC injection of study drug should be treated using clinical judgment to determine the appropriate response according to typical clinical practice.

8.4.1.2. Local Injection Site Reactions

Local injection site reactions must be reported as AESIs if they meet the severity criteria defined in Section 10.1.3. The corresponding NCI-CTCAE severity scale is provided in Section 10.2.4.

8.5. Method of Treatment Assignment

Participants will be randomized according to a central randomization scheme using an interactive web response system (IWRS).

Randomization will be stratified according to age categories (<18 years, ≥18 to ≤65 years, >65 years), region (US, rest of world), and use of stable IVIG or SCIG regimen prior to screening (yes, no)

8.6. Blinding

An unblinded pharmacist or qualified personnel at the site, not otherwise associated with the conduct of the study, will reconstitute the drug for administration. The drug solution must be provided in identical form for active and placebo treatments, so that they remain indistinguishable to both study personnel and participants.

Study participants, the principal investigators, and study site personnel (with the exception of the unblinded pharmacist at each site) will remain blinded to all randomization assignments throughout the study. The Regeneron medical/study director, study monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site will remain blinded to all participant randomization assignments.

Selected individuals from the Sponsor not involved in the conduct of the study may have access to unblinded data as needed for safety review or other data review. Any team performing interim data reviews will be separated from the ongoing study team. No study personnel involved in the day-to-day conduct of the study will have access to any unblinded data before the database is locked for this study.

Drug concentration, serology and other blood-based biomarker results will not be communicated to the sites, and the Sponsor's blinded operational team will not have access to results associated with participant identification until after the database is locked.

8.7. Emergency Unblinding

Unblinding of treatment assignment for a participant may be necessary due to a medical emergency, or any other significant medical event, when a treatment decision for that medical emergency/significant event is contingent upon knowing the participant's treatment assignment. Any participant who becomes RT-PCR positive during the study is eligible to receive post-infection treatment with casirivimab+imdevimab without unblinding.

If unblinding is required:

- The investigator will make the decision to unblind the treatment assignment, following consultation with the Sponsor or the global Principal Investigator
- Only the affected participant will be unblinded
- Unblinding is performed using the IWRS, which will notify the Sponsor. The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If the study pharmacist(s)/designee is not available, the investigator for the site will unblind the participant
- If the IWRS is unavailable, the investigator will ask the unblinded study pharmacist(s)/designee to perform manual unblinding. All manual unblinding procedure will be adequately documented, including the reason why the IWRS was not used
- The investigator will notify the Sponsor and/or designee as soon as possible after unblinding the participant

Treatment assignment is not to be provided to site personnel, other than the unblinded study pharmacist (when applicable), at any time during the conduct of the study, except in the case of a true emergency and when a treatment decision is contingent on knowing the participant's treatment assignment. In the event that there is no study pharmacist, the individual at the site fulfilling that role will be the only unblinded member of the site personnel.

8.8. Treatment Logistics and Accountability

8.8.1. Packaging, Labeling, and Storage

A medication numbering system will be used to label unblinded investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging. In order to maintain the blind, these lists will not be accessible to individuals involved in study conduct.

The unblinded pharmacist will prepare the unblinded investigational product and dispense it in a blinded manner to the blinded study staff for administration to the participant.

Study drug will be stored at the site at a temperature of 2ºC to 8ºC. Storage instructions will be provided in the pharmacy manual.

8.8.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed at the site with approval by the Sponsor or returned to the Sponsor or designee.

8.8.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication:

- Dispensed to each participant
- Returned from each participant (if applicable), and
- Disposed of at the site or returned to the Sponsor or designee.

All accountability records must be made available for inspection by the Sponsor and regulatory agency inspectors; photocopies must be provided to the Sponsor at the conclusion of the study.

8.8.4. Treatment Compliance

All drug compliance records must be kept current and made available for inspection by the Sponsor and regulatory agency inspectors.

8.9. Concomitant Medications and Procedures

Any treatment or procedure administered from the time of the first dose of study drug to the final study visit will be recorded as concomitant medication or concomitant procedure. This includes medications or procedures that were started before the study and are ongoing during the study.

8.9.1. Prohibited Medications

The following concomitant medications are prohibited and may result in permanent discontinuation of study drug:

- Investigational, authorized, or approved COVID-19 vaccines within 90 days of the last dose of study drug (or per current CDC recommendations) (CDC, 2021)
- Investigational or approved passive antibodies for SARS-CoV-2 infection (eg, convalescent plasma or sera, monoclonal antibodies, hyperimmune globulin), remdesivir, or other anti-SARS-CoV-2 agents when used as prophylaxis

8.9.2. Permitted Medications

Other than the prohibited medications listed in Section 8.9.1, concomitant medications are permitted during the study. If there is any question regarding whether a concomitant medication may be used during the study, the study site should contact the Sponsor medical monitor.

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized, and deviations from planned study procedures are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

Study assessments and procedures are presented by study period and visit in Table 1.

Table 1: Schedule of Events (No Longer Applicable as of Protocol Amendment 2)

Study Day	*Screening/Baseline*[1]				*Efficacy Assessment Period*[2]							*Follow-Up Period*[2]			Confirmatory Visit, Suspected COVID-19[3]	Post-Infection Treatment Visit, Lab-Confirmed Infection[3]	ET
	-14 to 1	1			8[2]	29	57	85	113	141	169	197 (FU 1)	225 (FU 2)	253 (EOS)			
	Screen	Pre-Dose	Dose	Post-Dose													
Window (Day)					±3	±7	±7	±7	±7	±7	±7	±14	±14	±14			
Screening/Baseline																	
Informed consent	X																
Inclusion/exclusion	X																
Medical history	X																
Demographics	X																
Weight and height	X																
Locally-acceptable sample for SARS-CoV-2 RT-PCR (local)[4]	X																
NP swab sample for SARS-CoV-2 RT-qPCR (central)[4]		X															
Randomization		X															
Treatment																	
Study drug administration[5]			X			X	X	X	X	X							
Safety																	
Vital signs[6]		X		X		X	X	X	X	X	X						
Treatment-emergent grade ≥3 AEs[7]				X	X	X	X	X	X	X	X	X	X	X			X
Treatment-emergent AEs leading to study drug discontinuation[7]				X	X	X	X	X	X	X	X	X	X	X			X
Treatment-emergent SAEs[7]				X	X	X	X	X	X	X	X	X	X	X			X
Treatment-emergent grade ≥2 hypersensitivity reactions[7]				X	X	X	X	X	X	X							X
Treatment-emergent grade ≥3 ISRs[7]				X	X	X	X	X	X	X							X
Concomitant medications and procedures	X				X	X	X	X	X	X	X	X	X	X			X
Pregnancy test, blood or urine (WOCBP only)	X					X		X		X							
Pregnancy status											X			X			X
Vital status					X						X	X	X	X			X
Safety information (newborns of study participants)														X			X
Efficacy																	
Clinician assessment of COVID-19 signs and symptoms			X			X	X	X	X	X	X	X	X	X			X[9]
Central Laboratory Pharmacodynamic/Biomarker Testing																	
Serum for central anti-SARS-CoV-2 serological assays		X[8]															
Serum for exploratory research		X[8]								X							
Plasma for exploratory research		X[8]								X							

Study Day		*Screening/Baseline*[1]				*Efficacy Assessment Period*[2]							*Follow-Up Period*[2]			Confirmatory Visit, Suspected COVID-19[3]	Post-Infection Treatment Visit, Lab-Confirmed Infection[3]	ET
		-14 to 1	1			8[2]	29	57	85	113	141	169	197 (FU 1)	225 (FU 2)	253 (EOS)			
		Screen	Pre-Dose	Dose	Post-Dose													
Window (Day)						±3	±7	±7	±7	±7	±7	±7	±14	±14	±14			
Pharmacokinetics and Immunogenicity Sampling (first 600 enrollees at participating sites)[10]																		
Serum for drug concentration (PK)[10,11]			X[8]			X	X		X			X		X				
Serum for immunogenicity (ADA)[10,12]			X[8]				X					X						
Participants with suspected COVID-19 only[13]																		
Clinician assessment of COVID-19 signs/symptoms																X		
Comprehensive vital sign assessment																X	X[6]	
Treatment-emergent grade ≥3 AEs																X	X	
Treatment-emergent SAEs[7]																X	X	
Concomitant medications and procedures																X	X	
If confirmed symptomatic[13]	Locally-acceptable sample for SARS-CoV-2 RT-PCR (local)															X		
	NP swab for SARS-CoV-2 RT-qPCR (central)															X		
If SARS-CoV-2 RT-PCR is positive[13]	Post-infection treatment																X	
	Clinician assessment of COVID-19 signs/symptoms					Every 7 (±1) days until 2 consecutive negative RT-qPCR results[13]												
	NP swab for SARS-CoV-2 RT-qPCR (central)															X		
	COVID-19-related MAV details					X	X	X	X	X	X	X	X	X	X			

ADA, anti-drug antibodies; AE; adverse event; EOS, end of study; FU, follow up; ISR, injection-site reactions; MAV, medically-attended visit; NP, nasopharyngeal; PK, pharmacokinetics; SAE, serious adverse event; RT-PCR, reverse transcription polymerase chain reaction; RT-qPCR, quantitative reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WOCBP, women of childbearing potential.

Table 2: Schedule of Events for Study Close-Out (Protocol Amendment 2; Applies to All Enrolled Participants)

Study Visit		**Dose Visit**	**Optional Confirmatory Visit(s), Suspected COVID-19**	**End-of-Study Follow-Up Visit (Telephone)**
Timing of Visit		**28 Days After the Most Recent Dose**	**Within 48 Hours of Symptom Onset, if Feasible**	**85 Days After the Most Recent Dose[1]**
Window (Days)		**±7**	**-**	**±14**
Informed consent		X[2]		
Optional study drug administration[3]		X		
Vital signs[4]		X		
Treatment-emergent AEs considered by the investigator to be unrelated to baseline conditions and unrelated to treatments for baseline conditions[5]		X		X
Treatment-emergent AEs leading to study drug discontinuation[5]		X		X
Treatment-emergent SAEs[5]		X		X
Treatment-emergent grade ≥2 hypersensitivity reactions[5]		X		
Treatment-emergent grade ≥3 injection site reactions (ISRs)[5]		X		
Concomitant medications and procedures		X		X
Pregnancy status				X
Vital status				X
Safety information (newborns of study participants)				X
Participants with suspected COVID-19 only (optional)[6]				
Clinician assessment of COVID-19 signs/symptoms[7]			X[6]	
Comprehensive vital sign assessment[8]			X[6]	
Treatment-emergent AEs considered by the investigator to be unrelated to baseline conditions and unrelated to treatments for baseline conditions[5]			X[6]	
Treatment-emergent SAEs[5]			X[6]	
Concomitant medications and procedures			X[6]	
If confirmed symptomatic:	Locally-acceptable sample for SARS-CoV-2 RT-PCR (local)[9]		X[6]	
	NP swab for SARS-CoV-2 RT-qPCR (central)[9]		X[6]	
If SARS-CoV-2 RT-PCR is positive:	Clinician assessment of COVID-19 signs/symptoms		Every 7 (±1) days until 2 consecutive negative RT-qPCR results[6]	
	NP swab for SARS-CoV-2 RT-qPCR (central)			
	COVID-19-related MAV details			

9.1.1. Footnotes for the Schedule of Events (Original Protocol)

1. The screening visit may occur up to 14 days prior to the baseline visit (day 1). For participants at sites with rapid RT-PCR testing, screening and baseline visits may occur on the same day.

   Participants who are unable to complete screening requirements within the screening period are allowed to be rescreened once, after consultation with the Sponsor.

2. During all EAP and follow-up visits, the site will remind participants to call the site as soon as possible if they experience any changes in their health, including any symptoms possibly related to COVID-19, and ensure that participants have the correct contact information to notify the site.

   On visit days when sample collection or dosing is not required, the information indicated in the schedule may be collected remotely without an in-person visit.

   For participants who do not require blood samples collected for drug concentration (PK), the day 8 visit may be performed remotely.

3. Participants will be offered post-infection treatment with casirivimab+imdevimab if the criteria provided in Section 6.4.4 are met. The post-infection treatment to be offered is also defined in Section 6.4.4. The confirmatory visit and post-infection treatment visit may occur on the same day. The confirmatory visit may also occur on the same day as a scheduled study visit. If visits occur on the same day, assessments for both visits must be collected (but not duplicated).

4. Collection for screening test must fulfill the window specified in the eligibility criteria (Section 7.2.1). If collection is performed outside of this window, testing must be repeated prior to randomization. Refer Section 9.2.1.4 for requirements related to screening test and baseline tests for SARS-CoV-2 infection. Participants who were negative according local testing but positive by central testing will discontinue study drug and enter the follow-up period. Refer to Section 6.4.7 for more information.

5. Dosing will be administered after all assessments and sample collections are completed.

6. Vital signs (defined in Section 9.2.5.1) will be collected before study drug administration. On day 1, participants will be observed for at least 15 minutes after completion of study drug administration.

7. Refer to Section 10.1 for AE monitoring and reporting guidelines.

8. The indicated blood samples may be collected at either day -1 or day 1 but must be collected prior to drug administration.

   Samples for serological assays will be used for retrospective analysis (Section 9.2.8.1) and the results will not be reported to study sites.

9. During any early termination visit, COVID-19 signs and symptoms will be assessed only for participants who were RT-PCR positive and entered follow-up without completing all study visits during the EAP.

10. Samples for drug concentration (PK) and immunogenicity (ADA) will only be collected in the first 600 participants who are enrolled at participating sites.
11. Actual dosing time and drug concentration sample (PK) collection times will be recorded. For PK sample collection on dosing days, samples must be collected prior to dosing.
12. The window for pre-dose immunogenicity (ADA) sample collection should be as close to administration of study drug as is reasonable. Actual dosing time and ADA sample collection times will be recorded.
13. The assessments and procedures in this section only apply to participants with suspected COVID-19, confirmed COVID-19 symptoms, or laboratory confirmed SARS-CoV-2 infection, as indicated. Note the following:
    - The collections and assessments indicated in this section will be performed **in addition** to collections and assessments indicated in the scheduled visits.
    - Refer to Section 6.4 for monitoring, evaluation, and additional procedures for participants with suspected COVID-19 or laboratory-confirmed SARS-CoV-2 infection.
    - Comprehensive vital sign assessment includes standard vital sign assessment (defined in Section 9.2.5.1), SpO_2, and respiratory rate.
    - NP swabs for central lab RT-qPCR testing are collected once every 7 days (±1 day) until 2 consecutive tests are negative.
    - Clinician assessment of COVID-19 signs and symptoms is performed every 7 days (±1 day) until 2 consecutive RT-qPCR tests are negative. Signs and symptoms will continue to be evaluated during the scheduled visits of the follow-up period.

9.1.2. Footnotes for the Schedule of Events (Protocol Amendment 2)

1. Approximately 85 days after the final dose of study drug (ie, the optional final dose of casirivimab+imdevimab defined in protocol amendment 2, or the final assigned casirivimab+imdevimab or placebo dose for participants who do not receive the optional dose).
2. Informed consent may be obtained at the dosing visit, or at any time prior to the visit via remote consent (if available and allowable at the study site).
3. Applicable to participants who consent to receive a final optional dose of 1200 mg SC casirivimab+imdevimab. The optional dose may be administered to all participants regardless of treatment assignment at randomization. However, participants will not be eligible to receive this dose if they have already received casirivimab+imdevimab as post-infection treatment. The dose will be recorded.
4. Vital signs (defined in Section 9.2.5.1) will be collected before study drug administration and at least 60 minutes after completion of study drug administration.
5. Refer to Section 10.1 for AE monitoring and reporting guidelines.

6. Note that all assessments and procedures related to participants with suspected COVID-19 are optional for both the study site and the study participant. Refer to Protocol Amendment 2 Procedures for additional information.
7. Clinician assessment of sign or symptoms may occur remotely. If remote assessment is performed, a confirmatory site visit for laboratory testing of SARS-CoV-2 can optionally occur after a clinician deems that the signs or symptoms are related to COVID-19.
8. Comprehensive vital sign assessment includes standard vital sign assessment (defined in Section 9.2.5.1), SpO_2, and respiratory rate.
9. Note that samples for local and central laboratory testing of SARS-CoV-2 may be collected on the same day; the results of local testing are not required prior to sample collection for central testing.

9.1.3. Early Termination Visit

Participants who withdraw from the study will be asked to have an early termination (ET) visit consisting of the assessments indicated in the Schedule of Events.

9.1.4. Unscheduled Visits

All attempts should be made to keep participants on the study schedule. Unscheduled visits may be required for participants with suspected COVID-19; refer to Section 6.4 for additional information.

Unscheduled visits may also be necessary to repeat testing following abnormal laboratory results, for collection of NP swabs, blood, serum, or plasma, for follow-up of treatment-emergent SAEs, treatment-emergent AESIs, or for any other reason, as warranted.

9.2. Study Procedures

This section describes the procedures and collections that will be performed in this study. Procedures and collections will occur according to the Schedule of Events.

9.2.1. Procedures Performed at Screening

The following procedures will be performed for the purpose of determining study eligibility or characterizing the baseline population: informed consent, medical history, demographics (including age, sex, race), weight, height, screening assessment for SARS-CoV-2 infection.

9.2.1.1. Informed Consent

Informed consent (and assent, as applicable) must be obtained according to the requirements described in Section 13.2.

9.2.1.2. Medical History

Medical history will include, but not be limited to the following:

- Prior COVID-19 infection
- COVID-19 vaccination record

- Menopausal history
- Pregnancy or breastfeeding status, if applicable

9.2.1.3. Weight and Height

Body weight will be assessed using calibrated scales. During weight assessment, participants should not wear shoes. Body weight will be recorded to the nearest 0.1 kg.

Height will also be recorded.

9.2.1.4. Screening and Baseline Assessments for SARS-CoV-2 Infection

During the screening period, the investigator or designee will verify that the participant has tested negative for SARS-CoV-2 within the time period specified in Section 7.2.1. The screening assessment for SARS-CoV-2 infection will be performed locally using an approved or authorized diagnostic RT-PCR assay, performed according to the study site's standards and procedures.

For local screening test, a nasopharyngeal (NP) swab sample is the preferred sample type, but other samples (eg, nasal, oropharyngeal, saliva) are acceptable if they are collected according to local standards. For tests performed at screening, the local testing result, specimen type, assay type, and date of the test will be recorded in the eCRF.

Baseline SARS-CoV-2 RT-qPCR testing will be performed by a central laboratory NP swab test on day 1. The qualitative results of this baseline central SARS-CoV-2 RT-qPCR will be reported back to the corresponding study site but will not be required prior to study drug administration on day 1.

9.2.2. Randomization

Refer to Section 8.5.

9.2.3. Study Drug Administration

Refer to Section 8.1.

9.2.4. Efficacy Procedures

9.2.4.1. Post-Baseline Assessments for SARS-CoV-2 Infection

Refer to Section 6.4 for additional information regarding post-baseline testing for SARS-CoV-2 infection.

9.2.4.2. Clinician Assessment of COVID-19 Signs and Symptoms

COVID-19 signs and symptoms will be evaluated by a study clinician (investigator or designee) during each study visit as indicated in the Schedule of Events. Participants with suspected COVID-19 will also undergo an evaluation of symptoms as soon as possible (within 48 hours of symptom onset, if feasible), and those with a positive SARS-CoV-2 RT-PCR will undergo weekly assessment of signs and symptoms (refer to Section 6.4 and the Schedule of Events for additional information).

Clinical Evaluation. The clinician (investigator or designee) will evaluate the participant for signs of COVID-19 and query participants and/or their parent(s) or guardian(s) for any symptoms of COVID-19.

Information regarding symptoms should be obtained in an unsolicited fashion, allowing the participant and/or participant's parent(s) or guardian(s) to spontaneously report events. Solicitation of specific symptoms should be avoided.

Source Documentation. For each symptom, the start (onset) date, end date, and severity will be recorded (mild, moderate, severe) in the participant's medical record (source document). It is important to record this information in the source document, to ensure that the temporal dimensions of each sign or symptom are captured.

Event of Interest. A sign or symptom recorded in the source document will subsequently be recorded as an event of interest (EI) if it meets all of the following conditions:

- The participant has laboratory-confirmed SARS-COV-2 infection (refer to Section 6.4 for details)
- The sign or symptom falls within the broad term definition (Table 3)
- The sign/symptom onset date and the date of collection for the positive sample occurring within ±7 days of one another

For each EI, and during each visit for which signs and symptoms are evaluated, the following minimum information will be recorded:

- The sign or symptom, with start (onset) calendar date, end calendar date, and severity (mild, moderate, severe)
- Confirmatory local RT-PCR test result and date of sample collection
- Confirmatory central RT-qPCR test result and date of sample collection
- Weekly central RT-qPCR test results and dates of sample collection
- Record of any post-infection treatment with casirivimab+imdevimab administered

Note that any sign or symptom corresponding to a grade ≥3 TEAE will also be recorded and used for safety evaluation as described in Section 10.1.

Table 3: Broad Term Definition of COVID-19 Signs and Symptoms

• Body aches such as muscle pain or joint pain	• Chest pain	• Chills
• Confusion	• Cough	• Diarrhea
• Dizziness	• Fatigue	• Feverish
• Fever ≥38.0°C	• Headache	• Loss of appetite
• Loss of taste / smell	• Nausea	• Pressure / tight chest
• Rash	• Red or watery eyes	• Runny nose
• Shortness of breath / difficulty breathing	• Sneezing	• Sore throat
• Sputum / phlegm	• Stomachache	• Vomiting

9.2.4.3. COVID-19-Related Medically-Attended Visit Details, Immunocompromised Population Definition (Exploratory Outcome)

A COVID-19-related medically-attended visit (MAV) will be defined as follows: hospitalization, ER visit, urgent care visit, physician's office visit, or telemedicine visit, with one of the reasons for the visit being COVID-19.

Medically-attended visits related to COVID-19, as determined by the investigator, will be recorded in the eCRF. Details will include at minimum:

- Type of visit (hospitalization, ER, urgent care, physician's office visit, telemedicine)
- Date of visit
- If hospitalized due to COVID-19, length of visit
- Reason (list all COVID-19-related clinical manifestation[s] that prompted the medically-attended visit)
- If hospitalized due to COVID-19, whether ICU care was given
- If hospitalized due to COVID-19, whether mechanical ventilation was required
- Treatments given for COVID-19 (including, but not limited to, supplemental oxygen, corticosteroids, remdesivir, baricitinib, etc)

9.2.5. Safety Procedures

9.2.5.1. Vital Signs

Standard vital signs will include body temperature, blood pressure, and heart rate. Comprehensive vital sign assessment will additionally include SpO_2 and respiratory rate.

Vital signs will be measured after the participant has been resting quietly for at least approximately 5 minutes and may be obtained in seated or supine position.

Temperature may be measured using the following methods: axilla, oral, tympanic, or temporal. Body temperature should be measured using the same method each time. Temperature should be measured after at least 5 minutes of rest (supine or sitting).

SpO_2 will be measured using a fingertip or similar non-invasive device following 5 minutes of rest (inactivity) while supine, semi-recumbent, or sitting and will only be measured in the presence of a good SpO_2 wave form.

9.2.5.2. Adverse Event Monitoring

Refer to Section 10.1.

9.2.5.3. Concomitant Medications and Procedures

Concomitant medications and procedures will be recorded as defined in Section 8.9.

9.2.5.4. Pregnancy Test for Women of Childbearing Potential

Pregnancy testing will be performed in women of childbearing potential (WOCBP) only. Serum or urine pregnancy test are both acceptable.

Participants who become pregnant will remain in the study and will continue to follow the Schedule of Events as planned. Refer to Section 10.1.3 for more information regarding pregnancy reporting.

9.2.5.5. Pregnancy Status

Pregnancy status and date of pregnancy, as applicable, will be recorded. Refer to Section 10.1.3 for reporting requirements.

9.2.5.6. Vital Status

Vital status (whether the participant is dead or alive) will be recorded, as well as the date of death, when applicable.

9.2.5.7. Safety Information in Newborns of Study Participants

The incidence and outcome of any SARS-CoV-2 infection will be collected for newborn infants of participants who were treated in the study and were pregnant at randomization or became pregnant at any time in the study. Note that this information is in addition to outcome reporting of all pregnancies (Section 10.1.3).

9.2.6. Drug Concentration and Measurements

Samples will be collected at the timepoints listed in the Schedule of Events. For information concerning unused samples and exploratory research, refer to Section 9.2.9.

9.2.7. Immunogenicity Measurements and Samples

Samples for immunogenicity assessment will be collected at the timepoints listed in the Schedule of Events. For information concerning unused samples and exploratory research, refer to Section 9.2.9.

9.2.8. Pharmacodynamic/Biomarker Procedures

9.2.8.1. Serological Assays for Endogenous Anti-SARS-CoV-2 Antibodies

Antibodies against the S protein RBD will be measured using the Elecsys® anti-SARS-CoV-2 S assay (anti-RBD total Ig, Roche) on samples collected at baseline. The results of this assay will be used to retrospectively analyze the data by the magnitude of baseline immune response to COVID-19 vaccines (see efficacy analysis set definitions in Section 11.3.1). Neutralizing antibodies against SARS-CoV-2 will also be measured at baseline in all enrolled participants in order to determine if any measurable, endogenous humoral response was functional.

VV-RIM-00181183-1.0 Approved - 25 Jan 2022 GMT-5:00

Additional anti-SARS-CoV-2 antibodies may also be measured on stored samples to further characterize participants' baseline serostatus. Any assays used post-baseline to measure antibody immunity will have been demonstrated not to be susceptible to interference from study drug.

9.2.8.2. Serum and Plasma for Exploratory Research

Serum and plasma collected and banked for exploratory research may be used for studies related to COVID-19 disease or vaccination, SARS-CoV-2, casirivimab, imdevimab, host and viral biological pathways, and other mechanisms related to safety, drug exposure, disease activity and clinical outcomes.

9.2.8.3. Exploratory Virology and Viral Sequencing

In support of public health initiatives to track SARS-CoV-2 genetic variants pre and post-treatment, viral genome sequencing will be performed on SARS-CoV-2 viral nucleic acid isolated from available nasopharyngeal (NP) swab samples collected during the study that have been confirmed positive by RT-qPCR for SARS-CoV-2 at the central laboratory.

The results of viral sequencing and related analyses may be reported outside of the study CSR in a separate report.

9.2.9. Unused and Residual Biological Samples

Any biological samples collected during the study which are not used for their planned purpose, or for which material remains after their planned analysis, may be kept for up 15 years after study completion (or for a shorter time period if required per regional laws and regulations) for use in exploratory research related to COVID-19 disease or vaccination, SARS-CoV-2, casirivimab+imdevimab, host and viral biological pathways, and other mechanisms related to safety, drug exposure, disease activity and clinical outcomes.

9.2.10. Exploratory Immunology Sub-Study (Optional; Separate Protocol)

Whole blood samples may be collected as part of an optional sub-study at a select site(s) to study patients' endogenous immune activity and responses to COVID-19 vaccination, SARS-CoV-2 infection and infection by other pathogens such as, but not limited to, influenza. The samples may be used to characterize the cells and plasma to study immune function in these patients pre- and post-treatment using flow cytometry, RNA sequencing, cytokine profiling, and other methods. This sub-study will be described in a separate protocol and results will not be included in the CSR.

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

This study will collect and record the following targeted TEAEs:

- Treatment-emergent grade ≥3 AEs
- Treatment-emergent AEs leading to study drug discontinuation
- Treatment-emergent SAEs
- Treatment-emergent grade ≥2 hypersensitivity reactions
- Treatment-emergent grade ≥3 injection-site reactions

Note: throughout Section 10, the term "AE" refers to the targeted list above.

10.1.1. General Guidelines

The investigator must promptly record all clinical events occurring during the study data collection, from the start of the pretreatment period to the end of on-treatment period (see Section 11.4.5.1). Medical conditions that existed or were diagnosed prior to the signing of the informed consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of informed consent should also be recorded as medical history. Any subsequent worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug should also be recorded as an AE.

At each visit, the investigator will determine whether any AEs have occurred by evaluating the participant. Adverse events may be directly observed, reported spontaneously by the participant or parent, or by questioning the participant or parent at each study visit. Participants and parents should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 10.2. The investigator's assessment must be clearly documented in the site's source documentation with the investigator's signature. The investigator should follow up on SAEs (and AESIs) until they have resolved or are considered clinically stable; AEs should be followed until they are resolved or last study visit, whichever comes first.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the Investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, dose reduction, require corrective treatment, or constitute an AE in the Investigator's clinical judgment.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (diagnosis or symptom requiring hospitalization). A procedure is not

an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the informed consent form) procedures, treatments requiring hospitalization for pre-existing conditions that do not worsen in severity, and admission for palliative or social care should not be reported as SAEs (see Section 10.2 for definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any SAE that may occur after the on-treatment period that the Investigator assesses as related to study drug should also be reported.

All AEs, SAEs, AESIs, and pregnancy reports are to be reported according to the procedures in Section 10.1.3.

10.1.2. Reporting Procedure

All events (serious and non-serious) must be reported with Investigator's assessment of the event's seriousness, severity, and causality to the (when applicable: blinded) study drug. For SAEs and AESIs, a detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE eCRF. Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc.) will be summarized in the narrative on the AE eCRF, and retained at the study center and available upon request.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

10.1.3. Events that Require Expedited Reporting to Sponsor

The following events also require reporting to the Sponsor (or designee) within 24 hours of learning of the event:

- **SAEs**
- **Adverse Events of Special Interest (AESI)**, defined as:
  - Grade ≥2 hypersensitivity reactions
  - Grade ≥3 injection-site reactions

  Note: refer to Table 5 *for grading scale.*
- **Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the Investigator to report to the Sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a study participants, during the study or within 8 months of the last dose of study drug. Any complication of pregnancy affecting a female participant, and/or fetus and/or newborn that meets the SAE criteria, must be reported

as an SAE. Outcome for all pregnancies should be reported to the Sponsor, including testing results for SARS-CoV-2 infection in the newborn, if performed.

A pregnancy report form will be completed for each participant who becomes pregnant or is pregnant at the time the parent or guardian signs consent.

10.2. Definitions

10.2.1. Adverse Event

An AE is any untoward medical occurrence in a participant administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

10.2.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a participant is a passenger).
- Is **life-threatening** – in the view of the Investigator, the participant is at immediate risk of death at the time of the event. This does not include an AE that, had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as a hospital admission (any duration) or an emergency room visit for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the Investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the participant or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Criteria for reporting SAEs must be followed for these events.

10.2.3. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical interest specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

10.2.4. Severity

The severity of adverse events (including test findings classified as adverse events) will be graded using the current version of the NCI-CTCAE v5.0 (DCTD, 2017).

Treatment-emergent AEs, SAEs, or AESIs not listed in the NCI-CTCAE will be graded according to the scale in Table 4. The NCI-CTCAE severity grading scale for anaphylaxis, allergic reactions, and injection site reactions is provided in Table 5.

Table 4: NCI-CTCAE Severity Grading System for Adverse Events (v5.0)

Grade	Severity	Description
1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate	Minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL)[1]
3	Severe	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[2]
4	Life-threatening	Life threatening consequences; urgent intervention indicated
5	Death	Death related to adverse events

[1] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[2] Self-care ADL refers to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Table 5: NCI-CTCAE Severity Grading (v5.0) for Anaphylaxis, Allergic Reactions, and Injection-Site Reactions

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anaphylaxis[1]	Not applicable	Not applicable	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Allergic reaction (hypersensitivity reaction)[2]	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Injection site reaction[3]	Tenderness with or without associated symptoms (eg, warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

[1] Disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death

[2] Disorder characterized by an adverse local or general response from exposure to an allergen.

[3] Disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection.

Source: (DCTD, 2017)

10.2.5. Causality

The Investigator must provide causality assessment as whether or not there is a reasonable possibility that the drug caused the adverse event, based on evidence or facts, his/her clinical judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset versus time drug was administered
- Nature of the reactions: immediate versus long term
- Clinical and pathological features of the events
- Existing information about the drug & same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses
- Response to dechallenge (drug discontinuation)
- Response to rechallenge (re-introduction of the drug)
- Participant's medical and social history

Causality to the study drug (including study drug administration):

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the nature of the reaction, participant's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

  or

  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its class of drugs, or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the nature of the reaction, participant's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

Causality to the study conduct (protocol specified procedure):

- Related:
  - The AE follows a reasonable temporal sequence from a protocol specified procedure, and cannot be reasonably explained by the nature of the reaction, participant's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.
- Not Related:
  - The AE does not follow a reasonable sequence from a protocol specified procedure, or can be reasonably explained by the nature of the reaction, participant's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

10.3. Safety Monitoring

The Investigator will monitor the safety of study participant at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the Sponsor in a timely fashion. The Sponsor will monitor the safety data from across all study sites. The Medical/Study Director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Global Patient Safety; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

10.4. Notifying Health Authorities, Institutional Review Boards, and Investigators

During the study, the Sponsor and/or the contract research organization (CRO) will inform health authorities, Institutional Review Boards (IRBs)/Ethics Committees (ECs), and the participating Investigators of any SUSARs (Suspected Unexpected Serious Adverse Reactions) occurring in other study centers or other studies of the active study drug, as appropriate per local reporting requirements. In addition, the Sponsor and/or CRO will comply with any additional local safety reporting requirements.

Upon receipt of the Sponsor's notification of a SUSAR that occurred with the study drug, the Investigator will inform the IRB/EC unless delegated to the Sponsor.

Event expectedness for study drug is assessed against the Reference Safety Information section of the Investigator's Brochure that is effective for expedited safety reporting.

At the completion of the study, the Sponsor will report all safety observations made during the conduct of the trial in the Clinical Study Report to health authorities and IRB/EC as appropriate.

11. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) of the study. The SAP will be revised prior to the end of the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the first interim analysis.

11.1. Statistical Hypothesis

For the primary objective (Section 2.1), the null hypothesis of the study is that the antibody efficacy (AbE) of casirivimab+imdevimab to prevent symptomatic SARS-CoV-2 infection, compared to placebo, is 0%.

The statistical hypotheses (null and alternative) for any antibody arm can be stated as:

H_0: *HR = 1 versus* H_1: *HR < 1*, where HR is the hazard ratio for antibody arm over placebo.

Equivalently, the null and alternative hypotheses can be stated as:

H_0: *AbE = 0% versus* H_1: *AbE >0%*, where AbE=100 x (1-HR).

Antibody efficacy is thus defined as the percent reduction in hazard ratio for an antibody arm over that of placebo when comparing incidence of symptomatic SARS-CoV-2 infection, using a time-to-event analysis approach.

For the alternative hypothesis, the target antibody efficacy of arm 1 (casirivimab+imdevimab 1200 mg (day 1) SC then 600 mg SC Q4W) is assumed to be at least 60% (ie, HR=0.4); AbE could be same or lower for the other 2 antibody arms, eg, 55% (HR=0.55), 45% (HR=0.45) (Table 6).

11.2. Justification of Sample Size

The sample size is driven by the number of cases to demonstrate the efficacy of the antibody arm, compared to placebo, in preventing symptomatic (broad term), RT-PCR-confirmed SARS-CoV-2 infection in immunocompromised participants.

The number of cases needed to detect the target antibody efficacy and corresponding power with log-rank test are provided in Table 6. These values assume that the time to symptomatic SARS-CoV-2 infection is distributed exponentially in each group, with a COVID-19 incidence rate in the placebo arm of 4.02% over 6 months in the immunocompromised population.

In this study, a total of 186 cases are targeted across all 4 treatment arms in the modified intention-to-treat (mITT) set. Accordingly, a total of 8752 participants are planned to be randomized, based upon the following assumptions:

- Study duration of 15 months, assuming 6 months follow-up for efficacy and accrual duration of 9 months,
- Probability of participant dropouts by 6 months is 0.05 (ie, 5%), and
- Approximately 10% participants at baseline will have failed to meet one (or both) of the conditions of the modified intent-to-treat (mITT) population (and will only be included in the ITT population; Section 11.3.1)

For the purpose of estimating events (sample size) for pairwise comparisons between antibody arm and placebo, it was assumed that there will be four interim looks at 20%, 33%, 50%, and 75% information fraction. Note, however, that actual number of interim looks conducted may vary.

Table 6: Power and Sample Size Estimates to Demonstrate Antibody Efficacy at Overall α=0.025 (1-sided)

Arm	Group	Target Antibody Efficacy	Power	Target Number of Cases (mITT)[a]	6-month COVID-19 incidence rates[b]	Number of participants, to randomize in 1:1:1:1 ratio[c]
-	Total	-	-	186	-	8752
1	Casirivimab+imdevimab 1200 mg (day 1) SC then 600 mg SC Q4W	60%	99.7%	31	1.628%	2188
2	Casirivimab+imdevimab 300 mg SC Q4W	55%	98.7%	35	1.829%	2188
3	Casirivimab+imdevimab 300 mg SC Q12W	45%	90%	43	2.231%	2188
4	Placebo	-	-	77	4.02%	2188

[a] Estimates based on log-rank test assuming at least 90% power for arm 3.
[b] Assuming exponential distribution, placebo rate and hazard ratio for antibody arm.
[c] Sample size adjusted upwards for 10% participants based on RT-qPCR and central lab serology test result at baseline (modified intent-to-treat [mITT] population).

The power and sample size calculations were performed using EaST software.

11.3. Analysis Sets

11.3.1. Efficacy Analysis Sets

The intent-to-treat (ITT) population is defined as all randomized participants.

The primary analysis population for efficacy will be the modified intent-to-treat (mITT) population, defined as all randomized participants who received at least one dose of the study drug and at baseline (day 1):

1. Have tested negative by RT-qPCR (central lab results), and
2. Have central serology test result (Elecsys® anti-S RBD total Ig) ≤50 U/mL

Participants who are deemed medically ineligible or contraindicated to receiving a full course of standard-of-care COVID-19 vaccine will also be included in the mITT.

Analysis will be performed according to the study drug allocated (as randomized).

Both, ITT and mITT populations will be used to summarize demographics and baseline characteristics of participants.

11.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all participants who received any study drug; it is based on the treatment received (as treated). Determination of "as treated" will be based on the actual study drug received, with details provided in the SAP. Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

11.3.3. Pharmacokinetic Analysis Set

The PK analysis population includes all participants who received any study drug and who had at least 1 non-missing result following the first dose of study drug. Participants will be analyzed based on the actual treatment received.

Participants who test positive for SARS-CoV-2 infection during the treatment period and discontinue study drug may be analyzed separately.

11.3.4. Immunogenicity Analysis Sets

The ADA analysis sets (AAS) includes all participants who received any amount of study drug (active or placebo [safety analysis set]) and had at least one non-missing ADA result following the first dose of the study drug. The AAS is based on the actual treatment received (as treated) rather than as randomized.

The NAb analysis sets (NAS) includes all treated participants who received any study drug (active or placebo), have at least one non-missing ADA result following the first dose of study drug (active or placebo), and either tested negative at all ADA sampling times or tested positive for ADA with at least one non-missing NAb result after first dose of the study drug (active or placebo). Participants who are ADA negative are set to negative in the NAb analysis set.

11.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of participants reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

Subgroups will be defined by key baseline factors (e.g., demographics, disease characteristics). Subgroup analyses will be performed on efficacy endpoints and safety endpoints, as needed. Details will be described in the Statistical Analysis Plan (SAP).

Statistical analyses will be performed using Statistical Analysis Software (SAS) Version 9.4 or higher.

11.4.1. Participant Disposition

The following will be provided:

- The total number of screened participants who have signed informed consent
- The total number of randomized participants: received a randomization number

- The total number of participants who discontinued the study, and the reasons for discontinuation
- The total number of participants who discontinued from study treatment, and the reasons for discontinuation
- A summary of analysis sets including ITT, mITT, SAF, PK, and AAS (see Section 11.3)

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group, and by all participants combined.

11.4.3. Efficacy Analyses

The mITT population will be the primary analysis population for efficacy. The ITT population will also be used for efficacy analysis. Participant data will be analyzed according to the group to which they were randomized.

11.4.3.1. Primary Efficacy Analysis

The primary endpoint of the study is cumulative incidence of symptomatic (broad term), RT-PCR-confirmed SARS-CoV-2 infection cases during the efficacy assessment period (EAP). See Section 6.2 for the definition of a symptomatic SARS-CoV-2 infection.

The EAP is defined as the day 2 to day 169 visit. The cumulative incidence of cases through the EAP will be estimated using the Kaplan-Meier method, and the antibody efficacy (*AbE*) will be estimated as the percent risk reduction (ie, *100 x [1-HR)*, where *HR* is the hazard ratio for comparison of the incidence of cases in the antibody arm versus placebo). A stratified Cox proportional hazard regression model with treatment group as a fixed effect, and adjusted for the stratification factors of age categories, region, and use of stable IVIG or SCIG regimen prior to screening, will be used to estimate the hazard ratio and 95% CI (2-sided).

For the primary analysis, cases will be counted from day 2 through day 176 (ie, day 169 +7 days), to allow for cases to accrue until the end of the EAP visit window per the Schedule of Events. Time of symptomatic SARS-CoV-2 infection will be the earlier of the sign/symptom onset date or the sample collection date for which RT-PCR result (local or central) was positive.

Two-sided p-values will be reported using the log-rank test for pairwise comparison between each antibody arm and placebo. See Section 11.4.4 and Section 11.5 for multiplicity adjustment.

The primary analysis population will be the mITT population. ITT population will also be used to analyze the primary endpoint.

Details of supportive analyses and subgroup analyses for the primary endpoint will be provided in the SAP.

11.4.4. Control of Multiplicity

The overall type 1 error rate will be strictly controlled at 0.025 (1-sided) due to multiple hypothesis tests for each of the antibody arms versus placebo, planned interim analyses for efficacy, and other testing as detailed in the SAP.

The hypothesis test for the primary endpoint will be performed first for comparison of arm 1 (casirivimab+imdevimab 1200 mg SC [day 1], then 600 mg SC Q4W) versus placebo, and then for comparison of arm 2 (casirivimab+imdevimab 300 mg SC Q4W) and arm 3 (casirivimab+imdevimab 300 mg SC Q12W) versus placebo. The overall testing strategy for all tests will be described in the SAP.

The Lan-DeMets implementation of the O'Brien-Fleming alpha spending function will be applied to control the false positive error rate of 0.025 (1-sided) over the interim analyses for efficacy and primary analysis (see Section 11.5).

11.4.5. Safety Analysis

11.4.5.1. Adverse Events

Definitions

For safety variables, the following observation periods are defined:

- The pretreatment period is defined as the time from the signing of the ICF to before study drug administration.
- The EAP is defined as the day from first dose of study drug to day 169 ± 7 days
- The Follow-up period is defined as the end of the EAP to the end of the Follow-up Period (ie, the last study visit).

Treatment-emergent adverse events (TEAEs) are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition.

This study will collect data on the following targeted TEAEs (Section 10.1): Grade ≥3 AEs, AEs leading to discontinuation, SAEs, grade ≥2 hypersensitivity reactions, and grade ≥3 injection-site reactions.

Analysis

All AEs reported in this study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®).

The number and percentage (proportion) of participants will be summarized by group in the Safety Set.

Summaries will be provided for the EAP, and combined across the EAP and Follow-up periods for the following:

- Overview of TEAEs, ie, overall number (%) of participants with any TEAE, grade ≥3 TEAE, Serious TEAE, AESI, serious AESI, TEAE leading to death, or TEAE leading to study discontinuation

- Grade 3 and Grade 4 TEAEs by primary system organ class (SOC) and preferred term (PT)
- TEAEs leading to discontinuation by primary SOC and PT
- TEAEs leading to death by primary SOC and PT
- Treatment-emergent SAEs by primary SOC and PT, as well as by SOC, PT, and severity (according to the grading scale outlined in Section 10.2.4)

In addition, following data will be analyzed:

- Summary of Treatment-emergent AESIs by PT during the EAP
- Incidence of Treatment-emergent AESIs by PT during the EAP
  - Grade ≥2 hypersensitivity reactions
  - Grade ≥3 injection-site reactions

Deaths and other SAEs will be summarized by treatment group.

11.4.5.2. Other Safety (Vital Signs and Laboratory Tests)

Definitions

The following definitions will be applied to laboratory parameters and vital signs:

The potentially clinically significant value (PCSV) criteria are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests and vital signs. The PCSV criteria will be provided in the SAP.

PCSV criteria will determine which subjects had at least 1 PCSV during the respective TEAE periods, taking into account all evaluations performed during the respective TEAE periods, including unscheduled or repeated evaluations. The number of all such subjects will be the numerator for the PCSV percentage.

Analysis

The incidence of PCSVs at any time during the TEAE period will be summarized regardless of the baseline level, and again in participants without PCSV in the corresponding category at baseline.

Summary tables, shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest. Summary of vital signs will be provided.

Listings will be provided for subjects meeting PCSV criteria.

Treatment Exposure

The duration of study treatment exposure will be defined as day 1 through 4 weeks, ie, 28 days, after the last dose for a participant in the Q4W arms and day 1 through 12 weeks, ie, 84 days after the last dose for a participant in the Q12W arm. The duration of the study will be through the follow-up period defined as end of EAP through day 253 (±14 days).

Treatment exposure and study duration will be evaluated in the SAF.

11.4.5.3. Treatment Compliance

Participant treatment compliance in terms of total dose, number of doses, and number of SC injections will be summarized for each group. Compliance with study drug will be calculated as follows:

$$\text{Compliance (\%)} = 100 \times \frac{\text{Number of actual injections}}{\text{Number of planned injections}}.$$

This will be presented by specific ranges for each group and the ranges of interest will be specified in the SAP.

11.4.6. Pharmacokinetics

11.4.6.1. Analysis of Drug Concentration Data

The concentrations of casirivimab and imdevimab in serum over time will be summarized descriptively for each of the treatment groups by age group (subjects ≥12 years of age, ≥40 kg; and subjects ≥18 years of age). Associations between covariates that may impact PK of casirivimab and imdevimab and concentrations of the antibodies in serum may be evaluated as appropriate.

No formal statistical hypothesis testing will be performed.

11.4.7. Analysis of Immunogenicity Data

The immunogenicity variables described in Section 5.5 will be summarized using descriptive statistics. Immunogenicity will be characterized by ADA status, ADA category, and maximum titer observed in participants in the AAS, and by NAb status observed in participants in the NSA.

The ADA status of each participant may be classified as one of the following:

- Positive
- Pre-existing – If the baseline sample is positive and all post baseline ADA titers are reported as less than 9-fold the baseline titer value
- Negative – If all samples are found to be negative in the ADA assay.

The ADA category of each positive participant is classified as one of the following:

- Treatment-boosted - A positive result at baseline in the ADA assay with at least one post baseline titer result ≥9-fold the baseline titer value
- Treatment-emergent - A negative result or missing result at baseline with at least one positive post baseline result in the ADA assay. Participants that are treatment-emergent may be further categorized.

The maximum titer category of each participant is classified as:

- Low (titer <1,000)
- Moderate (1,000≤ titer ≤10,000)
- High (titer >10,000)

Listings of all ADA titer levels will be provided for participants with pre-existing, treatment-emergent and treatment-boosted ADA response. The absolute occurrence (n) and percent of participants (%) with NAb status in the NAb analysis set will be provided by treatment groups.

Plots of drug concentrations will be examined and the influence of ADAs and NAbs on individual PK profiles evaluated. Assessment of impact of ADA and NAb on safety and efficacy may be provided.

11.5. Interim Analysis

This study will have planned interim analyses for efficacy. The primary objective of these interim analyses is the early detection of evidence of antibody efficacy (AbE) in arm 1, ie, casirivimab+imdevimab 1200 mg SC (day 1) then 600 mg SC Q4W compared to placebo and stopping for efficacy.

To control the overall Type 1 error rate (false-positive rate) at 0.025 (1-sided) due to interim looks, the Lan-DeMets implementation of the O'Brien-Fleming alpha spending function will be used. The actual alpha spending will be based on the actual number of cases for the primary endpoint included in the analyses and the target total number of cases for the treatment arms being analyzed (see Table 6), as determined by the O'Brien-Fleming spending function at the time of interim analysis.

An independent data monitoring committee (IDMC) will perform the interim analyses. If antibody efficacy is demonstrated at any interim analysis, the IDMC will inform the Sponsor's management and may make recommendations to stop the study for efficacy. At the time of each interim analysis, a memo will be issued to document the data cutoff date. In the event that the first hypothesis test on the primary endpoint is met during interim or final analysis, all other pre-specified comparisons and endpoints will be analyzed at that time at all remaining alpha.

In addition to the formal interim analyses for efficacy monitoring, the IDMC will also monitor for non-efficacy and safety, for which the guiding principles are stated in Section 6.5 and Section 6.8.1, with further details provided in the IDMC charter and the SAP.

11.6. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 15.1.

12. QUALITY CONTROL AND QUALITY ASSURANCE

In accordance with ICH E6, the Sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are described in this section.

12.1. Data Management and Electronic Systems

12.1.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation [quality-checking], cleaning, correcting, releasing) will be maintained and stored at Regeneron (Sponsor).

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical history) will be done using internationally recognized and accepted dictionaries.

The eCRF data for this study will be collected with an electronic data capture (EDC) system.

12.1.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IWRS system – study drug supply
- EDC system (data capture) – Medidata Rave
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

Regeneron uses a study-specific risk based approach to study monitoring and oversight, aligned with risk based quality principles, outlined in ICH E6 (R2) Guideline for Good Clinical Practice. Risk-Based Quality Monitoring (RBQM) methodology focuses on employing a fit-for-purpose monitoring strategy, supported either directly by Regeneron as Sponsor, or via our CRO partners. RBQM strategies include: reduced source data verification (SDV), targeted source data review (SDR), the use of off-site/remote and triggered on-site monitoring visits, and Centralized Monitoring to identify site level risks and study level trends. The Investigator must allow study-related monitoring activities to occur.

The study monitors will perform ongoing source data review to verify that data recorded in the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of participants are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate participant records (source documents). The site is responsible to ensure quality within their records and systems and are accountable for ensuring that all source data and eCRF data are timely, accurate and complete.

The Investigator must keep all source documents on file with the eCRF. Case report forms and source documents must be available at all times for inspection by authorized representatives of the Sponsor and regulatory authorities.

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic Case Report Forms (CRFs) within the EDC system by trained site personnel. All required eCRFs must be completed for each and every participant enrolled in the study. An unblinded site team member will enter study drug administration data in the EDC separately from blinded site team member, in order to maintain the blind. The Investigator must ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor in the eCRFs. After review of the clinical data for each participant, the Investigator must provide an electronic signature. A copy of each participant eCRF casebook is to be retained by the Investigator as part of the study record and must be available at all times for inspection by authorized representatives of the Sponsor and regulatory authorities.

Corrections to the eCRF will be entered in the eCRF by the Investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

12.3. Audits and Inspections

This study may be participant to a quality assurance audit or inspection by the Sponsor or regulatory authorities. Should this occur, the Investigator is responsible for:

- Informing the Sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the Sponsor’s participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the Sponsor immediately
- Taking all appropriate measures requested by the Sponsor to resolve the problems found during the audit or inspection

Documents participant to audit or inspection include but are not limited to all source documents, eCRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also participant to inspection. In addition, representatives of the Sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the Investigator's institution.

In all instances, the confidentiality of the data must be respected.

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the eCRF must be signed electronically by the Investigator. This signed declaration accompanies each set of participant's final eCRF that will be provided to the Sponsor.

12.4.2. Retention of Records

The Investigator must retain all essential study documents, including ICFs, source documents, Investigator copies of eCRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The Investigator must obtain written approval from the Sponsor before discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the Investigator's personal situation is such that archiving can no longer be ensured, the Investigator must inform the Sponsor (written notification) and the relevant records will be transferred to a mutually agreed-upon destination.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of both the Sponsor and the Investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

13.2. Informed Consent and Assent

The principles of informed consent are described in ICH guidelines for GCP.

Due to disease severity, quarantine restrictions, and/or other reasons related to COVID-19, it may be necessary to implement temporary or alternative measures to obtain informed consent per procedures outlined in the investigator site file.

The ICF used by the investigator must be reviewed and approved by the Sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC-approved ICF and documentation of approval must be provided to the Sponsor before study drug will be shipped to the study site.

Adult Participants

For participants at or above the legal age of adulthood, it is the responsibility of the investigator or authorized designee (if acceptable by local regulations) to obtain informed consent from each participant prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the participant in language that he/she can

understand. The ICF should be signed and dated by the participant and by the investigator or authorized designee who reviewed the ICF with the participant:

- Participants who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Participants who can understand but who can neither write nor read will have the ICF read to them in the presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the participant's study record, and a copy of the signed ICF must be given to the participant.

If new safety information results in significant changes in the risk/benefit assessment, or if there are significant changes to the study procedures, the ICF must be reviewed and updated appropriately. All study participants must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the participant's study record and a copy must be given to the participant.

Participants Under 18 Years of Age (or Under Country's Legal Age of Adulthood)

For participants under the legal age of adulthood, it is the responsibility of the investigator or authorized designee (if acceptable by local regulations) to obtain written informed consent from the participant's parent(s) or legal guardian(s) prior to the participant's participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the fullest possible extent in language that the participant's parent(s) or legal guardian(s) can understand. The ICF should be signed and dated by the participant's parent(s) or legal guardian(s) and by the same investigator or designee who explained the ICF.

Local law and site policies must be observed by the investigator in deciding whether the consent of 1 or both parents/guardians is required. If only 1 parent or guardian signs the ICF, the investigator must document the reason the other parent or guardian did not sign.

The investigator (or authorized designee) may also be required to obtain assent from the participant, as determined by the IRB/EC and in accordance with the local regulations and requirements:

- Participants who can write but cannot read will have the assent form read to them before writing their name on the form
- Participants who can understand but who can neither write nor read will have the assent form read to them by the person obtaining assent, who will sign and date the assent form to confirm that assent was given

The original assent form must be retained by the investigator as part of the participant's study record, and a copy of the signed assent form must be given to the participant's parent(s) or legal guardian(s).

13.3. Participant Confidentiality and Data Protection

The Investigator must take all appropriate measures to ensure that the anonymity of each study participant will be maintained. Participants should be identified by a participant identification number only, on eCRFs or other documents submitted to the Sponsor. Documents that will not be submitted to the Sponsor (eg, signed ICF) must be kept in strict confidence.

The participant 's and Investigator's personal data, which may be included in the Sponsor database, will be treated in compliance with all applicable laws and regulations. The Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4. Institutional Review Board / Ethics Committee

An appropriately constituted IRB/EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the participants (eg, advertising) before any participant may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the participant, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of participants or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the Sponsor prior to shipment of drug supplies to the Investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the Investigator.

13.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. Treatment codes will be disseminated to each investigation site thereafter.

14. PROTOCOL AMENDMENTS

The Sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC -approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

15.1. Premature Termination of the Study

The Sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the Sponsor decide to terminate the study, the Investigator(s) will be notified in writing.

15.2. Close-out of a Site

The Sponsor and the Investigator have the right to close-out a site prematurely.

Investigator's Decision

The Investigator must notify the Sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the Sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The Sponsor will notify the Investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The Investigator has received all items and information necessary to perform the study, but has not enrolled any participant within a reasonable period of time
- The Investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of participants required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the participants' interests.

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

Publication rights and procedures will be outlined in a separate clinical study agreement.

19. REFERENCES

ACIP. Advisory Committee on Immunization Practices (ACIP) Presentation Slides: August 13, 2021 Meeting. https://www.cdc.gov/vaccines/acip/meetings/slides-2021-08-13.html. Published 2021. Accessed 10 Sep 2021 2021.

Agha M, Blake M, Chilleo C, Wells A,Haidar G. Suboptimal response to COVID-19 mRNA vaccines in hematologic malignancies patients. medRxiv 2021:2021.2004.2006.21254949.

Babaha F,Rezaei N. Primary Immunodeficiency Diseases in COVID-19 Pandemic: A Predisposing or Protective Factor? Am J Med Sci 2020; 360(6):740-741.

Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 2021; 384(5):403-416.

Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, et al. Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients. JAMA 2021a; 325(21):2204-2206.

Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, et al. Immunogenicity of a Single Dose of SARS-CoV-2 Messenger RNA Vaccine in Solid Organ Transplant Recipients. JAMA 2021b; 325(17):1784-1786.

CDC. Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States.Centers for Disease Control and Prevention. https://www.cdc.gov/vaccines/covid-19/info-by-product/pfizer/clinical-considerations.html. Published 2021. Updated 05 Mar 2021. Accessed 21 Mar 2021 2021.

Copin R, Baum A, Wloga E, Pascal KE, Giordano S, Fulton BO, et al. The monoclonal antibody combination REGEN-COV protects against SARS-CoV-2 mutational escape in preclinical and human studies. Cell 2021.

DCTD. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.National Cancer Institute. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Published 2017. Accessed 2 Jul 2020.

Deepak P, Kim W, Paley MA, Yang M, Carvidi AB, Demissie EG, et al. Effect of Immunosuppression on the Immunogenicity of mRNA Vaccines to SARS-CoV-2 : A Prospective Cohort Study. Ann Intern Med 2021.

Gao Y, Chen Y, Liu M, Shi S,Tian J. Impacts of immunosuppression and immunodeficiency on COVID-19: A systematic review and meta-analysis. J Infect 2020; 81(2):e93-e95.

Herishanu Y, Avivi I, Aharon A, Shefer G, Levi S, Bronstein Y, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. Blood 2021; 137(23):3165-3173.

Hoffmann M, Kleine-Weber H,Pöhlmann S. A Multibasic Cleavage Site in the Spike Protein of SARS-CoV-2 Is Essential for Infection of Human Lung Cells. Mol Cell 2020; 78(4):779-784.e775.

Horby PW, Mafham M, Peto L, Campbell M, Pessoa-Amorim G, Spata E, et al. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. medRxiv 2021:2021.2006.2015.21258542.

Lewis NM, Chu VT, Ye D, Conners EE, Gharpure R, Laws RL, et al. Household Transmission of SARS-CoV-2 in the United States. Clin Infect Dis 2020.

Long QX, Liu BZ, Deng HJ, Wu GC, Deng K, Chen YK, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. Nat Med 2020; 26(6):845-848.

Magyarics Z, Leslie F, Bartko J, Rouha H, Luperchio S, Schörgenhofer C, et al. Randomized, Double-Blind, Placebo-Controlled, Single-Ascending-Dose Study of the Penetration of a Monoclonal Antibody Combination (ASN100) Targeting Staphylococcus aureus Cytotoxins in the Lung Epithelial Lining Fluid of Healthy Volunteers. Antimicrob Agents Chemother 2019; 63(8).

O'Brien MP, Forleo-Neto E, Musser BJ, Isa F, Chan K-C, Sarkar N, et al. Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. New England Journal of Medicine 2021a.

O'Brien MP, Forleo-Neto E, Sarkar N, Isa F, Hou P, Chan K-C, et al. Subcutaneous REGEN-COV Antibody Combination in Early SARS-CoV-2 Infection. medRxiv 2021b:2021.2006.2014.21258569.

O'Brien MP, Forleo Neto E, Musser BJ, Isa F, Chan K-C, Sarkar N, et al. Subcutaneous REGEN-COV Antibody Combination for Covid-19 Prevention. medRxiv 2021c:2021.2006.2014.21258567.

Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020; 383(27):2603-2615.

REGEN-COV™ (casirivimab with imdevimab) [HCP Fact Sheet]. 2021; Regeneron Pharmaceuticals, Inc., Tarrytown, NY. https://www.regeneron.com/sites/default/files/treatment-covid19-eua-fact-sheet-for-hcp.pdf.

Sadoff J, Gray G, Vandebosch A, Cárdenas V, Shukarev G, Grinsztejn B, et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. N Engl J Med 2021; 384(23):2187-2201.

Shah DP, Ghantoji SS, Shah JN, El Taoum KK, Jiang Y, Popat U, et al. Impact of aerosolized ribavirin on mortality in 280 allogeneic haematopoietic stem cell transplant recipients with respiratory syncytial virus infections. Journal of Antimicrobial Chemotherapy 2013; 68(8):1872-1880.

Sonani B, Aslam F, Goyal A, Patel J,Bansal P. COVID-19 vaccination in immunocompromised patients. Clin Rheumatol 2021; 40(2):797-798.

Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT,Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell 2020; 181(2):281-292.e286.

Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGEN-COV Antibody Cocktail in Outpatients with Covid-19. medRxiv 2021a:2021.2006.2009.21257915.

Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGEN-COV Antibody Cocktail Clinical Outcomes Study in Covid-19 Outpatients. medRxiv 2021b:2021.2005.2019.21257469.

WHO. Laboratory testing of 2019 novel coronavirus (2019-nCoV)in suspected human cases: interim guidance, 17 January 2020. https://www.who.int/publications/i/item/laboratory-testing-of-2019-novel-coronavirus-(-2019-ncov)-in-suspected-human-cases-interim-guidance-17-january-2020. Published 2020.

Wollacott AM, Boni MF, Szretter KJ, Sloan SE, Yousofshahi M, Viswanathan K, et al. Safety and Upper Respiratory Pharmacokinetics of the Hemagglutinin Stalk-Binding Antibody VIS410 Support Treatment and Prophylaxis Based on Population Modeling of Seasonal Influenza A Outbreaks. EBioMedicine 2016; 5:147-155.

20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol, *A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Anti-Spike SARS-CoV-2 Monoclonal Antibodies as Pre-Exposure Prophylaxis to Prevent COVID-19 in Immunocompromised Participants*, and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the planned conduct of the study.

Study Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Anti-Spike SARS-CoV-2 Monoclonal Antibodies as Pre-Exposure Prophylaxis to Prevent COVID-19 in Immunocompromised Participants

Protocol Number: R10933-10987-COV-2176

Protocol Version: ~~Original~~Amendment 2 US

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00181183 v1.0

Approval/eSignature	[redacted] 25-Jan-2022 15:24:05 GMT+0000
Approval/eSignature	[redacted] 25-Jan-2022 15:33:18 GMT+0000
Approval/eSignature	[redacted] 25-Jan-2022 16:34:45 GMT+0000
Approval/eSignature	[redacted] 25-Jan-2022 22:51:57 GMT+0000

Signature Page for VV-RIM-00181183 v1.0 Approved