REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN
VERSION: FINAL V1.0

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 (REGEN-COV; REGN10933+REGN10987)
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Clinical Phase:	Phase 3
Sponsor:	Regeneron Pharmaceuticals, Inc.
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The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
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
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

1. OVERVIEW

This is a randomized, double-blind, placebo-controlled, phase 3 study to assess the safety and efficacy of anti-SARS-CoV-2 mAb therapy, 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.

Regeneron decided to close enrollment of the COV-2176 Study on Dec 16 2021. This was based on several factors, including the recent Emergency Use Authorization of an alternative therapy in pre-exposure prophylaxis as well as emerging evidence surrounding Variants of Concern (VOC). While casirivimab+imdevimab retains activity against other known VOCs, including Delta, which was the most prevalent variant in the U.S., it has diminished potency against Omicron. Consequently, Regeneron stopped recruitment into this study.

As a result of the early termination of the study, the objectives could not be achieved and none of the hypotheses are evaluable. Although this SAP refers to primary and secondary endpoints and objectives based on their description in the protocol, these have all been designated exploratory due to the early termination.

1.1. Background/Rationale

Study R10933-10987-COV-2176 was terminated early by the Sponsor due to the high frequency of the Omicron variant 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 protocol amendment 2 followed the sponsor's decision to close enrollment early and the study was revised to allow one optional dose and obtain final safety assessments.

Optional Dose

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 (protocol amendment 2 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 (in the Documentation of Clinical Evaluation section). 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 protocol Section 6.4.4) at any time prior to receipt of the optional 1200mg SC dose (eg, during the 4 weeks between receipt of the last protocol-defined dose and 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. Participants with a positive SARS-CoV-2 RT-PCR may have additional assessments and sample collections, including 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 protocol 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 (protocol amendment 2 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.

Analysis Plan

At the time that enrollment was closed, 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. No interim analysis will be performed for this study, and no IDMC review meetings will occur.

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 below), and a 3-month follow-up period.

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).

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

Participants will be monitored for suspected COVID-19 symptoms throughout the study. Those with suspected COVID-19 will be evaluated by a study clinician for signs and symptoms of COVID-19 and will have RT-PCR testing to confirm SARS-CoV-2 infection.

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 were available at time of study initiation in the regions where the study is being conducted.

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.

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 at time of study initiation in the regions where the study is being conducted.

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.

Primary Efficacy Analysis

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 unstratified Cox

proportional hazard regression model with treatment group as a fixed effectwill 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.

Safety Analyses

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.

Per protocol amendment 2, this study will collect 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.

Other Safety Analyses

Vital Signs, Laboratory Tests, treatment exposure, and treatment compliance analyses will be performed.

1.2. Study Objectives

1.2.1. Primary Objectives

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.

1.2.2. 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

1.2.3. 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

1.2.4. Modifications from the Statistical Section in the Final Protocol

Some exploratory efficacy endpoints listed in protocol amendment 2 will not be reported.

1.2.5. Revision History for SAP Amendments

NA

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This is a randomized, double-blind, placebo-controlled, phase 3 study to assess the safety and efficacy of anti-SARS-CoV-2 mAb therapy, 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. The study consists of three periods: a screening period of up to 14 days, an efficacy assessment period (EAP) of approximately 6 months and a 3-month follow-up period. A diagram depicting the study design is provided in the protocol. In addition to the main study, an optional immunology sub-study will be conducted outside of the protocol.

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

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

Prior to closing enrollment early, 66 subjects (about 16~17 subjects per treatment group) were recruited and randomized from US sites.

2.2. Sample Size and Power Considerations

The trial was terminated by sponsor early and the actual sample size for the study was not 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 planned number of cases needed to detect the target antibody efficacy and corresponding power with log-rank test are not reached for this study due to early study termination. There's no interim analyses for this study. Study power may not be reached due to early termination.

2.3. Study Plan

The study event table is presented in Section 10.1.

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (ICH, 1998), the following population of analysis will be used for all statistical analysis:

3.1. The 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):

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

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

ITT will be used to summarize demographics and baseline characteristics of participants.

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,. Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

3.3. Pharmacokinetic Analysis Set

The PK analysis set is defined for each study drug separately, includes all participants who received active study drug, and who had at least 1 non-missing result of each respective analyte following the first dose of respective study drug. Participants will be analyzed based on the actual treatment received (as treated) rather than as randomized.

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

3.4. Immunogenicity Analysis Sets

The ADA analysis sets (AAS) are defined for each study drug separately and include 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 respective study drug or placebo. The AAS are based on the actual treatment received (as treated) rather than as randomized.

The NAb analysis sets (NAbAS) are defined for each study drug separately and include all treated participants (active or placebo) that are included in the ADA analysis set and that tested negative at all ADA sampling times or tested positive at one or more post-dose ADA sampling times and had at least one non-missing post-dose NAb result (either imputed or analysis result).

Samples that tested negative for ADA are not assayed in the NAb assay and the corresponding NAb results are imputed as negative and included as such in the NAb analysis set. Participants in the NAbAS with multiple post-dose ADA results which consist of both imputed NAb-negative result(s) for ADA negative samples and only missing NAb results for all ADA-positive result(s), are set to NAb negative. Participants in the NAbAS that have at least one post-dose positive NAb analysis result are set to NAb positive even if other NAb results are missing.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic variables will be summarized:

- Age at screening (year)
- Age groups for PK: ≥12 years and ≥40kg to <18 years; ≥18 years
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White and Other)
- Region (US)
- Ethnicity (Hispanic/Latino)
- Baseline Weight
- Baseline Body mass index (BMI) calculated from weight and height
- Use of stable IVIG or SCIG regimen prior to screening
- Baseline serology status and baseline median serology value from central lab
- Baseline viral load from central lab (copies/ml; log10 copies/ml)
- Baseline local RT-PCR qualitive results (U/mL)

4.2. Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA®).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

4.3. Concomitant Medication/Procedures

Medications will be coded using the WHO Drug Dictionary (WHODD, Drug Global version SEP2020 B3).

This includes medications that were started before the initiation of study treatment and are ongoing during the treatment-emergent EAP.

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4.4. Prohibited Medication During Study and Post-Infection treatment

4.4.1. Prohibited Medication During Study

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 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

4.4.2. Post-Infection treatment

.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

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

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) will be recorded, and participants will be asked to notify study personnel as soon as possible about such occurrences.

4.5. Efficacy Variable

4.5.1. Primary Efficacy Variable

Primary efficacy variable is cumulative incidence of symptomatic (broad term), RT-PCR-confirmed SARS-CoV-2 infection cases during the efficacy assessment period (EAP).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). The EAP is defined as the day 2 to day 169 +7 days . In addition, following rules will be applied to the primary analyses:

- Time to first symptotic infection is defined as the first date of having either central or local lab deterimined positive test result.
- Subjects do not experience any symptotic infection will be censored at last observed time point.
- Subjects who die at any time in the study or discontinue the study earlier (did not get any infections) will be censored at the end of study in case of final database lock.
- Subjects with COVID-19 symptoms that are missing a central lab determined RT-qPCR test during the EAP but have a positive SARS-COV-2 test from a local lab will be considered as having a symptomatic infection if any of the symptoms occurred within 7 days of the positive SARS-COV-2 test that was observed during the EAP.
- If subjects took optional dose of 1200mg, all the data after the dose will be removed from the efficacy analyses.

If subjects took investigational, authorized, or approved COVID-19 vaccines within 90 days of the last dose of study drug (or per current CDC recommendations) (CDC, 2021) or any covid-19 treatment medications for prevention after starting study treatment (Anti SARS-CoV-2 antibodies including Bamlanivimab/ Etesevimab, Casirvimab/ Imdevimab (REGEN-COV), Sotrovimab or Tixagevimab/ Cilgavimab (Evusheld); remdesivir; Nirmatrelvir/ Ritonavir (Paxlovid); Molnupiravir, all the efficacy data after these treatment will be removed from efficacy analyses.

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 the appendix 10.2 .

4.5.2. Other Efficacy Variable(s)

The exploratory efficacy variables are:

1. Cumulative incidence of symptomatic (broad term), RT-PCR-confirmed SARS-CoV-2 infection cases during the follow-up period is defined as time to first symptomatic infection (RT-PCR-confirmed SARS-CoV-2) during the follow-up period. Similar rules to primary efficacy variable are applied to this variable.
2. Cumulative incidence of RT-PCR-confirmed SARS-CoV-2 infection cases (regardless of symptoms) during the EAP is defined as time to first RT-PCR-confirmed SARS-CoV-2 infection cases (regardless of symptoms) during the EAP. Similar rules to primary efficacy variable are applied to this variable.
3. Proportion of participants with COVID-19-related hospitalization, emergency room visit, urgent care center visit or death during the EAP and follow-up period is defined as number of participants with COVID-19-related hospitalization, emergency room visit, urgent care center visit or death during the EAP and follow-up period divided by total number of participants of interest.
4. Maximum SARS-CoV-2 RT-qPCR viral load (log10 copies/mL) in NP swab samples among individuals with ≥1 RT-qPCR positive test that has an onset during the EAP is defined as the maximum value of viral load (log10 copies/mL) among all the NP swab samples from individuals with ≥1 RT-qPCR positive test that has an onset during the EAP.
5. Viral variant characteristics of SARS-CoV-2 in participants who become infected post-baseline

4.6. Safety Variables

4.6.1. Adverse Events, Serious Adverse Events

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: Grade ≥3 AEs, AEs leading to discontinuation, SAEs, grade ≥2 hypersensitivity reactions, and grade ≥3 injection-site reactions.

4.6.2. Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) is defined as:

− Grade ≥2 hypersensitivity reactions

− Grade ≥3 injection-site reactions

4.6.3. Vital Signs and Laboratory Tests

Standard vital signs including body temperature, blood pressure, and heart rate, comprehensive vital sign assessment including additionally include SpO_2 and respiratory rate will be collected. Temperature and SpO_2 will be collected. Local safety laborary tests collect absolute neutrophil count, platelet count, hemoglobin, ALT, AST, total bilirubin, and creatineine at baseline visit as well as study visits days 29,85 and 169.

4.7. Pharmacokinetic Variables

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

4.8. Immunogenicity Variables

The immunogenicity variables include ADA status, titer, and NAb status at nominal sampling time/visit. Serum samples for ADA will be collected at the clinic visits specified in the protocol SOE. Samples positive in the ADA assay will be further characterized for ADA titers and for the presence of NAb.

5. STATISTICAL METHODS

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

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

5.1. Demographics and Baseline Characteristics

The variables for baseline characteristics include standard demography and other baseline summaries of efficacy variables will be displayed for each treatment group and all participant combined.

5.2. Medical History

Summary for each treatment group and all participant combined will be provided.

5.3. Prior/concomitant Medications

Prior /concomitant illnesses and medications will be summarized based on the safety population. 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.

Medications will be coded to the ATC level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup) and summarized Subjects will be counted once in all

ATC categories linked to the medication. Concomitant medications/procedures during EAP: medications taken or procedures performed in the period from the day of the first dose of study drug up to D176 or to the last visit if a subject discontinue from the study, whichever is earlier. This includes medications that were started before the initiation of study treatment and are ongoing during the EAP. Concomitant medications/procedures during the follow-up period: medications taken, or procedures performed from the day after the end of EAP to the final study visit or started during the treatment-emergent EAP and are ongoing after EAP.

5.4. Prohibited Medications if applicable

Prohibited medications will be summarized based on ITT under protocol deviations. Listing of prohibited medications described in the protocol will be provided for subjects under protocol deviations.

5.5. Subject Disposition

Subject study status will be summarized by treatment group and overall for the study.

The following will be provided:

- Number of screened subjects, defined as signed the ICF
- Number of randomized subjects
- Number of subjects randomized but who did not receive study treatment

- Number of subjects who discontinued the study, and the reasons for discontinuation
- A listing of subjects treated but not randomized, subjects randomized but not treated, and subjects randomized but not treated as randomized
- A listing of subjects prematurely discontinued from the study, along with reasons for Discontinuation
- A summary of analysis sets including randomized subjects and randomized subjects by treatment groups, ITT, mITT, SAF, PK, immunogenicity (AAS).

5.6. Extent of Study Treatment Exposure and Compliance

5.6.1. Measurement of 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 for SAF during EAP by each group and by all subjects combined.

5.6.2. Exposure to Investigational Product

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.

5.7. Analyses of Efficacy Variables

The following null and alternate hypotheses will be tested for the primary endpoint unless otherwise specified:

H0: There is no treatment difference between REGN10933+REGN10987 and placebo

H1: There is a treatment difference between REGN10933+REGN10987 and placebo

Primary efficacy variable will be analyzed and compared between REGN-COV arms vs placebo.

5.7.1. Analysis of Primary Efficacy Endpoint

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

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 4.5.1 for the definition of a symptomatic SARS-CoV-2 infection.

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 unstratified Cox proportional hazard regression model with treatment group as a fixed effect, will be used to estimate the hazard ratio and 95% CI (2-sided). Nominal two-sided p-values will be reported for descriptive purpose using the log-rank test for pairwise comparison between each antibody arm and placebo.

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.

5.7.2. Analysis of Secondary Efficacy Endpoints

No secondary efficacy variables are collected for this study

5.7.3. Analysis of Other Exploratory Endpoints

The following exploratory endpoints will be summarized descriptively:

1. Cumulative incidence of symptomatic (broad term), RT-PCR-confirmed SARS-CoV-2 infection cases during the follow-up period
2. Cumulative incidence of RT-PCR-confirmed SARS-CoV-2 infection cases (regardless of symptoms) during the EAP
3. Proportion of participants with COVID-19-related hospitalization, emergency room visit, urgent care center visit or death during the EAP and follow-up period
4. Maximum SARS-CoV-2 RT-qPCR viral load (log10 copies/mL) in NP swab samples among individuals with ≥1 RT-qPCR positive test that has an onset during the EAP

5. Viral variant characteristics of SARS-CoV-2 in participants who become infected post-baseline

5.7.4. Adjustment for Multiple Comparison

Due to study early terminations, no multiple adjustments will be performed for any analyses.

5.8. Analysis of Safety Data

Secondary safety endpoints are

1. Proportion of participants with grade ≥3 treatment-emergent adverse events (TEAEs), during the EAP and follow-up period
2. Proportion of participants with TEAEs leading to study drug discontinuation, during the EAP and follow-up period
3. Proportion of participants with treatment-emergent serious adverse events (SAEs) during the EAP and-follow up period
4. Proportion of participants with adverse events of special interest (AESIs) during the EAP

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).

The safety analysis will be based on the reported AEs and other safety information (clinical laboratory evaluations, and vital signs). The summary of AE results will be presented for each treatment group for each of three TEAE periods: treatment-emergent EAP (TEEAP), treatment-emergent follow-up period (TEFUP), and overall study period (i.e., combined across the TEEAP and TEFUP). For laboratory and vital sign results they will be presented for each treatment group for each of three periods: EAP, follow-up, and overall study period.

5.8.1. Adverse Events

All AEs reported in this study will be reported by the preferred term (PT), and the primary system organ class (SOC). The number and percentage of subjects with TEAEs will be summarized by treatment group.

Summaries will include:

- Overview of TEAEs, i.e., overall number (%) of subjects with any TEAE, Serious

TEAE, TEAE leading to death, TEAE leading to study withdrawn

- Overview of non-COVID TEAEs (not related to the patients's underlying disease and/or not related to treatments for the underlying conditions), i.e., overall number (%) of subjects with any TEAE, Serious TEAE, TEAE leading to death, or TEAE leading to study withdrawn
- Overview of AESI, i.e., overall number (%) of subjects with any AESI, grade 3 or greater injection site reactions, grade 2 or greater hypersensitivity reactions, AESI leading to death, or AESI leading to study drug withdrawn)
- TEAEs by primary SOC and PT
- TEAEs by severity (according to the grading scale appendix Section 10.3), presented by primary SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by primary SOC and PT
- Treatment-emergent SAEs by primary SOC and PT
- Treatment-emergent AESIs by primary SOC and PT
- TEAEs leading to study withdrawn by primary SOC and PT
- Treatment-emergent AESIs leading to study withdrawn by primary SOC and PT
- Treatment-emergent AESIs by severity, presented by primary SOC and PT
- Number of subjects who died during TEEAP, TEFUP, and the study period, respectively, and reason for death
- TEAEs leading to death
- AESIs leading to death by SOC and PT.

In addition, the number (%) of subjects symptoms assessment collected in the COVID-19 symptoms assessment eCRF will be summarized by treatment group. The descriptive statistics of the duration (days) of each COVID-19 symptom will also be presented. Subject listing of COVID-19 symptoms including the details such as the start date, end date, and duration of each symptom will be provided. In addition, subject listing of SAEs, AESI, TEAEs related to study drug, and TEAEs leading to study drug withdrawn will also be presented.

5.8.2. Clinical Laboratory Measurements

5.8.3. Analysis of Vital Signs and Safety Laboratory Measures

Summary of vital signs including systolic blood pressure, diastolic blood pressure, heart rate, oxygen saturation, Temperature, Respiratory rate will be provided. In addition, local labatory results will be summarized by abnormality(low/high) and normality. Listings will be provided for all the local laboratory results.

5.8.4. Analysis Other Safety Variables

For subjects who become SARS-CoV-2 positive and require medically attended visits to the emergency department (ED), urgent care center (UCC), or hospitalization starting from the timepoint of SARS-CoV-2 RT-qPCR positive and through the end of the study, will have the following parameters or occurrences (worst or most abnormal finding) during the medically attended visit/stay collected (eCRF).

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)

A listing of subjects who have abnormal findings with any SARS-CoV-2 infection-related medically-attended visit will be provided including the corresponding study period information.

5.9. Analysis of Pharmacokinetic 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 to <18 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.

5.10. Analysis of Immunogenicity Data

5.10.1. Analysis of ADA data:

The immunogenicity variables described in Section 4.8 will be summarized using descriptive statistics. Immunogenicity will be characterized per drug molecule by ADA status, ADA category and maximum titer observed in participants in the ADA analysis sets. For samples confirmed as drug specific ADA positive, but found negative at the lowest titer dilution, the lowest dilution in the titer assay is imputed.

The ADA status of each participants 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 participants is classified as:

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. Patients that are treatment-emergent will be further categorized as follows:

Treatment-emergent is further sub-categorized as:

Persistent - A positive result in the ADA assay detected in at least 2 consecutive post baseline samples separated by at least a 16-week post baseline period [based on nominal sampling time], with no ADA-negative results in-between, regardless of any missing samples

Transient - Not persistent or indeterminate, regardless of any missing samples

Indeterminate - A positive result in the ADA assay at the last collection time point only, regardless of any missing samples

The maximum titer category of each participants is classified as:

Low (titer <1,000)

Moderate (1,000 ≤ titer ≤ 10,000)

High (titer >10,000)

The following will be summarized by treatment group and ADA titer level:

- Number (n) and percent (%) of ADA-negative participants
- Number (n) and percent (%) of pre-existing participants
- Number (n) and percent (%) of treatment-emergent ADA positive participants
  - Number (n) and percent (%) of persistent treatment-emergent ADA positive participants
  - Number (n) and percent (%) of indeterminate treatment-emergent ADA positive participants
  - Number (n) and percent (%) of transient treatment-emergent ADA positive participants
- Number (n) and percent (%) of treatment-boosted ADA positive participants

Listing of all ADA titer levels will be provided for participants with pre-existing, treatment-emergent and treatment-boosted ADA response.

5.10.2. Analysis of Neutralizing Antibody (NAb) Data

The absolute occurrence (n) and percent of participants (%) with NAb status in the NAb analysis set will be provided by treatment groups. The NAb status is categorized as follows:

- Negative: Samples tested negative in the ADA assay, or samples positive in the ADA assay but tested negative in the NAb assay.
- Positive: Samples tested positive in the NAb assay

5.11. Association of Immunogenicity with Exposure and Safety

5.11.1. Immunogenicity and Exposure

Potential association between immunogenicity and systemic exposure to casirivimab and imdevimab will be explored by treatment groups. Plots of individual casirivimab and imdevimab concentration time profiles may be provided to examine the potential impact of ADA category, maximum titer category and NAb status on these profiles.

5.11.2. Immunogenicity and Safety

Potential association between immunogenicity variables and safety may be explored with a primary focus on the following safety events during the TEAE period:

- Injection site reaction (serious or severe and lasting 24 hours or longer)
- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylaxis (SMQ: Anaphylactic Reaction [Narrow])

The safety analyses mentioned above will be conducted using the following categories:

  - ADA Positive
- Treatment-emergent
- Treatment-boosted
  - Maximum post-baseline titer category in ADA positive participants
  - NAb positive

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the Baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of investigational product.

6.2. Data Handling Convention for Efficacy Variables

Rules for handling missing RT-qPCR test results for primary and secondary efficacy variables are described in Section 5.7 .

6.3. Data Handling Convention for Missing Data

This section includes the methods for missing data imputation and methods for missing mechanism exploration, if necessary. Missing data will not be imputed in listings. This section includes the methods for missing data imputation for some summary analyses, if necessary.

Date and Time of Study Treatment Injections

Since the study drug is administered at the site, the date and time of study drug administrations are filled in eCRF. No missing data is expected. The information is filled in eCRF. If a patient's date of the last dose is totally missing or unknown, his/her last visit date will be substituted.

Adverse Event

If the severity of a TEAE is missing, it will be classified as "severe" or "Grade 3" in the frequency tables by intensity of TEAEs. If the assessment of relationship of a TEAE to the investigational product is missing, it will be classified as related to study drug. When the partial AE date/time information does not indicate that the AE started prior to study treatment or after the TEAE period, the AE will be classified as treatment-emergent.

Medication/Procedure

If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly or stopped prior to the first study treatment administration, it will be considered as concomitant medication/procedure by imputing the start date on the date of first study treatment administration.

6.4. Visit Windows

Assessments taken outside of protocol allowable windows will be displayed according to the case report form (CRF) assessment recorded by the investigator. Data analyzed by-visit-analysis will be summarized by the scheduled visit described in protocol Schedule of Events. Below are the definitions for the visit windows programmatically imposed on all available measures from unscheduled visits collected over the course of the study including early termination visit and end of study visit. No analysis visit windows will be applied for the study scheduled visits nor for drug concentration and immunogenicity data. The visit windows are constructed using ranges

applied to the number of days in study (study days) when the measure is collected. Below are the relevant definitions for the analysis visit windows:

1. The first study treatment occurs on Study Day 1.

2. Study day is defined as the number of days since the first study treatment administration+1.

3. Since the protocol specifies that measurements be collected before study treatment is administered on a given day, it is appropriate that baseline include Day 1.

4. For randomized but not treated subjects, Day 1 is the day of randomization.

Table 1: Efficacy Analysis Windows for Unscheduled Visits with RT-qPCR or Viral Load Results

Visit Label	Targeted Study Day	Window in Study Day
Baseline	1	≤ 1
Week 1	8	[2, 11]
Week 4	29	[22, 36]
Week 8	57	[50, 64]
Week 12	85	[78, 92]
Week 16	113	[106,120]
Week 20	141	[134, 148]
Week 24	169	[162,176]
Week 28	197	[183, 211)
Week 32	225	[211, 239)
Week 36	253	[239, 267]

If a subject has multiple efficacy assessment visits within an analysis visit window, the one with worst result (e.g., the positive test result will be used for analysis if one record is positive and the

other one is negative; the highest viral load result will be used if multiple viral load results are in the same analysis window.) will be selected. If the test results are all negative, the value of the latter visit will be used. If there are multiple positive RT-qPCR results within an analysis window, the record with the highest quantitative result will be used.

Table 2: Global Analysis Windows for Data Other Than RT-qPCR Test

Visit Label	Targeted Study Day	Window in Study Day
Baseline	1	≤ 1
Week 1	8	[5, 11]
Week 4	29	[22, 36]
Week 8	57	[50, 64]
Week 12	85	[78, 92]
Week 16	113	[106,120]
Week 20	141	[134, 148]
Week 24	169	[162,176]
Week 28	197	[183, 211)
Week 32	225	[211, 239)
Week 36	253	>=239

Unscheduled For efficacy, safety laboratory data, and vital signs, unscheduled visit measurements may be used to provide a measurement for a time point, including baseline, if appropriate according to their definitions. The measurements may also be used to determine abnormal values, AESIs

6.5. Pooling of Centers for Statistical Analyses

The randomization is stratified by region. Since there is only one country for the study, region variable as a fixed effect factor will not be included in the statistical analysis model.

6.6. Statistical Technical Issues

7. INTERIM ANALYSIS

This study is terminated early and there's no planned interim analysis.

8. SOFTWARE

All analyses will be done using SAS Version 9.4 or higher.

9. REFERENCES

1. ICH. (1998, February 5). ICH Harmonized tripartite guideline: Statistical principles for clinical trials (E9). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

10. APPENDIX

10.1. Schedule of Time and Events

Table 3: 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**															
	Screen	**Pre-Dose**	**Dose**	**Post-Dose**	**8[2]**	**29**	**57**	**85**	**113**	**141**	**169**	**197 (FU 1)**	**225 (FU 2)**	**253 (EOS)**			
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 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			
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

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															
	Screen	Pre-Dose	Dose	Post-Dose	8[2]	29	57	85	113	141	169	197 (FU 1)	225 (FU 2)	253 (EOS)			
Window (Day)					±3	±7	±7	±7	±7	±7	±7	±14	±14	±14			
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							
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						

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			
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[1][3]	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		

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			
	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 4: 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

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**
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]	
	Clinician assessment of COVID-19 signs/symptoms			

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**
If SARS-CoV-2 RT-PCR is positive:	NP swab for SARS-CoV-2 RT-qPCR (central)		Every 7 (±1) days until 2 consecutive negative RT-qPCR results[6]	
	COVID-19-related MAV details			

10.2. 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

10.3. 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.

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