NCT04666441

STATISTICAL ANALYSIS PLAN
VERSION: FINAL

Clinical Study Protocol Title: 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
Protocol Number:	R10933-10987-COV-20145
Clinical Phase:	Phase 2
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatistician:	[redacted]
Clinical Trial Manager:	[redacted]
Study Medical Director:	[redacted]
Version/Date:	Original Statistical Analysis Plan /01MAR2021

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

See appended electronic signature page

Study Biostatistician [redacted]

See appended electronic signature page

Study Clinical Pharmacology [redacted]

See appended electronic signature page

Study Bioanalytical Sciences [redacted]

See appended electronic signature page

Study Medical Director [redacted]

See appended electronic signature page

Project Biostatistician [redacted]

See appended electronic signature page

Head of BDM or designee [redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
CPK	Creatine phosphokinase
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
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate dehydrogenase
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
Regeneron	Regeneron Pharmaceuticals, Inc.
RT-qPCR	Quantatitive 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

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to database lock and unblinding of the treatment assignments. The SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of data for R10933-10987-COV-20145 study.

This analysis plan will be issued prior to the first database lock and unblinding of the treatment codes.

1.1. Background/Rationale

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.

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 IV single dose with an acceptable safety profile in this patient population. In this phase 2 study, additional IV single dose regimens, as well as SC single dose regimens, will be evaluated in outpatients with SARS-CoV-2 infection to provide additional assessment of virologic efficacy and safety at lower doses.

1.2. Study Objectives

1.2.1. Primary Objectives

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

1.2.2. 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

1.2.3. 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 vists (MAVs) in patients treated with REGN10933+REGN10987 compared to those treated with placebo

Note: 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.

- 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 COVID-19-related hospitalizations, COVID-19-related emergency room (ER) visits, or all-cause deaths in patients treated with REGN10933+REGN10987 compared to those treated with placebo

1.2.4. Endpoints

The efficacy analysis sets are defined in sections 5.7.1 and 5.7.3.

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 who are seronegative at baseline.

Secondary Endpoints

- 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

Exploratory Endpoints

- 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, COVID-19-related 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

1.2.5. Modifications from the Statistical Section in the Final Protocol

Not applicable.

1.2.6. Revision History for SAP Amendments

This is the first version of the SAP.

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This randomized, double-blinded, placebo-controlled, parallel group study will assess the virologic efficacy, as well as safety and tolerability, of REGN10933+REGN10987 at different IV and SC single-dose regimens in outpatients with SARS-CoV-2 infection. The purpose of this study is to identify the lowest dose regimen capable of demonstrating the same (or similar) virologic efficacy seen at the 2400 mg IV 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 R10933-10987-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 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 household transmission 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.

Up to 1400 total patients will be enrolled in up to approximately 80 sites in the United States. 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):

Table 1: Treatment Arms and Randomization Ratio

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

This randomization ratio means ~200 subjects in each arm receiving REGN10933+REGN10987 and ~200 subjectes receiving placebo (i.e., 100 with IV and 100 with SC). For the purpose of all

virological and efficacy analyses, the placebo arms from the two routes of administration will be pooled because the route of administration does not alter the pharmacodynamic response of patients receiving placebo. Treatment groups for active doses will not be pooled.

2.2. Power Considerations

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 R10933-10987-COV-2067, the mean (SD) was -0.73 (0.948) log_{10} copies/mL (see Investigator's Brochure). For the primary hypothesis comparing each dose to placebo, approximatey 57 patients per treatment group will provide ~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.

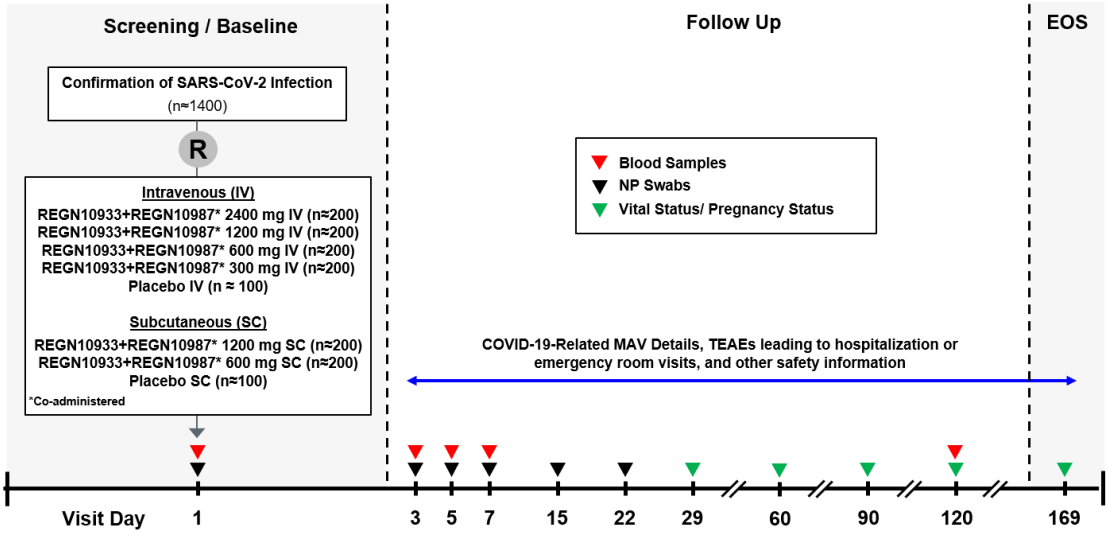
For comparisons between doses and regimens, the study plans to enroll 700 seronegative patients in order to have 100 patients per group. For between-group comparisons, the 95% CI half-width between any two treatment groups with 100 patients per group would be 0.27 log_{10} copies/mL. In order to enroll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

2.3. Study Plan

Patients will have NP swabs and blood samples collected every other day for the first week of the study. Additional NP swabs will be collected once-weekly for two 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 four 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



3. ANALYSIS POPULATIONS

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

3.1. The Seronegative Modified Full Analysis Set (mFAS)

The Overall modified Full Analysis Set (**Overall mFAS**) 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). If a pre-treatment qualitatitive test is missing then a qualitatitive 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 Overall mFAS populations, the placebo IVand placebo SC arms will be pooled for all analyses of virologic endpoints, Active dose groups will not be pooled.

3.2. Per Protocol Set (PPS)

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 will exclude 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 will be the same as the Overall mFAS.

3.3. The Safety Analysis Set (SAF)

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.

3.4. Pharmacokinetic Analysis Set

The PK Analysis Set (PKAS) includes all patients who received any study drug 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.

3.5. The Immunogenicity Analysis Set

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.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (age, gender, race, and ethnicity), and baseline viral load measured with both $\log_{10}$ copies/mL and Cycle Threshold (Ct), viral load threshold, presence/absence of COVID-19 related symptoms, serology (i.e., negative, positive, or other), medical history, and medication history for each patient.

4.2. Medical History

Medical history includes (and may be include more such as risk factors)

- 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 by NCI-CTCAE v5.0
- Whether the patient is receiving oxygen at home by nasal cannula
- Menopausal history
- Pregnancy or breastfeeding status, if applicable

4.3. Pre-Treatment / Concomitant Medication

Prior and comcomitant medications will be summarized separately.

4.4. Rescue Medication/or Prohibited Medication During Study

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. Medications that are prohibited by the protocol will be reviewed and identified by the study clinician and reported in the protocol deviations.

4.5. Efficacy Variable

4.5.1. Primary Efficacy Variable

The primary efficacy measurement is the viral load of patients in the Seronegative mFAS as measured by central laboratory RT-qPCR ($\log_{10}$ copies/mL). The primary efficacy variable is the time-weighted average (TWA) change from baseline in viral load ($\log_{10}$ copies/mL) from day 1 to day 7 as measured by RT-qPCR in NP swabs. The TWA is calculated using the trapezoidal rule as the area under the curve (AUC) divided by this observational period as follows:

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

where V_i is the result of change in viral load ($\log_{10}$ copies/mL) at time point t_i from baseline. As baseline is time point t_1, then $V_1 = 0$.

4.5.2. Secondary Efficacy Variables

The table below describes the primary and secondary efficacy variables labelled 'P' or 'S', respectively. An 'X' means that variable will not be analyzed. The two columns on the far right describe the analysis sets for the efficacy analysis.

Table 2: Efficacy Variables

Efficacy Variable	Endpoint Type	Baseline Viral Load Subgroup	Seronegative mFAS	Overall mFAS
Change from BL in viral load – TWA (days 1 to 7)	Continuous	All	P	S
	Continuous	$>10^4$ copies/mL	X	S
	Continuous	$>10^5$ copies/mL	X	S
	Continuous	$>10^6$ copies/mL	X	S
	Continuous	$>10^7$ copies/mL	X	S
Change from BL in viral load – TWA (days 1 to 5)	Continuous	All	S	S
	Continuous	$>10^4$ copies/mL	X	S
	Continuous	$>10^5$ copies/mL	X	S
	Continuous	$>10^6$ copies/mL	X	S
	Continuous	$>10^7$ copies/mL	X	S
Proportion of patients with viral load $>10^4$ copies/mL at each visit	Categorical	All	S	S
Proportion of patients with viral load $>10^5$ copies/mL at each visit	Categorical	All	S	S
Proportion of patients with viral load $>10^6$ copies/mL at each visit	Categorical	All	S	S
Proportion of patients with viral load $>10^7$ copies/mL at each visit	Categorical	All	S	S
Proportion of patients <LLOQ	Categorical	All	S	S
Proportion of patients <LOD	Categorical	All	S	S
Change from BL in viral load at each visit	Continuous	All	S	S

Denote baseline as BL, Limit of Detection as LOD, and Lower Limit of Quanitification as LLOQ.

4.5.3. Exploratory Efficacy Variables

These variables will be studied using the Seronegative mFAS.

Table 3: Exploratory Efficacy Variables

Efficacy Variable	Category	Time Period	Type
Change from BL in Ct – TWA	All	D7 and D5	Continuous
Change from BL in Ct at each visit	All	D22	Continuous
COVID-19 related MAVs or all-cause mortality	All	D29 and D169	Proportion with ≥1 event
	All	D29 and D169	Proportion with ≥2 events
≥1 COVID-19-related hospitalization or all-cause mortality	All	D29 and D169	Proportion
≥1 COVID-19-related hospitalization, ER visit, or all-cause mortality	All	D29 and D169	Proportion
COVID-19 related MAVs	All	D29 and D169	Proportion with ≥1 event
	Hospitalization	D29 and D169	Count
	ER Visit	D29 and D169	Count
	Urgent Care	D29 and D169	Count
	Physician's office visit	D29 and D169	Count
	Telemedicine	D29 and D169	Count
Days of COVID-19 hospitalization	All	Whole Study	Count
Patients admitted to ICU from COVID-19	All	D29 and D169	Proportion
Patients requiring supplemental oxygen from COVID-19	All	D29 and D169	Proportion
Patients requiring mechanical ventilation due to COVID-19	All	D29 and D169	Proportion
COVID-19-related MAVs	All	D29 and D169	Count

Denote Medically-Attended Visits as MAVs and the emergency room as ER. Count refers to the frequency of times event occurs per patient.

4.6. Safety Variables

4.6.1. Adverse Events and Serious Adverse Events

An Adverse Event (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 be study (ICH E2A Guideline).

A Serious Adverse Event (SAE) either results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, congenital anomaly/birth defect, or is an important medical event. The protocol provides the details.

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

4.6.2. Adverse Events of Special Interest

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

- Grade ≥ 2 infusion-related reactions up to day 4
- Grade ≥ 3 injection-site reactions up to day 4
- Grade ≥ 2 hypersensivity reactions up to day 29
- Any treatment-emergent AE (TEAE) that led to a hospitalization or emergency room visit, regardless of whether the visit is related to COVID-19

4.6.3. Laboratory Safety Variables

The laboratory safety variables are blood chemistry and hematology. The tests for blood chemistry include: Sodium, Potassium, Chloride, Carbon Dioxide, Glucose, Blood urea nitrogren (BUN), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Total bilirubin, Albumin, Alkaline phosphatase, Creatinine, Creatine phosphokinase (CPK), and Lactate dehydrogenase (LDH). Hematology tests include Hemoglobin, Hematocrit, Red blood cells (RBCs), White blood cells (WBCs), Platelet count, Differential Neutrophils, Lymphocytes, Monocytes, Basophils, and Eosinophils. Clinical laboratory values will be converted to standard international (SI) units and grouped by function in summary tables. Clinical laboratory values will be converted and analyzed in both standard international (SI) units and US conventional units provided by the central laboratory. Both actual test values and “change from baseline” values (defined as the post-baseline value minus the baseline value) over time will be summarized, where the post-baseline visits will

be assigned to the Global Analysis Windows. Potentially clinically significant values (PCSV) ranges will be applied to the laboratory test values as applicable (see PCSV criteria in Appendix 11.2).

4.6.4. 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. Potentially clinically significant values (PCSV) ranges will be applied to corresponding vital sign parameter values according to (see PCSV criteria in Appendix 11.2).

4.7. Pharmacokinetic Variables and Anti-Drug Antibody (ADA) Variables

The pharmacokinetic (PK) variables are the concentration of REGN10933 and REGN10987 in serum and time. Samples are collected at the timepoints outlined in the Schedule of Events (Appendix 11.1).

4.8. Immunogenicity Variables

The immunogenicity variables are ADA response status, titer, NAb status, and time-point/visit. Samples for ADA analysis are collected at the timepoints outlined in the Schedule of Events (Appendix 11.1).

5. STATISTICAL METHODS

For continuous variables, descriptive statistics will include the following: the number of patients reflected in the calculation (n), mean, median, standard deviation, Q1, 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 (i.e., either at screening or pre-dose assessment).

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group and overall for the study. For viral load, there will be summaries and visualizations of key disease-related characteristics.

5.2. Medical History

Medical history will be summarized by SOC and PT and by treatment group and all groups combined in the SAF population.

5.3. Prior / Concomitant Medications

All prior medications, dictionary coded by WHODRUG (WHO Drug Global version 01MAR2020 B3), will be descriptively summarized by treatment group and overall for the study, for subjects in SAF population. All procedures, dictionary coded by MedDRA v23.1, will be summarized in the same fashion as prior/concomitant medications.

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

All concomitant medications/procedures will be descriptively summarized by treatment group, for subjects in SAF.

5.4. Rescue / Prohibited Medications

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. Listing of prohibited medications will be provided for patients in SAF.

5.5. Patient Disposition

Using the SAF, appropriate summaries of the patient disposition will be displayed. Summaries of total screened patients, numbers of each analysis set by treatment and total will be available. 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
- Thte 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

Using the SAF, summaries of discontinuation and/or dropouts by reasons and treatments will be presented.

5.6. Extent of Study Treatment Exposure and Compliance

This is a single dose study, with the site administering the doses. A listing will be provided of patients who are randomized but not dosed as well as infusions or injections that were either interrupted or not completed. Treatment compliance in terms of total dose and infusion interruption will be summarized by treatment group.

The extent of follow-up in the SAF population will be summarized. The numbers of patients completing 29 days and 169 days of follow-up will be tabulated.

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.

5.7. Hypothesis Test

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 ($\log_{10}$ copies/mL) from day 1 to day 7, relative to placebo

The type I error rate is 0.05.

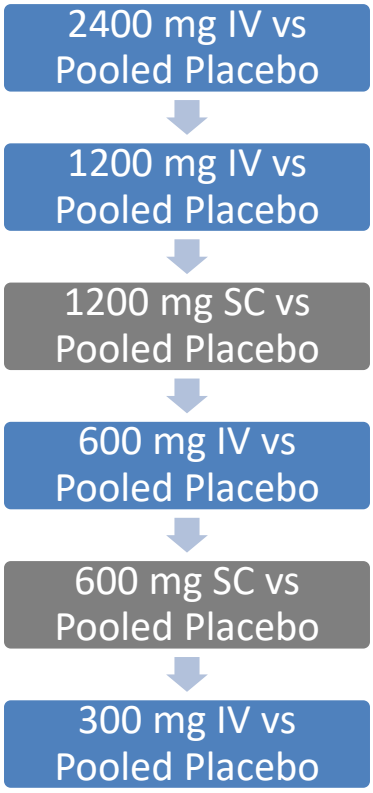
5.7.1. Analysis of Primary Efficacy Variable

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

A step-down testing approach will be used for comparing active treatment groups to the pooled placebo to control type I error rate at 0.05. The pairwise comparisons are performed using the t-

test. Figure 2 below illustrates this hierarchy. If a test is insignificant, then the formal testing procedure stops at that step.

Figure 2: Testing Hierarchy



The least squares mean estimates and 95% confidence intervals 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+REGN1097 treatment group and placebo along along with the p-values for the comaprisons. Accompanying descriptive analyses will be provided at the individual timepoints used to calculate the TWA.

No hypothesis testing is planned for the between active dose comparisons. Only estimates and 95% confidence intervals will be reported for the between active dose comparisons.

5.7.2. Analysis in Patients with High Viral Loads

Within the Overall mFAS population, analysis of the change from baseline in viral load at each visit will be performed in baseline viral load categories ($>10^4$ copies/mL, $>10^5$copies/mL, $>10^6$ copies/mL, $>10^7$copies/mL) using the same method as described above using ANCOVA.

5.7.3. Subgroup Analyses

Subgroup analysis by gender, symptomatic vs. asymptomatic, race (white vs. other), and baseline viral load (above or below median) may be performed in seronegative mFAS in order to assess the consistency of results.

5.7.4. Dose Response Modelling

Several dose response models will be explored for the TWA of change in baseline in viral load (log_{10} copies/mL) from day 1 to day 7, and then a single model is selected using Akaike's Information Criteria (AIC). The AIC considers a trade-off between increasing the number of parameters in terms of goodness-of-fit by introducing a penalty for the number of parameters. The model with the lowest AIC value is selected. The models under consideration are linear, hyperbolic E_{max}, and sigmoidal E_{max}. Additional models may be considered. As the dose response testing and modelling is for estimation, there will be no adjustment for multiplicity.

Table 4: Set of Candidate Dose Response Models

Name	Model	Description
Sigmoidal E_{max}	$y_i = E_0 + E_{max}\frac{D_i^h}{ED_{50}^h + D_i^h} + \epsilon_i$	i: the patient ID y_i: the response for the i^{th} patient E_0: the placebo effect E_{max}: The maximum effect attributable to the drug ED_{50}: The dose that produces one-half of E_{max} h: The hill parameter and determines the steepness of the slope D_i: The dose-level for the i^{th} patient ϵ_i: The error term for the i^{th} patient where each error term is independent and identically Normally distributed with mean 0 and standard deviation σ.
Hyperbolic E_{max}	$y_i = E_0 + E_{max}\frac{D_i}{ED_{50} + D_i} + \epsilon_i$	Special case of above model where $h = 1$
Linear	$y_i = E_0 + \beta_1 * D_i + \epsilon_i$	β_1: Linear effect term
Exponential	$y_i = E_0 + E_1\left(\exp\left(\frac{D_i}{\delta}\right) - 1\right) + \epsilon_i$	E_1: Exponential term δ: Scale

5.7.5. Analysis of Secondary Efficacy Variables

For the analysis of primary and secondary efficacy variables, the table below summarizes the quantities and corresponding methods for analysis. The details of methods are described the paragraphs that follow.

Table 5: Secondary Efficacy

Measurement	Units	Metric	Method
Viral load (D1-5)	log_{10} copies/mL	TWA	ANCOVA
Viral load	log_{10} copies/mL	Change from BL in viral load at each visit	MMRM
Viral load	log_{10} copies/mL	Proportions <LLOQ, <LOD, $>10^4$, $>10^5$, $>10^6$, or $>10^7$	Fisher's Exact Test/Logistic Regression
Percent change in Viral Load	copies/mL	Percent change in viral load (copies/mL) to each time point	MMRM

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 populations. The model will include 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 covariance matrix; heterogeneous autoregressive (1), or compound symmetry covariance matrix will be considered 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.

There may be additional analysis of the proportions of patients who have PCR below the limit of detection, below the lower limit of quantification, or have quantatitive PCR levels above $>10^4$, $>10^5$, $>10^6$, or $>10^7$ will be tabulated over time using logistic regression model with terms for treatment arm, baseline viral load, and the treatment-by-baseline viral load interaction. Adjusted odds ratios and corresponding p-values and confidence intervals may be estimated from the model.

5.7.6. Analysis of Other Secondary Efficacy

The table in subsection 4.5.2 describes the other secondary efficacy variables. All variables will be tabulated.

5.8. Analysis of Safety Data

The analysis of safety and tolerability will be performed in the SAF population.

5.8.1. Adverse Events

Safety data will be summarized in three periods:

1. The pretreatment period, i.e., from signing the ICF to before the study drug administration
2. The 29-day observation period, i.e., from the time of the administration of the study drug to the last follow-up visit.
3. The full observation period, i.e., from the time of the administration of the study drug to the last follow-up visit.

For patients that are vaccinated for SARS-CoV-2, only the safety data before vaccination will be used in the primary safety analysis. A secondary safety analysis will use all data collected.

Analysis

All SAEs and AESIs 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 adverse events (AEs) through day 29 by system organ class and PT
- The number (n) and percentage (%) of patients with at least 1 treatment-emergent serious adverse events (SAEs) through day 29 by system organ class and PT
- The number (n) and percentage (%) of patients with at least 1 infusion-related reactions (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 reactions (grade ≥2), through day 29 by PT
- 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) from day 30 to day 169
- Treatment-emergent SAEs, up to day 169

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 described in the protocol), 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
- The number (n) and percentage (%) of patients with Grade 3 or Grade 4 treatment-emergent adverse events.

Deaths and other SAEs will also be listed and summarized by treatment arm. Tables describing the adverse events will be made covering the two periods, except the observation period will be broken into two divisions: day 1 to day 29 and day 1 to day 169.

There will also be lists of every Treatment-Emergent Adverse Event (TEAE). Then there will be a list of TEAEs for the proportion that occurs greater than or equal to 5% and a list of TEAEs for the proportion that occurs greater than or equal to 10%.

5.8.2. Clinical Laboratory Measurements

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 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.

5.8.3. Vital Signs

Vital signs (temperature, blood pressure, heart rate (per minute), SpO_2) will be summarized at baseline and post-dose with descriptive statistics. Graphs of mean (+/- SE) value may be provided.

5.9. Analysis of Pharmacokinetic and Immunogenicity Data

5.9.1. Analysis of Pharmacokinetic Data

Concentrations of REGN10933 and REGN10987 in serum, separately and combined, will be summarized at each time point by treatment group using descriptive statistics. No formal statistical analysis will be performed.

Pharmacokinetic parameters will be determined for individual subjects by non-compartmental methods using Phoenix WinNonlin (version 8.1, Certara, L.P.), for both REGN10933 and REGN10987. Pharmacokinetic parameters will summarized by treatment group using descriptive statistics.

The following PK parameters to be estimated include are but not limited to, and if supported by the data:

IV doses: C_{max}, T_{max}, C_7, $AUC_{0\text{-}7\ days}$, AUC_{last}, AUC_{inf}, CL, MRT, V_z, V_{ss}, $t_{½}$.

SC doses: C_{max}, T_{max}, C_7, $AUC_{0\text{-}7\ days}$, AUC_{last}, AUC_{inf}, CL/F, V_z/F, $t_{½}$.

5.9.2. Analysis of Pharmacokinetic/Pharmacodynamic Data

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.

5.9.3. Analysis of Immunogenicity Data

5.9.3.1. Analysis of ADA Data

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

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

ADA Response Categories:

- ADA Negative, defined as an ADA negative response in the ADA assay at all time points collected, 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 a 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 (<1,000)
- – Moderate (≥1,000 to ≤10,000)
- – High (>10,000)

The following analysis 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.

5.9.3.2. Analysis of NAb Data

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

6. ASSOCIATION OF IMMUNOGENICITY WITH EXPOSURE, SAFETY AND EFFICACY

6.1. Immunogenicity and Exposure

Potential association between immunogenicity variables and systemic exposure to REGN10933 and REGN10987 will be explored by treatment groups. Plots of drug concentration time profiles may be provided to examine the potential impact of ADA response status, titer and NAb on these profiles.

6.2. Immunogenicity and Safety and Efficacy

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

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

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

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

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

7. DATA CONVENTIONS

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

7.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of investigational product (either screening or pre-dose).

For determining if a patient is positive for SARS-CoV-2, latest qualitatative PCR tests taken prior to the dose administration will be used. If the pre-dose qualitative PCR is not available, the tests up to 2 hours post-dose will be used to determine baseline PCR status. For analyses of *quantitative* RT-qPCR levels, only values from NP swabs take before dosing will be used.

7.2. Data Handling Convention for Efficacy Variables

For efficacy variables, only observed data will be used. If the viral load is not available at the scheduled time point t_i or missing due to failed test or other reasons, only the time points with non-missing values will be included for TWA calculation. The nominal visits and results from these visits will be used to compute the TWA (the primary endpoint). Patients without a baseline will be excluded from the analysis. Additionally, patients who do not have any viral measurements during first 7 days post baseline will be excluded.

Viral loads less the lower limit of quantification of the PCR assay but with positive qualitative results will be set to half of the lower limit of quantification of the PCR assay; values with nondetectable RNA will be set to 0 $\log_{10}$ copies/mL if the reason for the negative value is a not a failed test. Viral load values above the upper limit of quantification will be re-tested using the reflex test and the corresponding quantatitive value will be used in the analysis. If two or more measurements correspond to the same visit, the "worst" value will be used. For viral load, the "worst" value is the highest. For Ct analysis, the "worst" value is the lowest value.

7.3. Data Handling Convention for Missing Data

For efficacy variables, only observed data will be used. If samples are missing, then the TWA estimates adjust using irregular spacing of the timing.

Adverse Event

If the severity of a TEAE is missing, it will be classified as "severe" or "Grade 3" in the frequency tables by intensity of TEAEs. If the assessment of relationship of a TEAE to the investigational product is missing, it will be classified as related to study drug.

Every effort will be made to collect the start dates of all AEs and concomitant medications. If the end data of the AE is missing, then the data of the last follow-up date. When the partial AE date/time information does not indicate that the AE started prior to study treatment or after the TEAE period, the AE will be classified as treatment-emergent.

Medication/Procedure

If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly or stopped prior to the study treatment administration, it will be

considered as concomitant medication/procedure by imputing the start date on the date of first study treatment administration.

Potentially Clinically Significant Value (PCSV)

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

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

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

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

7.4. Visit Windows

Below are the definitions for the visit windows programmatically imposed on all available measures from unscheduled visits collected over the course of the study including early terminatin visit and the end of study vitsit. No analysis visit windows will be applied for the study scheduled visits.

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

1. The first study treatment occurs on study day 1.
2. Study day is defined as the number of days since the first study treatment administration +1.
3. Since the protocol specifies that measurements be collected before study treatment is administered on a given day, it is appropriate that baseline includes day 1.
4. For randomized but not treated subjects, day 1 is the day of randomization.

Table 6: Analysis Windows

Visit Label	Targeted Study Day	Analysis Window in Study Day
Baseline	1	≤ 1
Day 3	3	[2, 3]
Day 5	5	[4, 5]
Day 7 (Week 1)	7	[6, 10]
Day 15 (Week 2)	15	[11, 18]
Day 22 (Week 3)	22	[19, 25]
Day 29 (Week 4)	29	[26, 45]
Day 60	60	[46, 86]
Day 90	90	[87, 93]
Day 120	120	[94, 144]
Day 169	169	>144

If a subject has multiple efficacy assessment visits within an analysis vsit window, the one with worst result will be selected (e.g. highest quantitative viral load). Extra assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing adverse events) will be included in the listings, but not summaries except for the endpoint determination. If more than one laboratory value is available for a given visit, the "worst" will be used in summaries and all observations will be presented in listings.

7.5. Unscheduled Assessments

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

7.6. Pooling of Centers for Statistical Analyses

Not applicable.

8. INTERIM ANALYSIS

There is no formal interim analysis planned for this study.

When approximately 800 patients complete the day 7 visit, a first-step analysis will be performed. Since this is the final analysis of the primary endpoint, it is not considered an interim analysis.

9. SOFTWARE

All analyses will be done using SAS EG version 9.4 and R Version 3.5.1 or higher.

Non compartmental analysis of PK data will be performed using Phoenix WinNonlin (version 8.1, Certara, L.P.).

10. REFERENCES

1. ICH. (1996, July 30). ICH Harmonized tripartite guideline: Structure and content of clinical study reports (E3). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
2. ICH. (1997, July 17). ICH Harmonized tripartite guideline: General considerations for clinical trials (E8). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
3. ICH. (1998, February 5). ICH Harmonized tripartite guideline: Statistical principles for clinical trials (E9). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
4. Menon, S. M. and Zink, R. C. Ed. *Modern Approaches to Clinical Trials Using SAS®: Classical, Adaptive, and Bayesian Methods*. SAS Institute Inc., Cary, NC, USA. 2015.

11. APPENDIX

11.1. Schedule of Events

Table 7: 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	

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
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.

For footnotes on the Schedule of Events, please see the protocol.

11.2. Criteria for Potentially Clinically Significant Values (PCSV)

Table 8: Criteria for Potentially Clinicially Significant Values (PCSV)

Parameter	PCSV	Comments
Clinical Chemistry		
ALT	>3 and ≤ 5 ULN and baseline ≤ 3 ULN >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently.
AST	>3 and ≤ 5 ULN and baseline ≤ 3 ULN >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently.
Alkaline Phosphatase	>1.5 ULN and baseline ≤ 1.5 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007.
Total Bilirubin	>1.5 and ≤ 2 ULN and baseline ≤ 1.5 ULN >2 ULN and baseline ≤ 2.0 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007.
Conjugated Bilirubin	>35% Total Bilirubin and TBILI>1.5 ULN, and baseline Total Bilirubin ≤ 35% or TBILI ≤1.5 ULN	Conjugated bilirubin determined on a case-by-case basis.
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN, and baseline ALT ≤ 3 ULN or TBILI ≤ 2ULN	Concept paper on DILI – FDA draft Guidance Oct 2007.
CPK	>3 and ≤ 10 ULN and baseline ≤ 3ULN >10 ULN and baseline ≤10ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative.

Parameter	PCSV	Comments
Creatinine	≥150 µmol/L (Adults) or ≥ULN (if ULN≥150 µmol/L) and baseline < 150 µmol/L or <ULN (if ULN≥150 µmol/L) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994. 3 independent criteria
Creatinine Clearance (Cockcroft's formula)	<15 ml/min and baseline ≥15 ml/min (end stage renal impairment) ≥15 -<30 ml/min and baseline ≥30 ml/min (severe renal impairment) ≥30 - < 60 ml/min and baseline ≥60 ml/min (moderate renal impairment) ≥60 - < 90 ml/min and baseline ≥90 ml/min (mild renal impairment)	Use is optional. FDA draft guidance 2010 Four independent criteria, will provide additional shift table if needed
Uric Acid Hyperuricemia: Hypouricemia:	 >408 µmol/L or >ULN (if ULN≥408 µmol/L) and baseline ≤408 µmol/L or ≤ULN (if ULN≥408 µmol/L) <120 µmol/L or <LLN (if LLN≤120 µmol/L) and baseline ≥ 120 µmol/L or ≥LLN (if LLN≤120 µmol/L)	Harrison- Principles of Internal Medicine 17th Ed., 2008. Two independent criteria
Blood Urea Nitrogen	≥17 mmol/L or ≥ULN (if ULN≥17 mmol/L) and baseline <17 mmol/L or <ULN (if ULN≥17 mmol/L)	Two independent criteria
Chloride Hypochloremia: Hyperchloremia:	 <80 mmol/L or <LLN (if LLN≤80 mmol/L) and baseline ≥ 80 mmol/L or ≥LLN (if LLN≤80 mmol/L) >115 mmol/L or >ULN (if ULN≥115 mmol/L) and baseline ≤ 115 mmol/L or ≤ULN (if ULN≥115 mmol/L)	Two independent criteria

Parameter	PCSV	Comments
Sodium Hyponatremia: Hypernatremia:	 ≤129 mmol/L or ≤LLN (if LLN≤129 mmol/L) and baseline > 129 mmol/L or >LLN (if LLN≤129 mmol/L) ≥160 mmol/L or ≥ULN (if ULN≥160 mmol/L) and baseline <160 mmol/L or <ULN (if ULN≥160 mmol/L)	Two independent criteria
Potassium Hypokalemia Hyperkalemia	 <3 mmol/L or <LLN (if LLN≤3 mmol/L) and baseline ≥ 3 mmol/L or ≥LLN (if LLN≤3 mmol/L) ≥5.5 mmol/L or ≥ULN (if ULN≥5.5 mmol/L) and baseline <5.5 mmol/L or <ULN (if ULN≥5.5 mmol/L)	FDA Feb 2005. Two independent criteria
Glucose Hypoglycaemia Hyperglycaemia	 ≤3.9 mmol/L and <LLN and baseline >3.9 mmol/L or ≥ LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted) and baseline < 11.1 mmol/L (unfasted); <7 mmol/L (fasted)	ADA Jan 2008.
Albumin	≤25 g/L or ≤LLN (if LLN≤25 g/L) and baseline >25 g/L or >LLN (if LLN≤25 g/L)	
Hematology		

Parameter	PCSV	Comments
WBC	<3.0 Giga/L or <LLN (if LLN≤3.0 Giga/L) and baseline ≥3.0 Giga/L or ≥LLN (if LLN≤3.0 Giga/L) (Non-Black); <2.0 Giga/L or <LLN (if LLN≤2.0 Giga/L) and baseline ≥2.0 Giga/L or ≥LLN (if LLN≤2.0 Giga/L) (Black)* ≥16.0 Giga/L or ≥ULN (if ULN≥16.0 Giga/L) and baseline < 16 Giga/L or <ULN (if ULN≥16.0 Giga/L)	Increase in WBC: not relevant. *The default criteria. Summary by race (black and Non-black) are optional. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L or >ULN (if ULN≥4.0 Giga/L) and baseline ≤ 4.0 Giga/L or ≤ULN (if ULN≥4.0 Giga/L)	
Neutrophils	<1.5 Giga/L or <LLN (if LLN≤1.5 Giga/L) for Non-Black or <1.0 Giga/L or <LLN (if LLN≤1.0 Giga/L) for Black and baseline ≥1.5 Giga/L or ≥LLN (if LLN≤1.5 Giga/L) for Non-Black or ≥1.0 Giga/L or ≥LLN (if LLN≤1.0 Giga/L) for Black* <1.5 Giga/L or <LLN (if LLN≤1.5 Giga/L) and baseline ≥1.5 Giga/L or ≥LLN (if LLN≤1.5 Giga/L) (Non-Black); <1.0 Giga/L or <LLN (if LLN≤1.0 Giga/L) and baseline ≥1.0 Giga/L or ≥LLN (if LLN≤1.0 Giga/L) (Black) <0.5 Giga/L regardless of baseline value or race	International Consensus meeting on drug-induced blood cytopenias, 1991. *The default criteria. By race (black and Non-black) are optional.
Monocytes	>0.7 Giga/L or >ULN (if ULN≥0.7 Giga/L) and baseline ≤ 0.7 Giga/L or ≤ULN (if ULN≥0.7 Giga/L)	
Basophils	>0.1 Giga/L or >ULN (if ULN≥0.1 Giga/L) and baseline ≤ 0.1 Giga/L or ≤ULN (if ULN≥0.1 Giga/L)	
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L) and baseline ≤0.5 Giga/L or ≤ULN (if ULN≥0.5 Giga/L)	Harrison- Principles of Internal Medicine 17th Ed., 2008.

Parameter	PCSV	Comments
Hemoglobin	≤115 g/L or ≤LLN (if LLN≤115 g/L) for male or ≤95 g/L or ≤LLN (if LLN≤95 g/L) for female and baseline > 115 g/L or >LLN (if LLN≤115 g/L) for male or > 95 g/L or >LLN (if LLN≤95 g/L) for Female* ≤115 g/L or ≤LLN (if LLN≤115 g/L) and baseline > 115 g/L or >LLN (if LLN≤115 g/L) for male; ≤95 g/L or ≤LLN (if LLN≤95 g/L) and baseline > 95 g/L or >LLN (if LLN≤95 g/L) for Female. ≥185 g/L or ≥ULN (if ULN≥185 g/L) for male or ≥165 g/L or ≥ULN (if ULN≥165 g/L) for female and baseline <185 g/L or <ULN (if ULN≥185 g/L) for male or <165 g/L or <ULN (if ULN≥165 g/L) for Female* ≥185 g/L or ≥ULN (if ULN≥185 g/L) and baseline <185 g/L or <ULN (if ULN≥185 g/L) for Male; ≥165 g/L or ≥ULN (if ULN≥165 g/L) and baseline < 165 g/L or <ULN (if ULN≥165 g/L) for Female Decrease from Baseline ≥20 g/L	Three criteria are independent. *The default criteria. By gender (male and female) are optional. Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).

Parameter	PCSV	Comments
Hematocrit	≤0.37 v/v or ≤LLN (if LLN≤0.37 v/v) for Male or ≤0.32 v/v or ≤LLN (if LLN≤0.32 v/v) for Female and baseline > 0.37 v/v or >LLN (if LLN≤0.37 v/v) for Male or > 0.32 v/v or >LLN (if LLN≤0.32 v/v) for Female* ≤0.37 v/v or ≤LLN (if LLN≤0.37 v/v) and baseline > 0.37 v/v or >LLN (if LLN≤0.37 v/v) for Male; ≤0.32 v/v or ≤LLN (if LLN≤0.32 v/v) and baseline > 0.32 v/v or >LLN (if LLN≤0.32v/v) for Female ≥0.55 v/v or ≥ULN (if ULN≥0.55 v/v) for Male or ≥0.5 v/v or ≥ULN (if ULN≥0.5 v/v) for Female and baseline < 0.55 v/v or <ULN (if ULN≥0.55 v/v) for Male < 0.5 v/v or <ULN (if ULN≥0.5 v/v) for Female* ≥0.55 v/v or ≥ULN (if ULN≥0.55 v/v) and baseline < 0.55 v/v or <ULN (if ULN≥0.55 v/v) for Male ; ≥0.5 v/v or ≥ULN (if ULN≥0.5 v/v) and baseline < 0.5 v/v or <ULN (if ULN≥0.5 v/v) for Female	Two Criteria are independent *The default criteria. By gender (male and female) are optional.
RBC	≥6 Tera/L or ≥ULN (if ULN≥6 Tera/L) and baseline < 6 Tera/L or <ULN (if ULN≥6 Tera/L)	Unless specifically required for particular drug development, the analysis is redundant with that of Hb.
Platelets	<100 Giga/L or <LLN (if LLN≤100 Giga/L) and baseline ≥100 Giga/L or ≥LLN (if LLN≤100 Giga/L) ≥700 Giga/L or ≥ULN (if ULN≥700 Giga/L) and baseline < 700 Giga/L or <ULN (if ULN≥700 Giga/L)	International Consensus meeting on drug-induced blood cytopenias, 1991. Two independent criteria

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

11.3. SAS Code for Dose Response Modelling

We utilize SAS code from the chapter on Classical Dose-Response Study from *Modern Approaches to Clinical Trials Using SAS®: Classicial, Adaptive, and Bayesian Methods* edited by Sandeep M. Menon and Richard C. Zink (page 185). We assume the data set data1 contains the response for each dose and use arbitrary initial values for demonstration purposes.

```
*** Sigmoidal E_max model;
proc nlmixed data=data1 alpha=0.05;
        *** set up initial values
        parms e0=10 emax=80 ed50=5.5 h=1 v=400;
        *** Specify that ed50 must be positive;
        bounds ed50>0;
        *** Define model;
        if dose=0 then eta = e0;
        else eta = e0 + (emax*dose**h) / (ed50**h+dose**h));
        model resp ~ normal(eta, v);

        *** Estimate the difference in means;
        estimate “Diff Means (dose 2400 mg – placebo)”
                e0+((emax*2400**h)/(ed50**h+2400**h))-e0;
        estimate “Diff Means (dose 1200 mg – placebo)”
                e0+((emax*1200**h)/(ed50**h+1200**h))-e0;
        estimate “Diff Means (dose 600 mg – placebo)”
                e0+((emax*600**h)/(ed50**h+600**h))-e0;
        estimate “Diff Means (dose 300 mg – placebo)”
```

```
            e0+((emax*300**h)/(ed50**h+300**h))-e0;

        predict eta out=etahat;
        ****output estimations;
        ****dataset est has output for estimate of the mean differences;
        ****dataset parms has output for parameters: e0 emax ed50 h;
        ods output AdditionalEstimates=est ParameterEstimates=parms;
run;

*** Hyperbolic E_max model;
proc nlmixed data=data1 alpha=0.05;
        *** set up initial values
        parms e0=10 emax=80 ed50=5.5 v=400;
        *** Specify that ed50 must be positive;
        bounds ed50>0;
        *** Define model;
        if dose=0 then eta = e0;
        else eta = e0 + (emax*dose) / (ed50+dose));
        model resp ~ normal(eta, v);

        *** Estimate the difference in means;
        estimate “Diff Means (dose 2400 mg – placebo)”
            e0+((emax*2400)/(ed50+2400))-e0;
```

```
        estimate “Diff Means (dose 1200 mg – placebo)”
                e0+((emax*1200)/(ed50+1200))-e0;
        estimate “Diff Means (dose 600 mg – placebo)”
                e0+((emax*600)/(ed50+600))-e0;
        estimate “Diff Means (dose 300 mg – placebo)”
                e0+((emax*300)/(ed50+300))-e0;

        predict eta out=etahat;
        ****output estimations;
        ****dataset est has output for estimate of the mean differences;
        ****dataset parms has output for parameters: e0 emax ed50;
        ods output AdditionalEstimates=est ParameterEstimates=parms;
run;

*** Linear model;
proc nlmixed data=data1 alpha=0.05;
        *** set up initial values
        parms e0=10 beta1=80 beta2=80  v=400;

        *** Define model;
        if dose=0 then eta = e0;
        else eta = e0 + beta1 * dose;
        model resp ~ normal(eta, v);
```

```
        *** Estimate the difference in means;
        estimate “Diff Means (dose 2400 mg – placebo)”
                e0+ beta1 * 2400 - e0;
        estimate “Diff Means (dose 1200 mg – placebo)”
                e0+ beta1 * 1200  - e0;
        estimate “Diff Means (dose 600 mg – placebo)”
                e0+ beta1 * 600 - e0;
        estimate “Diff Means (dose 300 mg – placebo)”
                e0+ beta1 * 300 - e0;

        predict eta out=etahat;
        ****output estimations
        ****dataset est has output for estimate of the mean differences;
        ****dataset parms has output for parameters: e0 beta1;
        ods output AdditionalEstimates=est ParameterEstimates=parms;
run;
*** Exponential model;
proc nlmixed data=data1 alpha=0.05;
        *** set up initial values
        parms e0=10 e1=1 delta=1;

        *** Define model;
```

```
        if dose=0 then eta = e0;
        else eta = e0 + e1 * (exp(dose/delta)-1);
        model resp ~ normal(eta, v);
        *** Specify that delta must be positive;
        bounds delta>0;

        *** Estimate the difference in means;
        estimate “Diff Means (dose 2400 mg – placebo)”
                e0+ e1* (exp(2400/delta)-1) - e0;
        estimate “Diff Means (dose 1200 mg – placebo)”
                e0+ e1* (exp(1200/delta)-1) - e0;
        estimate “Diff Means (dose 600 mg – placebo)”
                e0+ e1* (exp(600/delta)-1) - e0;
        estimate “Diff Means (dose 300 mg – placebo)”
                e0+ e1* (exp(300/delta)-1) - e0;
        predict eta out=etahat;
        ****output estimations
        ****dataset est has output for estimate of the mean differences;
        ****dataset parms has output for parameters: e0 e1 delta;
        ods output AdditionalEstimates=est ParameterEstimates=parms;
run;
```

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