Clinical Study Protocol

A PHASE 2 STUDY TO ASSESS THE VIROLOGIC EFFICACY OF REGN10933+REGN10987 ACROSS DIFFERENT DOSE REGIMENS IN OUTPATIENTS WITH SARS-CoV-2 INFECTION

Compound:	REGN10933+REGN10987 (Casirivimab + Imdevimab)
Clinical Phase:	2
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[redacted]

AMENDMENT HISTORY

Amendment 2

The primary purpose of this amendment is to pre-specify a first-step analysis and make adjustments to the planned statistical methodology.

Description of Change	Brief Rationale	Section(s)
Study enrollment has been closed.	Based on assessment that the study is adequately powered with current enrollment	Section 6.1 Study Description and Duration
A primary efficacy analysis will be conducted as a first-step analysis using the first 816 patients enrolled in the study. This analysis represents the final analysis of the primary endpoint and is not considered an interim analysis.	To pre-specify the first-step analysis and other planned statistical analyses of the study	Section 6.3 Planned Interim Analysis Section 8.7 Blinding Section 11 Statistical Plan Section 11.2 Justification of Sample Size Section 11.4.9 Timing of Statistical Analyses [new] Section 11.5 Interim Analysis
The following additional changes have been made with respect to the statistical design of the study: • Virologic endpoints assessing changes in cycle threshold (Ct) are now exploratory; these were previously planned as secondary analyses • Exploratory endpoints have been added to assess the proportion of patients with ≥1 COVID-19-related hospitalization/all-cause death or ≥1 COVID-19-related hospitalization/emergency room visit/all-cause death • Exploratory endpoints assessing the cumulative incidence of various COVID-19-related medically-attended visits have been removed; corresponding proportion-based endpoints have been retained • Associated details (eg, study variables, primary and secondary efficacy analyses) have been updated to the reflect the planned statistical analysis	To clarify the planned study analyses	Section 4.2 Secondary Endpoints Section 4.3 Exploratory Endpoints Section 5.1 Demographic and Baseline Characteristics Figure 1 Study Flow Diagram Section 11.3.1 Efficacy Analysis Sets Section 11.3.1.1 The Seronegative Modified Full Analysis Set [new] Section 11.3.1.2 Per Protocol Set [new] Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.2 Secondary Efficacy Analysis Section 11.4.4 Control of Multiplicity Section 11.4.5.1 Adverse Events
Clarified in the schedule of events that study visits are not required solely to collect continuously-monitored assessments, if no other assessments are planned on that day.	To ensure operational clarity and avoid unnecessary study visits	Table 1 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events Table, #6
Clarified that for patients with symptoms of COVID-19 at screening, the severity of symptoms will be recorded and graded in the eCRF using the current version of the NCI-CTCAE v5.0.	To capture additional clinically-relevant information regarding COVID-19 illness	Table 1 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events Table, #12 Section 9.2.1.4 Medical History

Description of Change	Brief Rationale	Section(s)
Clarified that during each indicated collection visit (as provided in the schedule of events), all previously unrecorded COVID-19-related medically-attended visits and details will be recorded, beginning from the day of dosing up to and including the day of collection.	To ensure appropriate capturing of clinically-relevant information	Section 9.2.10.3 COVID-19-Related Medically-Attended Visit Details
The risk-benefit section has been updated to reflect the current Investigator's Brochure (edition 5). This update includes the addition of hypersensitivity reactions (including infusion-related reactions and injection site reactions) as an important identified risk.	To provide current information regarding the potential risks and benefits of REGN10933 + REGN10987	Section 3.3 Risk-Benefit
Provided updated CDC guidance regarding COVID-19 vaccination.	To ensure accurate and current medical information	Section 7.2.1 Inclusion Criteria, #7 Section 8.10.1 Prohibited and Permitted Medications
In light of the increasing number of therapeutic and preventative COVID-19 agents approved or conditionally authorized, reference to individual agents has been removed. References to FDA and EMA have been provided as a general resource for currently-available agents.	To ensure current, accurate, and consistent information	Section 1.6 A Randomized, Placebo-Controlled Study of Anti-SARS-CoV-2 S Protein Monoclonal Antibodies in Outpatients with SARS-CoV-2 Infection
Minor administrative changes, updates to background information, and other minor typographical corrections were made.	To ensure current, accurate, and consistent information	Throughout the document

Amendment 1

The primary purpose of this amendment is to modify the study design per health authority request.

Description of Change	Brief Rationale	Section(s)
In addition to current safety information collection, the following additional information will be collected: • All treatment-emergent adverse events (TEAEs) through day 29 • TEAEs that led to a hospitalization or emergency room visit, regardless of relatedness to COVID-19, through day 169 • Grade ≥3 TEAEs through day 169 • All serious adverse events (SAEs) through day 169 • Any clinically-significant laboratory findings Exploratory endpoints have been added and/or modified to accommodate the additional collection of safety information.	Per health authority request, for more comprehensive analysis of safety profile and to further assess patient safety by extending the follow-up period to cover approximately 5 half-lives of REGN10933 + REGN10987	Section 2.3 Exploratory Objectives Section 3.2.1 Rationale for Study Design Section 4.3 Exploratory Endpoints Section 5.3 Safety Variables Section 6.1 Study Description and Duration Table 1 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events Table, #5, 8 Section 9.2.4.2 Adverse Event Monitoring Section 9.2.5 Post-Day 22 Follow-up by Phone Section 9.2.7 Laboratory Testing Section 10.1.1 General Guidelines Section 10.1.3 Events that Require Expedited Reporting to Sponsor Section 11.4.5.1 Adverse Events
Details of COVID-19-related medically-attended visits will be collected through day 169. Collection previously ended at day 29.	For more comprehensive exploratory assessment of clinical outcomes	Table 1 Schedule of Events
Blood samples for drug concentration and immunogenicity assessments will be collected on day 120. Anti-drug antibody (ADA) and neutralizing antibody (NAb)-related objectives, endpoints, and analyses have been added accordingly.	For comprehensive analysis of drug concentrations and immunogenicity of REGN10933 and REGN10987 over time, at different dose levels and routes of administration	Section 2.2 Secondary Objectives Section 3.3 Risk-Benefit Section 4.2 Secondary Endpoints Section 5.5 Immunogenicity Variables [new] Section 6.1 Study Description and Duration Table 1 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events Table, #10 Section 11.3.4 Immunogenicity Analysis Set [new] Section 9.2.8 Drug Concentration Measurements and Samples Section 9.2.9 Immunogenicity Measurements and Samples [new] Section 11.4.8 Analysis of Immunogenicity Data [new] Section 11.4.8.1 Analysis of Neutralizing Antibody Data [new]
The following study visit modifications have been made: • Phone visits were added at day 90 and day 169 • An in-person visit was added at day 120	To accommodate the additional safety, drug concentration, and immunogenicity assessments	Section 3.3 Risk-Benefit Section 6.1 Study Description and Duration Figure 1 Study Flow Diagram Table 1 Schedule of Events

Description of Change	Brief Rationale	Section(s)
• The study duration has been extended from 61days to 170 days		Section 9.1.2 Early Termination from the Study
Grade ≥3 injection-site reactions (ISRs) will be reported as AESIs. Grade 2 ISRs will no longer be considered AESIs.	To collect the most medically-relevant AESIs	Section 8.5.2 Injection Reactions Table 1 Schedule of Events Section 10.1.1 General Guidelines Section 10.1.3 Events that Require Expedited Reporting to Sponsor
The followings changes and clarifications were made with respect to assessment of women of childbearing potential (WOCBP) and women who are pregnant: • In addition to the standard collection of pregnancy outcome information, for newborn infants of patients who were treated in the study and were pregnant at randomization or became pregnant at any time while in the study, the incidence and outcome of any SARS-CoV-2 infection [in the newborn] will be collected on day 120 and day 169 • Pregnancy testing at screening must be performed in all WOCBP, regardless of pregnancy status • Pregnancy or breastfeeding status at screening must be collected as medical history, if applicable • A paper pregnancy report form must be completed for each patient who becomes pregnant or is pregnant at the signing of consent.	To ensure accurate information is collected regarding pregnancy; per health authority request, to assess any treatment effects on vertical transmission of SARS-CoV-2	Table 1 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events Table, #7 Section 9.2.1.4 Medical History Section 9.2.5 Post-Day 22 Follow-up by Phone Section 10.1.3 Events that Require Expedited Reporting to Sponsor Section 9.2.6 Pregnancy Test for Women of Childbearing Potential
The following modifications have been made, and information provided, with respect to SARS-CoV-2 vaccination: • Patients will be excluded based on prior use, current use, or planned use (within time period given per CDC guidance but no sooner than 22 days after study drug administration) of any authorized or approved vaccine for SARS-CoV-2. • Patients will be excluded if they have any prior participation, current participation, or any future plans to participate in a clinical research study evaluating any authorized, approved, or investigational vaccine for SARS-CoV-2 • SARS-CoV-2 vaccines will be captured as targeted concomitant medication. In addition, current CDC guidance related to vaccination has been provided for reference. This guidance recommends deferral of SARS-CoV-2 vaccination for at least 90 days after administration of passive antibody treatment (eg, REGN10933+REGN10987) (CDC, 2020)	Per current CDC recommendations on SARS-CoV-2 vaccination	Section 7.2.2 Exclusion Criteria, #7, #11 [new] Section 8.10.1 Prohibited and Permitted Medications 9.2.4.3 Record Targeted Concomitant Medications
Clarified that viral variants suspected to confer decreased susceptibility to REGN10933 and/or	Per health authority request	Section 9.2.10.1 Virology

Description of Change	Brief Rationale	Section(s)
REGN10987 will be evaluated in nonclinical work separate from this protocol.		
Clarified that for the screening SARS-CoV-2 diagnostic test, the **sample** must be collected ≤72 hours of randomization. Samples are not valid for screening if collected >72 hours from randomization, even if the test is performed, or results reported, within the 72-hour window.	To ensure appropriate screening for SARS-CoV-2 infection	Section 7.2.1 Inclusion Criteria, #2
Removed language stating that if diagnostic SARS-CoV-2 testing was performed outside of the allowed window, a new test is required for study inclusion. Language had previously been retained in error. Per study exclusion criteria, patients will be excluded if they have a positive SARS-CoV-2 antigen or molecular diagnostic test from a sample collected >72 hours prior to randomization	To ensure accurate information	Section 9.2.1.2 Diagnostic Test for SARS-CoV-2
Members of the clinical site study team and/or their immediate family will be now considered a study exclusion criterion.	To avoid the appearance of conflict of interest or coercion, and to ensure integrity of study data	Section 7.2.2 Exclusion Criteria, #12 [new]
The schedule of events was corrected to reflect treatment-emergent grade ≥2 hypersensitivity reactions will be assessed through day 29. Previous schedule incorrectly stated that assessment would occur through day 22.	To ensure accurate information	Table 1 Schedule of Events
Updates to background information and other minor updates were made.	To ensure current, accurate, and consistent information	Throughout the document

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AAS	Anti-drug antibody analysis set
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
CRF	Case report form (electronic or paper)
CRO	Contract research organization
Ct	Cycle Threshold
CTCAE	Common Terminology Criteria for Adverse Events
EDC	Electronic data capture
EOS	End of study
ET	Early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IV	Intravenous
MAV	Medically-attended visit
mFAS	Modified full analysis set
NAb	Neutralizing antibody
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
PK	Pharmacokinetic
PPE	Personal protective equipment
RBQM	Risk-Based Quality Monitoring
RT-qPCR	Quantitative reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TWA	Time weighted average

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 2 Study to Assess the Virologic Efficacy of REGN10933+REGN10987 Across Different Dose Regimens in Outpatients with SARS-CoV-2 Infection
Site Locations	The study will be conducted in approximately 80 sites in the United States.
Principal Investigator	To be determined
Objectives	
Primary	• To assess the virologic efficacy of REGN10933+REGN10987 across different intravenous and subcutaneous doses compared to placebo
Secondary	• To evaluate additional indicators of virologic efficacy of REGN10933+REGN10987 compared to placebo • To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo • To assess the concentrations of REGN10933 and REGN10987 in serum over time • To assess the immunogenicity of REGN10933 and REGN10987
Study Design	*Note: as of protocol amendment 2, study enrollment is closed.* This is a randomized, double-blind, placebo-controlled, parallel group study to assess the dose response profile of single intravenous (IV) or single subcutaneous (SC) doses of REGN10933+REGN10987 in outpatients with SARS-CoV-2 infection. Eligible patients will be randomized to receive a single dose of REGN10933+REGN10987 or placebo by IV or SC route. On the day of dosing, patients will have NP swabs taken for SARS-CoV-2 RT-qPCR testing and blood drawn for safety, drug concentration, immunogenicity, and serologic analyses. After study drug administration, patients will have a post-dose blood collection (either at the end of intravenous infusion or at least 1 hour after subcutaneous administration). Patients will be monitored for at least 1 hour after study drug administration and then released from the study site, if medically appropriate. Information related to safety and COVID-19-related medically-attended visits will be recorded during planned study visits. Patients will also be asked to notify study personnel as soon as possible about any medically-attended visits. Note that the TEAEs that will be collected during the study will differ according to different periods of the study schedule. Refer to the safety reporting section in the protocol for more information on reporting of TEAEs and treatment-emergent laboratory abnormalities. Patients will have NP swabs and blood samples collected every other day for the first week of the study. Additional NP swab samples will be collected once-weekly for 2 more weeks to assess potential persistence of viral load. A phone visit will occur during the fourth week for collection of safety information. After the first month, patients will have visits approximately once-monthly for 4 additional months. The penultimate visit will be in-person to collect blood samples for drug concentration and immunogenicity. The final visit (EOS) will be a phone call.
Study Duration	The duration of the study is 170 days for each patient.
End of Study Definition	The end of study is defined as the date when the last living patient completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study patient can no longer be contacted by the investigator).
Population	
Sample Size	Up to approximately 1400 patients will be enrolled.
Target Population	This study will enroll adult, non-hospitalized patients who have a positive diagnostic test for SARS-CoV-2.

Inclusion criteria: A patient must meet the following criteria to be eligible for inclusion in the study. Other inclusion criteria also apply and are described in the main text.

- Is male or female ≥18 years of age (or country's legal age of adulthood) at randomization

  Note: upper age limit may apply; refer to other inclusion criteria.
- Has SARS-CoV-2-positive diagnostic test from a sample collected ≤72 hours prior to randomization, using a validated SARS-CoV-2 antigen, RT-PCR, or other molecular diagnostic assay and an appropriate sample such as nasopharyngeal (NP), nasal, oropharyngeal (OP), or saliva

  Note: Historical record of positive result is acceptable, as long as the sample was collected ≤72 hours prior to randomization.
- *Low-risk symptomatic patient:* Has symptoms consistent with COVID-19 (as determined by the investigator) with onset ≤7 days before randomization, and **meets all of the following 8 criteria:**
- Age ≤50
- No obesity, with obesity defined as BMI ≥30 kg/m^2
- Does not have cardiovascular disease or hypertension
- Does not have chronic lung disease or asthma
- Does not have type 1 or type 2 diabetes mellitus
- Does not have chronic kidney disease, with or without dialysis
- Does not have chronic liver disease
- Is not pregnant

  or

  Asymptomatic patient: Has had no symptoms consistent with COVID-19 (as determined by the investigator) occurring at any time <2 months prior to randomization

Exclusion criteria: A patient who meets any of the following criteria will be excluded from the study. Other exclusion criteria also apply and are described in the main text.

- Was admitted to a hospital for COVID-19 prior to randomization, or is hospitalized (inpatient) for any reason at randomization
- Has a known positive SARS-CoV-2 serologic test
- Has a positive SARS-CoV-2 antigen or molecular diagnostic test from a sample collected >72 hours prior to randomization
- Is immunosuppressed, based on investigator's assessment

  Note: examples include cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of AIDS), sickle cell anemia, thalassemia, and prolonged use of immune-weakening medications.
- Has participated, or is participating, in a clinical research study evaluating COVID-19 convalescent plasma, mAbs against SARS-CoV-2, or intravenous immunoglobulin (IVIG) within 3 months or within 5 half-lives of the investigational product (whichever is longer) prior to the screening visit
- Prior, current, or planned future use of any of the following treatments: COVID-19 convalescent plasma, mAbs against SARS-CoV-2 (eg, bamlanivimab), IVIG (any indication), systemic corticosteroids (any indication), or COVID-19 treatments (authorized, approved, or investigational)

  Note: prior use is defined as the past 30 days or within than 5 half-lives of the investigational product (whichever is longer) from screening.
- Prior use (prior to randomization), current use (at randomization), or planned use (within time period given per CDC guidance but no sooner than 22 days of study drug administration) of any authorized or approved vaccine for COVID-19

	Note: As of 02 March 2021, CDC guidance recommends deferral of SARS-CoV-2 vaccination for at least 90 days after administration of passive antibody therapy. Additional information can be found in the main text. • Has participated, is participating, or plans to participate in a clinical research study evaluating any authorized, approved, or investigational vaccine for SARS-CoV-2
Treatments	
IV Single Dose	Co-administered REGN10933+REGN10987 combination therapy intravenous (IV) single dose: • 2400 mg (1200 mg per monoclonal antibody [mAb]) • 1200 mg (600 mg per mAb) • 600 mg (300 mg per mAb) • 300 mg (150 mg per mAb) • Placebo IV single dose
SC Single Dose	Co-administered REGN10933+REGN10987 combination therapy subcutaneous (SC) single dose • 1200 mg (600 mg per mAb) • 600 mg (300 mg per mAb) • Placebo SC single dose
Endpoints	
Primary	Time-weighted average daily change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7, as measured by RT-qPCR in NP swab samples, in patients who have a central-lab determined RT-qPCR positive test and are seronegative at baseline
Secondary	• Time-weighted average daily change from baseline in viral load (log_{10} copies/mL) from day 1 to day 5 • Time-weighted average daily change from baseline in viral load (log_{10} copies/mL) in patients with high viral load at baseline ($>10^4$ copies/mL, $>10^5$ copies/mL, $>10^6$ copies/mL, $>10^7$ copies/mL) from day 1 to day 7 • Time-weighted average daily change from baseline in viral load (log_{10} copies/mL) in patients with high viral load at baseline ($>10^4$ copies/mL, $>10^5$ copies/mL, $>10^6$ copies/mL, $>10^7$ copies/mL) from day 1 to day 5 • Proportion of patients with high viral load ($>10^4$ copies/mL, $>10^5$ copies/mL, $>10^6$ copies/mL, $>10^7$ copies/mL) at each visit • Proportion of patients with viral loads below the limit of detection at each visit • Proportion of patients with viral loads below the lower limit of quantification at each visit • Change from baseline in viral load (log_{10} copies/mL) at each visit, as measured by RT-qPCR in NP samples • Proportion of patients with treatment-emergent SAEs through day 29 • Proportion of patients with infusion-related reactions (grade ≥2) through day 4 • Proportion of patients with injection-site reactions (grade ≥3) through day 4 • Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29 • Concentrations of REGN10933 and REGN10987 in serum over time • Immunogenicity as measured by anti-drug antibodies (ADAs) and neutralizing antibodies (NAb) to REGN10933 and REGN10987
Procedures and Assessments	Procedures and assessments will include: • NP swabs for SARS-CoV-2 RT-qPCR • COVID-19-related medically-attended visits

	• TEAEs, treatment-emergent SAEs, and treatment-emergent AESIs (grade ≥2 infusion-related reactions, grade ≥3 injection-site reactions, grade ≥2 hypersensitivity reactions, and any TEAE that led to a hospitalization or emergency room visit, regardless of whether the visit is related to COVID-19) • Targeted concomitant medications, safety labs, vital signs, and pregnancy status
Statistical Plan	
Statistical Hypothesis	• H_0: There is no difference between patients treated with one or more dose regimens of REGN10933+REGN10987 and patients treated with placebo in time weighted average daily change from baseline in viral load from day 1 to day 7 • H_1: REGN10933+REGN10987 reduces time weighted average daily change from baseline in viral load (log10 copies/mL) from day 1 to day 7, relative to placebo
Justification of Sample Size	The sample size is based on the primary virologic endpoint of the time-weighted average (TWA) daily change from baseline in viral load (log10 copies/mL) from day 1 to day 7, in patients who are seronegative and who have a positive RT-qPCR value at baseline. In the Phase 2 portion of Study COV-2067, the mean (SD) was -0.73 (0.948) log10 copies/mL. For the primary hypothesis comparing each dose to placebo, approximately 57 patients per treatment group. With this sample size, the study has ~98% power to detect a difference of -0.73 log10 copies/mL between any active treatment group and placebo. In order to enroll 400 seronegative patients, the study will randomize approximately 800 patients, assuming that 50% are seronegative. For comparisons between doses and regimens, the study plans to enroll 700 seronegative patients in order to have 100 patients per group. For between-group comparisons, the 95% CI half-width between any two treatment groups with this sample size would be 0.27 log10 copies/mL. In order to enroll 700 seronegative patients, approximately 1400 patients will be randomized. Placebo IV and placebo SC arms will be pooled in the efficacy analyses of the viral load endpoints as the route of administration does not alter the pharmacodynamic response of patients receiving placebo.
Primary Efficacy Analysis	The primary virologic efficacy variable is the time-weighted average change from baseline in viral load from day 1 to day 7, as measured by RT-qPCR in NP swab samples. The primary analysis will be conducted in the Seronegative mFAS population. The analyses will be based on the observed data with no imputation for missing data. Viral load values less than the lower limit of quantification of the PCR assay but with positive qualitative results will be set to half of lower limit of quantification of the PCR assay; values with nondetectable RNA will be set to 0 log10 copies/mL if the reason for the negative value is not a failed test. Viral load values above the upper limit of quantification will be re-tested using the reflex test. The primary efficacy variable will be calculated using the linear trapezoidal rule, ie, area under the curve for change from baseline at each time point from day 1 to last observation divided by the number of days from day 1 to day of last observation. The TWA estimates the average over the time range of interest, adjusting for any irregular spacing of the timing when samples are taken (eg, if samples are missing). An Analysis of Covariance (ANCOVA) model with treatment group as a fixed effect and baseline viral load and treatment by baseline interaction as covariates will be fit to the data as the primary analysis.
Timing of Statistical Analyses	The primary efficacy analysis will be conducted as a first-step analysis using the first 816 patients enrolled in the study up to day 7, in order to evaluate approximately 400 patients who are seronegative at baseline. This analysis represents the final analysis of the primary endpoint and is not considered an interim analysis. An analysis may also occur after all enrolled patients have reached at least day 7, and a subsequent analysis will occur once the last patient enrolled in the study completes their last study visit. A SAP will be issued prior to the first database lock.

1. INTRODUCTION

1.1. Emergence of SARS-CoV-2 and COVID-19

Coronaviruses are a family of enveloped, single-stranded RNA viruses. In recent decades, two highly pathogenic strains of coronavirus were identified in humans: severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). These viruses were found to cause severe, and sometimes fatal, respiratory illness (Cui, 2019) (Fehr, 2015).

In December 2019, pneumonia of unknown cause was identified in clusters of patients in Wuhan City, China. A novel enveloped RNA betacoronavirus – severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – was identified in these patients, and the disease caused by SARS-CoV-2 infection was later designated coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO, 2020) (Zhu, 2020). Millions of SARS-CoV-2 infections have been confirmed worldwide, and the rapidly spreading, worldwide outbreak has prompted the WHO to declare COVID-19 a pandemic and public health emergency of international concern.

1.2. Clinical Outcomes in Hospitalized Patients with COVID-19

Patients with COVID-19 are at risk for developing a variety of respiratory conditions, ranging from relatively mild symptoms to respiratory failure and death (Wu, 2020). Among hospitalized patients, intensive care and/or supplemental oxygen intervention (eg, mechanical ventilation) is often required, and reported fatality rates are high.

In a report from the Chinese Center for Disease Control and Prevention that included 44,500 confirmed infections, nearly 20% of patients presented with advanced respiratory symptoms (14% with dyspnea, hypoxia, and >50% lung involvement on imaging; 5% with respiratory failure, shock, or multiorgan failure) (Wu, 2020). Another analysis of patients with COVID-19 in China found that, among 1,099 hospitalized patients, 5% had been admitted to an intensive care unit (ICU), 2.3% required invasive mechanical ventilation, and 1.4% died. Among patients with advanced disease on admission (defined as pneumonia, hypoxemia, and tachypnea), these negative outcomes rose to 19%, 14.5%, and 8.1%, respectively (Guan, 2020). A report of 2634 hospitalized patients with COVID-19 in the United States identified similar clinical outcomes: 14.2% were admitted to an ICU, 12.2% required invasive mechanical ventilation, and 21% died (Guan, 2020). Other reports have found that approximately 20% to 30% of hospitalized patients with COVID-19 and pneumonia require intensive care for respiratory support (Richardson, 2020).

1.3. Outpatient Care as a Potential COVID-19 Treatment Setting

Although severe COVID-19 can occur across all age groups, accumulating data have identified several factors that can place patients at risk of more serious illness and potentially lead to hospitalization, emergency room visits, or other medically-attended visits (MAVs). These include age, pregnancy, as well as variety of comorbidities such as obesity and cardiovascular disease (Chen, 2020). An anti-viral therapeutic that could be administered to outpatients has the potential to significantly reduce COVID-19-related medically-attended visits, particularly among those with 1 or more baseline risk factors Currently, there is a great need for therapies capable of reducing viral load and slowing or preventing COVID-19 disease progression.

1.4. The Role of Spike (S) Protein in SARS-CoV-2 Pathogenesis

Coronaviruses consist of an RNA genome packaged in nucleocapsid (N) protein surrounded by an outer envelope. The envelope is comprised of membrane (M) protein and envelope (E) protein, which are involved in virus assembly, and spike (S) protein, which mediates entry into host cells. S proteins form large trimeric projections, providing the hallmark crown-like appearance of coronaviruses. S protein trimers bind to a host receptor and, after priming by cellular proteases, mediate host–virus membrane fusion (Huang, 2020). The S protein appears to be central to viral infectivity by SARS-CoV-2. SARS-CoV-2 S protein binds the host receptor angiotensin-converting enzyme 2 (ACE2) with high affinity, and in cell assays and animal models can utilize ACE2 as a functional receptor for host cell entry (Hoffmann, 2020) (Ou, 2020) (Walls, 2020).

Blockade of host cell entry through the use of neutralizing antibodies against S protein is a viable mechanistic strategy shown to reduce viral infectivity of SARS-CoV and MERS-CoV (Jiang, 2020). In light of the likely pivotal role of S protein in the pathogenesis of SARS-CoV-2 (Datta, 2020), a number of efforts are underway to develop antibodies and vaccines that target the S protein of this novel coronavirus.

1.5. REGN10933+REGN10987: Human Monoclonal Antibodies that Target SARS-CoV-2 S Protein

Regeneron Pharmaceuticals, Inc (Regeneron) is currently developing human, neutralizing monoclonal antibodies (mAb)s directed against the S protein of SARS-CoV-2, for the treatment and prevention of SARS-CoV-2 infection. REGN10933 and REGN10987 are human, IgG1 mAbs that bind the receptor binding domain (RBD) of the SARS-CoV-2 S protein and block interaction with ACE2. REGN10933 and REGN10987 exhibit potent neutralization and can bind simultaneously to the S protein RBD. When co-administered as combination therapy, REGN10933+REGN10987 treatment is anticipated to neutralize SARS-CoV-2 with a reduced likelihood of viral escape due to genetic mutations. Importantly, these mAbs retain neutralization potency against multiple SARS-CoV-2 variants identified through clinical isolates, including recently-emerging variants such as the D614G variant, B.1.1.7 variant (first identified in the UK), and B.1.351 variant (first identified in South Africa) (Baum, 2020) (Korber, 2020) (Wang, 2021). REGN10933+REGN10987 combination therapy (also referred to as casirivimab+imdevimab) thus represents a promising therapeutic strategy to reduce SARS-CoV-2 viral load and COVID-19 disease progression.

1.6. A Randomized, Placebo-Controlled Study of Anti-SARS-CoV-2 S Protein Monoclonal Antibodies in Outpatients with SARS-CoV-2 Infection

Several therapeutic and preventative agents are under investigation for the treatment or prevention of COVID-19. While a number of these agents have received approvals or conditional authorizations (EMA, 2021) (FDA, 2021) there remains a significant unmet medical need for COVID-19 treatments. Multiple COVID-19 therapies will be required, both to address the medical requirements of distinct patient populations and to bolster treatment supplies as caseloads continue to rise. The availability of multiple treatment options, and the continued collection of data on conditionally authorized treatments, are critically important in the setting of a global pandemic.

Studies are currently ongoing to assess the efficacy and safety of co-administered REGN10933+REGN10987 combination therapy ("REGN10933+REGN10987") in the treatment and prevention of COVID-19. Available data in outpatients have shown that REGN10933+REGN10987 provides similar virologic and clinical efficacy when given as 2400 mg or 8000 mg intravenous (IV) single dose (Section 3.2), with an acceptable safety profile in this patient population. In this phase 2 study, additional IV dose regimens, as well as subcutaneous (SC) dose regimens, will be evaluated in outpatients with SARS-CoV-2 infection to provide additional assessment of virologic efficacy and safety at lower doses.

For more information regarding the rationale for the study design and dose selection, refer to Section 3.2. Additional background information on the study drug and the overall development program can be found in the Investigator's Brochure.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to assess the virologic efficacy of REGN10933+REGN10987 across different intravenous and subcutaneous doses compared to placebo.

2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate additional indicators of virologic efficacy of REGN10933+REGN10987 compared to placebo
- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo
- To assess the concentrations of REGN10933 and REGN10987 in serum over time
- To assess the immunogenicity of REGN10933 and REGN10987

2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To explore the occurrence of COVID-19-related hospitalizations, emergency room visits, and other medically-attended visits (MAVs) in patients treated with REGN10933+REGN10987 compared to those treated with placebo

  Note: The definition of a COVID-19-related MAV is provided in Section 9.2.10.3.
- To assess viral genetic variation in patients with a positive SARS-CoV-2 quantitative reverse transcription polymerase chain reaction (RT-qPCR)
- To explore relationships between REGN10933+REGN10987 exposure and selected efficacy endpoints, safety endpoints, and/or biomarkers
- To explore the occurrence of all-cause hospitalizations, emergency room (ER) visits, or deaths in patients treated with REGN10933+REGN10987 compared to those treated with placebo

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

Treatment with REGN10933+REGN10987 is well tolerated and reduces SARS-CoV-2 viral load across multiple dose regimens compared to placebo.

Information concerning statistical hypotheses can be found in Section 11.1.

3.2. Rationale

3.2.1. Rationale for Study Design

In an ongoing study in outpatients with COVID-19 (R10933-10987-COV-2067; hereafter COV-2067), interim phase 1/2 and primary phase 2 analyses found that patients treated with 2400 mg or 8000 mg of REGN10933+REGN10987 IV single dose had a greater reduction in viral load compared with those who received placebo. These virologic effects translated into clinical benefit, significantly reducing COVID-19-related MAVs in these patients (with MAV defined in the study as hospitalization, emergency room visit, urgent care visit, physician's office visit, or telemedicine visit, with the primary reason for the visit being COVID-19). Notably, virologic and clinical efficacy were similar among those treated with either 2400 mg or 8000 mg, suggesting that maximal benefit may have already been reached at the 2400 mg dose (refer to the Investigator's Brochure for more information on these analyses).

This randomized, double-blinded, placebo-controlled, parallel group study (R10933-10987-COV-20145) will assess the virologic efficacy, as well as safety and tolerability, of REGN10933+REGN10987 at different single dose regimens in outpatients with SARS-CoV-2 infection. The purpose of this study is to identify a lower dose regimen capable of demonstrating the same (or similar) virologic efficacy seen at the 2400 mg IV single dose level in outpatients with COVID-19. These data, taken together with data on the safety profile of REGN10933+REGN10987 and any correlation between virologic and clinical efficacy at 1200 mg, 2400 mg, and 8000 mg IV doses observed in Study COV-2067, will aid in identifying a dose regimen with the optimal risk-benefit profile in this patient population. Moreover, identifying lower doses that are capable of reducing viral load will bolster the ability to provide therapeutic doses of REGN10933+REGN10987 in the setting of a global pandemic, where supplies of therapeutic agents are increasingly limited as caseloads rise.

An additional aim of this study is to assess to virologic efficacy, as well as safety and tolerability, of REGN10933+REGN10987 given subcutaneously in outpatients with SARS-CoV-2. Currently, SC administration is being explored only in the prophylaxis setting (R10933-10987-COV-2069). Availability of subcutaneously-administered single-dose REGN10933+REGN10987 in the treatment setting could potentially improve access for patients who are unable to access facilities capable of administering intravenous infusions.

Since the primary endpoint of this study is virologic, the study will enroll patients with SARS-CoV-2 infection regardless of whether they have symptoms of COVID-19. This will allow for a broader assessment of the potential impact of REGN10933+REGN10987 on SARS-CoV-2 viral burden. Study COV-2067 is currently assessing a more targeted population of symptomatic patients who have one or more risk factors for developing severe COVID-19.

As of protocol amendment 1, patients will be followed for safety monitoring for approximately 6 months after study drug administration. This extended study duration will include approximately 5 half-lives of REGN10933+REGN10987 (with a half-life of approximately 30 days) and allow an assessment of safety during the drug elimination period.

3.2.2. Rationale for Dose Selection

Initial phase 1 and phase 2 studies in outpatients with SARS-CoV-2 infection (Study COV-2067) assessed single IV dose administration of REGN10933+REGN10987 at 2400 mg (1200 mg per mAb) and 8000 mg (4000 mg per mAb). The original strategy in selecting these doses was to identify a target concentration in lung epithelial fluid (ELF) that approximates the effective concentration required for 99% viral neutralization (EC_{99})* of SARS-CoV-2 in vitro, and then identify doses anticipated to meet or exceed this concentration in lung ELF. Using observed EC_{99} estimates of 0.14 µg/mL (REGN10933) and 0.78 µg/mL (REGN10987), assuming drug concentration in lung ELF to be 0.15x that of serum (Magyarics, 2019), and accounting for uncertainties related to drug PK and mAb penetration into lung ELF, 20 µg/mL (per mAb) was selected as the initial target concentration in serum, and a 2400 mg dose was chosen with the assumption that ≥95% of patients would exceed the target concentration in serum for at least 28 days. An 8000 mg dose also was evaluated, in the event that a higher dose was required for efficacy.

Data from the phase 1 and phase 2 studies confirmed that ≥95% of patients exceeded 20 µg/mL per mAb in serum for 28 days at the 2400 mg dose, and dose-proportional increases in exposure were observed at 8000 mg. Moreover, treatment with either 2400 mg or 8000 mg REGN10933+REGN10987 reduced viral load and led to positive trends in clinical outcomes, as demonstrated by similar and significant reductions in COVID-19-related MAVs at both dose levels (Weinreich, 2020)(for more information, refer to the Investigator's Brochure). Based on the flat dose response observed for the 2400 mg and 8000 mg doses, as well as a linear PK relationship between the doses, the 2400 mg IV dose was chosen as the highest dose to be investigated in phase 3 of Study COV-2067. A 1200 mg IV dose is also being investigated in that study and is expected to achieve approximately 50% of the concentrations observed for 2400 mg, assuming that the linear PK relationship between 2400 mg and 8000 mg is also observed at this lower dose.

The purpose of the current study is to characterize the dose response relationship for REGN10933+REGN10987, as measured by changes in time-weighted viral load up to study day 7. The mean total concentrations for the selected doses are anticipated to meet or exceed the target concentration in serum during this time period. Based on currently-available concentration data and assuming linear PK, the expected mean total drug concentrations in serum (sum of REGN10933 and REGN10987) on study day 7 for the selected IV doses of 300, 600, 1200, and 2400 mg are 30.7, 61.3, 123, and 245 µg/mL, respectively. Assuming a lung ELF-to-serum ratio of 0.15x, the mean total concentration of antibody is expected to exceed either EC_{99} in the ELF for at least 6 days for all IV doses selected. On Day 15, the expected mean concentrations are 21.3, 42.6, 85.2, and 170 µg/mL, respectively.

In addition to intravenously administered REGN10933+REGN10987, SC doses of 600 mg and 1200 mg will also be evaluated. From study day 2 to study day 8, the expected mean total concentration in serum (sum of REGN10933 and REGN10987) is expected to range between 25.8 to 52.6 µg/mL for the 600 mg SC dose and between 51.6 and 105 µg/mL for the 1200mg SC dose.

On study day 15, the expected mean concentration is 41 μg/mL for the 600 mg SC dose and 81 μg/mL for the 1200 mg SC dose.

*Note: the EC_{99} values discussed here are identical to the inhibitory concentration (IC_{99}) values discussed in the Investigator's Brochure.

3.3. Risk-Benefit

In Study COV-2067, virologic and clinical efficacy was observed for REGN10933+REGN10987 in the overall population of patients that were SARS-CoV-2 RT-qPCR-positive at baseline, although it was more striking in individuals who had at least 1 pre-existing risk factor for severe COVID-19, were seronegative at baseline, or in those whose immune response was not sufficiently strong to reduce viral load as evidenced by high baseline viral loads. Treatment with REGN10933+REGN10987 was able to compensate for the absent or insufficient immune response and was able to reduce the mean viral load and decrease the number of MAVs. Overall, these data provide promising evidence for the use of REGN10933+REGN10987 in outpatients with SARS-CoV-2 infection.

These positive efficacy results are balanced by an acceptable safety profile. Nonclinical toxicology studies in nonhuman primates showed that REGN10933+REGN10987 was well-tolerated without adverse findings. Important identified risks, important potential risks, and other theoretical considerations are described below.

Important Identified Risks. As with other protein therapeutics, hypersensitivity reactions, including acute infusion-related reactions (IV intravenous [IV] administration) or injection site reactions (SC subcutaneous [SC] administration), may develop immediately or within a few hours to days after study drug administration. Hypersensitivity reactions, including infusion-related reactions or injection site reactions, have been observed in patients who received REGN10988+REGN10933 during ongoing clinical trials.

Important Potential Risks. The important potential risks of REGN10933+REGN10987 are the clinical consequences of immunogenicity and embryo-fetal toxicity.

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

Reproductive and developmental toxicology studies have not been conducted; therefore, the effects of REGN10933, REGN10987, and REGN10933+REGN10987 combination therapy on the fetus and reproductive organs in males and females are unknown. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier and are present in breast milk; therefore, the REGN10933+REGN10987 combination therapy have the potential to be transferred from the mother to the developing fetus or a breastfed child. Given the high affinity and specificity of REGN10933 and REGN10987, off-target pharmacological effects are not anticipated in either the mother or the fetus, and no off-target binding of REGN10933 or REGN10987 was observed in any of the human or monkey tissues evaluated ex vivo in tissue cross-reactivity studies. However, it is unknown whether the potential transfer of the combination of REGN10933+REGN10987 therapy provides any treatment benefit or risk to the developing fetus or a breastfed child.

There is currently limited clinical experience in the use of REGN10933, REGN10987, and REGN10933+REGN10987 combination therapy in female patients who are pregnant or

breastfeeding. The combination of REGN10933+REGN10987 therapy should be used during pregnancy or breastfeeding only if the potential benefit justifies the potential risk for the mother and the fetus or breastfed child considering all associated health factors. If a female patient is pregnant or were to become pregnant while receiving REGN10933+REGN10987 combination, the pregnancy should be followed until outcome and any safety issue observed get reported.

Other Theoretical Considerations. Theoretical risks of administration of the REGN10933+REGN10987 combination include interference with the patient's endogenous immune response to either SARS-CoV-2 infection or vaccination against COVID-19. In this study, risk mitigation includes exclusion criteria for certain vaccination scenarios (refer to Section 7.2.2). A reference to current CDC guidance is provided (Section 8.10.1) to aid investigators on appropriate management of COVID-19 vaccination.

Antibody-dependent enhancement (ADE) has been observed for some therapeutics targeting exogenous viral proteins. For antibody therapies, ADE is thought to occur when binding of antibody to the target viral protein enhances FcγR-mediated host cell entry of the virus (Iwasaki, 2020). This could potentially lead to worsening of disease and, in the case of SARS, acute lung injury (Liu, 2019). REGN10933 and REGN10987 retain the Fc region, as this may play a role in protecting against viral infection (Yasui, 2014), there is no strong evidence of ADE in other coronavirus models (Kam, 2007) (Liu, 2019) (Luo, 2018). To date, Fc-containing mAbs developed by the Sponsor for Ebola virus and MERS-CoV have demonstrated specificity to their exogenous targets with no significant unexpected safety findings in preclinical or clinical studies. All patients will have follow-up assessments up to day 169 (end of study; EOS). In addition, any SAEs reported after EOS will be recorded.

Summary. Overall, the anticipated benefit of REGN10933+REGN10987 combination therapy in treatment of infection with SARS-CoV-2 virus, along with the risk minimization measures in place, support clinical development of the product and the initiation and conduct of clinical trials.

For additional information, refer to the Investigator's Brochure.

4. ENDPOINTS

4.1. Primary Endpoint

The primary endpoint is time-weighted average daily change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7, as measured by RT-qPCR in nasopharyngeal (NP) swab samples, in patients who have a central-lab determined RT-qPCR positive test and are seronegative at baseline.

4.2. Secondary Endpoints

The secondary endpoints are:

- Time-weighted average daily change from baseline in viral load (log_{10} copies/mL) from day 1 to day 5
- Time-weighted average daily change from baseline in viral load (log_{10} copies/mL) in patients with high viral load at baseline ($>10^4$ copies/mL, $>10^5$ copies/mL, $>10^6$ copies/mL, $>10^7$ copies/mL) from day 1 to day 7
- Time-weighted average daily change from baseline in viral load (log_{10} copies/mL) in patients with high viral load at baseline ($>10^4$ copies/mL, $>10^5$ copies/mL, $>10^6$ copies/mL, $>10^7$ copies/mL) from day 1 to day 5
- Proportion of patients with high viral load ($>10^4$ copies/mL, $>10^5$ copies/mL, $>10^6$ copies/mL, $>10^7$ copies/mL) at each visit
- Proportion of patients with viral loads below the limit of detection at each visit
- Proportion of patients with viral loads below the lower limit of quantification at each visit
- Change from baseline in viral load (log_{10} copies/mL) at each visit, as measured by RT-qPCR in NP samples
- Proportion of patients with treatment-emergent SAEs through day 29
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with injection-site reactions (grade ≥3) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29
- Concentrations of REGN10933 and REGN10987 in serum over time
- Immunogenicity as measured by ADAs and NAb to REGN10933 and REGN10987

4.3. Exploratory Endpoints

Note: The definition of a COVID-19-related medically-attended visit is provided in Section 9.2.10.3.

The exploratory endpoints are:

- Time-weighted average daily change from baseline in cycle threshold (Ct) from day 1 to day 7, as measured by RT-qPCR in NP samples
- Time-weighted average daily change from baseline in Ct from day 1 to day 5, as measured by RT-qPCR in NP samples
- Change from baseline in Ct at each visit, as measured by RT-qPCR in NP samples
- Proportion of patients (through day 29 and day 169) with ≥1 COVID-19-related hospitalization or all-cause mortality
- Proportion of patients (through day 29 and day 169) with ≥1 COVID-19-related hospitalization, emergency room (ER) visit, or all-cause mortality
- Proportion of patients (through day 29 and day 169) with ≥1 COVID-19-related medically-attended visit or all-cause mortality
- Proportion of patients (through day 29 and day 169) with ≥1 COVID-19-related medically-attended visit by type of visit (hospitalization, emergency room visit, urgent care, physician's office visit, and/or telemedicine visit)
- Proportion of patients (through day 29 and day 169) with ≥2 COVID-19-related medically-attended visits or all-cause mortality
- Days of hospitalization due to COVID-19
- Proportion of patients (by day 29 and day 169) admitted to an intensive care unit (ICU) due to COVID-19
- Proportion of patients (by day 29 and day 169) requiring supplemental oxygen due to COVID-19
- Proportion of patients (by day 29 and day 169) requiring mechanical ventilation due to COVID-19
- Total number of COVID-19-related MAVs through day 29 and 169
- All-cause mortality by day 29 and day 169
- Proportion of patients with treatment-emergent SAEs through day 169

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height), disease characteristics (eg, baseline viral load [$\log_{10}$ copies/mL, viral load threshold, and Ct], presence/absence of COVID-19-related symptoms, days since symptom onset), serology (negative, positive, or other), medical history, and medication history for each patient.

5.2. Efficacy Variables

Efficacy variables include viral load ($\log_{10}$ copies/mL and Ct).

5.3. Safety Variables

Safety variables include incidence of TEAEs, incidence of treatment-emergent SAEs, and incidence of treatment-emergent AESIs as described in Section 10.1.1.

5.4. Pharmacokinetic Variables

The variables are the concentration of REGN10933 and REGN10987 in serum and time. Samples will be collected at the visits specified in Table 1.

5.5. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, as well as NAb status, and time point/visit. Samples will be collected at the visits specified in Table 1.

6. STUDY DESIGN

6.1. Study Description and Duration

Note: as of protocol amendment 2, study enrollment is closed.

This is a randomized, double-blind, placebo-controlled, parallel group study to assess the dose response profile of single IV or single SC doses of REGN10933+REGN10987 in outpatients with SARS-CoV-2 infection. The schedule of events is provided in Table 1, and the study design is provided in Figure 1.

Eligible patients will be randomized to receive a single dose of REGN10933+REGN10987 or placebo by IV or SC route (refer to Section 8.6 for more information on treatment allocation). On the day of dosing, patients will have NP swabs taken for SARS-CoV-2 RT-qPCR testing and blood drawn for safety, drug concentration, immunogenicity, and serologic analyses. After study drug administration, patients will have a post-dose blood collection (either at the end of intravenous infusion or at least 1 hour after subcutaneous administration). Patients will be monitored for at least 1 hour after study drug administration and then released from the study site, if medically appropriate.

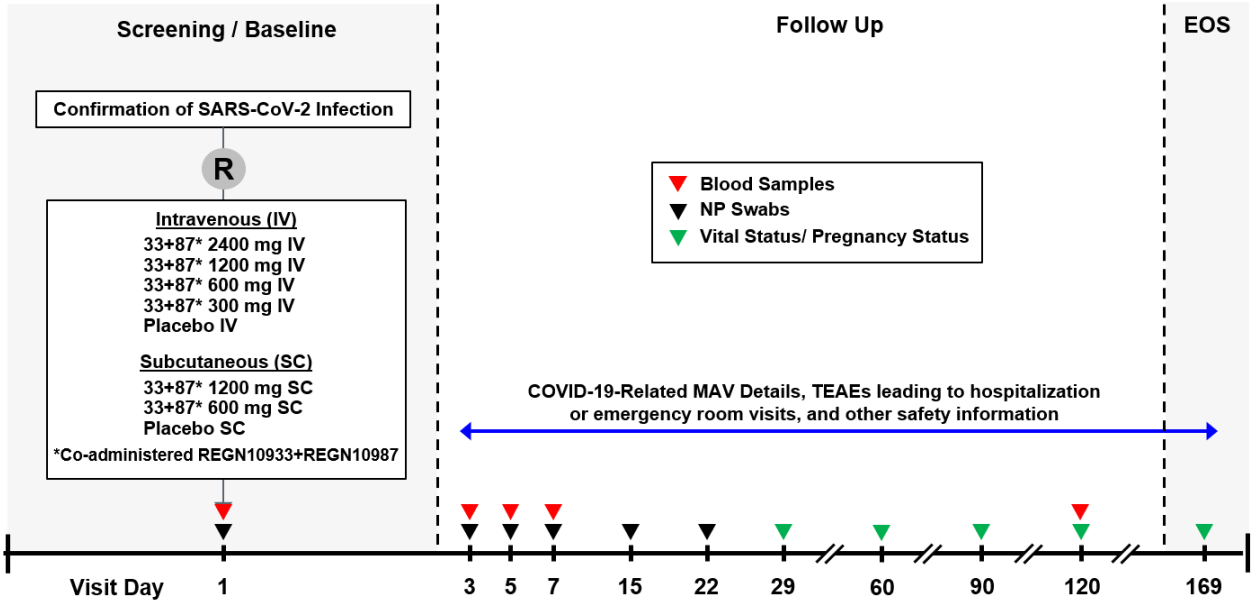
Subsequent assessments and sample collections may potentially occur through a variety of in-person and remote methods. This may include (but is not limited to) visits at the study site or place of infusion, home-based visits (defined as visits by home health staff, at mobile units, and/or testing centers), or by phone/telemedicine. Throughout the study, biological samples will be obtained by study personnel only at study locations where appropriate personal protective equipment (PPE) can be used.

Information related to safety and COVID-19-related medically-attended visits will be recorded during planned study visits. Patients will also be asked to notify study personnel as soon as possible about any medically-attended visits. Note that the TEAEs (as defined in Section 10.1.1) that will be collected during the study will differ according to different periods of the study schedule (Table 1). Refer to Section 10.1.1 for more information on reporting of TEAEs and treatment-emergent laboratory abnormalities.

Patients will have NP swabs and blood samples collected every other day for the first week of the study. Additional NP swab samples will be collected once-weekly for 2 more weeks to assess potential persistence of viral load. A phone visit will occur during the fourth week for collection of safety information.

After the first month, patients will have visits approximately once-monthly for 4 additional months. The penultimate visit will be in-person to collect blood samples for drug concentration and immunogenicity. The final visit (EOS) will be a phone call.

Figure 1: Study Flow Diagram



6.2. End of Study Definition

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

6.3. Planned Interim Analysis

No formal interim analysis will be conducted. Refer to Section 11.4.9 for information on the timing of planned analyses for this study.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

Up to approximately 1400 patients will be enrolled. Refer to Section 11.2 for more information.

7.2. Study Population

This study will enroll adult, non-hospitalized patients who have a positive diagnostic test for SARS-CoV-2.

7.2.1. Inclusion Criteria

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

1. Is male or female ≥18 years of age (or country's legal age of adulthood) at randomization

   Note: upper age limit may apply; refer to other inclusion criteria.

2. Has SARS-CoV-2-positive diagnostic test from a sample collected ≤72 hours prior to randomization, using a validated SARS-CoV-2 antigen, RT-PCR, or other molecular diagnostic assay and an appropriate sample such as nasopharyngeal (NP), nasal, oropharyngeal (OP), or saliva

   Note: Historical record of positive result is acceptable, as long as the sample was collected ≤72 hours prior to randomization.

3. *Low-risk symptomatic patient:* Has symptoms consistent with COVID-19 (as determined by the investigator) with onset ≤7 days before randomization, and **meets all of the following 8 criteria:**

   a. Age ≤50
   b. No obesity, with obesity defined as BMI ≥30 kg/m^2
   c. Does not have cardiovascular disease or hypertension
   d. Does not have chronic lung disease or asthma
   e. Does not have type 1 or type 2 diabetes mellitus
   f. Does not have chronic kidney disease, with or without dialysis
   g. Does not have chronic liver disease
   h. Is not pregnant

   or

   Asymptomatic patient: Has had no symptoms consistent with COVID-19 (as determined by the investigator) occurring at any time <2 months prior to randomization

4. Maintains O_2 saturation ≥93% on room air
5. Is willing and able to provide informed consent signed by study patient or legally acceptable representative
6. Is willing and able to comply with study procedures, including providing samples for viral shedding testing

7.2.2. Exclusion Criteria

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

1. Was admitted to a hospital for COVID-19 prior to randomization, or is hospitalized (inpatient) for any reason at randomization
2. Has a known positive SARS-CoV-2 serologic test
3. Has a positive SARS-CoV-2 antigen or molecular diagnostic test from a sample collected >72 hours prior to randomization
4. Is immunosuppressed, based on investigator's assessment

   Note: examples include cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of AIDS), sickle cell anemia, thalassemia, and prolonged use of immune-weakening medications.
5. Has participated, or is participating, in a clinical research study evaluating COVID-19 convalescent plasma, mAbs against SARS-CoV-2, or intravenous immunoglobulin (IVIG) within 3 months or within 5 half-lives of the investigational product (whichever is longer) prior to the screening visit
6. Prior, current, or planned future use of any of the following treatments: COVID-19 convalescent plasma, mAbs against SARS-CoV-2 (eg, bamlanivimab), IVIG (any indication), systemic corticosteroids (any indication), or COVID-19 treatments (authorized, approved, or investigational)

   Note: prior use is defined as the past 30 days or within than 5 half-lives of the investigational product (whichever is longer) from screening.
7. Prior use (prior to randomization), current use (at randomization), or planned use (within time period given per CDC guidance but no sooner than 22 days of study drug administration) of any authorized or approved vaccine for COVID-19

   Note: As of 02 March 2021, CDC guidance recommends deferral of SARS-CoV-2 vaccination for at least 90 days after administration of passive antibody therapy. Refer to Section 8.10.1 for more information.
8. Has known active infection with influenza or other non-SARS-CoV-2 respiratory pathogen, confirmed by a diagnostic test
9. Has known allergy or hypersensitivity to components of study drug
10. Has been discharged, or is planned to be discharged, to a quarantine center
11. Has participated, is participating, or plans to participate in a clinical research study evaluating any authorized, approved, or investigational vaccine for COVID-19
12. Is a member of the clinical site study team or is an immediate family member of the site study team

7.3. Premature Withdrawal from the Study

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

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

Patient who are withdrawn prematurely from the study will be asked to complete an early termination visit and follow up contact, as described in Section 9.1.2.

7.4. Replacement of Patients

Patient prematurely discontinued from the study will not be replaced.

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

Instructions on dose preparation are provided in the pharmacy manual. See Section 8.6 for dose levels and method of treatment allocation.

- Co-administered REGN10933+REGN10987 combination therapy
- Placebo

In this study, both intravenous infusion and subcutaneous administration will be used. All patients allocated to a subcutaneous regimen will receive 4 injections of study drug on day 1, each containing 2.5 mL of active study drug or placebo.

It is recommended that subcutaneous injection sites should be chosen among the different quadrants of the abdomen (avoiding navel and waist areas) and upper thighs. During the dose administration, each injection must be given in a different anatomical location (1 injection administered in the right lower quadrant of the abdomen, another in the left lower quadrant of the abdomen, etc).

8.2. Background Treatment(s)

No background treatment will be allowed. Patients may self-administer non-prescribed medications (eg, antipyretics).

8.3. Rescue Treatment(s)

Patients can receive rescue therapy for COVID-19 per local standard-of-care. Rescue treatment(s) will not be provided as part of the study.

8.4. Dose Modification and Study Treatment Discontinuation Rules

8.4.1. Dose Modification

This is a single dose study; dose modification is not allowed.

8.4.2. Study Drug Discontinuation

This is a single dose study; study drug discontinuation is not applicable.

8.5. Management of Acute Reactions

8.5.1. Infusion-Related Reactions and Hypersensitivity Reactions

Emergency equipment and medication for the treatment of infusion reactions must be available for immediate use if required for treatment. All grade ≥2 infusion-related reactions and grade ≥2 hypersensitivity reactions must be reported as AESIs (see Section 10.2.3). Refer to CTCAE severity scale in Section 10.2.5.

8.5.1.1. Interruption of the Intravenous Infusion

The infusion should be interrupted if any of the following AEs are observed:

- Sustained/severe cough
- Rigors/chills
- Rash, pruritus (itching)
- Urticaria (hives, welts, wheals)
- Diaphoresis (sweating)
- Hypotension
- Dyspnea (shortness of breath)
- Vomiting
- Flushing

The reaction(s) should be treated symptomatically, and the infusion may be restarted at 50% of the original rate.

If investigators feel there is a medical need for treatment or discontinuation of the infusion other than described above, they should use clinical judgment to provide the appropriate response according to typical clinical practice.

8.5.1.2. Termination of the Intravenous Infusion

The infusion should be terminated and **not** restarted if any of the following AEs occur:

- Anaphylaxis*
- Laryngeal/pharyngeal edema
- Severe bronchospasm
- Chest pain
- Seizure
- Severe hypotension

- Other neurological symptoms (confusion, loss of consciousness, paresthesia, paralysis, etc)
- Any other symptom or sign that, in the opinion of the investigator, warrants termination of the IV infusion

*Consider anaphylaxis if the following is observed (Sampson, 2006): acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) **and at least one of the following:**

- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

8.5.2. Injection Reactions

Emergency equipment and medication for the treatment of systemic injection reactions (ie, hypersensitivity) must be available for immediate use.

All grade ≥3 injection reactions (local or systemic) must be reported as AESIs. Refer to CTCAE severity scale in Section 10.2.5.

8.6. Method of Treatment Assignment

Patients will be randomized to one of the treatment arms listed below, according to a central randomization scheme using an interactive web response system (IWRS):

Dose of Co-administered REGN10933+REGN10987 Combination Therapy	Route of Administration	Randomization Ratio
2400 mg (1200 mg each of REGN10933 and REGN10987)	IV	2
1200 mg (600 mg each of REGN10933 and REGN10987)	IV	2
600 mg (300 mg each of REGN10933 and REGN10987)	IV	2
300 mg (150 mg each of REGN10933 and REGN10987)	IV	2
Placebo	IV	1
1200 mg (600 mg each of REGN10933 and REGN10987)	SC	2
600 mg (300 mg each of REGN10933 and REGN10987)	SC	2
Placebo	SC	1

8.7. Blinding

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

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

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

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

8.8. Emergency Unblinding

Unblinding of treatment assignment for a patient may be necessary due to a medical emergency or any other significant medical event and when a treatment decision is contingent on knowing the patient's treatment assignment.

If unblinding is required:

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

Treatment assignment is not to be provided to site personnel, other than the unblinded study pharmacist (when applicable), at any time during the conduct of the study, except in the case of a true emergency and when a treatment decision is contingent on knowing the patient's treatment

assignment. In the event that there is no study pharmacist, the individual at the site fulfilling that role will be the only unblinded member of the site personnel.

8.9. Treatment Logistics and Accountability

8.9.1. Packaging, Labeling, and Storage

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

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

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

8.9.2. Supply and Disposition of Treatments

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

8.9.3. Treatment Accountability

All drug accountability records must be kept current.

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

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

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

8.9.4. Treatment Compliance

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

8.10. Concomitant Medications

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

For more information on recording of concomitant medications, refer to Section 9.2.4.3.

8.10.1. Prohibited and Permitted Medications

Patients are not permitted to receive any medication specified in the exclusion criteria for study enrollment unless medically indicated (Section 7.2.2).

Based on CDC guidance and investigator discretion, deferring the use of any authorized or approved COVID-19 vaccine for at least 90 days after dosing may be considered to reduce potential interference of the study drug with vaccine-induced immune responses. For more information, refer to the current CDC guidance (CDC, 2020). Refer to Section 7.2.2 for more information on exclusion criteria related to COVID-19 vaccination.

Patients may otherwise continue their normal regimen of medications and procedures.

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

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

Table 1: Schedule of Events

Day	Screening/Baseline[1]				Follow Up[2]										EOS
	-1 to 1				3	4	5	7	15	22	29[2]	60[2]	90[2]	120	169[2]
	Screen	Pre-Dose	Dose	Post-Dose											
Window (Days)									±1	±1	±3	±3	±3	±28	±28
Screening/Baseline Only															
Informed consent	X														
Inclusion/exclusion	X														
Antigen or molecular diagnostic test for SARS-CoV-2[3]	X														
Demographics	X														
Medical history (including COVID-19 symptoms, if applicable)[12]	X														
Weight and height	X														
Randomization		X													
Treatment															
Study drug administration			X												
Efficacy															
Nasopharyngeal (NP) swab for SARS-CoV-2 RT-qPCR		X			X		X	X	X	X					
Safety															
Vital signs		X[4]		X[4]											
Treatment-emergent grade ≥2 IRRs[5,6]			← cont. monitoring →												
Treatment-emergent grade ≥3 ISRs[5,6]			← cont. monitoring →												
Treatment-emergent grade ≥2 hypersensitivity[5]reactions[5,6]			← continuous monitoring →												
Treatment-emergent AEs[5,6]			← continuous monitoring →												
Treatment-emergent grade 3 or 4 AEs[5]												X	X	X	X
Treatment-emergent SAEs[5,6]			← continuous monitoring →												
TEAEs that led to any hospitalization or emergency room visit[5,6]			← continuous monitoring →												
Targeted concomitant medications[5,6]	X		← continuous monitoring →												
Pregnancy test (WOCBP)[7]	X														
Vital status											X	X	X	X	X
Pregnancy status[7]											X	X	X	X	X
Safety information (newborns of study participants)[7]														X	X
Central Laboratory Safety Testing and Serologic Testing															
Hematology (including differential)[8]	X[8]							X							
Blood chemistry[8]	X[8]							X							
Serum for serology	X														
Drug Concentration and Immunogenicity Testing															
Serum for drug concentration (PK)[9]	X[9]			X[9]	X		X	X						X	
Serum for immunogenicity (ADA)[10]	X[10]													X	
Exploratory Patient Outcome Assessment															
COVID-19-related MAV details[11]				← continuous monitoring →											

ADA, anti-drug antibodies; AE, adverse event; cont, continuous; EOS, end of study; IRR, infusion-related reaction; ISR, injection-site reaction; MAV, medically-attended visit; PK, pharmacokinetics; SAE, serious adverse event; RT-qPCR, quantitative reverse transcription polymerase chain reaction; WOCBP, women of childbearing potential.

9.1.1. Footnotes for the Schedule of Events Table

1. Screening visit may occur on the same day as the baseline visit (day 1), or the day prior to the baseline visit (day -1).
2. On visit days when sample collection is not required, the information indicated in the schedule may be collected by phone without an in-person visit.
3. Refer to Section 9.2.1.2 for diagnostic test requirements during screening.
4. Vital signs, including temperature, blood pressure, heart rate, and SpO_2, will be collected as described in Section 9.2.4.1. Vital signs will be taken once before study drug administration and once after study drug administration is completed. After infusion or injection of study drug, patients will be observed for at least 1 hour.
5. From day 1 to day 29, the following will be recorded: all TEAEs, treatment-emergent SAEs, and treatment-emergent AESIs (grade ≥2 IRRs, grade ≥3 ISRs, grade ≥2 hypersensitivity reactions, and any treatment-emergent adverse event that led to a hospitalization or emergency room visit, regardless of whether the visit is related to COVID-19).

   From day 30 to day 169, the following will be recorded: treatment-emergent grade 3 or 4 AEs, treatment-emergent SAEs, and treatment-emergent AESIs (any treatment-emergent adverse event that led to a hospitalization or emergency room visit, regardless of whether the visit is related to COVID-19). Refer to Section 10.1 for more information on AE reporting and recording requirements.

   Medications will be also be reviewed and recorded. Only the targeted medications listed in Section 9.2.4.3 will be recorded in the eCRF.
6. Study visits are not required solely to collect continuously-monitored assessments, if no other assessments are planned on that day.
7. Pregnancy testing will be performed in women of childbearing potential (WOCBP) only. For WOCBP who have symptoms of COVID-19 at screening (see Section 7.2.1), negative pregnancy test must be confirmed prior to study drug administration. WOCBP who are asymptomatic at screening may receive study drug regardless of pregnancy status. Serum or urine pregnancy test are both acceptable. Refer to Section 9.2.6 for more information, including definition of WOCBP. Note that a paper pregnancy report form must be completed for each patient who becomes pregnant or is pregnant at the signing of consent. Safety information in newborns of study participants will be collected as described in Section 9.2.5.
8. The indicated blood samples may be collected at either day -1 or day 1 (screening or pre-dose), but must be collected prior to randomization. Refer to Section 9.2.7 for more information on abnormal laboratory findings.
9. Actual dosing time and drug concentration sample collection times will be recorded.

   For patients receiving IV infusion: at the screening/baseline visit, blood for assessment of drug concentration in serum will be taken prior to dosing (either at day -1 or day 1) and within 60 minutes after the end of infusion (EOI). The EOI sample should be collected

from the arm contralateral to that used for IV infusion. If not medically feasible, the EOI sample can be drawn from the same arm, but not from the infusion catheter.

For patients receiving SC injection: at the screening/baseline visit, blood for assessment of drug concentration in serum will be taken prior to dosing (either at day -1 or day 1). The post-dose blood collection should occur at least 1 hour after study drug administration.

10. The window for predose ADA sample collection should be as close to administration of study drug as is reasonable. Actual dosing time and ADA sample collection times, as applicable, will be recorded.
11. Details of COVID-19-related MAVs will be collected as described in Section 9.2.10.3.
12. When applicable, COVID-19 symptoms will be recorded and graded in eCRF. Symptom severity will also be recorded, using the current version of the NCI-CTCAE v5.0 (refer to Section 10.2.5).

9.1.2. Early Termination from the Study

Patients who withdraw prior to day 7 will be asked to allow an early termination (ET) visit consisting of day 7 assessments and sample collections. Patients who withdraw after day 7 but prior to day 22 will be asked to allow an ET visit consisting of day 22 assessments and sample collections.

Patients who withdraw consent for the study prior to day 29 will be contacted by phone on day 29 to obtain vital status. Patients withdrawn from the study after day 29 will be asked to complete an ET visit consisting of day 169 (EOS) assessments and sample collections.

9.1.3. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of treatment-emergent SAEs, and treatment-emergent AESIs, or for any other reason, as warranted.

9.2. Study Procedures

This section describes the procedures and collections that will be performed in this study. Procedures and collections will occur according to the schedule of events (Table 1).

9.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population.

9.2.1.1. Informed Consent

Informed consent must be obtained according to the requirements described in Section 13.2.

9.2.1.2. Diagnostic Test for SARS-CoV-2

The investigator or sub-investigator will verify that the patient has tested positive for SARS-CoV-2, either at screening or by historical record (refer to Section 7.2.1 for detailed screening

requirements). For tests performed at screening, the local testing result, specimen type, assay type, and date of the test will be recorded in the eCRF.

9.2.1.3. Demographics

Refer to Section 5.1.

9.2.1.4. Medical History

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

- COVID-19 with start date as the date of onset of first symptoms related to COVID-19, as well as associated symptoms and their severity graded per NCI-CTCAE v5.0 (refer to Section 10.2.5)
- Whether the patient is receiving oxygen at home by nasal cannula
- Menopausal history
- Pregnancy or breastfeeding status, if applicable

9.2.1.5. Weight and Height

Weight and height will be recorded at the screening/baseline visit.

9.2.2. Treatment

See Section 8.1.

9.2.3. Efficacy Procedures

9.2.3.1. Nasopharyngeal Swab Collection

Virologic samples will be collected from patients to determine presence or absence of SARS-CoV-2 virus, including at baseline, and to measure viral load. Samples will be used for RT-qPCR analysis. Samples may additionally be used for exploratory viral RNA sequencing plaque forming unit assays (PFU) assays and/or viral culture. Additional details regarding sample collection and analysis can be found in Section 9.2.10.1 and the laboratory manual.

9.2.4. Safety Procedures

9.2.4.1. Vital Signs

Vital signs will include temperature, blood pressure, heart rate (per minute), SpO_2.

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

Blood pressure should be measured after the patient has been resting quietly for at least 5 minutes and may be obtained from a seated or supine position.

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

9.2.4.2. Adverse Event Monitoring

The TEAEs listed in Section 10.1.1 will be recorded.

9.2.4.3. Record Targeted Concomitant Medications

A targeted list of the following concomitant medications will be recorded in the eCRF:

- Putative COVID-19 treatments (eg, remdesivir, bamlanivimab, convalescent serum, IVIG, IL-6 receptor inhibitors [eg, sarilumab, tocilizumab], JAK inhibitors [eg, baricitinib], ivermectin)
- SARS-CoV-2 vaccines
- Antipyretics (eg, aspirin, acetaminophen, ibuprofen)
- Anticoagulants (eg, enoxaparin, warfarin, rivaroxaban)
- Immunosuppressants (eg, cyclosporine A, corticosteroids)
- Interferon beta
- Theophylline
- Antiepileptics (eg, carbamazepine, divalproex, phenytoin)
- Antiarrhythmics (eg, digoxin, disopyramide, procainamide)
- Antivirals, antibacterial, and antifungals
- Antiparasitics (chloroquine or hydroxychloroquine)
- Angiotensin receptor blockers (eg, losartan, valsartan)
- Angiotensin converting enzyme inhibitors (eg, benazepril, lisinopril).
- Influenza vaccinations

For more information on concomitant medications, refer to Section 8.10.

9.2.5. Post-Day 22 Follow-up by Phone

Patients will be contacted by phone for post-day 22 safety assessments at the time points listed in Table 1. These assessments will include vital status, pregnancy status, and targeted safety information.

Vital Status. Record vital status (whether the patient is dead or alive) and record the date of death, when applicable.

Pregnancy Status. Record pregnancy status and date of pregnancy, when applicable. Refer to Section 10.1.3 for reporting requirements.

Targeted Safety Information. Refer to Section 10.1 for more information on reporting and recording requirements.

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

9.2.6. Pregnancy Test for Women of Childbearing Potential

Pregnancy testing may be satisfied by either serum pregnancy test or by urine β-HCG. Pregnancy tests are a requirement for WOCBP only and should be completed regardless of pregnancy status. Pregnancy test will be performed at the local laboratory.

For WOCBP who have symptoms of COVID-19 at screening (see Section 7.2.1), negative pregnancy test must be confirmed prior to study drug administration. WOCBP who are asymptomatic at screening may receive study drug regardless of pregnancy status.

WOCBP are defined as females who are fertile following menarche until becoming postmenopausal, unless permanently sterile. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a postmenopausal state. The above definitions are according to Clinical Trial Facilitation Group (CTFG) guidance. Pregnancy testing is not required for women with documented hysterectomy or tubal ligation.

Information about pregnancy will be recorded as described in Section 10.1.3.

9.2.7. Laboratory Testing

Hematology and blood chemistry will be analyzed by a central laboratory. Detailed instructions are provided in the laboratory manual.

Blood Chemistry

Tests will include:

Sodium	Blood urea nitrogen (BUN)	Alkaline phosphatase
Potassium	Aspartate aminotransferase (AST)	Creatinine
Chloride	Alanine aminotransferase (ALT)	Creatine phosphokinase (CPK)
Carbon dioxide	Total bilirubin	Lactate dehydrogenase (LDH)
Glucose	Albumin	

Hematology

Tests will include:

Hemoglobin	*Differential:*	Neutrophils
Hematocrit		Lymphocytes
Red blood cells (RBCs)		Monocytes
White blood cells (WBCs)		Basophils
Platelet count		Eosinophils

Abnormal Laboratory Values and Laboratory Adverse Events

All laboratory values must be reviewed by the investigator or authorized designee.

Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the Medical/Study Director must be consulted.

The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values are provided in Section 10.1.1.

9.2.8. Drug Concentration Measurements and Samples

Samples for assessment of drug concentration will be collected at the time points indicated in the schedule of events. For information concerning unused samples and exploratory research, refer to Section 9.2.9.

9.2.9. Immunogenicity Measurements and Samples

Samples for immunogenicity assessment will be collected at the time points listed in the schedule of events.

9.2.10. Exploratory Pharmacodynamic/Biomarker Analyses

This section describes planned exploratory analyses, some of which may not be reported in the CSR.

Note that any biological samples collected during the study which are not used for their planned purpose, or for which material remains after their planned analysis, may be used for assessment of immunogenicity if necessary. [redacted]

9.2.10.1. Virology

Viral Sequencing

In support of public health initiatives to track SARS-CoV-2 genetic variants, as well as to monitor for possible viral resistance, viral genome sequencing may be performed on viral nucleic acid isolated from nasopharyngeal swab, nasal swab, and/or saliva samples, at baseline and in cases of a positive RT-qPCR result. Sequencing analyses will consist of the entire viral genome, including the full gene sequence that encodes the SARS-CoV-2 S protein.

Viral sequencing may be performed on post-treatment samples to assess the emergence of sequence variants and to understand the potential relationship between genetic mutations and mAb functional activity. Viral sequencing may also be done on placebo controls to determine whether any genetic mutations observed in the mAb treatment group are naturally emergent genetic variants.

Viral variants suspected to confer decreased susceptibility to REGN10933 and/or REGN10987 will be evaluated in nonclinical work separate from this protocol.

The results of the viral sequencing may not be included in the clinical study report.

Viral Infectivity

To explore the effects of REGN10933+REGN10987 on infectivity of SARS-CoV-2, we may use PFU, viral culture or viral subgenomic mRNA RT-qPCR assays. In vitro SARS-CoV-2 infectivity of cultured cells may be explored using NP samples. Infectivity of cells grown in culture may be assessed by PFU assays and/or immunofluorescence assays. We may also use sub-genomic viral mRNA transcript assays, such as RT-qPCR or subgenomic mRNA sequencing, or other measures of in vivo infectivity potential. Viral sub-genomic mRNA is transcribed only in infected cells and is not packaged into virions, and therefore may be an indicator of actively-infected cells. These data may be associated with RT-qPCR measuring viral load.

The results of the viral infectivity assays may not be included in the clinical study report.

9.2.10.2. Serological Immunoassays for Anti-SARS-CoV-2 Antibodies

To explore the impact of baseline humoral activity against SARS-CoV-2 on the response to REGN10933+REGN10987, serological immunoassays will be used to detect antibodies at baseline against the SARS-CoV-2 S protein and/or N protein. Neutralization assays may also be used to evaluate the function of endogenous baseline anti-SARS-CoV-2 antibodies. Associations will be evaluated with virology and other clinical outcomes.

9.2.10.3. COVID-19-Related Medically-Attended Visit Details

A COVID-19-related medically-attended visit will be defined as follows: hospitalization, ER visit, urgent care visit, physician's office visit, or telemedicine visit, with the primary reason for the visit being COVID-19.

Medically-attended visits related to COVID-19, as determined by the investigator, will be recorded in the eCRF. During each indicated collection visit (refer to Table 1), all previously unrecorded COVID-19-related medically-attended visits and details will be recorded, beginning from the day of dosing up to and including the day of collection.

Details will include at minimum:

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

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

In this study, the following TEAEs will be recorded:

- Treatment-emergent AEs, up to day 29
- Treatment-emergent AESIs (Section 10.1.3) as follows:
  - Grade ≥2 infusion-related reactions, up to day 4
  - Grade ≥3 injection-site reactions, up to day 4
  - Grade ≥2 hypersensitivity reactions, up to day 29
  - Any TEAE that led to a hospitalization or emergency room visit, regardless of whether the visit is related to COVID-19, up to day 169
- Treatment-emergent AEs (grade 3 or 4 only), from day 30 to day 169
- Treatment-emergent SAEs, up to day 169

The investigator must promptly record the above TEAEs occurring during the observation period (see Section 11.4.5.1). Note that the length of this period differs in each study phase, owing to different final study visit days. Medical conditions that existed or were diagnosed prior to the signing of the informed consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of informed consent should also be recorded as medical history. Any subsequent worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug should also be recorded as TEAE, provided that it fulfills the above criteria.

Throughout the study, the investigator will determine whether any TEAEs occurred by evaluating the patient. These events may be directly observed, reported spontaneously by the patient, or by questioning the patient at each study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator must assess all TEAEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 10.2. The investigator's assessment must be clearly documented in the site's source documentation with the investigator's signature. The investigator should follow up on TEAEs until they have resolved or are considered clinically stable.

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

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the Investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, require corrective treatment, or constitute an AE in the investigator's clinical judgement. For events that are serious due to hospitalization or ER visit, the reason must

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

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

Any SAE that may occur subsequent to the reporting period (end of study) that the investigator assesses as related to study drug should also be reported.

All treatment-emergent SAEs, AESIs, and pregnancies are to be reported according to the procedures in Section 10.1.3.

10.1.2. Reporting Procedure

The treatment-emergent AEs defined in Section 10.1.1 must be reported with investigator's assessment of the event's seriousness, severity, and causality to the blinded study drug. A detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE eCRF. Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc) will be summarized in the narrative on the AE eCRF and retained at the study center and available upon request.

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

10.1.3. Events that Require Expedited Reporting to Sponsor

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

- **Treatment-emergent SAEs**.
- **Treatment-emergent AESI** (serious and nonserious), defined as**:**
  - Grade ≥2 infusion-related reactions
  - Grade ≥3 injection-site reactions
  - Grade ≥2 hypersensitivity reactions
  - Any TEAE that led to a hospitalization or emergency room visit, regardless of whether the visit is related to COVID-19
- **Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the Sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female study patient during the study or existing at the

time of signing the informed consent form. A paper pregnancy report form must be completed for each patient who becomes pregnant or is pregnant at the signing of consent.

Any complication of pregnancy affecting a female study patient and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the Sponsor, including testing results for SARS-CoV-2 infection in the newborn, if performed.

10.2. Definitions

10.2.1. Adverse Event

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

10.2.2. Serious Adverse Event

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

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

Criteria for reporting SAEs must be followed for these events (refer to Section 10.1.1 Section 10.1.2).

10.2.3. Adverse Events of Special Interest

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

Adverse events of special interest for this study are defined in Section 10.1.3.

10.2.4. Infusion-Related Reactions, Injection-Site Reactions, and Hypersensitivity Reactions

Infusion-related reactions are defined as any relevant adverse event that occurs during intravenous infusion or up to day 4.

Injection-site reactions are defined as any relevant adverse event that occurs during subcutaneous injection or up to day 4.

Hypersensitivity reactions are defined as any relevant adverse event that occurs during intravenous infusion or subcutaneous injection or up to study day 29.

10.2.5. Severity

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

Treatment-emergent AEs, SAEs, or AESIs not listed in the NCI-CTCAE will be graded according to the scale in Table 2. The grading systems for anaphylaxis, allergic reaction (hypersensitivity), infusion-related reaction, and injection-site reaction are provided in Table 3.

Table 2: NCI-CTCAE (v5.0) Severity Grading System for Adverse Events: General Guideline

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

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

Table 3: NCI-CTCAE (v5.0) Severity Grading System for Anaphylaxis, Allergic Reaction, Infusion-Related Reaction, and Injection-Site Reaction

Grade	CTCAE Term			
	Anaphylaxis[1]	**Allergic Reaction** *(hypersensitivity)*[2]	**Infusion-Related Reaction**[3]	**Injection-Site Reaction**[4]
1	N/A	Systemic intervention not indicated	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Tenderness with or without associated symptoms (eg, warmth, erythema, itching)
2	N/A	Oral intervention indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Pain; lipodystrophy; edema; phlebitis
3	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Ulceration or necrosis; severe tissue damage; operative intervention indicated
4	Life-threatening consequences; urgent intervention indicated	Life-threatening consequences; urgent intervention indicated	Life-threatening consequences; urgent intervention indicated	Life-threatening consequences; urgent intervention indicated
5	Death	Death	Death	Death

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

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

[3] Disorder characterized by adverse reaction to the infusion of pharmacological or biological substances

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

10.2.6. Causality

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

The following factors should be considered when assessing causality:

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

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

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

  or

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

Causality to the study conduct (protocol specified procedure):

- Related:
  - The adverse event follows a reasonable temporal sequence from a protocol specified procedure and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

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

10.3. Safety Monitoring

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

10.4. Notifying Health Authorities, Institutional Review Board and Investigators

During the study, the Sponsor and/or the CRO will inform health authorities, Institutional Review Board (IRBs), and the participating investigators of any SUSARs (Suspected Unexpected Serious Adverse Reactions) occurring in other study centers or other studies of the active study drug, as appropriate per local reporting requirements. In addition, the Sponsor and/or CRO will comply with any additional local safety reporting requirements. All notifications to investigators will contain only blinded information.

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

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

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

11. STATISTICAL PLAN

This section summarizes the statistical analyses for this study and provides the basis for the statistical analysis plan (SAP) for the study.

Endpoints are listed in Section 4. Analysis variables are listed in Section 5.

11.1. Statistical Hypothesis

The statistical hypothesis for the primary virologic efficacy endpoint is:

- H_0: There is no difference between patients treated with one or more dose regimens of REGN10933+REGN10987 and patients treated with placebo in time weighted average daily change from baseline in viral load from day 1 to day 7
- H_1: REGN10933+REGN10987 reduces time weighted average daily change from baseline in viral load (log10 copies/mL) from day 1 to day 7, relative to placebo

11.2. Justification of Sample Size

The sample size is based on the primary virologic endpoint of the time-weighted average (TWA) daily change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7, in patients who are seronegative and who have a positive RT-qPCR value at baseline. In the Phase 2 portion of Study COV-2067, the mean (SD) was -0.73 (0.948) log_{10} copies/mL (see the Investigator's Brochure). For the primary hypothesis comparing each dose to placebo, approximately 57 patients per treatment group. With this sample size, the study has ~98% power to detect a difference of -0.73 log_{10} copies/mL between any active treatment group and placebo. In order to enroll 400 seronegative patients, the study will randomize approximately 800 patients, assuming that 50% are seronegative.

For comparisons between doses and regimens, the study plans to enroll 700 seronegative patients in order to have 100 patients per group. For between-group comparisons, the 95% CI half-width between any two treatment groups with this sample size would be 0.27 log_{10} copies/mL. In order to enroll 700 seronegative patients, approximately 1400 patients will be randomized.

Placebo IV and placebo SC arms will be pooled in the efficacy analyses of the viral load endpoints as the route of administration does not alter the pharmacodynamic response of patients receiving placebo.

11.3. Analysis Sets

11.3.1. Efficacy Analysis Sets

11.3.1.1. The Seronegative Modified Full Analysis Set

The **Overall modified Full Analysis Set (mFAS)** includes all randomized patients with a positive central-lab determined SARS-CoV-2 RT-qPCR result from NP swab samples at randomization and is based on the treatment received (as treated). If a pre-treatment qualitative test is missing, then a qualitative test that is within post-treatment plus 2 hours may be used.

The **Seronegative mFAS** is the subset of patients in the mFAS population who are seronegative at baseline. The Seronegative mFAS will be used for all efficacy and pharmacodynamic analyses.

The Seronegative mFAS is the primary analysis population; secondary analyses will be conducted in the Overall mFAS population.

Note that since the primary objective of this study is to estimate the dose- and exposure-response of REGN10933+REGN10987 in reducing viral load, patients are included in the treatment actually received, not as randomized.

In the Seronegative mFAS and mFAS populations, the placebo IV and placebo SC arms will be pooled for all analyses of virologic endpoints. Active dose groups will not be pooled.

11.3.1.2. Per Protocol Set

The Per Protocol Set (PPS) includes all randomized patients who receive treatment with positive central-lab determined SARS-CoV-2 RT-qPCR result from NP swab samples at randomization and is based on the treatment received (as treated).

The PPS further excludes patients (1) who do not receive the full dose, (2) receive convalescent plasma therapy or SARS-CoV-2 antivirals, and (3) receive COVID-19 vaccination on or prior to the day 7 visit. Like the mFAS, the placebo IV and placebo SC arms will be pooled. Active dose groups will not be pooled. If all the patients in the mFAS are fully dosed and there are no applicable protocol deviations regarding (2) and (3), the PPS is the Overall mFAS.

11.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized patients who received any study drug; it is based on the treatment received (as treated). Determination of "as treated" will be based on the actual study drug received on day 1. Demographic and baseline characteristics, treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

In the SAF population, the placebo arms for the IV and SC routes of administration will be summarized separately.

11.3.3. Pharmacokinetic Analysis Set

The PK Analysis Set (PKAS) includes all randomized patients who received any study drug (SAF) and who have at least 1 non-missing drug concentration measurement following study drug administration. Patients will be analyzed according to the actual treatment received.

11.3.4. Immunogenicity Analysis Sets

The immunogenicity analysis set for a potential interim analysis is dependent on assay availability.

The ADA Analysis Set (AAS) includes all treated patients who received any study drug and have at least 1 non-missing ADA result after first dose of the study drug.

The NAb Analysis Set (NAS) includes all patients who received any study drug and who are negative in the ADA Assay or with at least one non-missing result in the NAb assay after first dose of the study drug. Patients who are ADA negative are set to negative in the NAb Analysis Set.

Patients will be analyzed according to the actual treatment received.

11.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum. For categorical or ordinal data, frequencies and percentages will be displayed for each category.

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

11.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients: met the inclusion/exclusion criteria regarding the target indication and signed the ICF
- The total number of randomized patients: received a randomization number
- The total number of patients who discontinued the study, and the reasons for discontinuation
- The total number of patients who discontinued from study treatment, and the reasons for discontinuation
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation

11.4.2. Demography and Baseline Characteristics

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

11.4.3. Efficacy Analyses

11.4.3.1. Primary Efficacy Analysis

The primary virologic efficacy variable is the time-weighted average change from baseline in viral load from day 1 to day 7, as measured by RT-qPCR in NP swab samples. The primary analysis will be conducted in the Seronegative mFAS population.

The analyses will be based on the observed data with no imputation for missing data. Viral load values less than the lower limit of quantification of the PCR assay but with positive qualitative results will be set to half of lower limit of quantification of the PCR assay; values with nondetectable RNA will be set to 0 $\log_{10}$ copies/mL if the reason for the negative value is not a failed test. Viral load values above the upper limit of quantification will be re-tested using the reflex test.

The primary efficacy variable will be calculated using the linear trapezoidal rule, ie, area under the curve for change from baseline at each time point from day 1 to last observation divided by the number of days from day 1 to day of last observation. The TWA estimates the average over the

time range of interest, adjusting for any irregular spacing of the timing when samples are taken (eg, if samples are missing).

An Analysis of Covariance (ANCOVA) model with treatment group as a fixed effect and baseline viral load and treatment by baseline interaction as covariates will be fit to the data as the primary analysis.

In addition, the least squares mean estimates for the TWA mean change from baseline in viral load will be presented for each treatment group, as well as for the difference between each REGN10933+REGN10987 treatment group and placebo as well as between active treatment groups. p-Values will be presented comparing the active arms to placebo. 95% confidence intervals will be reported between the active doses. Accompanying descriptive analyses will be provided at the individual time points used to calculate the TWA. To explore the dose response, other modeling approaches such as E_{max} will be described in the SAP.

For efficacy analyses, the placebo IV and placebo SC arms are pooled.

11.4.3.2. Secondary Efficacy Analysis

A mixed effect model for repeated measures (MMRM) will assess the time course of treatment effect in viral load, the change from baseline in viral load (log_{10} copies/mL) at each visit for both the Seronegative mFAS and the Overall mFAS. There will be terms for baseline, treatment, visit, treatment-by-baseline interaction, baseline-by-visit interaction, and treatment-by visit interaction. Within-patient errors will be modeled with an unstructured, heterogeneous autoregressive (1), or compound symmetry covariance matrix in that order if a model does not converge. The least squares means estimates for the mean at each visit and mean change from baseline to each visit as well as the difference of these estimates between each anti-spike mAb treatment arm and placebo will be provided along with the corresponding standard error, p-value, and associated 95% confidence interval.

In the Seronegative mFAS, the proportion of patients who have PCR below the limit of detection (LOD), below the lower limit of quantification (LLOQ), or have qPCR levels >10^4, >10^5, >10^6, or >10^7 will be tabulated over time. The numbers of patients in each category will be tested using Fisher's Exact test. Corresponding p-values and confidence intervals will be presented.

Analyses of the virologic endpoints with in the Overall mFAS population will also be performed in subsets defined by the baseline viral load ($>10^4$ copies/mL, $>10^5$ copies/mL, $>10^6$ copies/mL, $>10^7$ copies/mL). The TWA, the time course of change, and other virologic endpoints will be summarized and/or analyzed within each of these categories.

11.4.4. Control of Multiplicity

The overall type I error rate will be controlled for the primary hypothesis at the two-sided 0.05 level by the use of a step-down testing approach, starting at the top dose (Table 4). Each test compares a specific treatment group to pooled placebo. The highest dose will be tested first; if significant, the second highest dose will be tested; and so on. No multiplicity adjustments will be made for secondary endpoints, nor for comparisons between active doses.

Table 4: Statistical Testing Hierarchy

Hierarchy Number	Description
1	2400 mg IV versus pooled placebo
2	1200 mg IV versus pooled placebo
3	1200 mg SC versus pooled placebo
4	600 mg IV versus pooled placebo
5	600 mg SC versus pooled placebo
6	300 mg IV versus pooled placebo

11.4.5. Safety Analysis

11.4.5.1. Adverse Events

Definitions

For safety variables, 3 periods are defined:

- The **pretreatment period** is defined as the time from signing the ICF to before study drug administration
- The **29-day observation period** is defined as the time of study drug administration to day 29.
- The **full observation period** is defined as the time of the administration of the study drug to the last follow-up visit.

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

Analysis

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

Summaries by treatment group will include the following:

- The number (n) and percentage (%) of patients with at least 1 treatment-emergent AE through day 29 by SOC and PT
- The number (n) and percentage (%) of patients with at least 1 treatment-emergent grade 3 or 4 AE through day 169 by SOC and PT
- The number (n) and percentage (%) of patients with at least 1 treatment-emergent SAE through day 29 by SOC and PT
- The number (n) and percentage (%) of patients with at least 1 infusion-related reaction (grade ≥2), through day 4 by PT
- The number (n) and percentage (%) of patients with at least 1 injection-site reaction (grade ≥3), through day 4 by PT

- The number (n) and percentage (%) of patients with at least 1 hypersensitivity reaction (grade ≥2), through day 29 by PT

Summaries of SAEs and AESIs by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 event by SOC and PT
- SAEs and AESIs by severity (according to the grading scale outlined in Section 10.2.5), presented by SOC and PT
- SAEs and AESIs by relationship to treatment (related, not related), presented by SOC and PT
- Treatment-emergent SAEs and AESIs

Deaths and other SAEs will be listed and summarized by treatment arm.

11.4.5.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Laboratory Tests

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Number and percentage of patients with a potentially clinically significant value (PCSV) at any post-randomization time point will be summarized for each clinical laboratory test for all patients and separately for patients in whom the PCSV criterion was normal or missing at baseline.

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.

Listings will be provided with flags indicating the out of laboratory range values.

11.4.5.3. Treatment Exposure

The number and percentage of patients randomized and exposed to double-blind study drug, and duration of exposure to treatment during the study will be presented by treatment group.

11.4.5.4. Treatment Compliance

Treatment compliance in terms of total dose and infusion interruption will be summarized. The analysis methods will be detailed in the SAP.

11.4.6. Pharmacokinetics

11.4.6.1. Analysis of Drug Concentration Data

The concentrations of REGN10933 and REGN10987 in serum over time will be summarized descriptively for each of the treatment groups

11.4.7. Pharmacokinetics and Pharmacokinetics/Pharmacodynamics Analyses

Exposure-response analyses for select efficacy and safety endpoints and/or biomarkers may be performed, as appropriate. Details of the exposure-response analyses will be documented separately.

11.4.8. Analysis of Immunogenicity Data

Immunogenicity will be characterized by the ADA and Nab response and titers observed in patients in the ADA and NAb analysis sets. ADA response categories and titer categories are defined as follows:

ADA Response Categories:

- ADA Negative, defined as ADA negative response in the ADA assays for 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.
- 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 analyses will be provided:

- Number (n) and percent (%) of ADA-negative patients (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 patients by treatment groups and ADA titer categories
- Number (n) and percent (%) of treatment-boosted ADA positive patients by treatment groups and ADA titer categories

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

11.4.8.1. Analysis of Neutralizing Antibody Data

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

11.4.9. Timing of Statistical Analyses

The primary efficacy analysis will be conducted as a first-step analysis using the first 816 patients enrolled in the study up to day 7, in order to evaluate approximately 400 patients who are seronegative at baseline (refer to Section 11.2 for more information). This analysis represents the final analysis of the primary endpoint and is not considered an interim analysis.

An analysis may also occur after all enrolled patients have reached at least day 7, and a subsequent analysis will occur once the last patient enrolled in the study completes their last study visit. A SAP will be issued prior to the first database lock.

Note: Individuals unblinded to patient-level data for the first-step analysis or subsequent analyses will no longer be directly involved in the day-to-day conduct of the study. Patient-level results will not be released to any site-facing personnel or anyone who is directly involved in the day-to-day conduct of the study.

11.5. Interim Analysis

No formal interim analysis will be conducted. Refer to Section 11.4.9 for information on the timing of planned analyses for this study.

11.6. Statistical Considerations Surrounding the Premature Termination of a Study

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

12. QUALITY CONTROL AND QUALITY ASSURANCE

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

12.1. Data Management and Electronic Systems

12.1.1. Data Management

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

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

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

12.1.2. Electronic Systems

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

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

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

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

The investigator must allow study related monitoring activities to occur. The study monitors will perform ongoing source data review to verify that data recorded in the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current

approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2.2. Source Document Requirements

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

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

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic Case Report Forms (eCRFs) within the EDC system by trained site personnel. All required eCRFs must be completed for each and every patient enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor in the eCRFs. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient eCRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the Sponsor and regulatory authorities.

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

12.3. Audits and Inspections

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

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

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

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

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

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

12.4.2. Retention of Records

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

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

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

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

13.2. Informed Consent

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

An informed consent form (ICF) can be defined as either a paper consent form or an electronically-delivered consent (eConsent). An eConsent may be provided only where allowable by local laws and regulations and by site policies.

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

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

For patients at or above the legal age of adulthood, it is the responsibility of the investigator or authorized designee (if acceptable by local regulations) to obtain informed consent from each

patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient:

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

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

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

13.3. Patient Confidentiality and Data Protection

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

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

13.4. Institutional Review Board/Ethics Committee

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

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

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

A copy of the IRB approval letter with a current list of the IRB members and their functions must be received by the Sponsor prior to shipment of drug supplies to the investigator. The approval

letter should include the study number and title, the documents reviewed, and the date of the review.

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

13.5. Clinical Study Data Transparency

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

14. PROTOCOL AMENDMENTS

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

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

15.1. Premature Termination of the Study

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

15.2. Closeout of a Site

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

Investigator's Decision

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

Sponsor's Decision

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

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

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

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

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

19. REFERENCES

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20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol, "A Phase 2 Study to Assess the Virologic Efficacy of REGN10933+REGN10987 Across Different Dose Regimens in Outpatients with SARS-CoV-2 Infection", and agree to abide by all provisions set forth therein.

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

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

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

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

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

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

Study Title: A Phase 2 Study to Assess the Virologic Efficacy of REGN10933+REGN10987 Across Different Dose Regimens in Outpatients with SARS-CoV-2 Infection

Protocol Number: R10933-10987-COV-20145

Protocol Version: Amendment 2

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00145951 v1.0

ESig Approval	[redacted]
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Signature Page for VV-RIM-00145951 v1.0 Approved