Clinical Development and Regulatory Affairs
Biostatistics and Data Management

REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN
VERSION: FINAL

Clinical Study Protocol Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Assessing the Efficacy and Safety of Anti-Spike SARS-CoV-2 Monoclonal Antibodies in Preventing SARS-Cov-2 Infection in Household Contacts of Individuals Infected with SARS-CoV-2

Compound:	REGN10933+REGN10987
Protocol Number:	R10933-10987-COV-2069
Clinical Phase:	Phase 3
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatistician:	[redacted]
Clinical Trial Manager:	[redacted]
Study Medical Director:	[redacted]
Version/Date:	1.0/25MAR2021

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

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
EAP	Efficacy assessment period
EOS	End of study
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	Generalized estimation equation
ICF	Informed consent form
ICH	International Council for Harmonisation
IWRS	Interactive web response system
mAb	Monoclonal antibody
NAb	Neutralizing anti-drug antibody
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
PK	Pharmacokinetic
PCSV	Potentially clinically significant value
RBC	Red blood cell
RBD	Receptor binding domain
RT-qPCR	Quantitative reverse transcription polymerase chain reaction (test; refers to the central lab testing in this protocol)
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of childbearing potential

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to database lock and unblinding. The SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of data for R10933-10987-COV-2069 study. The SAP includes multiple steps of analyses described in Section 7.

This plan may be revised during the study to accommodate protocol amendments and/or to make changes to adapt to unexpected issues in study execution and/or data that affect planned analyses. These revisions will be based on blinded data review, and a final plan will be issued prior to the first step database lock and unblinding of the individual treatment assignment.

1.1. Background/Rationale

This study will assess the use of REGN10933+REGN10987 in preventing household transmission of SARS-CoV-2. A household is defined as a group of people who live together at the same residence and share multiple living spaces (e.g., living room, bedroom, kitchen, bathroom).

1.2. Study Objectives

All subjects in the study will have household contact with the first household member known to be infected with SARS-CoV-2 infection (index case) but who are themselves either not infected or who are asymptomatic (having no active respiratory or non-respiratory symptoms consistent with COVID-19) at the time of screening. In this study, the household contact must share the same residence and have a close exposure to the first individual in the household with a known SARS-CoV-2 infection (index case).

For the analyses, there are four cohorts defined based on the subject's SARS-CoV-2 infection status at baseline, as measured by central lab SARS-CoV-2 RT-qPCR (quantitative reverse transcription polymerase chain reaction), and on the subject's age:

- For subjects with SARS-CoV-2 RT-qPCR negative at baseline, they are assigned into two cohorts:
  - Cohort A (adult and adolescent subjects [≥12 years])
  - Cohort A1 (pediatric subjects [<12 years])

or

- For subjects with SARS-CoV-2 RT-qPCR positive at baseline, they are assigned into two cohorts:
  - Cohort B (adult and adolescent subjects [≥12 years])
  - Cohort B1 (pediatric subjects [<12 years])

1.2.1. Primary Objectives

The primary objectives are for subjects who are seronegative at baseline (based on central lab test) unless stated otherwise.

Efficacy – Cohort A (Adult and adolescent subjects (≥12 years) who are SARS-CoV-2 RT-qPCR negative at baseline)

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing symptomatic SARS-CoV-2 infection (broad-term) confirmed by RT-qPCR

Efficacy – Cohort B (Adult and adolescent subjects (≥12 years) who are SARS-CoV-2 RT-qPCR positive at baseline)

- To evaluate the efficacy of REGN109333+REGN10987 compared to placebo in preventing COVID-19 symptoms (broad-term)

Safety – Cohort A and Cohort A1, Cohort B and B1

To evaluate the safety and tolerability of REGN10933+REGN10987 following subcutaneous (SC) administration compared to placebo

1.2.2. Secondary Objectives

Cohort A and Cohort A1

The following secondary objectives are for subjects who are seronegative at baseline (based on central lab test) unless stated otherwise.

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing a SARS-CoV-2 infection with a high viral load (i.e. viral load >4 (log10 copies/mL))
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of signs and symptoms in subjects with symptomatic SARS-CoV-2 infection (broad-term) confirmed by RT-qPCR
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of SARS-CoV-2 infection with a high viral load (i.e. viral load >4 (log10 copies/mL))
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of SARS-CoV-2 infection
- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing asymptomatic or symptomatic SARS-CoV-2 infection confirmed by RT-qPCR
- To evaluate the impact of treating the index case with REGN10933+REGN10987 on the incidence of SARS-CoV-2 infection among their household contacts in placebo group (note: This is a cross-study analysis based on only subjects in placebo group of R10933-10987-COV-2069 whose index cases participated in R10933-10987-COV-2067)

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing symptomatic SARS-CoV-2 infection (Centers for Disease Control and Prevention (CDC) definition) confirmed by RT-qPCR
- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing symptomatic SARS-CoV-2 infection (strict-term) confirmed by RT-qPCR
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on SARS-CoV-2 RT-qPCR viral load
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on SARS-CoV-2 infection:
  - On health care utilization
  - On absenteeism from daily responsibilities (where applicable)
- To evaluate the impact of treating any SARS-CoV-2 RT-qPCR positive household member with REGN10933+REGN10987 on the incidence of SARS-CoV-2 infection among their household contacts in placebo group (note: This is a cross-study analysis based on only subjects in placebo group of R10933-10987-COV-2069 whose index or other household member participated in R10933-10987-COV-2067 or in cohort B)
- To characterize the drug concentration-time profiles of REGN10933 and REGN10987 in serum and selected PK parameters
- To assess the immunogenicity of REGN10933 and REGN10987
- To evaluate the safety and tolerability of REGN10933+REGN10987 following SC administration in seropositive subjects
- To estimate the incidence and severity of symptomatic SARS-CoV-2 infection over time, including the period following study drug treatment, in REGN10933+REGN10987-treated seronegative and seropositive subjects compared with placebo-treated subjects
- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing symptomatic SARS-CoV-2 infection (broad-term) confirmed by RT-qPCR (cohort A1)

Cohort B and Cohort B1

Secondary objectives for Cohort B and Cohort B1 are for all seronegative subjects at baseline (by central lab test) unless stated otherwise.

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing development of:
  - Symptomatic SARS-CoV-2 infection (strict-term)
  - Symptomatic SARS-CoV-2 infection (broad-term; cohort B1)
  - Symptomatic SARS-CoV-2 infection (CDC definition)

- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of signs and symptoms in subjects with symptomatic SARS-CoV-2 infection confirmed by RT-qPCR
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of SARS-CoV-2 infection with a high viral load
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on SARS-CoV-2 viral load
- To evaluate the impact of REGN10933+REGN10987 compared to placebo in SARS-CoV-2 infection:
- On health care utilization
- On absenteeism from daily responsibilities (where applicable)
- To characterize the drug concentration-time profiles of REGN10933 and REGN10987 in serum and selected PK parameters
- To assess the immunogenicity of REGN10933 and REGN10987
- To evaluate the safety and tolerability of REGN10933+REGN10987 following SC administration
- To estimate the incidence and severity of symptomatic SARS-CoV-2 infection over time, including the period following study drug treatment, in REGN10933+REGN10987-treated subjects compared with placebo-treated subjects

1.2.3. Exploratory Objectives

Cohort A and Cohort A1

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing SARS-CoV-2 infection assessed by seroconversion in baseline seronegative subjects
- To explore the impact of REGN10987+REGN10933 compared to placebo:
  - On humoral immune response to SARS-CoV-2 infection
  - On measures of infectivity of SARS-CoV-2 as assessed in experimental laboratory assays
- To evaluate the impact of REGN10933+REGN10987 compared to placebo in SARS-CoV-2 infection in subjects who are seropositive at baseline:
  - Prevention of symptomatic infection (strict-term)
  - Prevention of symptomatic infection (broad-term)
  - Prevention of symptomatic infection (CDC definition)
  - Prevention of asymptomatic infection or symptomatic re-infection (strict-term, CDC definition, or broad-term)

- To explore the relationships between REGN10933+REGN10987 exposure and selected clinical efficacy and safety endpoints and/or biomarkers in seropositive and seronegative subjects
- To assess viral genetic variation in SARS-CoV-2 in subjects with a positive SARS-CoV-2 RT-qPCR
- To explore biomarkers (including host genome variants) associated with safety and efficacy of REGN10933+REGN10987 and to study SARS-CoV-2 (cohort A only)
- To evaluate the impact of treating any household member with anti-SARS CoV-2 monoclonal antibody on the incidence of SARS-CoV-2 infection among their household contacts. The monoclonal antibody treatment considered for this analysis are any EUA approved antibody including REGN10933+REGN10987 (within or outside of the study R10933-R10987-COV-2067)

Cohort B and Cohort B1

- To evaluate the impact of REGN10933+REGN10987 compared to placebo in seropositive subjects in preventing:
  - Symptomatic SARS-CoV-2 infection (strict-term)
  - Symptomatic SARS-CoV-2 infection (broad-term)
  - Symptomatic SARS-CoV-2 infection (CDC definition)
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of signs and symptoms in seropositive subjects with symptomatic SARS-CoV-2 infection confirmed by RT-qPCR
- To evaluate the impact of REGN10933+REGN10987 compared to placebo in seropositive subjects on SARS-CoV-2 RT-qPCR viral load
- To evaluate the impact of REGN10933+REGN10987 compared to placebo in seropositive subjects on SARS-CoV-2 infection:
  - On health care utilization
  - On absenteeism from daily responsibilities (where applicable)
- To explore the impact of REGN10987+REGN10933 compared to placebo in subjects, by their baseline serology test status (e.g., seropositive or seronegative, based on central lab test) on SARS-CoV-2 infection:
  - On humoral immune response
  - On measures of infectivity of SARS-CoV-2 as assessed in experimental laboratory assays
- To explore the relationships between REGN10933+REGN10987 exposure and selected clinical efficacy and safety endpoints and/or biomarkers in seropositive and seronegative subjects

- To assess viral genetic variation in SARS-CoV-2 in subjects with a positive SARS-CoV-2 RT-qPCR.
- To explore biomarkers (including host genome variants) associated with safety and efficacy of REGN10933+REGN10987 and to study SARS-CoV-2

1.2.4. Modifications from the Statistical Section in the Final Protocol

There are no modifications compared to protocol amendment 6.

1.2.5. Revision History for SAP Amendments

This is the first version of SAP.

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This is a phase 3 randomized, double-blind, placebo-controlled study in adults/adolescent subjects (≥12 years) and pediatric subjects (<12 years of age) who are household contacts of the first known household member infected with SARS-CoV-2 (index case). All subjects in the study are asymptomatic (having no active respiratory or non-respiratory symptoms consistent with COVID-19) at the time of screening. The index case will have a diagnosis of SARS-CoV-2 infection using a diagnostic test, e.g., RT-PCR, antigen test, or other test format (approved or with Emergency Use Authorization issued by the US FDA or by local health authority). Randomization will be performed by individual study subjects, not by households. Some of the index cases of household contacts in this study may be participating in a separate treatment study (R10933-10987-COV-2067).

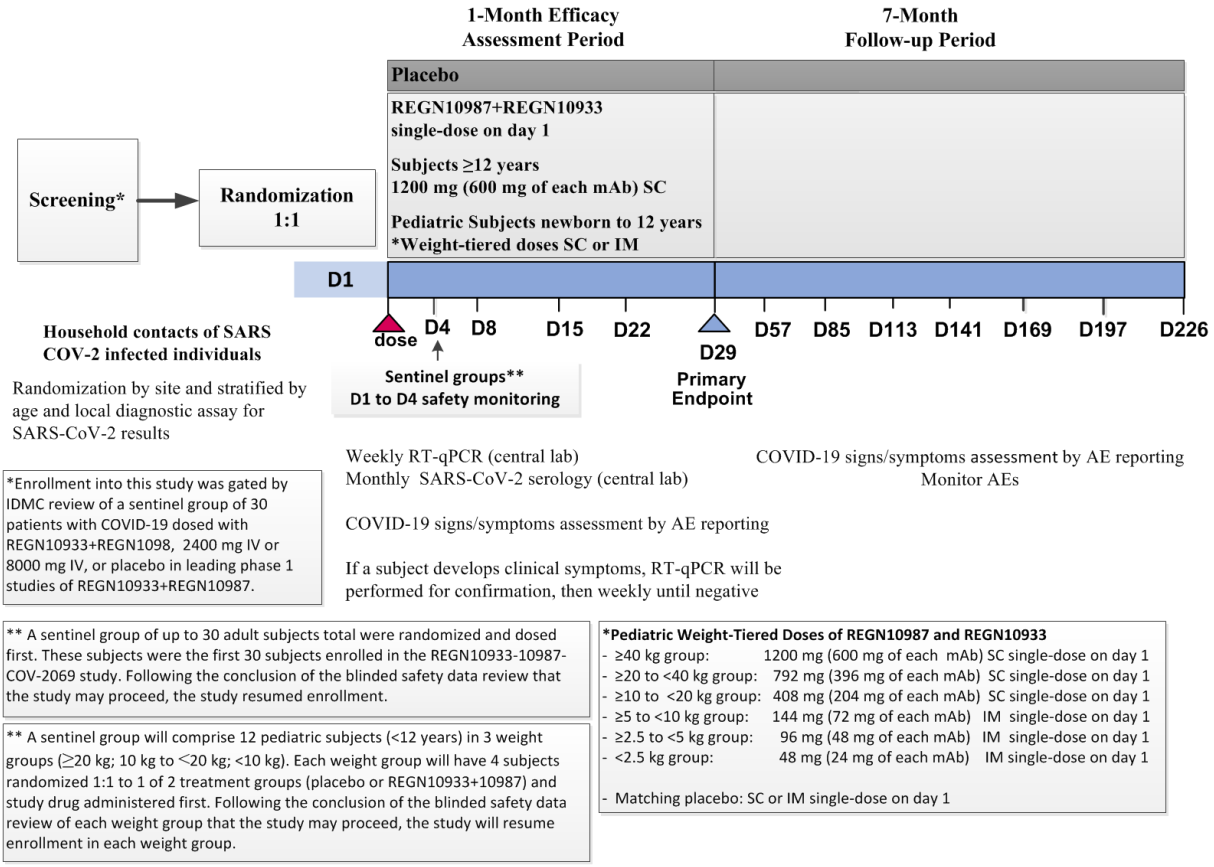
Randomization will be performed by site and stratified for assigning subjects in a 1:1 allocation ratio to placebo or REGN10933+REGN10987 [1200 mg (600 mg of each mAb SC). Randomization stratifications are test results (positive, negative, or unavailable) of a local diagnostic assay for SARS-CoV-2 (e.g., molecular assay such as RT-PCR assay for SARS-CoV-2 or a SARS-CoV-2 antigen test) from appropriate samples, e.g., nasopharyngeal (NP), oropharyngeal (OP), nasal, or saliva, and age group (<12 years, ≥12 to <18 years, ≥18 to <50 years, or ≥50 years). For pediatric subjects (<12 years), the weight group (≥20 kg, ≥10 to <20 kg, and <10 kg) will be used as an additional stratification factor.

The study was originally planned to enroll 2000 adult and adolescent subjects. A blinded analysis of approximately 25% of enrolled subjects in this study was performed, demonstrating that higher than expected seropositivity was observed in cohort A. In addition, an unblinded administrative analyses was performed on the data based on 554 subjects to verify assumptions and adequacy of sample size. The subjects who were included in the administrative assessment will not be included in the final efficacy analysis. Thus, sample size was increased to accommodate higher seropositivity rate and the unblinded administrative assessment. The total study population was planned to be approximately 3500 adult and adolescent subjects (~3150 subjects in cohort A and ~350 subjects in cohort B) including 554 cohort A subjects in the administrative assessment and approximately 250 pediatric subjects <12 years old (~225 subjects in cohort A1 and 25 subjects in cohort B1), with household contact exposure to individual with a confirmed SARS-CoV-2 infection.

Statistical analyses will be conducted separately in each cohort. For the purpose of the study analysis, cohorts A, A1, B, and B1 are independent. As specified earlier, the 554 subjects in the administrative assessment will not be included in the final efficacy analyses (first step analysis) however, these subjects will be included in the safety analyses. Also, the final efficacy analysis (first step analysis) will include only subjects randomized on or before January 28, 2021. The total number of subjects to be included in the first step analysis is approximately 2459. The subjects randomized after January 28, 2021 will remain blinded until the final analysis but will not be part of any formal statistical testing.

For each subject, the study comprises 3 periods: a 1-day screening/baseline period, a 1-month EAP, and a 7-month follow-up period (See Figure 1).

Figure 1: Study Flow Diagram



The schedule of events tables for this study can be found in the Appendix 10.2.

2.2. Sample Size and Power Considerations

2.2.1. Cohort A

The primary hypothesis is the reduction in the proportion of symptomatic RT-qPCR (broad-term) confirmed SARS-CoV-2 infections in seronegative subjects. To calculate the sample size to achieve at least 90% power for seronegative subjects in cohort A, it is assumed that the statistical hypothesis will be tested in a 2-sided test. Based on the administrative assessment results among 409 seronegative subjects in cohort A, an approximately 50% reduction of infection (symptomatic or asymptomatic) compared to placebo group and a 100% reduction of symptomatic infection compared to placebo group was observed. Due to the small sample size in the administrative assessment, it was assumed, for the purpose of assessing study power, that an approximately 50% reduction or greater in symptomatic infections compared to the placebo group will be expected for the final primary efficacy analysis.

In this household study design, the number of subjects per household, the correlation between subjects and symptomatic infection rates within a household are unknown. To detect a relative risk of 0.5 (i.e., 50% reduction of the assumed 10% attack rate in the placebo arm), equivalent to an odds ratio of 0.47, power was calculated compared to the p-value of 0.05 based on 2000

simulations in 1248 subjects from 430 households (i.e., assuming an average household size of 2.9 seronegative subjects). Table 1 provides power calculations by varying degrees of correlation within household. In all cases, the power of the study is >90% using a generalized linear model with the generalized estimation equation (GEE) approach assuming a compound symmetry covariance matrix.

Table 1: Simulated Power for Household Design (1248 Subjects over 430 Households)

Placebo Attack Rate	REGN10933+ REGN10987 Attack Rate	Correlation within Household	Average Odds Ratio REGN10933+REGN10987 versus Placebo	Power
10%	5%	0.1	0.485	0.914
10%	5%	0.2	0.485	0.934
10%	5%	0.3	0.480	0.956
10%	5%	0.4	0.481	0.972
10%	5%	0.5	0.476	0.983
10%	5%	0.6	0.478	0.999

At least 1980 subjects will need to be enrolled in cohort A to have a minimum of 1248 seronegative subjects, assuming that 10% of subjects drop out, and 30% of subjects are seropositive at baseline.

The correlation among subjects within each household, the rates for seronegativity, and the rates for seropositivity will be monitored in a blinded fashion. The 2 assumptions, that 90% of randomized subjects will have a baseline negative RT-qPCR and be assigned to cohort A and that 70% of these subjects in cohort A are seronegative, will be monitored periodically to ensure that there will be a sufficient number of seronegative subjects (~1248) enrolled in Cohort A to be included in the primary analysis. This will maintain the planned statistical power.

2.2.2. Cohort B

The primary endpoint in asymptomatic seronegative subjects in cohort B is the proportions of subjects who subsequently develop signs and symptoms (broad term) within 14 days of a positive RT-qPCR test result at baseline or during the EAP.

The sample size of Cohort B is based on the frequency of finding positive subjects while enrolling Cohort A and assumes that approximately 10% of subjects in a household are already positive for SARS-CoV-2 by RT-qPCR at baseline. Among approximately 3500 adult and adolescent subjects that will be enrolled in cohort A or cohort B, the number of subjects expected in Cohort B is approximately 220 or higher, including 200 seronegative subjects. Assuming that 50% of infected placebo subjects at baseline will develop symptoms, 200 seronegative subjects in cohort B will provide >90% power to detect a relative risk of 0.5, using a 2-sided Fisher's exact test at an alpha level of 0.05.

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

Seronegative Modified Full Analysis Set (Seronegative mFAS-A) – Cohort A

The seronegative modified full analysis set for Cohort A (Seronegative mFAS-A) includes all randomized subjects aged 12 years and older who are laboratory confirmed negative for SARS-CoV-2 (per central lab PCR test) and who test negative for antibodies for SARS-CoV-2 (per central lab serology testing) at baseline.

Subjects included in the administrative assessment analysis are excluded from the Seronegative mFAS-A population.

Subjects will be analyzed based on the randomized treatment assignment. The seronegative mFAS-A population is the primary analysis population for the primary and secondary endpoints for Cohort A of this study unless specified otherwise.

Note: There are three antibody assays used for serology test: EuroImmun anti-S IgA, EuroImmun anti-S IgG, and Abbott anti-N IgG (Architect). Seronegative is defined as all available test results are negative. Seropositive is defined as 1 or more available test results are positive.

Seronegative Modified Full Analysis Set (Seronegative mFAS-A1) – Cohort A1

The seronegative modified full analysis set for Cohort A1 (seronegative mFAS-A1) includes all randomized subjects aged less than 12 years who are laboratory confirmed negative for SARS-CoV-2 (per central lab PCR test) and who test negative for antibodies for SARS-CoV-2 (per central lab serology testing) at baseline.

Subjects will be analyzed based on the randomized treatment assignment. The efficacy endpoints for Cohort A1 will be analyzed using the seronegative mFAS-A1 unless specified otherwise.

Seronegative Modified Full Analysis Set (Seronegative mFAS-B) – Cohort B

The seronegative modified full analysis set for Cohort B (seronegative mFAS-B) includes all randomized subjects aged 12 years and older who have laboratory confirmed positive tests at baseline for SARS-CoV-2 RT-qPCR and negative SARS-CoV-2 serology (both based on central lab testing) at baseline and are asymptomatic. Subjects will be analyzed based on the randomized treatment assignment. The primary and secondary efficacy endpoints for cohort B will be analyzed using the seronegative mFAS-B unless specified otherwise.

Seronegative Modified Full Analysis Set (Seronegative mFAS-B1) – Cohort B1

The seronegative modified full analysis set for Cohort B1 (seronegative mFAS-B1) includes all randomized subjects aged less than 12 years who have laboratory confirmed positive tests at baseline for SARS-CoV-2 RT-qPCR and negative SARS-CoV-2 serology (both based on central lab testing) at baseline and are asymptomatic. Subjects will be analyzed based on the randomized

treatment assignment. The efficacy endpoints for Cohort B1 will be analyzed using the seronegative mFAS-B1 unless specified otherwise.

3.2. The Safety Analysis Set (SAF)

The safety analysis set (SAF) includes all randomized subjects who received at least 1 dose or part of a dose of study drug. Subjects in the SAF will be analyzed based on the treatment received (as treated). In general, safety will be evaluated by study cohort: SAF-A (Cohort A), SAF-B (Cohort B), SAF-A1(Cohort A1), and SAF-B1 (Cohort B1). However, injection site reactions will also be based on all cohorts combined.

3.3. Pharmacokinetic Analysis Set

The PK analysis set includes all subjects who received any study drug and who had at least 1 non-missing drug concentration measurement following study drug administration. Subjects will be analyzed based on actual treatment received.

3.4. Immunogenicity Analysis Sets

3.4.1. Anti-drug Antibodies Analysis Set

The ADA analysis set (AAS) includes all subjects who received study drug and had at least 1 non-missing ADA result after study drug administration. Subjects will be analyzed based on the actual treatment received

3.4.2. Neutralizing Antibody Analysis Set

The NAb analysis set (NAS) includes all subjects who received any study drug and who are either negative in the ADA assay or positive for ADA with at least one non-missing result in the NAb assay after first dose of the study drug. Subjects who are ADA negative are set to negative in the NAb analysis set. Subjects will be analyzed according to the treatment actually received.

4. ANALYSIS VARIABLES

For each subject, demographic and baseline characteristics will be obtained from the last available value up to the date of the first study treatment administration (i.e., baseline definition). For subjects randomized but not treated, the baseline value is defined as the last available value prior to or on the date of randomization. If a subject was randomized over once, the latest randomization record will be used for analysis.

4.1. Demographic and Baseline Characteristics

The following demographic variables will be summarized:

- Age in years (continuous and categorical variable for subjects≥12 years will be categorized as follows: ≥12 to <18, ≥18 to <50, ≥50 to <65, ≥65 to <80, ≥80 years)
- Sex (Male, Female)
- Race (American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White and Other, where "Other" may include, for example, not reported, unknown, and multiracial, etc.)
- Ethnicity (Hispanic or Latino with further subgroups [Black Hispanic or Latino and White Hispanic or Latino], not Hispanic or Latino with further subgroups [Black not Hispanic or Latino and White not Hispanic or Latino], not reported, and unknown)

Baseline characteristic variables include:

- Weight (kg) (quantitative and qualitative variable for pediatric subjects: <10, ≥10 to <20, and ≥20)
- Height (cm)
- Body mass index (BMI) (kg/m^2) (quantitative and qualitative variable for subjects ≥12 years: <30 and ≥30)
- Randomization strata: local RT-qPCR status and age
- Region (US vs ex-US) and country
- Total household size including the house member(s) not participating this study
- Number of study subjects within household and cohort
- Index case interaction and household risk factors (e.g., share a bedroom, share a common room, no one wears a mask in home, etc.) per eCRF
- Status of index case participating R10933-10987-COV-2067
- Total household members, including index case, who participate the R10933-10987-COV-2067
- Infection risks (e.g. healthcare worker (Yes/ No), received influenza vaccine in last 14 days (Yes/No), first responder (Yes/No), Need to contact strangers on a regular basis (Yes/No), etc.) per exposure risk factors eCRFs

- Baseline overall serology status and observed combinations of three serology antibody assays
- Viral load (log10 copies/mL) at baseline for subject in cohort B
- Days between baseline central RT-qPCR test and study drug administration
- Baseline high risk subjects with at least one of the following criteria:
  - ≥65 years of age
  - BMI ≥35
  - Chronic kidney disease
  - Diabetes
  - Immunosuppressive disease
  - Are currently receiving immunosuppressive treatment

Are ≥55 years of age AND have cardiovascular disease OR hypertension OR chronic obstructive pulmonary disease

4.2. Medical History

Medical history will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the latest available version of Medical Dictionary for Regulatory Activities (MedDRA®).

4.3. Pre-Treatment / Concomitant Medication

Medications/Procedures will be recorded from the day of informed consent until the end-of-study (EOS) visit. Medications will be coded to the ATC level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug Dictionary (WHODD, Drug Global version SEP2020 B3). Subjects will be counted once in all ATC categories linked to the medication.

Prior medications/procedures: medications taken, or procedures performed prior to administration of the first study drug.

Concomitant medications/procedures during treatment-emergent EAP: medications taken or procedures performed in the period from the day of the first dose of study drug to 28 days after the last dose of study drug 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 treatment-emergent EAP.

Concomitant medications/procedures during the treatment-emergent follow-up period: medications taken, or procedures performed from the day after the end of treatment-emergent EAP to the final study visit or started during the treatment-emergent EAP and are ongoing after treatment-emergent EAP.

4.4. Prohibited Medications

The definition of prohibited medications is described in the section 8.9 of the protocol. They will be reviewed and identified by the study clinician and reported in protocol deviations.

4.5. Efficacy Variable

Unless otherwise specified, the baseline assessment is the last available measurement prior to the date of the study treatment administration. For subjects randomized but not treated, the baseline value is defined as the last available value prior to the date of randomization. Unless otherwise specified, all efficacy endpoints will be analyzed based on seronegative subjects in the corresponding cohort.

The definitions of broad-term, strict-term, and CDC definition symptoms are as follows:

Strict term:

- Fever (≥38°C) PLUS ≥1 respiratory symptom (sore throat, cough, shortness of breath)

OR

- 2 respiratory symptoms (sore throat, cough, shortness of breath)

OR

- 1 respiratory symptom (sore throat, cough, shortness of breath) PLUS ≥2 non-respiratory symptoms (chills, nausea, vomiting, diarrhea, headache, conjunctivitis, myalgia, arthralgia, loss of taste or smell, fatigue or general malaise)

Broad term:

ANY of the following:

1. Fever ≥38°C
2. Feverish
3. Sore throat
4. Cough
5. Shortness of breath/difficulty breathing *(nasal flaring*)*
6. Chills
7. Nausea
8. Vomiting
9. Diarrhea
10. Headache
11. Red or watery eyes *(conjunctivitis)*
12. Body aches such as muscle pain or joint pain *(myalgia, arthralgia)*
13. Loss of taste/smell
14. Fatigue *(fatigue or general malaise or lethargy*)*
15. Loss of appetite or poor eating/feeding
16. Confusion
17. Dizziness
18. Pressure/tightness in chest
19. Chest pain

20. Stomachache (*Abdominal pain**)
21. Rash
22. Sneezing
23. Runny nose
24. Sputum/phlegm
25. Other

**Signs and symptoms observed in pediatric subjects (age<12 years)*

CDC definition

At least two of the following symptoms: fever (measured, i.e., fever ≥38°C, or subjective, i.e., feverish), chills, rigors, myalgia, headache, sore throat, nausea or vomiting, diarrhea, fatigue, congestion or runny nose

OR

Any one of the following symptoms: cough, shortness of breath, difficulty breathing, new olfactory disorder, new taste disorder

OR

Severe respiratory illness with at least one of the following, clinical or radiographic evidence of pneumonia, acute respiratory distress syndrome (ARDS)

Note: Fever information will be collected from the fever assessment eCRF, and signs and symptoms will be collected from COVID-19 symptoms eCRF.

The following general rules will be used for efficacy variables and all SARS-CoV-2 RT-qPCR test results are based on the central lab testing:

- For cohort determination, qualitative PCR results from swabs taken prior to or within 2 hours of study drug administration will be used if there are no available test results prior to study drug administration.
- Quantitative values of viral load will be determined based on NP swabs only. For baseline viral load, only RT-qPCR results from swabs taken prior to dosing will be used.
- A positive infection will be defined based on any available RT-qPCR result (either NP, nasal or saliva) which is reported as "detected". A negative infection will be defined based on all available RT-qPCR results (either NP, nasal or saliva) which are reported as "not detected".
- Symptomatic SARS-CoV-2 infection (broad-term) is defined as a positive central lab SARS-CoV-2 RT-qPCR result (either NP, nasal or saliva) associated with signs and symptoms with the onset date occurring within 14 days of a positive RT-qPCR during the EAP.
- For subjects in Cohort B, symptomatic SARS-CoV-2 infection (broad-term) is defined as having at least one signs and symptoms with the onset date occurring within 14 days of a positive RT-qPCR (either NP, nasal or saliva) at baseline or during the EAP.

- Viral loads less than the lower limit of quantification of the PCR assay but with positive qualitative results will be set to half of the lower limit of quantification of the PCR assay; values with nondetectable RNA will be set to 0 $\log_{10}$ copies/mL Viral load values above the upper limit of quantification will be re-tested using the reflex test and the corresponding quantitative value will be used in the analysis.

4.5.1. Cohort A Primary Efficacy Variable

The primary efficacy variable in Cohort A is:

- Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP

A symptomatic RT-qPCR confirmed SARS-CoV-2 infection during the EAP will be any positive post-baseline RT-qPCR obtained during the EAP in which the subject experiences COVID-19 related signs or symptoms within 14 days of a positive test.

4.5.2. Cohort A Key Secondary Efficacy Variables

The key secondary efficacy variables listed below include two types of variables: binary (B) and continuous (C) variables.

Key Secondary Efficacy Variables	Type	Cohort A
Proportion of subjects with viral load >4 (log10 copies/mL) in NP swab samples during the EAP	B	X
Number of weeks of symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP	C	X
Number of weeks of high viral load >4 (log10 copies/mL) in NP swab samples during the EAP	C	X
Number of weeks of RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP	C	X
Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP	B	X
Proportion of subjects in placebo group with a RT-qPCR confirmed SARS-CoV-2 infection during the EAP with an index case participating in Study R10933-10987-COV-2067 (comparison of those whose index cases receive REGN10933+REGN10987 vs placebo in Study R1033-10987-COV-2067)	C	X

Duration of symptomatic infection (weeks) is defined as (the end date of all symptoms minus the date of the first symptom+1)/7, where a symptom is defined in Section 4.5. If the symptom is ongoing at the time of the first step analysis, the end date of the symptom will be set as the cutoff date for the first step analysis.

4.5.3. Cohort A and Cohort A1 Other Secondary Efficacy Variables

The secondary efficacy variables listed below include two types of variables: binary (B) and continuous (C) variables and marked for the corresponding cohort.

Other Secondary Efficacy Variables	Type	Cohort	
		A	A1
Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (CDC definition) during the EAP	B	X	X
Number of weeks of symptomatic RT-qPCR-confirmed SARS-CoV-2 infection (CDC definition) during the EAP	C	X	X
Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (strict-term) during the EAP	B	X	X
Number of weeks of symptomatic RT-qPCR-confirmed SARS-CoV-2 infection (strict-term) during the EAP	C	X	X
Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection at each week in the EAP	B	X	X
Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad term) at each week in the EAP	B	X	X
Time-weighted average of viral load (log10 copies/mL) from the first positive SARS-CoV-2 RT-qPCR in NP swab samples (that has an onset during the EAP) until the third weekly visit after the first positive test during the EAP *Note: Only for RT-qPCR positive subjects during the EAP in the Seronegative mFAS-A set*	C	X	X
Time-weighted average of viral load (log10 copies/mL) from the first positive SARS-CoV-2 RT-qPCR in NP swab samples (that has an onset during the EAP) until the second weekly visit after the first positive test during the EAP *Note: Only for RT-qPCR positive subjects during the EAP in the Seronegative mFAS-A set*	C	X	X
Maximum SARS-CoV-2 RT-qPCR viral load (log10 viral copies/mL) in NP swab samples among individuals with ≥1 RT-qPCR positive that has an onset during the EAP	C	X	X
SARS-CoV-2 RT-qPCR viral load (log10 viral copies/mL) in NP swab samples corresponding to the onset of first positive RT-qPCR during the EAP	C	X	X
Area under the curve (AUC) in viral load (log10 copies/mL) from the first positive SARS-CoV-2 RT-qPCR NP swab samples detected during the EAP until the first confirmed negative test (testing that occurs after the EAP will be included if necessary to achieve a negative test result).	C	X	X

Note: Only for RT-qPCR positive subjects during the EAP in the Seronegative mFAS-A set			
Number of medically attended visits in emergency rooms or urgent care centers related to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP	C	X	X
Proportion of subjects with at least one COVID-19 related hospitalization or emergency room visit associated with a positive RT-qPCR during the EAP, or all-cause death	B	X	X
Proportion of subjects requiring medically attended visits in emergency rooms or urgent care centers related to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP	B	X	X
Proportion of subjects hospitalized related to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP	B	X	X
Number of days of hospital and intensive care unit (ICU) stay in subjects hospitalized for a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP	C	X	X
Number of days missed for daily responsibilities (where applicable), including work (employed adults) or school (students), daycare or family obligations/responsibilities (childcare or eldercare) due to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP	C	X	X
Proportion of subjects in placebo group with a RT-qPCR confirmed SARS-CoV-2 infection during the EAP with at least one household member participating either in R10933-10987-COV-2067 or in cohort B (comparison of those whose households members receive REGN10933+REGN10987 vs placebo in R1033-10987-COV-2067 or in Cohort B)	B	X	X
Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP	B		X
Proportion of subjects with viral load >4 (log10 copies/mL) in NP swab samples during the EAP	B		X
Number of weeks of symptomatic RT-qPCR-confirmed SARS-CoV-2 infection (broad-term) during the EAP	C		X
Number of weeks of high-viral load >4 (log10 copies/mL) in NP swab samples during the EAP	C		X
Number of weeks of RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP	C		X
Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP	B		X

Proportion of subjects in placebo group with a RT-qPCR confirmed SARS-CoV-2 infection during the EAP with an index case participating in R10933-10987-COV-2067 (comparison of those whose index cases receive REGN10933+REGN10987 vs placebo in R1033-10987-COV-2067)	C		X

Time-weighted average (TWA) of viral load (log10 copies/mL) in NP swab samples from the day of the first positive SARS-CoV-2 RT-qPCR (central lab) to the third weekly visit after the first positive test visit: all observed viral load data from the first positive visit to the third weekly visit will be calculated using the trapezoidal rule as the area under the curve divided by this observational period as follows:

$$TWA = AUC/(t_k - t_1) = [\sum_{i=2}^{k=3} (t_i - t_{i-1}) * (V_i + V_{i-1})/2]/(t_k - t_1)$$

where V_i is the result of viral load (log10 copies/mL) at time point t_i. V_1 is the result of the viral load (log10 copies/mL) for the first positive SARS-CoV-2 RT-qPCR at timepoint t_1. If the V_i is not available at the scheduled time point t_i or missing due to failed test or other reasons, only the time points with non-missing values will be included for TWA calculation. If there are duplicate samples at a time point, the highest viral result will be used for analysis.

Note: For TWA of viral from the first positive to the second weekly visit after the first positive test visit endpoint, all observed viral load data from the first positive visit to the second weekly visits will be calculated using the same formula described above.

4.5.4. Cohort A and Cohort A1 Exploratory Efficacy Variables

The following exploratory variables are for both Cohort A and Cohort A1. Some of the endpoints will mature and be assessed after all subjects complete the study. For continuous variables the analysis only applies to subjects who have a positive central lab SARS-CoV-2 RT-qPCR test (based on observed data) during the EAP.

Exploratory Variables	Type
Proportion of baseline-seronegative subjects who have a first RT-qPCR confirmed SARS-CoV-2 infection in the follow-up period (i.e. after Day 29 visit)	B
Proportion of baseline-seronegative subjects who become seropositive (based on central lab test) up to day 57 (Note: For post-treatment serology, only antibody assay(s) that do not bind to REGN10933 or REGN10987 will be used to define the endpoint)	B
Proportion of baseline-seropositive subjects (based on central lab test) who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (strict-term) SARS-CoV-2 infection during the EAP	B
Proportion of subjects with negative RT-qPCR (based on central lab test) regardless of the serology status at baseline who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (strict-term) SARS-CoV-2 infection during the EAP	B

Proportion of baseline-seronegative or baseline-seropositive subjects with negative RT-qPCR (based on central lab test) who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (strict-term) SARS-CoV-2 infection during the EAP	B
Proportion of baseline-seropositive subjects (based on central lab test) who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (broad-term) SARS-CoV-2 infection during the EAP	B
Proportion of subjects with negative RT-qPCR (based on central lab test) regardless of serology status at baseline who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (broad-term) SARS-CoV-2 infection during the EAP	B
Proportion of baseline-seronegative or baseline-seropositive subjects with negative RT-qPCR (based on central lab test) who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (broad-term) SARS-CoV-2 infection during the EAP	B
Proportion of baseline-seropositive subjects (based on central lab test) who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (CDC definition) SARS-CoV-2 infection during the EAP	B
Proportion of subjects with negative RT-qPCR (based on central lab test) regardless of serology status at baseline who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (CDC definition) SARS-CoV-2 infection during the EAP	B
Proportion of baseline-seronegative or baseline-seropositive subjects with negative RT-qPCR (based on central lab test) who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (CDC definition) SARS-CoV-2 infection during the EAP	B
Proportion of baseline-seropositive subjects (based on central lab test) who subsequently have a positive SARS-CoV-2 RT-qPCR during the EAP	B
Time-weighted average of viral load (log10 copies/mL) from the first positive SARS-CoV-2 RT-qPCR in NP swab sample (that has an onset during the EAP) until third weekly visit after the first positive test in seropositive subjects (based on central lab test) during the EAP	C
Time-weighted average of viral load (log10 copies/mL) from the first positive SARS-CoV-2 RT-qPCR in NP swab sample (that has an onset during the EAP) until the second weekly visit after the first positive test in seropositive subjects (based on central lab test) during the EAP	C
Area under the curve (AUC) in viral load (log10 copies/mL) in NP swab samples from the first positive SARS-CoV-2 RT-qPCR NP swab sample until the first confirmed negative test, in seropositive subjects (based on central lab test) that has an onset during the EAP *Note: Only for RT-qPCR positive subjects during the EAP with confirmed negative tests in the seronegative mFAS*	C
Proportion of subjects in placebo group who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP by the status of household members participating in study R10933-10987-COV-2067 and receiving REGN10933+REGN10987 or whose household member did not receive treatment with REGN10933+REGN10987	B
Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP by the status of household members participating in study R10933-10987-COV-2067 and receiving REGN10933+REGN10987	B
Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP by the status of household members receiving an approved monoclonal antibody treatment for COVID-19	B

Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP by the status of household members receiving an approved monoclonal antibody treatment for COVID-19 or REGN10933+REGN10987 in study R10933-R10987-COV-2067	B
Maximum RT-qPCR viral load (log10 copies/mL) in NP swab samples during the EAP in subjects who have asymptomatic infection during the EAP	C
Maximum RT-qPCR viral load (log10 copies/mL) in NP swab samples during the EAP in subjects who have symptomatic infection during the EAP	C
Maximum RT-qPCR viral load (log10 copies/mL) in NP swab samples during the EAP in subjects who have a medically attended visit	C

4.5.5. Cohort B Primary Efficacy Variable

The primary efficacy variable for Cohort B is:

- Proportion of subjects who subsequently develop signs and symptoms (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP

4.5.6. Cohort B Key Secondary Efficacy Variables

The key secondary efficacy variables listed below are continuous (C) variables.

Key Secondary Efficacy Variables	Type
Number of weeks of symptomatic SARS-CoV-2 infection (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP	C
Number of weeks of high viral load >4 (log10 copies/mL) in NP swab samples during the EAP	C

4.5.7. Cohort B and Cohort B1 Other Secondary Efficacy Variables

The secondary efficacy variables listed below include two types of variables: binary (B) and continuous (C) variables and marked for the corresponding cohort.

Other Secondary Efficacy Variables	**Type**	**Cohort**	
		B	**B1**
Proportion of subjects who subsequently develop signs and symptoms (CDC definition) within 14 days of a positive RT-qPCR at baseline or during the EAP	B	X	X
Proportion of subjects who subsequently develop signs and symptoms (strict-term) within 14 days of a positive RT-qPCR at baseline or during the EAP	B	X	X

Number of weeks of symptomatic SARS-CoV-2 infection (CDC definition) within 14 days of a positive RT-qPCR at baseline or during the EAP	C	X	X
Number of weeks of symptomatic SARS-CoV-2 infection (strict-term) within 14 days of a positive RT-qPCR at baseline or during the EAP	C	X	X
Proportion of subjects with viral load >4 (log10 copies/mL) in NP swab samples during the EAP	B	X	X
Change in viral load (log10 copies/mL) from baseline to Day 8 visit in NP swab samples	C	X	X
Change in viral load (log10 copies/mL) from baseline to Day 15 visit in NP swab samples	C	X	X
Time-weighted average change from baseline in viral load (log10 copies/mL) in NP swab samples until the Day 22 visit	C	X	X
Area under the curve (AUC) in viral load (log10 copies/mL) in NP swab samples from baseline to the first confirmed negative test	C	X	X
Maximum SARS-CoV-2 RT-qPCR viral load (log10 copies/mL) in NP swab samples during the EAP	C	X	X
Number of medically attended visits in emergency rooms or urgent care centers related to RT-qPCR confirmed SARS-CoV-2 infection that has an onset at baseline or during the EAP	C	X	X
Proportion of subjects requiring medically attended visits in emergency rooms or urgent care centers related to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset at baseline or during the EAP	B	X	X
Proportion of subjects hospitalized related to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset at baseline or during the EAP	B	X	X
Number of days of hospital and ICU stay in subjects hospitalized for a RT-qPCR confirmed SARS-CoV-2 infection that has an onset at baseline or during the EAP	C	X	X
Number of days missed for daily responsibilities (where applicable), including work (employed adults) or school	C	X	X

(students), or family obligations/responsibilities (childcare or eldercare) due to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset at baseline or during the EAP			
Proportion of subjects with at least one COVID-19 related hospitalization or emergency room visit associated with a positive RT-qPCR at baseline or during the EAP, or all-cause death	B	X	X
Proportion of subjects who subsequently develop signs and symptoms (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP	B		X
Number of weeks of symptomatic SARS-CoV-2 infection (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP	C		X
Number of weeks of high viral load >4 (log10 copies/mL) in NP swab samples during the EAP	C		X

Time-weighted average (TWA) of change from baseline in viral load until the Day 22 visit: All observed viral load data from baseline to Day 22 visit will be calculated for each subject using the trapezoidal rule as the AUC for change from baseline at each time point divided by the time interval of this observational period as follows:

$$TWA = AUC/(t_k - t_1) = [\sum_{i=2}^{k=4}(t_i - t_{i-1}) * (D_i + D_{i-1})/2]/(t_k - t_1)$$

Where D_i is the change from baseline (t_1) in viral load (log10 copies/mL) obtained at time t_i and D_1 =0. If the D_i is not available or missing due to failed test or other reasons, only the time points with non-missing values will be included for TWA calculation. If there are duplicate samples at a time point, the highest viral result (log10 copies/ml) will be used for analysis.

For TWA of percent change from baseline, variable Pi will be applied to the formula above instead of Di, where Pi=Di/baseline.

4.5.8. Cohort B and Cohort B1 Exploratory Variables

The following exploratory variables are for both Cohort B and Cohort B1.

Exploratory Variables	Type
Proportion of subjects who subsequently have symptomatic (strict-term) SARS-CoV-2 infection confirmed by RT-qPCR within the EAP according to their baseline serology test status (i.e., seropositive or other, based on central lab test)	B

Proportion of subjects who subsequently have symptomatic (broad-term) SARS-CoV-2 infection confirmed by RT-qPCR within the EAP according to their baseline serology test status (i.e., seropositive or other, based on central lab test)	B
Proportion of subjects who subsequently have symptomatic (CDC definition) SARS-CoV-2 infection confirmed by RT-qPCR within the EAP according to baseline serology test status (i.e., seropositive or other, based on central lab test)	B
Number of weeks of symptomatic SARS-CoV-2 infection (strict-term) within 14 days of a positive RT-qPCR at baseline or during the EAP, according to baseline serology test status (i.e., seropositive or other, based on central lab test)	C
Number of weeks of symptomatic SARS-CoV-2 infection (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP, according to baseline serology test status (i.e., seropositive or other, based on central lab test)	C
Number of weeks of symptomatic SARS-CoV-2 infection (CDC definition) within 14 days of a positive RT-qPCR at baseline or during the EAP, according to baseline serology test status (i.e., seropositive or other, based on central lab test)	C
Time-weighted average change and percent change from baseline viral load (log10 copies/mL) in NP swab samples until the Day 22 visit according to baseline serology test status (i.e., seropositive or other, based on central lab test)	C
Area under the curve (AUC) in viral load (log10 copies/mL) in NP swab samples from baseline to the first confirmed negative test according to baseline serology test status (i.e., seropositive or other, based on central lab test)	C
Maximum SARS-CoV-2 RT-qPCR (log10 viral copies/mL) in NP swab samples during the EAP according to baseline serology test status (i.e., seropositive or other, based on central lab test)	C
Number of medically attended visits in emergency rooms or urgent care centers related to RT-qPCR confirmed SARS-CoV-2 infection at baseline or during the EAP, according to baseline serology test status (i.e., seropositive or other, based on central lab test)	C
Proportion of subjects requiring medically attended visits in emergency rooms or urgent care centers related to a RT-qPCR confirmed SARS-CoV-2 infection at baseline or during the EAP, according to baseline serology test status (i.e., seropositive or other, based on central lab test)	B
Proportion of subjects hospitalized related to a RT-qPCR confirmed SARS-CoV-2 infection at baseline or during the EAP, according to baseline serology test status (i.e., seropositive or other, based on central lab test)	B

Number of days of hospital and ICU stay in subjects hospitalized for a RT-qPCR confirmed SARS-CoV-2 infection at baseline or during the EAP, according to baseline serology test status (i.e., seropositive or other, based on central lab test)	C
Number of days missed for daily responsibilities (where applicable), including work (employed adults) or school (matriculating students), or family obligations/responsibilities (childcare or eldercare) due to a RT-qPCR confirmed SARS-CoV-2 infection at baseline or during the EAP, according to baseline serology test status (i.e., seropositive or other, based on central lab test)	C
Maximum RT-qPCR viral load (log10 copies/mL) in NP swab samples during the EAP in subjects who have asymptomatic infection during the EAP	C
Maximum RT-qPCR viral load (log10 copies/mL) in NP swab samples during the EAP in subjects who have symptomatic infection during the EAP	C
Maximum RT-qPCR viral load (log10 copies/mL) in NP swab samples during the EAP in subjects who have a medically attended visit related to a RT-qPCR confirmed SARS-CoV-2 infection at baseline or during the EAP	C

4.6. Safety Variables

4.6.1. Adverse Events and Serious Adverse Events

Adverse events and serious adverse events will be collected from the time of informed consent signature and then at each visit until the end of the study. All adverse events are to be coded to a "Preferred Term (PT)" and associated primary "System Organ Class (SOC)" according to the Medical Dictionary for Regulatory Activities (MedDRA version 23.1). The severity of AEs (including test findings classified as AEs) and injection-site -related reactions will be graded by the investigator using the current version of the NCI–CTCAE v5.0 0. The NCI-CTCAE severity grading systems for anaphylaxis, allergic reaction, and injection site reaction are specifically in section 10.2.4 of the protocol.

An adverse event is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

A serious adverse event is an adverse event (AE) that is classified as serious according to the criteria specified in the protocol.

For safety variables, the following observation periods are defined:

- The pre-treatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment-emergent EAP (TEEAP) is defined as the day from first dose of study drug to 28 days after the last dose of study drug (Note: There is only one planned dose.)
- The treatment-emergent follow-up period (TEFUP) is defined from the day after the end of the TEEAP to the end of the Follow-up Period (i.e., 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.

Treatment-emergent adverse events (TEAEs) will be summarized for each of the following periods: treatment-emergent EAP, treatment-emergent follow-up period, and the study period (i.e. combination of the treatment-emergent EAP and follow-up periods). Adverse events that occur prior to treatment will be listed.

Laboratory results, physical examination, and vital signs are to be recorded as AEs if they are medically relevant: symptomatic, requiring corrective therapy, leading to study discontinuation and/or fulfilling a seriousness criterion.

4.6.2. Adverse Events of Special Interest

Adverse events of special interest (AESI) are AEs (serious or non-serious) required to be monitored, documented, and managed in a pre-specified manner as described in the protocol. In this study, AESI are listed below (as provided in the protocol), along with each AESI detailed definition:

- Grade 3 or greater injection site reactions or hypersensitivity reactions including but not limited to anaphylaxis, laryngeal/pharyngeal edema, severe bronchospasm, chest pain, seizure, or severe hypotension (eCRF specific tick box on the AE page)

4.6.3. Events Causing Death

Subject deaths are per the observation periods will be summarized as follows.

- Deaths during the TEEAP
- Deaths during the TEFUP
- Deaths during the overall study period

4.6.4. Laboratory Safety Variables

Samples for laboratory testing will be collected at visits according to the schedule of events tables in the protocol. Samples will be analyzed by a central laboratory. The clinical laboratory data consists of serum chemistry, hematology, urinalysis and other specified in section 9.2.3.2 of the protocol.

Clinical laboratory values will be converted and analyzed in both standard international (SI) units and US conventional units provided by the central laboratory. Both actual test values and "change from baseline" values (defined as the post-baseline value minus the baseline value) over time will be summarized, where the post-baseline visits will be assigned to the Global Analysis Windows (See Section 6.4).

Potentially clinically significant values (PCSV) ranges will be applied to the laboratory test values as applicable (see PCSV criteria in Appendix 10.3).

Vital Signs

Both actual test values and "change from baseline" (defined as the post-baseline value minus the baseline value) over time in vital signs parameters (e.g., weight (kg), height (cm), BMI (kg/m^2),

temperature (^{0}C or ^{0}F), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg)) will be summarized as laboratory safety variables. Potentially clinically significant values (PCSV) ranges will be applied to the vital sign parameter values as applicable (see Appendix 10.3 for PCSV criteria).

4.6.5. Physical Examination Variables

Physical examination will be conducted as the protocol scheduled visits. If any abnormal findings during the screening period, they will be recorded in medical history eCRF form and AE eCRF form for any findings during post-screening period.

4.7. Pharmacokinetic Variables

The pharmacokinetic variables are the concentrations of REGN10933 and REGN10987 in serum and time when a sample was collected. The sampling time points for dense and sparse collection schedules are specified in the schedule of events tables in the protocol.

4.8. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, NAb status, and time-point/visit. Serum samples for Immunogenicity will be collected at the clinic visits specified in the schedule of events tables in the protocol.

5. STATISTICAL METHODS

For continuous variables, descriptive statistics will include the following: the number of subjects 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.

Baseline is defined as the last assessment obtained before the first dose of study drug.

Statistical hypotheses will be performed in seronegative subjects in Cohort A and Cohort B independently with separate type I error controls.

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group and overall, for the study. These will be analyzed by cohort for both seronegative mFAS and SAF populations.

5.2. Medical History

Medical history will be summarized by SOC and PT and by treatment group and all groups combined for the seronegative mFAS populations defined in Section 3.1.

5.3. Prior/concomitant Medications or Procedures

All prior medications will be descriptively summarized by treatment group and overall, for the study, for subjects in SAF population.

Summaries will present subject counts (and percentages) for all prior medications, by decreasing frequency of the overall group incidence of ATC followed by ATC level 2, ATC level 4 and preferred term. For prior procedure, summaries will be by SOC and PT, sorted by decreasing frequency of SOC and PT based on the incidence in the overall group incidence. Subjects will be counted only once for each SOC and PT linked to the procedure.

All concomitant medications/procedures will be descriptively summarized by treatment group and observation period defined in Section 4.6.1, for subjects in SAF.

5.4. Prohibited Medications

Listing of prohibited medications described in Section 4.4 will be provided for subjects in SAF.

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 cohort, mFAS sets, SAF, PK, immunogenicity (ADA).

5.6. Extent of Study Treatment Exposure and Compliance

5.6.1. Measurement of Compliance

Subject treatment compliance is not applicable for this study, since the study drug is administered once at the site and will be the same as treatment exposure.

5.6.2. Exposure to Investigational Product

The duration of study treatment will be defined as 28 days after the last dose for a subject in SAF.

5.7. Analyses of Efficacy Variables

The following null and alternate hypotheses will be tested for the primary and secondary endpoints 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

5.7.1. Analysis of Primary Efficacy Variables

Cohort A

The Cohort A primary efficacy endpoint described in Section 4.5.1 will be analyzed in the seronegative mFAS-A population. All post-baseline efficacy assessments obtained in the EAP will be included for the primary analysis.

In order to account for the correlation among subjects within a household and control the associated type 1 error inflation, a generalized linear model will be used to estimate the odds ratio between the treatment groups by using the GEE approach (See Appendix 10.4 for an example of SAS procedure). This model estimates a single within-household correlation coefficient. The model will include the fixed category effects of treatment group (placebo versus REGN10933+REGN10987), region (US versus ex-US), and age (≥12 to <50, ≥50 years). The model will use a compound symmetry covariance matrix and estimate the odds ratio between the treatment groups and corresponding 95% CI and p-value.

If the GEE model fails to converge due to most households containing only a single study subject in seronegative mFAS-A or the percentage of households in Cohort A with only a single study subject is 70% or more, then a logistic regression model will be used with treatment, region, and age group as fixed effects. The threshold of 70% was based on simulations of within-household correlation which show the type I error rate is inflated and the power is decreased when the

proportion of single-subject households is high (details provided in Section 6.6). If the logistic regression model does not converge, an exact logistic regression will be used. The estimates of odds ratio, the corresponding 95% CI and p-value will be provided from logistic regression (or exact logistic regression) for comparison of REGN10933+REGN10987 against placebo group.

In Cohort A, a subject will be considered having a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP if any of the post-baseline RT-qPCR results during the EAP are positive with at least one symptom within 14 days of a positive RT-qPCR result (Section 4.5).

Cohort B

The Cohort B primary efficacy endpoint described in Section 4.5.5 will be analyzed in the seronegative mFAS-B population. The same statistical methods as described for Cohort A will be used to obtain the estimate of odds ratio and p-value for comparison between the treatment groups.

In Cohort B, a subject will be considered having a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP if subjects have at least one symptom within 14 days of a positive RT-qPCR result at baseline or during the EAP.

Handling of Missing Central Lab SAR-CoV-2 RT-qPCR Data for Both Cohort A and Cohort B

Subjects with COVID-19 symptoms that are missing a central lab determined RT-qPCR test during the EAP (eg. are too sick to go to the study site) but have a positive SARS-COV-2 test from a local lab (eg. in the hospital) will be considered as having a symptomatic infection if any of the symptoms occurred within 14 days of the positive SARS-COV-2 test that was observed during the EAP.

The graphical display using Kaplan-Meier curve for the time to first symptom will also be provided.

5.7.1.1. Sensitivity Analyses

Robustness of the primary analyses results in Cohort A and Cohort B will be assessed through sensitivity analyses as follows:

Sensitivity analysis by excluding subjects who develop asymptomatic or symptomatic SARS-CoV-2 infection within 72 hours of the study drug administration

This analysis assesses for the sensitivity of the results to subjects who may have had undetected infections prior to dosing. That is, a subject had any onset of a positive RT-qPCR within 72 hours of the study drug administration will be excluded for this sensitivity analysis.

This sensitivity analysis will only be performed for Cohort A primary endpoint.

Sensitivity analysis by excluding subjects from non-good clinical practice (GCP) Compliant Site(s)

To access the impact of sites that had non-GCP compliance issues on the primary efficacy points, the primary analyses will be performed by excluding non-GCP compliant site(s).

This sensitivity analysis will be performed for both Cohort A and Cohort B primary endpoints.

5.7.1.2. Subgroup Analyses

To assess the homogeneity of the treatment effect across various subgroups, the primary analysis model with GEE approach will be applied to each subgroup if applicable; otherwise, the logistic regression model will be used. Odds ratio between the treatment groups and corresponding 95% CI will be provided, as well as the within-household correlation coefficient from GEE approach, within each subgroup.

The following subgroups of interest for Cohort A and Cohort B primary endpoints will be evaluated:

- Stratification age (years) group (≥12 to <18, ≥18 to <50, ≥50), and the additional age group: ≥12 to <18, and ≥18 years
- Sex
- Race (American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White and Other, where "Other" may include, for example, not reported, unknown, and multiracial, etc.) and an additional race group (White Hispanic or Latino, White not Hispanic or Latino, Black Hispanic or Latino, Back not Hispanic or Latino, and Other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, and not reported or unknown)
- BMI (<30, ≥30)
- Number of study subjects in cohort B within a household (0, ≥1) (Cohort A only)
- Total household size including the household member(s) not participating this study (2, and >2)
- Region (US, ex-US)
- Baseline high risk factor (Yes versus No) (as defined in Section 4.1)
- Healthcare worker (Yes/No) per exposure risk factor eCRF
- High viral load (> 4 log 10 copies/ml) at baseline (Yes/No) (Cohort B only)

5.7.2. Adjustment for Multiple Comparison

The overall type I error will be controlled in each of seronegative mFAS-A and seronegative mFAS-B independently at 2-sided 5% significance level.

Seronegative mFAS-A Subjects

The overall type I error will be controlled for the primary hypothesis in Cohort A based on a 2-sided test at an alpha level of 0.05 as follows:

> H0: There is no treatment difference between REGN10933+REGN10987 and placebo in the proportion of subjects with a symptomatic RT-qPCR confirmed SARS-CoV-2 infection during the EAP.

H1: There is a treatment difference between REGN10933+REGN10987 and placebo in the proportion of subjects with a symptomatic RT-qPCR confirmed SARS-CoV-2 infection during the EAP

If the primary efficacy endpoint in Cohort A is statistically significant, the alpha level of 0.05 will be released for the key secondary endpoints in Cohort A. The hierarchy testing sequence of key secondary endpoints is presented in the following table.

Table 2: Hierarchy Testing Sequence of Key Secondary Efficacy Endpoints in Seronegative mFAS-A

Key Secondary Efficacy Variables
Proportion of subjects with viral load >4 (log10 copies/mL) in NP swab samples during the EAP
Number of weeks of symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP
Number of weeks of high-viral load >4 (log10 copies/mL) in NP swab samples during the EAP
Number of weeks of RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP
Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP
Proportion of subjects in placebo group with a RT-qPCR confirmed SARS-CoV-2 infection during the EAP with an index case participating in study R10933-10987-COV-2067 (comparison of those whose index cases receive REGN10933+REGN10987 vs placebo in R1033-10987-COV-2067)

Seronegative mFAS-B Subjects

The overall type I error will be controlled for the primary hypothesis in Cohort B based on a 2-sided test at an alpha level of 0.05 as follows:

H0: There is no treatment difference between REGN10933+REGN10987 and placebo in the proportion of subjects who subsequently develop signs and symptoms (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP

H1: There is a treatment difference between REGN10933+REGN10987 and placebo in the proportion of subjects who subsequently develop signs and symptoms (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP

If statistical significance is established for the primary efficacy endpoint in cohort B, a hierarchical testing procedure will be applied to the key secondary endpoints in Cohort B at a 2-sided 0.05 significance level. The order of testing sequence for key secondary endpoints is presented in the following table.

Table 3: Hierarchy Testing Sequence of Key Secondary Efficacy Endpoints in Seronegative mFAS-B

Key Secondary Efficacy Variables
Number of weeks of symptomatic SARS-CoV-2 infection (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP
Number of weeks of high viral load (log10 copies/mL) >4 in NP swab samples during the EAP

5.7.3. Analyses of Key Secondary Variables

For Cohort A, the key binary endpoint of the proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP, the same statistical method used in the primary analysis will be applied. If a subject's overall infection status during the EAP cannot be determined due to missing RT-qPCR results, the following rules will be applied to impute the missing RT-qPCR data.

1. For subjects satisfying the criteria specified in the handling missing central lab SARS-CoV-2 RT-qPCR data of the analysis of primary efficacy variables, the corresponding visit(s) will be considered as having a positive RT-qPCR test.
2. After the first step above, each planned visit with missing RT-qPCR data will be imputed 100 times to generate 100 complete datasets based on the predicted probability using the fully conditional specification (FCS) (Van Buuren, S, 2005)[7] through the logistic regression. The logistic regression model includes the fixed effect factors of treatment group, region, age group, and RT-qPCR testing status at other analysis visits during the EAP. This imputation will repeat by iterating for each analysis visit with missing RT-qPCR testing status. Appendix 10.4 provides details on the use of FCS from the SAS MI procedure. These 100 complete datasets will be analyzed using the model specified above for the primary analysis. Results from 100 analyses will be combined using Rubin's formulae to obtain the final estimate of log(odds ratio), 95% CI and the associated p-value. The odds ratio and 95% CI will be derived by taking the exponential of these estimates.

For the key binary endpoint of the proportion of subjects with viral load >4 (log10 copies/mL), if NP swab viral load data is missing for a visit, it will not be imputed regardless of symptoms. Only non-missing available NP swab viral load data will be used for the analysis of this endpoint. Only subjects with at least one post-baseline viral load (log10 copies/mL) data in NP swab samples will be included in the analysis.

For Cohort A the key binary endpoint regarding the index case linkage to R10933-10987-COV-2067, the Fisher's exact test will be used.

For continuous key secondary endpoints in Cohort A and Cohort B (e.g., number of weeks of high viral load >4 (log10 copies/mL) in NP swab samples and number of weeks of symptomatic RT-qPCR-confirmed SARS-CoV-2 infection (broad-term) during the EAP, etc.), visits with missing viral load regardless of symptoms and visits with missing RT-qPCR that do not have any broad-term symptoms within 14 days will not be considered as meeting these endpoint criteria, respectively. For endpoints regarding viral load, only subjects with at least one post-baseline data

will be included in the analysis. These endpoints will be analyzed by the non-parametric method, a stratified Wilcoxon rank sum test (Van Elteren Test) with the region and age group. Descriptive statistics will be provided for number (%) of subjects with each interval of duration in weeks (i.e., 0 week, > 0 to ≤ 1 week, > 1 to ≤2 weeks, etc.) within each treatment group. The total weeks of infection and normalized duration (e.g., average duration infection per 1000 subjects) per treatment group will also be reported.

5.7.4. Analyses of Other Secondary and Exploratory Efficacy Variables

Other secondary efficacy endpoints will be analyzed by type of endpoint defined in Sections 4.5.2 to 4.5.8 for all cohorts. The analysis methods for key secondary efficacy endpoints in both cohort A and cohort B will also be applied to exploratory endpoints in both cohort A and cohort B if appropriate. Otherwise, the primary approach to the data will be descriptive statistics. For the comprehensive evaluation of efficacy, nominal p-values may be reported. Raw data descriptive statistics will also be presented.

Other secondary efficacy and exploratory endpoints for cohort A1 and cohort B1 may also be analyzed by type of endpoint. If the sample size is sufficient, continuous variables will be summarized by the descriptive statistics (e.g., n, mean, SD, Q1, median, Q3, minimum and maximum, etc.). Binary variables will be summarized using the number and percentage of subjects in each treatment group. No statistical hypothesis testing will be performed for cohort A1 and cohort B1. This approach may also be applied to adolescent subjects.

Binary Endpoints

Binary endpoints in cohort A and cohort B will be analyzed by applying the same approach used for the primary efficacy endpoints.

For endpoints regarding viral loads, visits with missing viral load (log10 copies/mL) in NP swab samples will not be included in the analyses. For binary endpoints regarding the index case or household members linkage to R10933-10987-COV-2067 or subjects in cohort B, and endpoints regarding the medically attended visits, Fisher's exact test will be used. KM curves will be used to assess the exploratory endpoint of proportion of baseline-seronegative subjects who have a first RT-qPCR confirmed SARS-CoV-2 infection in the follow-up period.

Continuous Endpoints

The secondary and exploratory continuous efficacy endpoints such as TWA, AUC, and maximum viral load (log10 copies/mL) will be analyzed using the ANOVA including treatment group, region, and age group as fixed effects in the model. The continuous endpoints regarding change from baseline in cohort B (e.g., TWA of change/percent change from baseline) will be analyzed using the ANCOVA model with treatment group, region, and age group as fixed effects, and the relevant baseline values as covariate as well as treatment-by-covariate interaction. The REGN10933+REGN10987 group will be compared to the placebo group and corresponding least square of mean difference, standard error (SE) and 95% confidence interval will be provided. For

other endpoints with non-normal/skewed distribution (e.g. number of days of symptoms (strict-term, and CDC definition, etc.)), Van Elteren test will be used.

5.7.5. Interim Analysis

No interim analysis will be conducted for this study.

5.8. Analysis of Safety Data

The analysis of safety and tolerability will be performed in SAF, as defined in Section 3.2. For each cohort, the safety analysis will also be performed by subject baseline serology status and age group (≥ 12 to <18 years and ≥18), respectively.

The safety analysis will be based on the reported AEs and other safety information (clinical laboratory evaluations, and vital signs).

Thresholds for PCSV in laboratory variables, and vital signs are defined in Appendix 10.3.

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), and by study cohort. 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.

General common rules

All safety analyses will be performed, unless otherwise specified, using the following common rules:

- Safety data in subjects who do not belong to the safety analysis set (i.e., exposed but not randomized) will be listed separately.
- PCSV values are thosevalues 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 (PCSV criteria described in Appendix 10.3). Considering that the threshold defined in the PCSV list for monocytes and basophils can be below the ULN, the following PCSV criterion will be used for the PCSV analysis of monocytes and basophils:
  - PCSV criterion for monocytes: >0.7 Giga/L or >ULN (if ULN ≥0.7 Giga/L).
  - PCSV criterion for basophils: >0.1 Giga/L or >ULN (if ULN ≥0.1 Giga/L).
- PCSV criteria will determine which subjects had at least 1 PCSV during the respective TEAE periods, taking into account all evaluations including unscheduled or repeated evaluations.
- The treatment-emergent PCSV denominator by treatment group for a given parameter will be based on the number of subjects assessed for that given parameter at least once during the respective TEAE periods.

- All unscheduled measurements will be assigned to Global Analysis Windows defined in Table 5 of Section 6.4 in order to provide an assessment for the screening/baseline visit through follow-up visit time points.
- For quantitative safety parameters including central laboratory measurements and vital sign scores, descriptive statistics will be used to summarize observed values and change from baseline values by visit.

5.8.1. Adverse Events

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). The preferred term (PT), and the primary system organ class (SOC) will be listed.

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 drug withdrawn, or subjects with any COVID-19 TEAE or asymptomatic COVID-19 TEAE
- Overview of non-COVID TEAEs (excluding COVID-19 and asymptomatic COVID-19), i.e., overall number (%) of subjects with any TEAE, Serious TEAE, TEAE leading to death, or TEAE leading to study drug withdrawn
- Overview of AESI, i.e., overall number (%) of subjects with any AESI, grade 3 or greater injection site reactions, grade 3 or greater hypersensitivity reactions, AESI leading to death, or AESI leading to study drug withdrawn)
- TEAEs by primary SOC and PT
- Number of subjects experiencing common TEAE(s) by primary SOC and PT (PT incidence≥5% in any treatment group)
- TEAEs by severity (according to the grading scale outlined in section 10.2.4 of the protocol), 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 drug withdrawn by primary SOC and PT
- Treatment-emergent AESIs leading to study drug 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 (death as an outcome on the AE CRF page, as reported by the Investigator) by SOC and PT

- AESIs leading to death (death as an outcome on the AE CRF page, as reported by the Investigator) by SOC and PT.

In addition, the number (%) of subjects with any post-baseline fever reported from the fever assessment eCRF, any subject self-recorded 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

For the respective EAP, FUP, and overall study period, clinical laboratory parameter actual values (quantitative) and change from baseline values will be descriptively summarized at baseline and each post-baseline visit by treatment group.

Individual subject laboratory parameter measurements will be additionally evaluated by PCSV criteria (See Appendix 10.3), specifically identifying subjects with at least one post-baseline measurement that meets the PCSV criteria. These laboratory parameters will be presented by the biological functions. The incidence of PCSVs at any time during the respective treatment-emergent periods (EAP and FUP) will be summarized regardless of the baseline level, and again according to the following baseline categories:

- Normal (according to PCSV criterion/criteria)/missing
- Abnormal according to PCSV criterion or criteria

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.

Subject listings of laboratory measurements that meet PCSV criteria will be provided for the report appendix.

A listing of all women of childbearing potential with a confirmed serum pregnancy test during the study will be provided.

5.8.3. Analysis of Vital Signs

For the respective EAP, FUP, and overall study period, the vital sign actual values (quantitative) and change from baseline values will be descriptively summarized at baseline and each post-baseline visit will be summarized by treatment group.

Individual subject laboratory parameter measurements will be additionally evaluated by PCSV criteria (See Appendix 10.3), specifically identifying subjects with at least one post-baseline measurement that meets the PCSV criteria.

Subject listings of vital sign measurements that meet PCSV criteria will be provided for the report appendix.

5.8.4. Analysis of Other Safety Variables - Abnormal Findings during SARS-CoV-2 Infection-related Medically Attended Visits

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).

- Nature of visit (ED, UCC, hospital stay)
- Abnormal vital signs: respiratory rate ≥30 per minute, heart rate ≥125 per minute, peripheral capillary oxygen saturation (SpO2) ≤93% on room air at sea level, or oxygen partial pressure (PaO2)/fractional inspired oxygen (FiO2) <300 mm Hg)
- Respiratory failure: needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, extracorporeal membrane oxygenation (ECMO)
- Evidence of shock: systolic blood pressure (SBP) <90 mm Hg, diastolic blood pressure (DBP) <60 mm Hg or requiring vasopressors (*Note: these limits for abnormal vital signs are for adult and adolescent subjects.)*
- Multiorgan dysfunction: Significant acute renal, hepatic, or neurologic dysfunction
- Multisystem inflammatory syndrome in children (MIS-C). (Note: for pediatric subjects <12 years only.)
- Admission to an ICU

Number and percentage of subjects who presented at least one of abnormal findings and then by each of these 5 abnormal findings will be provided by treatment group and TEAE period (TEEAP, TEFUP, and overall study period). Within each abnormal findings, number and percentages of subjects will also be reported for each observed criterion.

A listing of subjects who have any of these 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

5.9.1. Analysis of drug concentration data

Concentrations of REGN10933 and REGN10987 over time will be summarized by descriptive statistics for each cohort. No formal statistical hypothesis testing will be performed.

Dense PK sentinel cohort

The PK parameters to be determined after the first dose for REGN10933 and REGN10987 may include, but are not limited to:

- C_{max}
- C_{max}/Dose

- t_{max}
- t_{last}
- C_{last}
- AUC_{inf}
- AUC_{inf}/Dose
- $t_{1/2}$
- C_{28} (concentration in serum 28 days after dosing)

Selected PK parameters will be summarized by descriptive statistics for each cohort. Results from two different cohorts may be combined if appropriate.

Sparse PK

Concentrations of REGN10933 and REGN10987 in serum over time will be summarized by descriptive statistics for each cohort. No formal statistical hypothesis testing will be performed.

5.10. Analysis of Immunogenicity Data

The immunogenicity variables described in Section 4.8 will be summarized using descriptive statistics.

Immunogenicity will be characterized by ADA responses and titers observed in subjects in the ADA analysis set. ADA response categories and titer categories are defined as follows:

ADA response categories:

- ADA Negative, defined as ADA negative response in the ADA assay at all time points, regardless of any missing samples.
- Pre-existing immunoreactivity, defined as either an ADA positive response in the ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline with all post first dose ADA responses less than 9-fold over baseline titer levels.
- Treatment-emergent response, defined as an ADA positive response in the ADA assay post first dose when baseline results are negative or missing. The treatment-emergent responses will be further characterized as Persistent, Indeterminate or Transient.
  - Persistent Response – Treatment-emergent ADA positive response with two or more consecutive ADA positive sampling time points, separated by at least 16-week period (based on nominal sampling time), with no ADA negative samples in between, regardless of any missing samples.
  - Indeterminate Response –Treatment-emergent ADA positive response with only the last collected sample positive in the ADA assay, regardless of any missing samples.
  - Transient Response –Treatment-emergent ADA positive response that is not considered persistent or indeterminate, regardless of any missing samples.

- Treatment-boosted response, defined as a positive response in the ADA assay post first dose that is greater than or equal to 9-fold over baseline titer levels, when baseline results are positive

Titer categories (Maximum titer values)

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

The following analysis will be provided:

- Number (n) and percent (%) of ADA-negative subjects (pre-existing immunoreactivity or negative in the ADA assay at all time points) by treatment groups
- Number (n) and percent (%) of treatment-emergent ADA positive subjects by treatment groups and ADA titer categories and at the
  - Number (n) and percent (%) of persistent treatment-emergent ADA positive subjects
  - Number (n) and percent (%) of indeterminate treatment-emergent ADA positive subjects
  - Number (n) and percent (%) of transient treatment-emergent ADA positive subjects
- Number (n) and percent (%) of treatment-boosted ADA positive subjects by treatment groups and ADA titer categories

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

5.10.1. Analysis of Neutralizing Antibody (NAb) Data

The absolute occurrence (n) and percent of subjects (%) with NAb status in the NAb analysis set will be provided by treatment groups.

5.11. Association of Immunogenicity with Exposure, Safety and Efficacy

5.11.1. Immunogenicity and Exposure

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

5.11.2. Immunogenicity and Safety and Efficacy

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 reaction (SMQ: Anaphylaxis [Narrow])

Potential association between immunogenicity variables and efficacy endpoints may be explored (e.g., scatter plot or spaghetti plot).

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

- ADA positive subjects: subjects with treatment-emergent or treatment-boosted response.
- ADA negative subjects: subjects with pre-existing immunoreactivity or negative in the ADA assay at all time points.
- Subjects with persistent treatment-emergent ADA response
- NAb positive subjects: ADA positive subjects who were positive in the NAb assay at any time point analyzed.
- Maximum post-baseline titer in treatment-emergent or treatment-boosted ADA positive subjects:
  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤10,000)
  - High (titer >10,000)

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 measurement taken prior to the administration of study drug.

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 5.7.1.

6.3. Data Handling Convention for Missing Data

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 Injection

Since the study drug is administered at the site, the date and time of study drug administration are filled in eCRF. No missing data is expected. The information is filled in eCRF.

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.

Potentially Clinically Significant Value (PCSV)

If a subject has a missing baseline value, this subject will be grouped in the category "normal/missing at baseline."

For PCSVs with 2 conditions, one based on a change from baseline value and the other on a threshold value or a normal range, with the first condition being missing, the PCSV will be based only on the second condition.

For a PCSV defined on a threshold and/or a normal range, this PCSV will be derived using this threshold if the normal range is missing; e.g., for eosinophils the PCSV is >0.5 giga/L or >ULN if ULN ≥0.5 giga/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSVs.

6.4. Windows for Analysis Time Points

Data analyzed by-visit-analysis will be summarized by the scheduled visit described in protocol section 9.1 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 4: Efficacy Analysis Windows for Unscheduled Visits with RT-qPCR or Viral Load Results

Visit Label	Targeted Study Day	Analysis Window in Study Day
Baseline	1	≤ 1
Week 1	8	[2, 11]
Week 2	15	[12, 18]
Week 3	22	[19, 25]
Week 4	29	[26, 32]
Week 5	36	[33, 39]
Week 6	43	[40, 46]
…	…	…
Week x	29+7x	[26+7(x-4), 32+7(x-4)]

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

Visit Label	Targeted Study Day	Analysis Window in Study Day
Baseline	1	≤ 1
Day 2	2	[2, 2]
Day 4	4	[3, 4]
Week 1	8	[5, 11]
Week 2	15	[12, 18]
Week 3	22	[19, 25]
Week 4	29	[26, 42]
Week 8	57	[43, 70]
Week 12	85	[71, 98]
Week 16	113	[99, 126]
Week 20	141	[127, 154]
Week 24	169	[155, 182]
Week 28	197	[183, 210]
Week 32	225	>=211

Unscheduled Assessments

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, and PCSVs.

6.5. Pooling of Centers for Statistical Analyses

Currently, the randomization is stratified by site. Since a potential differential treatment effect among countries may exist, region variable as a fixed effect factor will be included in the statistical analysis model. A subgroup analysis regarding region will also be performed for the primary efficacy endpoint. Results will also be summarized descriptively by country.

6.6. Statistical Technical Issues

To consider the potential impact that not all of study subjects come from a household with more than one member participating this trial, a simulation has been conducted to explore the potential impact to the type I error rate and power by the percent of households with a single study subject only.

This simulation is based on the same sample size of 1248 (See Table 1 in Section 2.2.1) assuming the attack rates are 10% and 5% in placebo and REGN10933+REGN10987 treatment group, respectively. The correlated Bernoulli response data (e.g. 1=infected vs 0=not infected) within a household was generated by using Gaussian multivariate cumulative distribution function proposed by Emrich and Piedmonte (1991). For example, the table below exhibits the correlation between the bivariate normal data with correlation ρ used to generate the Bernoulli correlated data and the corresponding Bernoulli correlation γ in the cases where the attack rates are both 10% (e.g., $p_1 = p_2 = 0.1$ under the null hypothesis), and 10% and 5% (e.g., $p_1 = 0.1, p_2 = 0.05$ under the alternative hypothesis).

$p_1 = p_2 = 0.1$	
ρ Normal	γ Bernoulli
0.1	0.03706
0.2	0.07996
0.3	0.12907
0.4	0.18504
0.5	0.24891
0.6	0.32242
0.7	0.40866
0.8	0.51381
0.9	0.65405

$p_1 = 0.1, p_2 =$0.05	
ρ Normal	γ Bernoulli
0.1	0.03065
0.2	0.06748
0.3	0.11089
0.4	0.16150
0.5	0.22020
0.6	0.28834
0.7	0.36813
0.8	0.46328
0.9	0.58016

Given the percent of subjects from households with single study subject (HHS), the rest of household size was randomly generated by using a truncated Poisson ($l = 4$) (i.e., resampling if $\leq$1). The simulation is repeatedly 2000 times by different HHS to compare the power between GEE model and logistic regression model based on boundary p-value=0.044 after 2 planned interim analyses.

Summary of power and type I error rate between the GEE model and logistic regression model by different HHS, considering the extreme high correlated data. The power is based on the testing p-value compared to the boundary p-value of 0.044 after 2 interim analyses at 50% and 75% information fraction for the final analysis.

Comparisons of Power

$\gamma = 0.58$ ($p_1 = 0.1, p_2 = 0.05$)		
HHS(%)	power-GEE	power-Logistic
10	0.9920	0.9035
20	0.9905	0.9040
30	0.9855	0.9140

Comparisons of Type I Error

$\gamma = 0.65$ ($p_1 = 0.1, p_2 = 0.1$)		
HHS(%)	α-GEE	α -Logistic
10	0.0480	0.0435
20	0.0490	0.0440
30	0.0495	0.0475

40	0.9590	0.8980
50	0.9245	0.9075
60	0.9035	0.9085
70	0.8640	0.9175
80	0.8460	0.9155

40	0.0510	0.0445
50	0.0410	0.0360
60	0.0600	0.0490
70	0.0575	0.0390
80	0.0735	0.0370

Based on the potential inflation of type I error (α) and decreasing power as HHS over 50%, conservatively the percent of households with a single study subject could be higher than 70%. Thus, if this situation occurs, the logistic regression will be used instead of using GEE approach.

7. TIMING OF STATISTICAL ANALYSES

There are multiple steps of analyses planned for this study.

- An administrative descriptive analysis based on approximately first 554 randomized Cohort A subjects has been conducted. No formal statistical hypothesis testing will be performed. The individuals who have the subject treatment information will be described in the communication plan.
- The first step analysis: The database lock will occur when all Cohort A and Cohort B subjects complete the EAP and all their data during the EAP have been collected and validated. The individual treatment codes will be unblinded and final analyses of the primary and some secondary efficacy endpoints of cohort A and Cohort B will be conducted. The subjects who are included in the administrative analysis will not be included in the first step efficacy analysis. Also, subjects who are randomized after January 28th (approximately 269) will not be included in this analysis.

  Note: The results of primary and some secondary efficacy endpoints in the first step analysis maybe used for a submission dossier to health authorities.
- The second step analysis (final analysis): The database lock will occur after the last subject completes the study. All treated subjects including 554 subjects in the administrative assessment, subjects in the first step analysis, and those subjects (~269) who were randomized after 28 January, 2021, will be included in the safety analysis. The second-step analysis for efficacy will include all subjects except those subjects who were included in the administrative assessment.

8. SOFTWARE

All analyses will be done using SAS Version 9.4 or higher, and R 3.5.3 or higher.

9. REFERENCES

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10. APPENDIX

10.1. Summary of Statistical Analyses

Primary Efficacy Analysis:

Endpoint	Analysis Population	Estimand	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP	Seronegative mFAS-A	A broad-term symptom occurring within a 14-days window of any positive RT-qPCR during the EAP regardless of adherence to study treatment will be included for the primary analysis.	A generalized linear model with the generalized estimation equation (GEE) approach or logistic regression If percent of households with single study subject greater than or equal to 70%. Missing RT-qPCR will be imputed as positive RT-qPCR if a subject with COVID-19 signs and symptoms (broad-term) occurring within a 14-day window of a visit with missing RT-qPCR data.	Yes	Yes	1. Excluding those subjects who develop asymptomatic or symptomatic SARS-CoV-2 infection within 72 hours of the study drug administration 2. Exclude subjects from non-GCP compliance sites
Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) at baseline or during the EAP	Seronegative mFAS-B	Same as above including a positive RT-qPCR at baseline	Same as above including a positive RT-qPCR at baseline	Yes	No	1. Exclude subjects from non-GCP compliance sites

10.2. Schedule of Events

Table 6: Schedule of Events Cohorts A and B ([Adult / Adolescent Subjects], RT-qPCR-Negative and Positive)

Visit	Screening / Baseline[1]	Additional Safety (Sentinel Only)[2]				Efficacy Assessment Period (EAP)[3]				Follow-up Period							ET	Unscheduled Visit[4]
Visit Location Site (S), Phone (P)[5]	**S**	**S**	**S**	**P**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**		
Visit Number	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**EOS**		
Day	1	1	2	3	4	8	15	22	29	57	85	113	141	169	197	225		
Week	0	0	0	0	0	1	2	3	4	8	12	16	20	24	28	32		
Window (day)						±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Screening/Baseline:																		
Inclusion/exclusion	X																	
Informed consent (adult subject or parent/guardian)/pediatric assent (adolescent subject)	X																	
Informed consent (adults or parent/guardian)/pediatric assent for PGx sub-study(optional)[6]	X																	
Medical history	X																	
Demographics and risk factors for SARS-CoV-2 infection	X																	
Household assessment	X[16]								X									
Appropriate sample, diagnostic assay for SARS-CoV-2 (local lab)	X[7]																	
Randomization	X																	
Treatment:																		
Study drug administration	X[8]																	
Efficacy (Virology):																		
NP swab, SARS-CoV-2 RT-qPCR (central lab)[7,17]	X[8]					X	X	X	X	X[3,4,9]	X[3,4,9]	X[3,4,9]	X[3,4,9]	X[3,4,9]	X[3,4,9]	X[3,4,9]	X	X
Efficacy (Subject-Reported) only for RT-qPCR positive subjects:																		
Assessment of ED, UCC, hospital visits[18]						X	X	X	X	X	X	X	X	X	X	X		
Absenteeism assessment[18]						X	X	X	X							X		
Safety:																		
Vital signs	X[2,11]	X[2]							X							X		X
Targeted PE[11]	X		X		X				X							X		X
Adverse events[15,19]	X	X[2]	X[2]	X[2]	X[2,10]	X	X	X	X	X	X	X	X	X	X	X	X	X
Con Meds, Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test for WOCBP (dipstick, local lab)[12]	X															X		X
Laboratory Testing[13]:																		
Clinical Laboratory, Hematology, Blood Chemistry, Urinalysis	Refer to Table 7																	
Pharmacokinetics and Immunogencity[13]:																		
Drug concentration	Refer to Table 7																	
Anti-drug antibodies (ADA)																		

Biomarkers:																		
Serum for serology (central lab)[14]	X								X	X						X		
Research plasma	X								X[20]	X[20]						X[20]		
Research serum	X								X[20]	X[20]						X[20]		
Pharmacogenomics Sub-Study:																		
Whole Blood for RNA (Optional)[6]	X								X[20]	X[20]						X[20]		
Whole Blood for DNA (Optional)[6]	X																	

EAP, Efficacy assessment period; EOS, end of study; ED, emergency departments; ET, Early termination; UCC, urgent care centers; PE, physical exam; PGx, pharmacogenomics; 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.

10.2.1. Schedule of Events Table 6 (Cohorts A and B [Adult / Adolescent Subjects], RT-qPCR-Negative and Positive) Footnotes

1. The screening visit and baseline visit should both occur on the same day. If needed, a remote visit may occur to sign the ICF and collect medical history and concomitant medication use, on the day prior to, but within 24 hours of study drug administration, so that the in-person screening and randomization visit may be abbreviated, due to COVID-19 considerations. Study drug administration must occur within 96 hours of collection of the index cases' positive SARS-CoV-2 diagnostic test sample.
2. The sentinel group (see Section 6.1.1 of the protocol) had additional safety monitoring on day 1 and through day 4.

   Vital signs: On day 1, vital signs (blood pressure, pulse rate, body temperature, and respiratory rate) will be measured at predose, approximately every 30 minutes during the first 2 hours after dose, at hour 3, and at hour 4 before dismissal.

   Adverse Events (injection site reactions and hypersensitivity): after the administration of the first dose of study drug, subjects will be monitored on site for a minimum of 4 hours and then by daily visits to the study site or phone calls for the first 4 days (96 hours), particularly focusing on the assessment of injection site reactions and hypersensitivity after study drug administration.
3. Subjects who have a positive RT-PCR result during screening, or who have a positive RT-qPCR result any time after screening, will have the additional assessments done as indicated (**RT-qPCR positive subjects only**). A PK sample and an ADA sample will be collected (1) as soon as possible or within 7 days of receiving first positive SARS-CoV-2 RT-qPCR result for cohort A subjects and (2) as soon as possible or within 7 days of first new positive SARS-CoV-2 RT-qPCR result after achieving 2 consecutive negative results for all subjects.

   For subjects who become RT-qPCR positive after screening, the visit schedule will proceed as follows: (a) If the positive RT-qPCR result is from a scheduled visit for sample collection, the next weekly visit will occur as planned. (b) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) but within the window (±3 days) of the next weekly visit, this visit will be recorded as the scheduled next weekly visit. (c) If the positive RT-qPCR result is from an

unscheduled sample collection (eg, between scheduled visits) and not within the window (±3 days) of the next weekly visit, this visit will be recorded as an unscheduled visit, and the next weekly visit will occur as planned.

4. Unscheduled visits: If, at any time after randomization until end of study, a subject develops fever, an acute respiratory illness or other symptoms they may feel could be related to COVID-19 or is hospitalized for suspected COVID-19, the subject or parent/guardian (adolescent pediatric subject) should alert the investigator or designee immediately who will assess the subject's symptoms and condition (can be performed by phone contact, telemedicine, online meeting, home health care, etc) to decide if the subject should have an unscheduled visit for collection of NP swab sample for RT-qPCR testing. The subject or parent/guardian (adolescent pediatric subject) may also be asked to provide blood samples if it corresponds to a scheduled visit, according to the Schedule of Events (specified in Section 9.1 of the protocol). The investigator or designee should query the subject about AEs in general and AEs consistent of COVID-19 and record the information on CRF (see detailed description of the procedure in Section 9.2.2.2 of the protocol).

   (a) If the positive RT-qPCR result is from a scheduled visit for sample collection, the next weekly visit will occur as planned. (b) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) but within the window (±3 days) of the next weekly visit, this visit will be recorded as the scheduled next weekly visit. (c) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) and not within the window (±3 days) of the next weekly visit, this visit will be recorded as an unscheduled visit, and the next weekly visit will occur as planned.

5. Visit may occur by phone or electronic means

6. Separate consent (adult subject or parent/guardian of adolescent pediatric subject)/pediatric assent is required for participation in the optional genomic sub-study and collection of blood samples for DNA and RNA. The sample for RNA, should be collected on day 1/baseline (pre-dose). Genomic DNA should be collected on day 1/baseline. If not collected at baseline, the sample for genomic DNA may be collected at any visit.

7. Sample for diagnostic assay for SARS-CoV-2 (local lab) (see Section 9.1.2 of the protocol) and RT-qPCR (NP swab; central lab) should be collected before administration of study drug. Samples for RT-qPCR (NP swab) will be collected by swabbing through both nostrils (see Section 9.2.2.1 of the protocol). The remnant samples may additionally be used for exploratory viral RNA sequencing and viral infectivity analyses. The requirement for a local diagnostic assay for SARS-CoV-2 may be waived if the results are not expected to be available in a timely manner for randomization.

8. Study drug should be administered after all biological samples at screening/baseline have been collected.

9. Subjects who are RT-qPCR positive at the end of the EAP will continue to have samples collected weekly (NP swab; central lab) for RT-qPCR. Subjects will continue assessments/sample collections until 2 negative RT-qPCR test results have been

obtained ≥24 hours apart (all samples must be negative). Subjects who are RT-qPCR negative at the end of the EAP will have samples collected only if they become symptomatic with COVID-19 in the follow-up period.

10. For subjects who are not in the sentinel group (subset 1; completed), vital signs will be monitored on site as follows: Safety group (subset 2; completed): at baseline predose and then every hour for 2 hours after study drug administration and a phone call on day 4 to assess AEs, specifically injection site reactions and hypersensitivity; all other subjects (subset 3): at baseline and 1 hour after study drug administration. All subjects will be advised to call the site if signs/symptoms of injection site or hypersensitivity reactions occur. If the subject experiences a true medical emergency, they should visit their local hospital ED and contact the site personnel later.
11. The investigator may perform a targeted physical exam, request an exam and/or vital signs at any time. These assessments can be performed using a clinic visit or a remote visit with the investigator or sub-investigator, or designee (ie, nurse practitioner in countries where allowed by local law).
12. For all women of childbearing potential (WOCBP) and girls at or beyond menarche, except subjects with a confirmed pregnancy. If the local urine pregnancy test is positive, the site must perform a serum pregnancy test for confirmation.
13. Samples for drug concentration and, immunogenicity, and laboratory testing will be collected based on the subject subset designation as indicated in Table 7.
14. The serology test results will not be communicated to the sites. The sponsor's blinded study team will not have access to post-baseline results associated with subject identification until after the database is locked.
15. During each scheduled or unscheduled visit/contact, the investigator or designee will query subject about AEs in general (see Section 10.1.1 of the protocol) and evaluate if the AEs are associated with SARS-CoV-2 infection, including fever (see Section 9.2.2.2 of the protocol). The investigator should recommend that subjects (themselves or by their parent/guardian) measure their temperature daily during EAP, approximately at the same time, and also every time when the subject feels feverish, chills, or sick. Subjects with symptomatic SARS-CoV-2 infection should be queried on their symptoms weekly until symptoms resolve, even during follow-up period, then follow the regular schedule.
16. The information for the household assessment, including household members who receive an EUA approved monoclonal antibody treatment for COVID-19 or household members participating in the R10933-10987-COV-2067 study, should preferably be collected at the baseline visit. There will be a follow-up assessment at day 29.
17. All subjects will have a weekly NP swab sample collected during the EAP. Only subjects who are RT-qPCR positive will continue to have weekly NP swab samples collected during the follow-up period until 2 consecutive negative (≥24 hr) RT-qPCR results or the end of study visit.

18. Only for RT-qPCR positive subjects (cohort A and cohort B): Complete assessments from the time the subject first becomes RT-qPCR positive or from the time they develop symptoms suspected to be COVID-19 (later confirmed by RT-qPCR positive results) until the subject has had 2 negative tests or COVID-19 related symptoms have resolved (whichever lasts longer), or until the end of study visit.
19. All subjects or parent/guardians of adolescent pediatric subjects will complete the TEAE assessment weekly during the EAP. Subjects who are RT-qPCR negative will complete the TEAE assessment monthly during the follow-up period. Subjects who have symptomatic SARS-CoV-2 infection will complete the TEAE assessment weekly during the follow-up period until the COVID-19 related symptoms resolve after which the subject will complete the TEAE assessment monthly until the end of study visit.
20. Samples will be collected only from RT-qPCR positive subjects (cohort A and cohort B) from the time the subject first becomes RT-qPCR positive until the end of study. Note: this includes subjects who have returned to RT-qPCR negative by this visit.

Table 7: Schedule of Events: Cohorts A and B (Adult / Adolescent Subjects) for Drug Concentration, Immunogenicity, and Laboratory Testing

Samples for drug concentration (dense PK, sparse PK), immunogenicity assessment (ADA), and clinical laboratory testing (hematology, blood chemistry, and urinalysis) will be collected based on subset designation using subject number (assigned by IWRS):

- Sentinel group (Subset 1; completed): First 30 subjects
- Safety group (Subset 2; completed): 31st to 400th subject

All other subjects (Subset 3): 401st to last subject

Visit	Screening / Baseline[1]	Sentinel Group Only		Efficacy Assessment Period (EAP)				Follow-up Period							ET Visit[5]	Unscheduled Visit
Site (S)	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**			
Visit Number	**1**	**2**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**EOS 15**		
Day	1	2	4	8	15	22	29	57	85	113	141	169	197	225		
Week	0	0	0	1	2	3	4	8	12	16	20	24	28	32		
Window (day)				±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Sentinel Group (Subset 1)																
Dense PK[2]	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[6,7]
ADA[2,3]	X[1]						X			X				X	X	X[6,7]
Hematology[4]	X[1]	X	X				X	X	X	X	X	X	X	X	X	
Blood chemistry[4]	X[1]	X	X				X	X	X	X	X	X	X	X	X	
Urinalysis[4]	X[1]	X	X				X	X	X	X	X	X	X	X	X	
Safety group (Subset 2)																
Sparse PK[2]	X[1]						X	X		X		X		X	X	X[6,7]
ADA[2,3]	X[1]						X			X				X	X	X[6,7]
Hematology[4]	X[1]						X	X	X	X	X	X	X	X	X	
Blood chemistry[4]	X[1]						X	X	X	X	X	X	X	X	X	
Urinalysis[4]	X[1]						X	X	X	X	X	X	X	X	X	
All other subjects (Subset 3)																
PK[2]																X[6,7]
ADA[2,3]	X[1]						X			X				X	X	X[6,7]
Hematology[4]	X[1]						X									
Blood chemistry[4]	X[1]						X									
Urinalysis[4]	X[1]						X									

ADA, anti-drug antibodies; EAP, Efficacy assessment period; EOS, end of study; ET, Early termination; PK, Pharmacokinetics

10.2.2. Schedule of Events Table 4: All Cohorts A and B (Adult / Adolescent Subjects) for Drug Concentrations, Immunogenicity, and Laboratory Testing

1. Samples should be collected before the administration of study drug. Administration of study drug must be performed on the on same day as sample collection.
2. Actual dosing time and dense PK, sparse PK, and ADA sample collection times will be recorded.
3. At the screening/baseline visit, the window for baseline pre-dose ADA sample collection is as close to administration of study drug as is reasonable. Actual dosing times and ADA sample collection times will be recorded.
4. Whole blood samples for hematology and blood chemistry and urine samples for urinalysis will be analyzed at central lab.
5. Subjects who prematurely discontinue the study should have sample collection listed in the ET visit before exiting the study.
6. A PK serum sample and an ADA serum sample will be collected as soon as possible or within 7 days of receiving the first positive SARS-CoV-2 RT-qPCR result for cohort A subjects. The ADA serum samples may be analyzed for ADA and NAb, if feasible.
7. A PK serum sample and an ADA serum sample will be collected as soon as possible or within 7 days of first new positive SARS-CoV-2 RT-qPCR result after achieving 2 consecutive negative results for all subjects.

Table 8: Schedule of Events: Cohorts A1 and B1 (Pediatric Subjects [<12 years], RT-qPCR-Negative and Positive)

Visit	Screening / Baseline[1]	Additional Safety (Sentinel Only)[2]				Efficacy Assessment Period (EAP)[3]				Follow-up Period							ET	Unscheduled Visit[4]
Visit Location Site (S), Phone (P)[5]	**S**	**S**	**S**	**P[5]**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**		
Visit Number	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**EOS**		
Day	1	1	2	3	4	8	15	22	29	57	85	113	141	169	197	225		
Week	0	0	0	0	0	1	2	3	4	8	12	16	20	24	28	32		
Window (day)						±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Screening/Baseline:																		
Inclusion/exclusion	X																	
Informed consent (parent/guardian)/pediatric assent (subject)	X																	
Informed consent(adults or parent/guardian)/pediatric assent for PGx sub-study(optional)[19]	X																	
Medical history	X																	
Demographics and risk factors for SARS-CoV-2 infection	X																	
Household assessment	X[15]								X									
Appropriate sample, diagnostic assay for SARS-CoV-2 (local lab)	X[6]																	
Randomization	X																	
Treatment:																		
Study drug administration	X[7]																	
Efficacy (Virology):																		
NP swab, SARS-CoV-2 RT-qPCR (central lab)[6,16]	X[7]					X	X	X	X	X[3,4,8]	X[3,4,8]	X[3,4,8]	X[3,4,8]	X[3,4,8]	X[3,4,8]	X[3,4,8]	X	X
Efficacy (Subject-Reported) only for RT-qPCR positive subjects:																		
Assessment of ED, UCC, hospital visits[17]						X	X	X	X	X	X	X	X	X	X	X		
Absenteeism assessment[17]						X	X	X	X							X		
Safety:																		
Vital signs	X[2,10]	X[2]							X							X		X
Targeted PE[10]	X		X		X				X							X		X
Adverse events[14,18]	X[9]	X[2]	X[2]	X[2]	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	X
Con Meds, Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test for WOCBP (dipstick, local lab)[11]	X															X	X	
Laboratory Testing[12]:																		
Clinical Laboratory, Hematology, Blood Chemistry	Refer to Table 9																	
Pharmacokinetics and Immunogencity[12]:																		
Drug concentration / Anti-drug antibodies (ADA)	Refer to Table 9																	
Biomarkers:																		
Serum for serology (central lab)[12,13]	Refer to Table 9																	
Pharmacogenomics Sub-Study:																		
Whole Blood for RNA (Optional)[12,19]	Refer to Table 9																	
Whole Blood for DNA (Optional)[12,19]	Refer to Table 9																	

EAP, Efficacy assessment period; EOS, end of study; ED, emergency departments; ET, Early termination; UCC, urgent care centers; PE, physical exam; 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.

10.2.3. Schedule of Events Table 5 Cohorts A1 and B1 (Pediatric Subjects [<12 years], RT-qPCR-Negative and Positive) Footnotes

1. The screening visit and baseline visit should both occur on the same day. If needed, a remote visit may occur to sign the ICF and collect medical history and concomitant medication use, on the day prior to, but within 24 hours of study drug administration, so that the in-person screening and randomization visit may be abbreviated, due to COVID-19 considerations. Study drug administration must occur within 96 hours of collection of the index cases' positive SARS-CoV-2 diagnostic test sample.
2. The pediatric sentinel group (subset 4) (see Section 6.1.2 of the protocol) will have additional safety monitoring on day 1 and through day 4.

   Vital signs: On day 1, vital signs (pulse rate, respiratory rate, body temperature and blood pressure [if feasible, according to the child's age]) will be measured at predose, approximately every 30 minutes during the first 2 hours after dose before dismissal.

   Adverse Events (injection site reactions and hypersensitivity): after the administration of the first dose of study drug, subjects will be monitored on site for a minimum of 2 hours and then by daily visits to the study site or phone calls for the first 4 days (96 hours), particularly focusing on the assessment of injection site reactions and hypersensitivity after study drug administration.
3. Pediatric subjects who have a positive RT-PCR result during screening, or who have a positive RT-qPCR result any time after screening, will have the additional assessments done as indicated (**RT-qPCR positive pediatric subjects only**). A PK sample and an ADA sample will be collected (1) as soon as possible or within 7 days of receiving first positive SARS-CoV-2 RT-qPCR result for cohort A1 pediatric subjects and (2) as soon as possible or within 7 days of first new positive SARS-CoV-2 RT-qPCR result after achieving 2 consecutive negative results for all pediatric subjects.

   For pediatric subjects who become RT-qPCR positive after screening, the visit schedule will proceed as follows: (a) If the positive RT-qPCR result is from a scheduled visit for sample collection, the next weekly visit will occur as planned. (b) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) but within the window (±3 days) of the next weekly visit, this visit will be recorded as the scheduled next weekly visit. (c) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) and not within the window (±3 days) of the next weekly visit, this visit will be recorded as an unscheduled visit, and the next weekly visit will occur as planned.
4. Unscheduled visits: If, at any time after randomization until end of study, a pediatric subject develops fever, an acute respiratory illness or other symptoms they may feel could be related to COVID-19 or is hospitalized for suspected COVID-19, the pediatric

subject and/or parent/guardian should alert the investigator or designee immediately who will assess the subject's symptoms and condition (can be performed by phone contact, telemedicine, online meeting, home health care, etc) to decide if the pediatric subject should have an unscheduled visit for collection of NP swab sample for RT-qPCR testing. The pediatric subject and/or parent/guardian may also be asked to provide blood samples if it corresponds to a scheduled visit, according to the Schedule of Events (specified in Section 9.1 of the protocol). The investigator or designee should query the subject and/or parents/guardians about AEs in general and AEs consistent of COVID-19 and record the information on CRF (see detailed description of the procedure in Section 9.2.2.2 of the protocol).

(a) If the positive RT-qPCR result is from a scheduled visit for sample collection, the next weekly visit will occur as planned. (b) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) but within the window (±3 days) of the next weekly visit, this visit will be recorded as the scheduled next weekly visit. (c) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) and not within the window (±3 days) of the next weekly visit, this visit will be recorded as an unscheduled visit, and the next weekly visit will occur as planned.

5. Visit may occur by phone or electronic means
6. Sample for diagnostic assay for SARS-CoV-2 (local lab) (see Section 9.2.1.2 of the protocol) and RT-qPCR (NP swab; central lab) should be collected before administration of study drug. Samples for RT-qPCR (NP swab) will be collected by swabbing a single nostril (see Section 9.2.2.1 of the protocol). The remnant samples may additionally be used for exploratory viral RNA sequencing and viral infectivity analyses. The requirement for a local diagnostic assay for SARS-CoV-2 may be waived if the results are not expected to be available in a timely manner for randomization.
7. Study drug should be administered after all biological samples at screening/baseline have been collected.
8. Pediatric subjects who are RT-qPCR positive at the end of the EAP will continue to have samples collected weekly (NP swab; central lab) for RT-qPCR. Pediatric subjects will continue assessments/sample collections until 2 negative RT-qPCR test results have been obtained ≥24 hours apart (all samples must be negative). Subjects who are RT-qPCR negative at the end of the EAP will have samples collected only if they become symptomatic with COVID-19 in the follow-up period.
9. All other pediatric subjects (subset 5) will have additional safety monitoring on day 1 at baseline and 1 hour after study drug administration. All pediatric subjects or their parent/guardian will be advised to call the site if signs/symptoms of injection site or hypersensitivity reactions occur. If the pediatric subject experiences a true medical emergency, they and their parent/guardian should visit their local hospital ED and contact the site personnel later.
10. The investigator may perform a targeted physical exam, request an exam and/or vital signs at any time. These assessments can be performed using a clinic visit or a remote visit with the investigator or sub-investigator, or designee (ie, nurse practitioner in countries where allowed by local law).

11. For all girls at or beyond menarche. If the local urine pregnancy test is positive, the site must perform a serum pregnancy test for confirmation.
12. Samples for drug concentration, immunogenicity, laboratory testing, serology, and pharmacogenomics sub-study will be collected based on the pediatric subject subset designation as indicated in Table 9 .
13. The serology test results will not be communicated to the sites. The sponsor's blinded study team will not have access to post-baseline results associated with pediatric subject identification until after the database is locked.
14. During each scheduled or unscheduled visit/contact, the investigator or designee will query the pediatric subject and/or parent/guardian about AEs in general (see Section 10 of the protocol) and evaluate if the AEs are associated with SARS-CoV-2 infection (see Section 9.2.2.2. of the protocol). Pediatric subjects and/or parent/guardian with symptomatic SARS-CoV-2 infection should be queried on their symptoms weekly until symptoms resolve, even during follow-up period, then follow the regular schedule.
15. The information for the household assessment, including household members who received EUA approved monoclonal antibody treatment for COVID-19 or household members participating in the R10933-10987-COV-2067 study should preferably be collected at the baseline visit. There will be a follow-up assessment at day 29.
16. All pediatric subjects will have a weekly NP swab sample collected during the EAP. Only pediatric subjects who are RT-qPCR positive will continue to have weekly NP swab samples collected during the follow-up period until 2 consecutive negative (≥24 hr) RT-qPCR results or the end of study visit.
17. Only for RT-qPCR positive subjects (cohort A1 and cohort B1): Complete assessments from the time the subject first becomes RT-qPCR positive or from the time they develop symptoms suspected to be COVID-19 (later confirmed by RT-qPCR positive results) until the subject has had 2 negative tests or COVID-19 related symptoms have resolved (whichever lasts longer), or until the end of study visit.
18. All pediatric subjects and/or parent/guardian will complete the TEAE assessment weekly during the EAP. Subjects who are RT-qPCR negative will complete the TEAE assessment monthly during the follow-up period. Pediatric subjects and/or parent/guardian who have symptomatic SARS-CoV-2 infection will complete the TEAE assessment weekly during the follow-up period until the COVID-19 related symptoms resolve after which the pediatric subject and/or parent/guardian will complete the TEAE assessment monthly until the end of study visit.
19. Separate consent (parent/guardian of pediatric subject)/pediatric assent is required for participation of pediatric subjects who weigh ≥10 kg in the optional genomic sub-study and collection of blood samples for DNA and RNA.

Table 9: Schedule of Events: Cohorts A1 and B1 (Pediatric Subjects [<12 years]) for Drug Concentration, Immunogenicity, and Laboratory Testing

Samples for drug concentration (PK), immunogenicity assessment (ADA), and clinical laboratory testing (hematology, blood chemistry, and serology) will be collected based on subset designation and sample schedule (A, B, C, D) using subject number (assigned by IWRS):

- **Pediatric sentinel group (Subset 4)**: First 12 pediatric subjects (4 subjects per weight group (≥20 kg; 10 kg to <20 kg; <10 kg)
- **All other pediatric subjects (Subset 5):** All other pediatric subjects

Visit	Screening / Baseline[1]	Sentinel Group Only	Efficacy Assessment Period (EAP)			Follow-up Period							ET Visit[5]	Unscheduled Visit
Site (S)	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**			
Visit Number	**1**	**2**	**5**	**6**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**EOS 15**		
Day	1	2	8	15	29	57	85	113	141	169	197	225		
Week	0	0	1	2	4	8	12	16	20	24	28	32		
Window (day)		+2	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Sentinel Group (Subset 4)														
PK-ADA[2,3,9]; Hematology[4]; Blood Chemistry[4], Serology[4,8]														
Schedule A	X[1,8]	X			X[8]								X	X[6,7]
All other subjects (Subset 5)														
PK-ADA[2,3,9]; Hematology[4], Blood Chemistry[4], Serology[8]														
Schedule A	X[1,8]	X			X[8]								X	X[6,7]
Schedule B	X[1,8]		X		X[8]								X	X[6,7]
Schedule C	X[1,8]			X	X[8]								X	X[6,7]
Schedule D	X[1,8]				X[8]			X[8]					X	X[6,7]
Pharmacogenomics Sub-Study (only subjects ≥10 kg)														
Whole Blood for RNA (Optional)	X[10]													
Whole Blood for DNA (Optional)	X[10]													

ADA, anti-drug antibodies; EAP, Efficacy assessment period; EOS, end of study; ET, Early termination; PK, Pharmacokinetics

10.2.4. Schedule of Events Table 6: Cohorts A1 and B1 (Pediatric Subjects [<12 years]) for Drug Concentration, Immunogenicity, and Laboratory Testing

1. Samples should be collected before the administration of study drug. Administration of study drug must be performed on the on same day as sample collection.
2. Actual dosing time and sample collection times will be recorded for PK-ADA samples.
3. At the screening/baseline visit, the window for baseline pre-dose PK-ADA sample collection is as close to administration of study drug as is reasonable.
4. Whole blood samples for hematology and blood chemistry will be analyzed at central lab.
5. Pediatric subjects who prematurely discontinue the study should have sample collection listed in the ET visit before exiting the study.
6. A PK-ADA serum sample will be collected as soon as possible or within 7 days of receiving the first positive SARS-CoV-2 RT-qPCR result for cohort A pediatric subjects.
7. A PK-ADA serum sample will be collected as soon as possible or within 7 days of first new positive SARS-CoV-2 RT-qPCR result after achieving 2 consecutive negative results for all pediatric subjects.
8. Serum samples for serology will be collected at baseline and day 29. For pediatric subjects <10 kg, the serum sample for serology on the day 29 visit will not be collected due to restrictions in total blood volumes collection. For pediatric subjects <3 kg, the serum sample for serology on the baseline and day 29 visit will not be collected due to restrictions in total blood volumes collection.
9. The PK-ADA serum samples may be analyzed for ADA and NAb, if feasible.
10. Only for pediatric subjects who weigh ≥10 kg: The whole blood sample for RNA, should be collected on day 1/baseline (pre-dose). The whole blood for genomic DNA should be collected on day 1/baseline. If not collected at baseline, the sample for genomic DNA may be collected at any visit.

10.2.5. Early Termination Visit

Subjects who are withdrawn from the study will be asked to provide final blood samples for drug concentration and immunogenicity analysis.

10.2.6. Unscheduled Visits

All attempts should be made to keep subjects on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, for SARS-CoV-2 RT-qPCR and serology testing when subjects experience symptoms consistent with SARS-CoV-2 infection (per the broad-term list specified in Section 9.2.2.2 of the protocol), or for any other reason, as warranted.

10.3. Criteria for Potentially Clinically Significant Values (PCSV)

Parameter	PCSV For Studies in healthy subjects only	Comments
Clinical chemistry		
ALT	>3 and ≤5 ULN and baseline ≤3 ULN >5 and ≤10 ULN and baseline ≤5 ULN >10 and ≤20 ULN and baseline ≤10 ULN >20 ULN and baseline ≤20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Each category is calculated independently.
AST	>3 and ≤5 ULN and baseline ≤3 ULN >5 and ≤10 ULN and baseline ≤5 ULN >10 and ≤20 ULN and baseline ≤10 ULN >20 ULN and baseline ≤20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Each category is calculated independently.
Alkaline Phosphatase	>1.5 ULN and baseline ≤1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L.
Total Bilirubin	>1.5 and ≤2 ULN and baseline ≤1.5 ULN >2 ULN and baseline ≤2.0 ULN	Must be expressed in ULN, not in µmol/L or mg/L.
Conjugated bilirubin	>35% Total Bilirubin and TBILI >1.5 ULN, and baseline Total Bilirubin ≤35% or TBILI ≤1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis
ALT and Total Bilirubin	ALT>3 ULN and TBILI >2 ULN, and baseline ALT ≤3 ULN or TBILI ≤2ULN	
CPK	>3 and ≤10 ULN and baseline ≤3ULN >10 ULN and baseline ≤10ULN	
Creatinine	≥150 µmol/L (Adults) or ≥ULN (if ULN ≥150 µmol/L) and baseline <150 µmol/L or <ULN (if ULN ≥150 µmol/L) ≥30% change from baseline ≥100% change from baseline	3 independent criteria
Creatinine Clearance (Cockcroft's formula)	<15 ml/min and baseline ≥15 ml/min (end stage renal impairment) ≥15 to <30 ml/min and baseline ≥30 ml/min (severe renal impairment) ≥30 to < 60 ml/min and baseline ≥60 ml/min (moderate renal impairment) ≥60 to < 90 ml/min and baseline ≥90 ml/min (mild renal impairment)	Four independent criteria

Parameter	PCSV For Studies in healthy subjects only	Comments
Uric Acid Hyperuricemia: Hypouricemia:	 >408 µmol/L or >ULN (if ULN ≥408 µmol/L) and baseline ≤408 µmol/L or ≤ULN (if ULN ≥408 µmol/L) <120 µmol/L or <LLN (if LLN ≤120 µmol/L) and baseline ≥120 µmol/L or ≥LLN (if LLN ≤120 µmol/L)	Two independent criteria
Blood Urea Nitrogen	≥17 mmol/L or ≥ULN (if ULN ≥17 mmol/L) and baseline <17 mmol/L or <ULN (if ULN≥17 mmol/L)	Two independent criteria
Chloride Hypochloremia: Hyperchloremia:	 <80 mmol/L or <LLN (if LLN ≤80 mmol/L) and baseline ≥80 mmol/L or ≥LLN (if LLN ≤80 mmol/L) >115 mmol/L or >ULN (if ULN ≥115 mmol/L) and baseline ≤115 mmol/L or ≤ULN (if ULN ≥115 mmol/L)	Two independent criteria
Sodium Hyponatremia: Hypernatremia:	 ≤129 mmol/L or ≤LLN (if LLN ≤129 mmol/L) and baseline >129 mmol/L or >LLN (if LLN ≤129 mmol/L) ≥160 mmol/L or ≥ULN (if ULN ≥160 mmol/L) and baseline <160 mmol/L or <ULN (if ULN ≥160 mmol/L)	Two independent criteria
Potassium Hypokalemia Hyperkalemia	 <3 mmol/L or <LLN (if LLN ≤3 mmol/L) and baseline ≥3 mmol/L or ≥LLN (if LLN ≤3 mmol/L) ≥5.5 mmol/L or ≥ULN (if ULN ≥5.5 mmol/L) and baseline <5.5 mmol/L or <ULN (if ULN ≥5.5 mmol/L)	Two independent criteria
Total Cholesterol	≥7.74 mmol/L or ≥ULN (if ULN ≥7.74 mmol/L) and baseline <7.74 mmol/L or <ULN (if ULN ≥7.74 mmol/L)	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L or ≥ULN (if ULN ≥4.6 mmol/L) and baseline <4.6 mmol/L or <ULN (if ULN ≥4.6 mmol/L)	Threshold for therapeutic intervention

Parameter	PCSV For Studies in healthy subjects only	Comments
Glucose Hypoglycemia Hyperglycemia	 ≤3.9 mmol/L and <LLN and baseline >3.9 mmol/L or ≥ LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted) and baseline <11.1 mmol/L (unfasted); <7 mmol/L (fasted)	
HbA1c	>8% and baseline ≤ 8%	
Albumin	≤25 g/L or ≤LLN (if LLN≤25 g/L) and baseline >25 g/L or >LLN (if LLN ≤25 g/L)	
CRP	>2 ULN or >10 mg/L (if ULN not provided) and baseline ≤2 ULN or ≤10 mg/L (if ULN not provided)	
Hematology		
WBC	<3.0 Giga/L or <LLN (if LLN ≤3.0 Giga/L) and baseline ≥3.0 Giga/L or ≥LLN (if LLN≤3.0 Giga/L) (Non-Black); <2.0 Giga/L or <LLN (if LLN ≤2.0 Giga/L) and baseline ≥2.0 Giga/L or ≥LLN (if LLN≤2.0 Giga/L) (Black) ≥16.0 Giga/L or ≥ULN (if ULN ≥16.0 Giga/L) and baseline < 16 Giga/L or <ULN (if ULN ≥16.0 Giga/L)	
Lymphocytes	>4.0 Giga/L or >ULN (if ULN ≥4.0 Giga/L) and baseline ≤4.0 Giga/L or ≤ULN (if ULN ≥4.0 Giga/L)	
Neutrophils	<1.5 Giga/L or <LLN (if LLN ≤1.5 Giga/L) and baseline ≥1.5 Giga/L or ≥LLN (if LLN ≤1.5 Giga/L) (Non-Black); <1.0 Giga/L or <LLN (if LLN ≤1.0 Giga/L) and baseline ≥1.0 Giga/L or ≥LLN (if LLN ≤1.0 Giga/L) (Black)	
Monocytes	>0.7 Giga/L or >ULN (if ULN ≥0.7 Giga/L) and baseline ≤0.7 Giga/L or ≤ULN (if ULN ≥0.7 Giga/L)	

Parameter	PCSV For Studies in healthy subjects only	Comments
Basophils	>0.1 Giga/L or >ULN (if ULN ≥0.1 Giga/L) and baseline ≤0.1 Giga/L or ≤ULN (if ULN ≥0.1 Giga/L)	
Eosinophils	>0.5 Giga/L or >ULN (if ULN ≥0.5 Giga/L) and baseline ≤0.5 Giga/L or ≤ULN (if ULN ≥0.5 Giga/L)	
Hemoglobin	≤115 g/L or ≤LLN (if LLN ≤115 g/L) and baseline >115 g/L or >LLN (if LLN ≤115 g/L) for male; ≤95 g/L or ≤LLN (if LLN ≤95 g/L) and baseline >95 g/L or >LLN (if LLN ≤95 g/L) for Female. ≥185 g/L or ≥ULN (if ULN ≥185 g/L) and baseline <185 g/L or <ULN (if ULN ≥185 g/L) for Male; ≥165 g/L or ≥ULN (if ULN ≥165 g/L) and baseline <165 g/L or <ULN (if ULN ≥165 g/L) for Female Decrease from Baseline ≥20 g/L	Three criteria are independent.
Hematocrit	≤0.37 v/v or ≤LLN (if LLN ≤0.37 v/v) and baseline >0.37 v/v or >LLN (if LLN ≤0.37 v/v) for Male; ≤0.32 v/v or ≤LLN (if LLN ≤0.32 v/v) and baseline > 0.32 v/v or >LLN (if LLN ≤0.32 v/v) for Female ≥0.55 v/v or ≥ULN (if ULN ≥0.55 v/v) and baseline <0.55 v/v or <ULN (if ULN ≥0.55 v/v) for Male; ≥0.5 v/v or ≥ULN (if ULN ≥0.5 v/v) and baseline < 0.5 v/v or <ULN (if ULN ≥0.5 v/v) for Female	Two Criteria are independent
RBC	≥6 Tera/L or ≥ULN (if ULN ≥6 Tera/L) and baseline < 6 Tera/L or <ULN (if ULN ≥6 Tera/L)	
Platelets	<100 Giga/L or <LLN (if LLN ≤100 Giga/L) and baseline ≥100 Giga/L or ≥LLN (if LLN≤100 Giga/L) ≥700 Giga/L or ≥ULN (if ULN ≥700 Giga/L) and baseline <700 Giga/L or <ULN (if ULN ≥700 Giga/L)	Two independent criteria

Parameter	PCSV For Studies in healthy subjects only	Comments
Vital signs		
HR	<45 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	To be applied for all positions except STANDING
SBP	≤95 mmHg and decrease from baseline ≥20 mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions except STANDING
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions except STANDING

10.4. Example of SAS Procedures for Primary Analysis and Missing Data Imputations by FCS

Primary Analysis - GEE Model

Below is an example of SAS code using a generalized linear model to estimate the odds ratio between the treatment groups with the generalized estimation equation (GEE) approach after 100 imputations.

```
proc genmod data=DATA_IN;
class treatment(ref='0') Age_group region;/*eg.treatment= 0:placebo */
by _imputation_;
model response(event='1') =treatment region age_group/dist=bin link=logit;
repeat subject=household_id/type=cs;
lsmeans treatment/diff om cl ilink;
ods output diffs=logOR geeexchcorr=icc;
run;
```

Primary Analysis - Logistic Regression Model

Below is an example of SAS code using a logistic regression model instead of using GEE approach when the percentage of households with a single study subject is 70% or more to estimate the odds ratio between the treatment groups after 100 imputations.

```
proc genmod data=DATA_IN descending;
class treatment(ref='0') Age_group region;
by _imputation_;
model response(event='1') =treatment region age_group/dist=bin link=logit;
lsmeans treatment/diff om cl ilink;
ods output diffs=logOR ParameterEstimates=parameterestimates;
```

```
run;
```

Missing Data Imputations – FCS

Assume the missing RT-qPCR test results occurred across Visit 5 (Day 8) to Visit 8 (Day 29) (e.g. 1=positive vs 0=negative). An example of SAS code for FCS MI with the random seed=2069 is presented below.

```
proc mi data=DATAIN out=DATAOUT seed=2069 nimpute=100;
class treatment age_group   region v5 v6 v7 v8;
var treatment age_group region v5 v6 v7 v8;
fcs logistic(v5/LIKELIHOOD=AUGMENT);
fcs logistic(v6/LIKELIHOOD=AUGMENT);
fcs logistic(v7/LIKELIHOOD=AUGMENT);
fcs logistic(v8/LIKELIHOOD=AUGMENT);
run;
```

After FCS MI to generate 100 complete datasets, each subject's overall RT-qPCR test status during the EAP can be determined by any of imputed value V5 to V8 is equal to 1. The same model using GEE approach or logistic regression for the primary analysis will be applied.

The results from the 100 analyses will be combined using Rubin's formulae through PROC MIANALYZE procedure shown below.

```
proc mianalyze data=logOR;
ods output parameterestimates=final_logor;
modeleffects estimate;
stderr stderr;
run;
```

The estimates of log(odds ratio) and the corresponding 95% confidence interval (CI) will be provided in the FINAL_LOGOR dataset. The results of odds ratio and 95% CI will be derived by taking the exponential of these estimates.

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