NCT04425629

STATISTICAL ANALYSIS PLAN
PHASE 3
VERSION: FINAL V1.0

A MASTER PROTOCOL ASSESSING THE SAFETY, TOLERABILITY, AND EFFICACY OF ANTI-SPIKE (S) SARS-COV-2 MONOCLONAL ANTIBODIES FOR THE TREATMENT OF AMBULATORY PATIENTS WITH COVID-19

Compound:	REGN10933+REGN10987 (REGN-CoV2; REGEN-COV)
Protocol Number:	R10933-10987-COV-2067
Clinical Phase:	Phase 1/2/3
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatisticians:	PPD
	PPD
Clinical Trial Manager:	PPD
Study Medical Directors:	PPD
	PPD
	PPD
Version/Date:	Original (Version 1.0) / 12 Mar 2021

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 Biostatisticians PPD

See appended electronic signature page

Study Medical Director PPD

See appended electronic signature page

Study Clinical Pharmacologist PPD)

See appended electronic signature page

Study Bioanalytical Scientist PPD

See appended electronic signature page

Project Biostatistician PPD)

See appended electronic signature page

Head of BDM PPD

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
COVID-19	Coronavirus Disease 2019
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRP	C-reactive protein
ECG	Electrocardiogram
FAS	Full Analysis Set
ICH	International Council for Harmonisation
IWRS	Interactive Web Response System
IV	Intravenous
mFAS	Modified full analysis set
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects Model for Repeated Measures
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
OP	Oropharyngeal
NP	Nasopharyngeal
PCR	Polymerase Chain Reaction
PCSV	Potentially Clinically Significant Value
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred Term
RBC	Red Blood Cell
RMST	Restricted Mean Survival Time

Abbreviation	Definition
RNA	Ribonucleic Acid
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
SC	Subcutaneous
SOC	System organ class
TEAE	Treatment-emergent adverse event
ULN	Upper Limit Normal
US	United States (of America)
WBC	White blood cell
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

1. EXECUTIVE SUMMARY

The purpose of the statistical analysis plan (SAP) is to ensure the integrity of the study results by pre-specifying the statistical approaches for the analysis of study data prior to a database lock of this phase 1/2/3 adaptive study R10933-10987-COV-2067 of anti-Spike SARS-CoV-2 monoclonal antibodies in ambulatory patients with COVID-19.

Study R10933-10987-COV-2067 is an adaptive phase 1/2/3, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy and safety of co-administered REGN10933+REGN10987 combination therapy ("REGN10933+REGN10987"; REGN-COV2; REGEN-COV) in outpatient (ie, ambulatory) adults with COVID-19. An initial descriptive analysis of phase 1/2 data from the first 275 patients enrolled in this study was conducted based on a database lock on 23 September 2020. The primary phase 2 analysis was conducted based on a database lock on 24 October 2020, in which virologic efficacy was evaluated in the next 524 patients enrolled in the symptomatic cohort and clinical efficacy was evaluated in the combined analysis groups comprised of the first 799 randomized symptomatic patients. These analyses informed the phase 3 study design and provided insight into how the phase 3 analysis plan should be organized.

This version of the SAP implements the final phase 3 analysis plan for the study according to protocol amendment 8. The phase 3 portion of the study consists of patients separated into 3 cohorts: cohort 1 (symptomatic patients ≥18 years of age after 799 symptomatic patients from phase 1/2, not pregnant at randomization), cohort 2 (<18 years of age, not pregnant at randomization), and cohort 3 (pregnant at randomization). The analyses described herein apply only to the three cohorts in phase 3.

Based on the concept that the effects of REGN10933+REGN10987 are mediated by anti-viral activity and that benefit would be best observed by focusing analyses on patients who had not cleared virus at baseline and are at high risk for severe COVID-19, efficacy analyses will be conducted in a subset of the full analysis set (FAS), termed the modified full analysis set (mFAS), which includes patients who have detectable SARS-CoV-2 RNA by RT-qPCR in nasopharyngeal swabs at randomization and at least 1 risk factor for severe COVID-19. Analyses in the FAS that are not dependent on having detectable virus at baseline will be provided as supportive analysis. (The FAS represents all patients randomized and analyzed as randomized; it is equivalent to the ITT population for this study).

The Independent Data Monitoring Committee (IDMC) recently made a recommendation to stop enrollment into the placebo group based on clear efficacy. The Sponsor stopped enrolling patients in the placebo group as of 25 February 2021, and the study continues to enroll patients 1:1 into either of the REGN10933+REGN10987 treatment arms (1200 mg or 2400 mg). Based on the IDMC's recommendation, the Sponsor has decided to perform the final primary efficacy analysis of the REGN10933+REGN10987 2400 mg treatment group versus placebo, where the primary endpoint will be the proportion of patients with a hospitalization related to COVID-19 or all-cause death. The efficacy analysis will be conducted in phase 3, cohort 1 patients with at least 1 risk factor for severe COVID-19 who were randomized on or before 17 January 2021, with a data cut date of 18 Feburary 2021, ensuring all patients had an opportunity to reach day 29. This will be the final primary efficacy analysis for the REGN10933+REGN10987 2400 mg treatment group compared to placebo because it is estimated that there is sufficient power for the analysis of the

proportion of patients with hospitalization related to COVID-19 or all-cause death endpoint. An interim analysis of the REGN10933+REGN10987 1200 mg treatment versus placebo comparisons using patients randomized on or before 17 January 2021 will also be performed. The final analysis of REGN10933+REGN10987 1200 mg versus placebo comparisons will be based on all phase 3 patients randomized on or before 24 February 2021.

1.1. Background/Rationale

This study is an adaptive phase 1/2/3, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy and safety of co-administered REGN10933+REGN10987 combination therapy ("REGN10933+REGN10987") in outpatient (ie, ambulatory) adults with COVID-19. Treatments referenced in the protocol that were not utilized in the study will not be analyzed and are not discussed in this SAP.

1.2. Study Objectives

1.2.1. Primary Objectives

Cohort 1 (≥ 18 Years, Not Pregnant at Randomization)

- The primary objective of phase 3 is to evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo, as measured by COVID-19-related hospitalizations or all-cause death.

Cohort 2 (< 18 Years, Not Pregnant at Randomization)

- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo
- To further characterize the concentrations of REGN10933 and REGN10987 in serum over time

Cohort 3 (Pregnant at Randomization)

- To evaluate the safety and tolerability of REGN10933+REGN10987

1.2.2. Secondary Objectives

The secondary objectives of the phase 3 are:

Cohort 1

- To evaluate the impact of REGN10933+REGN10987 on the resolution of self-reported COVID-19 symptoms compared to placebo
- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo using various measures of COVID-19-related medically-attended visits, including COVID-19-related hospitalizations, emergency room visits, or all-cause death
- To describe the virologic effects of REGN10933+REGN10987 compared to placebo

- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo
- To further characterize the concentrations of REGN10933 and REGN10987 in serum over time
- To assess the immunogenicity of REGN10933 and REGN10987

Cohort 2

- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo using various measures of COVID-19-related medically-attended visits, including COVID-19-related hospitalizations or all-cause death
- To describe the virologic effects of REGN10933+REGN10987 compared to placebo
- To assess the immunogenicity of REGN10933 and REGN10987

Cohort 3

- To characterize 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 phase 3 are:

- To evaluate viral variants at baseline and post-treatment
- To explore the potential association of baseline humoral immune response to SARS-CoV-2 on response to REGN10933+REGN10987
- To evaluate the effects of REGN10933+REGN10987 compared to placebo on generation of a humoral immune response to SARS-CoV-2 (as measured by anti-SARS-CoV-2 N protein)
- To explore the effects of REGN10933+REGN10987 on measures of SARS-CoV-2 infectivity as assessed in experimental laboratory assays
- To explore biomarkers predictive of REGN10933+REGN10987 safety, efficacy, and/or disease progression and COVID-19 clinical outcomes
- To explore the underlying mechanisms of action and biology of REGN10933+REGN10987, SARS-CoV-2, and COVID-19
- To explore relationships between REGN10933+REGN10987 exposure and selected efficacy endpoints, safety endpoints, and/or biomarkers
- To evaluate the impact on self-reported symptoms of REGN10933+REGN10987 compared to placebo
- To assess the clinical efficacy of different dose levels of REGN10933+REGN10987, as measured by COVID-19-related hospitalizations or all-cause death

- To describe the relationship between virologic effects of REGN10933+REGN10987 and risk of COVID-19-related medically-attended visit or all-cause death
- To evaluate the effects of REGN10933+REGN10987 compared to placebo on the generation of endogenous humoral and/or cellular immune responses to SARS-CoV-2 (optional sub-study) (cohort 1)
- To evaluate the impact of REGN10933+REGN10987 on the resolution of self-reported COVID-19 symptoms compared to placebo (cohort 2 age ≥12 years)
- To describe the clinical outcomes of patients treated with REGN10933+REGN10987 using various measures of COVID-19-related medically-attended visits, including COVID-19-related hospitalizations or all-cause death (cohort 3)

1.2.4. Modifications from the Statistical Section in the Final Protocol

There is no modification from the statistical section in the protocol amendment 8.

1.2.5. Revision History for SAP Amendments

None.

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This is an adaptive, phase 1/2/3, randomized, double-blinded, placebo-controlled study to evaluate the efficacy, safety, and tolerability of REGN10933+REGN10987 combination therapy in ambulatory patients (ie, outpatients) with early-stage COVID-19.

In phase 1, only symptomatic patients with COVID-19 were enrolled. In phase 2, symptomatic patients and asymptomatic patients were enrolled into separate cohorts. In phase 3, only symptomatic patients are enrolled. The phase 3 patients are enrolled into the following cohorts.

- cohort 1 (≥ 18 years of age, not pregnant at randomization),
- cohort 2 (< 18 years of age, not pregnant at randomization) and
- cohort 3 (pregnant at randomization).

Cohort 1

Prior to protocol amendment 6, patients were randomized in a 1:1:1 allocation ratio to one of the treatments listed below:

- Co-administered REGN10933+REGN10987 combination therapy, 2400 mg (1200 mg each of REGN10933 and REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy, 8000 mg (4000 mg each of REGN10933 and REGN10987) IV single dose
- Placebo IV single dose

Randomization was stratified by:

- Presence/absence of COVID-19 symptoms (ie, symptomatic versus asymptomatic cohort). Any asymptomatic patient enrolled are considered to be part of phase 2.
- Country
- Risk factors for severe COVID-19 (no risk factors for severe COVID 19 versus ≥1 risk factor for severe COVID-19).

Starting with Protocol Amendment 6, patients were randomized in a 1:1:1 allocation ratio to one of the treatments listed below, according to a central randomization scheme using an interactive web response system (IWRS) and randomization was stratified by country. The stratification factors for presence/absence of COVID-19 symptoms and risk factors for hospitalization due to COVID-19 were removed because asymptomatic patients and those without risk factors were no longer eligible for the study:

- Co-administered REGN10933+REGN10987 combination therapy, 1200 mg (600 mg each of REGN10933 and REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy, 2400 mg (1200 mg each of REGN10933 and REGN10987) IV single dose
- Placebo IV single dose

Starting with protocol amendment 8, cohort 1 will be randomized 1:1 to a single dose of REGN10933+REGN10987 1200 mg IV or REGN10933+REGN10987 2400 mg IV and randomization stratified by country. Patients in this cohort will no longer be randomized to placebo.

Cohort 2

Starting with Protocol Amendment 6, pediatric patients were enrolled into cohort 2, randomized in a 1:1:1 allocation ratio to a single IV dose of REGN10933+REGN10987 at a lower dose level, at a higher dose level, or to placebo, where the exact dose was tiered according to body weight to match REGN10933+REGN10987 2400 mg or REGN10933+REGN10987 1200 mg, as defined in Table 1.

Starting with protocol amendment 8, cohort 2 will be randomized 1:1 to a single IV dose of REGN10933+REGN10987 high dose or REGN10933+REGN10987 low dose, as defined in Table 1. Patients in this cohort will no longer be randomized to placebo.

Table 1: REGN10933+REGN10987 IV Doses for Each Weight Group, Phase 3 Cohort 2 (Ages 0 to <18 Years)

Body Weight Group	Dose Equivalent for REGN10933+REGN10987 1200 mg IV Dose (600 mg per mAb)	Dose Equivalent for REGN10933+REGN10987 2400 mg IV Dose (1200 mg per mAb)
≥40 kg	1200 mg (600 mg per mAb)	2400 mg (1200 mg per mAb)
≥20 kg to <40 kg	450 mg (225 mg per mAb)	900 mg (450 mg per mAb)
≥10 kg to <20 kg	224 mg (112 mg per mAb)	450 mg (225 mg per mAb)
≥5 kg to <10 kg	120 mg (60 mg per mAb)	240 mg (120 mg per mAb)
≥2.5 kg to <5 kg	60 mg (30 mg per mAb)	120 mg (60 mg per mAb)
<2.5 kg	30 mg (15 mg per mAb)	60 mg (30 mg per mAb)

In phase 3 cohort 2, randomization will be stratified by country

Cohort 3

Patients in cohort 3 will be randomized in a 1:1 allocation ratio to co-administered REGN10933+REGN10987 combination therapy IV single dose (no placebo). Patients in cohort 3 who are ≥18 years of age will follow the REGN10933+REGN10987 dose levels described for cohort 1 (1200 mg and 2400 mg). Patients in cohort 3 who are <18 years of age will follow the adjusted REGN10933+REGN10987 dose levels described in Table 1.

In phase 3, cohort 3, randomization will not be stratified.

The study design schematic before protocol amendment 8 is presented in Figure 1 and Figure 2.

Figure 1: Study Flow Diagram, Phase 3 (Cohort 1 Patients; Cohort 3 Patients ≥18 Years)

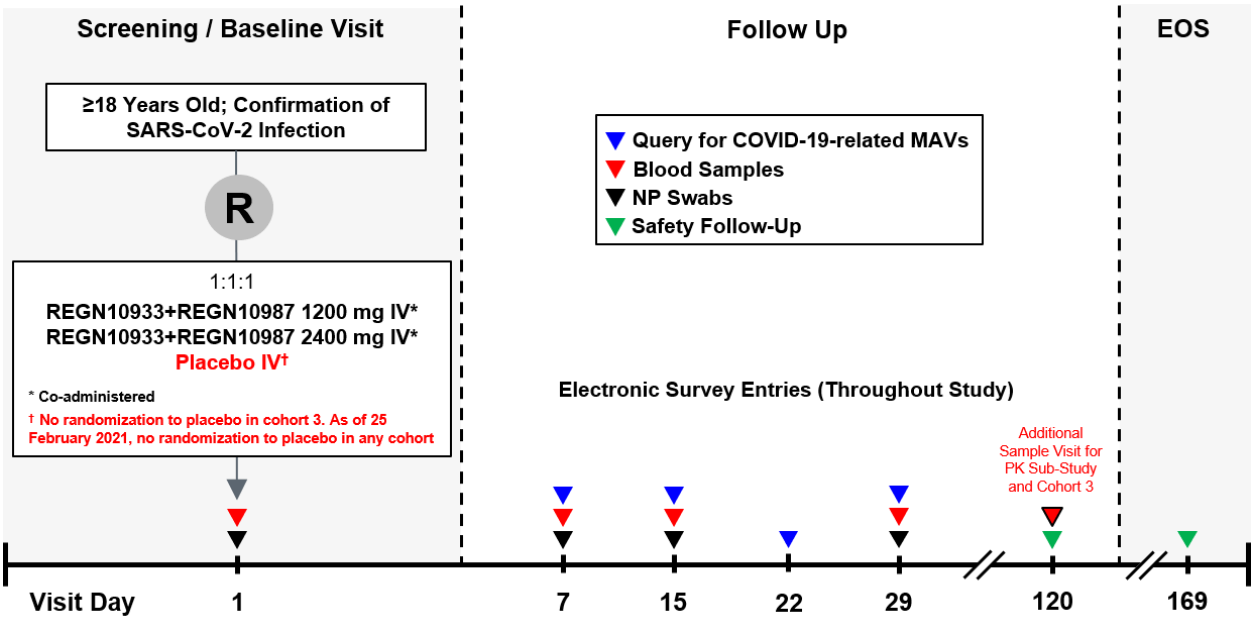
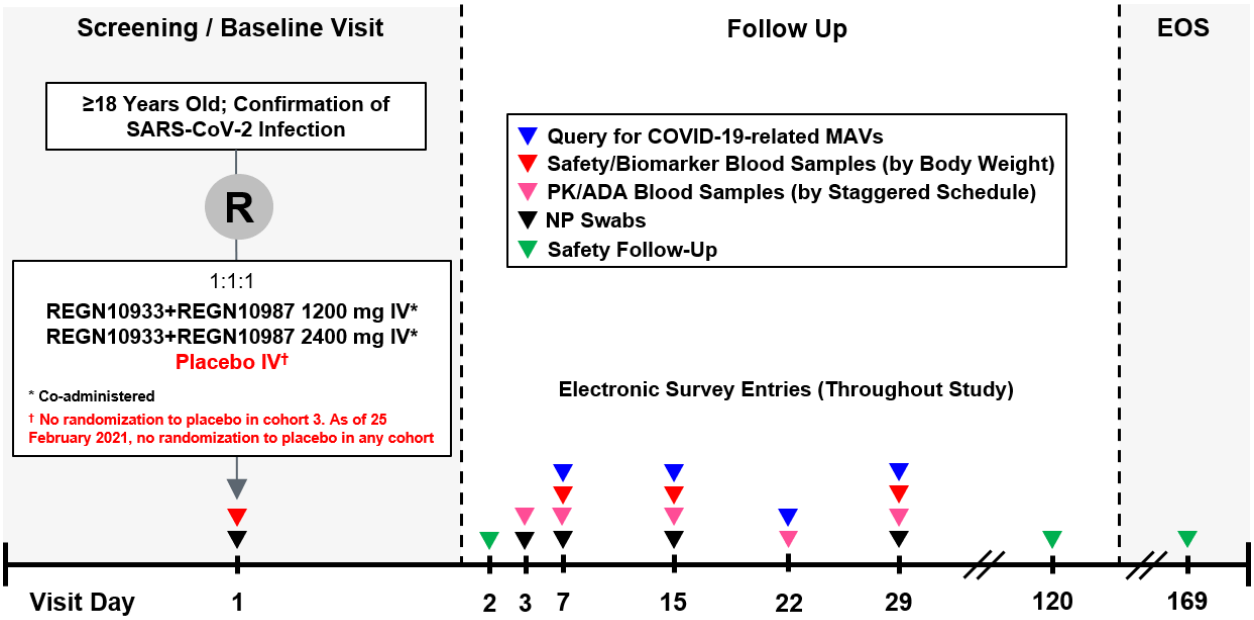


Figure 2: Study Flow Diagram, Phase 3 (Cohort 2 Patients; Cohort 3 Patients <18 Years)



2.2. Sample Size and Power Considerations for Phase 3

The phase 3 sample size of the study is based on having sufficient power to analyze the primary endpoint of proportion of patients with a COVID-19-related hospitalization or all-cause death in the modified full analysis set (mFAS). Based on data from the phase 2 analysis involving the first 799 symptomatic patients enrolled and blinded phase 3 data, the sponsor assumes an event rate of 3.4% for COVID-19-related hospitalization or all-cause death among patients on placebo in the mFAS (patients with at least 1 risk factor for severe COVID-19 and a positive SARS-CoV-2 RT-qPCR test at baseline), and that 83% of all randomized patients (FAS) will have a positive SARS-CoV-2 RT-qPCR test at baseline.

The following table presents estimated number of randomized patients with at least 1 risk factor for severe COVID-19 at each analysis time point for cohort 1 efficacy analysis.

Table 2: Estimated sample sizes at each analysis time point for Phase 3 patients with at least 1 risk factor for severe COVID-19

	Placebo FAS[1] (mFAS)	1200 mg FAS[1] (mFAS)	2400 mg FAS[1] (mFAS)	8000 mg FAS[1] (mFAS)	Total FAS[1] (mFAS)
Pre-Amendment 6 patients	662 (550)	Not applicable	662 (550)	662 (550)	1986 (1650)
Amendment 6/7 patients randomized by 17 January 2021	841 (698)	841 (698)	841 (698)	Not applicable	2523 (2094)
Final analysis for 2400 mg vs. placebo (patients randomized by 17 January 2021)	1503 (1248)		1503 (1248)		
Interim analysis for 1200 mg vs. placebo (patients randomized by 17 January 2021)	841 (698)	841 (698)			
Amendment 6/7 patients randomized by 24 February 2021	1352 (1122)	1352 (1122)	1352 (1122)	Not applicable	4056 (3366)
Final analysis for 1200 mg vs. placebo (patients randomized by 24 February 2021)	1352 (1122)	1352 (1122)			

[1] FAS estimates only include those in FAS with ≥1 risk factor for severe COVID-19.

The final primary efficacy analysis for the 2400 mg dose group versus placebo comparison will be performed based on patients randomized on or before 17 January 2021, which includes approximately 1503 randomized patients with COVID-19 risk factors per group in the 2400 mg dose group and the placebo group (1248 per group in mFAS). The study will have approximately 76% power to detect a significant treatment effect in the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death in mFAS at a 2-sided α of 0.05, assuming 3.4% of

patients in the placebo group and 1.7% of patients in the 2400 mg group have an event (ie, a 50% reduction with R10933+R10987 treatment). If there is a greater treatment difference, such as a 60% reduction, the study will have at least 90% power to detect a significant treatment effect in the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death.

The final efficacy analysis of the 1200 mg dose group versus placebo comparison will be performed in approximately 1352 patients with COVID-19 risk factors per dose group (approximately 1122 per dose group estimated in mFAS), representing the cohort of patients enrolled starting in Protocol Amendment 6 (i.e., when the 1200 mg dose was introduced) through February 24, 2021, the last date that enrollment into the placebo group was allowed. This analysis will only include patients who were concurrently randomized to either the 1200 mg dose group or the placebo group. The study will have approximately 72% power to detect a significant treatment effect in the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death in the mFAS at a 2-sided α of 0.05 assuming 3.4% of patients in the placebo group and 1.7% of patient in the 1200 mg group have an event (i.e., a 50% reduction). If there is a greater treatment difference, such as a 60% reduction, the study will have approximately 88% power to detect a significant treatment effect in the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death.

From 25 February 2021 onward, the Sponsor plans to randomize up to approximately 1500 patients 1:1 to either the 1200 mg dose group or the 2400 mg dose group in addition to the patients enrolled under Amendment 6 or 7, to have adequate precision to estimate the difference in the proportion of patients with a COVID-19-related hospitalization or death between the 2 dose groups. For example, assuming an event rate of 1.7% in each group, with a total of approximately 2100 concurrently randomized patients per arm (1744 per arm in mFAS) in 1200 mg and 2400 mg dose groups, a 2-sided 95% confidence interval for the difference will extend approximately 1% from the observed difference. Blinded sample size reestimation may be performed based on the pooled observed event rates.

The EAST v6.0 software was used for sample size calculation.

Phase 3 Cohort 2 and Cohort 3

Up to approximately 180 pediatric patients in cohort 2 is planned with a goal of approximately 52 patients exposed to each dose of study drug, which is considered adequate to describe the drug concentrations over time. In cohort 2, there will be an enrollment of approximately 20 patients <10 kg (10 per treatment group) and 20 patients between ≥10 kg and <40 kg (10 per treatment group).

In cohort 3, no minimum or maximum enrollment is planned.

Cohorts 2 and 3 will be analyzed descriptively for safety, and may be analyzed descriptively for clinical and virologic outcomes.

Note that cohort 2 and cohort 3 may continue to enroll after enrollment of cohort 1 has been completed.

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference for 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 analyses in the phase 1/2 portion of this study.

3.1. Efficacy Analysis Sets

Cohort 1

All symptomatic patients from the 800th randomized symptomatic patient will be included in the phase 3 portion of the study. The full analysis set (FAS) includes all randomized patients in phase 3 cohort 1, including those with or without risk factors for severe COVID-19, and is based on the treatment allocated (as randomized).

The modified full analysis set (mFAS) for phase 3 includes all randomized patients with a positive central lab-determined RT-qPCR test from nasopharyngeal (NP) swab samples at randomization, and *with at least one risk factor for severe COVID-19 at baseline*. If pre-dose virologic results from the qualitative test are missing, then results from post-dose sample may be used to determine the qualitative PCR status at baseline, as long as the sample was collected within 2 hours after starting the study drug infusion. The mFAS is based on the treatment allocated (as randomized). The seronegative mFAS is defined as all randomized patients with documented seronegative status (eg, SARS-CoV-2 serum antibody negative) at baseline in the mFAS.

Both mFAS and FAS will be used for the summaries of demographic and baseline characteristics. The mFAS will be used for the analysis of clinical, symptoms, and virologic endpoints. The seronegative mFAS will be used for the analysis of certain virologic endpoints and in analyses of certain clinical endpoints. Data from patients with no risk factors will be summarized descriptively.

For the analyses of 1200 mg group comparing to placebo, only patients concurrently randomized (ie, after Protocol Amendment 6 is implemented) will be included.

Cohort 2

The FAS includes all randomized patients in phase 3 cohort 2 and is based on the treatment allocated (as randomized). The modified full analysis set (mFAS) includes all randomized patients with positive RT-qPCR in NP swab samples at randomization and is based on the treatment allocated (as randomized). If pre-dose results from the qualitative test are missing, then results from post-dose sample may be used to determine the qualitative PCR status at baseline, as long as the sample was collected within 2 hours after starting the study drug infusion. The seronegative mFAS is defined as all randomized patients with documented seronegative status at baseline in the mFAS.

Cohort 3

Data on all patients in Cohort 3 (pregnant population) will be utilized in the analyses.

3.2. Safety (SAF) 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.

3.3. Pharmacokinetics Analysis Sets

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

3.4. Immunogenicity Analysis Sets

The immunogenicity analysis set is dependent on assay availability.

The anti-drug antibody (ADA) analysis set (AAS) includes all subjects who received any study drug (safety population) and had at least one non-missing ADA result from the ADA assay after first dose of the study drug(s). Subjects will be analyzed according to the treatment actually received.

Samples positive in the ADA assay will be characterized further for ADA titers and for the presence of neutralizing antibody (Nab). The NAb analysis set (NAS) includes all patients who received any study drug and who are either negative in the ADA assay or positive for ADA with at least one non-missing result in the NAb assay after first dose of the study drug. Subjects who are negative for ADA are set to negative in the NAb analysis set

Subjects will be analyzed according to the treatment actually received.

4. ANALYSIS VARIABLES

4.1. Demographics and Baseline Characteristics

Demographic and baseline characteristic variables include the following:

- Age at screening (years)
- Age group (<18, 18 to <65, ≥50, ≥65, ≥75)
- Sex (Male, Female)
- Race (Asian, American Indian/Alaska Native, Black/African American, Native Hawaiian/Other Pacific Islander, White and Other)
- Ethnicity (Hispanic or Latino, Not-Hispanic or Latino)
- Baseline Weight (kg)
- Baseline Height (cm)
- Baseline Body mass index (BMI) (kg/m^2) calculated from weight and height
- Obesity (not obese, BMI <=30 kg/m^2; obese, BMI >30 kg/m^2)
- Risk factor for severe COVID-19, per CRF (no risk factor, ≥1 risk factor)
- Baseline SARS-CoV-2 results from central lab (excluding assessment at screening visit)
- Baseline viral load based on RT-qPCR result (copies/mL as well as log10 copies/mL)
- Baseline viral load categories (>10^7, >10^6, >10^5, etc. copies/mL)
- Baseline qualitative RT-PCR results (positive, negative, other)
- Baseline serostatus (positive, negative, other)

  A patient's serostatus is considered to be positive if any anti-SARS-CoV-2 antibody test (eg, anti-SARS-CoV-2 IgA or IgG) is positive, negative if all available tests are negative, and other if serostatus is not positive or negative (eg, borderline result) or is unknown.
- Baseline C-Reactive Protein (mg/L)
- Time from onset of first COVD-19-related symptom, as determined by the investigator, to randomization (days)

4.2. Medical History

Medical history will include the following:

- COVID-19 with start date as the date of onset of first symptom related to COVID-19
- Risk factors for severe COVID-19/hospitalization due to COVID-19 as defined below
- Whether the patient is receiving oxygen at home by nasal cannula

- Pregnancy or breastfeeding status, if applicable

Risk factors for severe COVID-19 are defined as follows:

a. Age ≥50 years (cohort 1 only)
b. Obesity, defined as:
   BMI ≥30 kg/m^2 **(cohort 1 only)**
   BMI (kg/m2) ≥95th percentile for age and sex based on CDC growth charts **(cohort 2 ≥2 years only)**
c. Cardiovascular disease, including hypertension
d. Chronic lung disease, including asthma
e. Type 1 or type 2 diabetes mellitus
f. Chronic kidney disease, including those on dialysis
g. Chronic liver disease
h. Pregnancy
i. Immunosuppressed, based on investigator's assessment
   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
j. Any underlying genetic condition, neurologic condition, metabolic condition, or congenital heart disease deemed by the investigator to be a risk factor for severe COVID-19 **(cohort 2 only)**

4.3. Prior / Concomitant Medications or Procedures

Medications/Procedures will be recorded from the day of informed consent until the final study assessment (Day 169 or early study discontinuation or death). Medications will be coded to the ATC level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to WHO Drug Dictionary (WHODD) version 202003 or later. Patients will be counted once in all ATC categories linked to the medication.

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

Concomitant medications/procedures are: medications taken or procedures performed following the first dose of study drug through the final study assessment (Day 169 or early study discontinuation or death). This includes medications taken that started before the study and are ongoing during the study.

Only select concomitant medications will be captured in this trial. The select list of medications include, but are not limited to, corticosteroids, remdesivir, lopinavir-ritonavir, chloroquine, hydroxychloroquine, interferon beta, and convalescent serum. In addition, any concomitant procedures used to treat an adverse event will be captured in this trial.

Analysis of medications data will be focused on the targeted medications (specified in the protocol) that are expected to be reviewed and recorded by sites.

4.4. Rescue Medication/or Prohibited Medication During Study

Patients can receive rescue therapy for COVID-19 per local standard-of-care. Rescue treatments are not provided as part of the study.

Patients are not permitted to receive any medication specified in the exclusion criteria (of the protocol) for study enrollment, unless medically indicated. Patients may otherwise continue their normal regimen of medications and procedures. All data collected on medications/procedures (pre-treatment and concomitant) will be summarized.

4.5. Efficacy Endpoints

4.5.1. Primary Efficacy Endpoint

Cohort 1

The primary clinical efficacy endpoint for phase 3 is the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29.

4.5.2. Secondary Efficacy Endpoints

The secondary endpoints for phase 3 are:

Cohort 1

The key secondary endpoints for phase 3 are

- Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death from day 4 through day 29
- Time to COVID-19 symptoms resolution.

The other secondary efficacy endpoints for phase 3 are:

- Proportion of patients with ≥1 COVID-19-related hospitalization, emergency room (ER) visit, or all-cause death through day 29
- Proportion of patients with ≥1 COVID-19-related medically-attended visit or all-cause death through day 29
- Proportion of patients with COVID-19 related medically-attended visits by type of visit(s) (hospitalization, ER visit, urgent care, and/or physician's office/telemedicine visit) through day 29
- Proportion of patients with ≥2 COVID-19 related medically-attended visits through day 29
- Cumulative incidence of ≥1 COVID-19-related hospitalization or all-cause death through day 29
- Cumulative incidence of COVID-19-related hospitalizations or ER visits through day 29

- Cumulative incidence of patients with ≥1 COVID-19-related medically-attended visit or all-cause death through day 29
- Days of hospitalization due to COVID-19
- Proportion of patients admitted to an ICU due to COVID-19 by day 29
- Proportion of patients requiring supplemental oxygen due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29
- Total number of COVID-19-related medically-attended visits through day 29
- Time to all-cause death
- All-cause death by day 29, day 120, and day 169
- Time-weighted average 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 (patients enrolled prior to protocol amendment 6 only)
- Change from baseline in viral load at each visit, as measured by RT-qPCR in NP samples

Cohort 2

The secondary endpoints for phase 3 are:

- Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29
- Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death from day 4 through day 29
- Proportion of patients with ≥1 COVID-19-related hospitalization, ER visit, or all-cause death through day 29
- Proportion of patients with ≥1 COVID-19-related medically-attended visit or all-cause death through day 29
- Proportion of patients with ≥1 COVID-19-related medically-attended visit by type of visit(s) (hospitalization, ER visit, urgent care, and/or physician's office/telemedicine visit) through day 29
- Proportion of patients with ≥2 COVID-19-related medically-attended visits through day 29
- Cumulative incidence of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29
- Cumulative incidence of patients with ≥1 COVID-19-related hospitalization, ER visit, or all-cause death through day 29
- Cumulative incidence of patients with ≥1 COVID-19-related medically-attended visit or all-cause death through day 29

- Days of hospitalization due to COVID-19
- Proportion of patients admitted to an ICU due to COVID-19 by day 29
- Proportion of patients requiring supplemental oxygen due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29
- Total number of COVID-19-related medically-attended visits through day 29
- Time to all-cause death
- All-cause death by day 29, day 120, and day 169.
- Time-weighted average 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.
- Change from baseline in viral load at each visit, as measured by RT-qPCR in NP samples
- Immunogenicity, as measured by ADA and NAbs to REGN10933 and REGN10987

Cohort 3

The secondary endpoints for phase 3 are:

- Concentrations of REGN10933 and REGN10987 in serum over time
- Immunogenicity, as measured by anti-drug antibodies and neutralizing antibodies to REGN10933 and REGN10987

Endpoint definitions

Time to COVID-19 symptoms resolution will be defined as time from randomization to the first day during which the subject scored none on all symptoms except fatigue, headache, and cough, which can be mild/moderate or none. Patients with missing baseline assessment will not be included in the analysis.

Time-weighted average of change from baseline viral load in the nasopharyngeal (NP) swab samples from day 1 through day 7 will be calculated for each patient with intensive viral load data collection (ie, those randomized under protocol amendment 5 or earlier) using the linear trapezoidal rule as the area under the curve for change from baseline at each time point divided by the time interval for the observation period. Accompanying descriptive analyses will be provided at the individual timepoints used to calculate the TWA.

For example, the time-weighted average change from baseline in viral load in the nasopharyngeal (NP) swab samples till the last observation day t_k will be calculated using formula

$$TWA_{[0-k]} = [\sum_{i=1}^{k} (t_i - t_{i-1}) * (D_i + D_{i-1})/2]/(t_k - t_0)$$

Where

- *k=11* refers to 11 post-baseline assessments

- D_i is the change from baseline in viral load value (log10 copies/mL) obtained at time t_i, D_0 =0
- t_i is the time (day) for which D_i is measured, such as t_0 = 1 (day) for baseline and $\{t_i\}$ = 3, 5, 7, 9, 11, 13, 15, 18, 22, 25, 29, for i=1 to 11 where the postbaseline assessment is taken.
- If the D_i is not available per protocol or missing due to failed test or other reasons, only the time points with non-missing values will be included into the calculation. For example, we will calculate the TWA till day 7. In this case, data is not available at day 1, 2, 4, and 6 per the protocol schedule of events. Suppose the scheduled assessment result is missing at day 5 due to a failed test but non-missing at day 3 and day 7, then

$$TWA_{[0-7]} = [(t_3 - t_0) * (D_3 + D_0)/2 + (t_7 - t_3) * (D_7 + D_3)/2]/(t_7 - t_0)$$

Baseline is defined as the last non-missing value prior to the study drug infusion. Patients with missing baseline will be excluded from the analysis of virologic endpoints. Virologic data after start of study drug infusion will be used as post-baseline assessments.

4.5.3. Pharmacokinetics

- Concentrations of REGN10933 and REGN10987 in serum and select PK parameters

4.5.4. Immunogenicity

- Immunogenicity as measured by anti-drug antibodies (ADA) to REGN10933 and REGN10987

4.5.5. Exploratory Endpoints

Exploratory endpoints for phase 3 are:

- Viral load over time in patients with and without COVID-19-related medically-attended visits
- Change in WPAI+CIQ over time
- Change in EQ-5D-5L over time
- Time to COVID-19 symptoms resolution (cohort 2 ages ≥12 years)

4.6. Safety Variables

Safety endpoints

- 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 hypersensitivity reactions (grade ≥2) through day 29

4.6.1. Adverse Events and Serious Adverse Events

Serious adverse events and AESIs will be collected according to the Schedule of Events (Section 10.1). All adverse events are to be coded to a "Preferred Term (PT)" and associated primary "System Organ Class (SOC)" according to the Medical Dictionary for Regulatory Activities (MedDRA version 23.0 or later).

Infusion reactions are defined as any relevant AE that occurs during the infusion or up to day 4.

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.

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 (Division of Cancer Treatment and Diagnosis [DCTD], 2020).

Treatment-emergent SAEs or AESIs not listed in the NCI-CTCAE will be graded according to the scale in Table 3.

Table 3: NCI-CTCAE Severity Grading System for Adverse Events

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)*
3	Severe	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL†
4	Life-threatening	Life threatening consequences; urgent intervention indicated
5	Death	Death related to adverse events

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

4.6.2. Adverse Events of Special Interest

Adverse events of special interest (AESI) are AEs (serious or non-serious) of scientific and medical interest specific to this drug program, for which ongoing monitoring and rapid communication by the investigator to the sponsor will be appropriate.

Treatment-emergent adverse events of special interest for this study are grade ≥2 hypersensitivity and grade ≥2 infusion-related reactions and any treatment-emergent adverse event that led to a medically-attended visit (phase 3 only), regardless of whether the visit is related to COVID-19.

4.6.3. Laboratory Safety Variables

The clinical laboratory data consists of blood chemistry (including C-Reactive Protein, liver function tests, creatinine and other), hematology, urinalysis, infection testing, SARS-CoV-2 RT-PCR and other (as specified in the protocol).

Clinical laboratory values will be converted to standard international (SI) units and grouped by function in summary tables. Conventional unit may be provided. Functions are defined as follows:

- Liver function including ALT, AST, alkaline phosphatase, total bilirubin,
- Renal function including creatinine, uric acid,
- Electrolytes including sodium, potassium,
- C-Reactive Protein (CRP),
- Creatine Phosphokinase (CPK)
- Metabolic parameters including total proteins, albumin,
- White blood cells (WBCs) including WBCs count and differential count (neutrophils, lymphocytes, eosinophils, basophils, monocytes),
- Red blood cells (RBCs) and platelets including red blood cells count, hemoglobin, hematocrit and platelets count,
- Coagulation parameters including INR, PT, aPTT
- Other

4.6.4. Vital Signs

Vital signs, including temperature, blood pressure, heart rate, and SpO2 are recorded at multiple time points according to Schedule of Time and Events table (See Section 10.1).

4.7. Pharmacokinetic Variables

The PK variables are the concentrations of REGN10933 andREGN10987 in serum and time when a sample was collected as specified in the Schedule of Events table (please refer to table 10.1 in the appendix). (See Section 10.1).

4.8. Pharmacodynamic and Other Biomarker Variables

Exploratory biomarker variables may be reported outside of the clinical study report (CSR).

4.9. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, NAb status, and time-point/visit. Samples will be collected at the visits as specified in Section 10.1.

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 (SD), Q1, median, Q3, minimum, and maximum.

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

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics variables given in Section 4.1 will be summarized descriptively by treatment group, and all groups combined using full analysis set (FAS), mFAS and safety set for each cohort.

5.2. Medical History

Medical history will be summarized by SOC and PT and by treatment group and all groups combined using FAS for each cohort.

5.3. Prior / Concomitant Medications or Procedures

Prior or concomitant medications/procedures will be summarized by treatment groups using FAS for each cohort. Summaries will present patient counts (and percentages) for all medications, dictionary coded by WHODRUG, by decreasing frequency of the overall group incidence (or high dose group incidence in tables where the overall is not presented) of ATC followed by ATC level 2, ATC level 4 and preferred term. Focus of the results will be on the list of targeted medications (Section 4.3).

5.4. Prohibited Medications

Number and percentage of patients with prohibited medications will be summarized by treatment groups in the FAS population for each cohort, similar to the concomitant medications.

5.5. Subject Disposition

The following will be provided using FAS and mFAS for each cohort:

- The total number of screened patients: 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 summary of analysis sets including FAS, mFAS, SAF, PK, immunogenicity (ADA), and exploratory biomarkers (Section 3).

5.6. Extent of Study Treatment Exposure and Compliance

5.6.1. Measurement of Compliance

Proportion of patients with fully completed infusions of study drug will be reported as the treatment compliance since the patients will only receive one infusion during the study. Treatment compliance and proportion of patients with infusion interruptions will be summarized by treatment group using descriptive statistics based on the SAF population for each cohort.

5.6.2. Exposure to Investigational Product

Exposure to study drug will be examined for each patient as recorded on the Study Drug Administration-IV CRF. The following variables will be analyzed by treatment group:

- Duration of intravenous infusion
- Total volume of drug administered (units: mL)
- Number of patients with total planned dose administered (yes/no)

  If no, reason for not administration of total planned dose (equipment failure, adverse event, other)
- Number of patients with infusion interruptions

The number and percentage of patients randomized and exposed to double-blind study drug will be presented for each treatment group.

5.7. Analyses of Efficacy Variables

5.7.1. Analysis of Primary Efficacy Variables

Cohort 1

The primary efficacy analysis for the clinical endpoint, proportion of patients with COVID-19-related hospitalization or all-cause death through day 29, will be performed based on the mFAS.

The analyses of proportion of patients with COVID-19-related hospitalization or all-cause death through day 29 will be performed for the following null and alternative statistical hypotheses:

- H_0: The risk of having COVID-19-related hospitalization or all-cause death through day 29 for REGN10933+REGN10987 2400 mg group is the same as that for placebo
- H_1: The risk of having COVID-19-related hospitalization or all-cause death through day 29 for REGN10933+REGN10987 2400 mg group is not the same as that for placebo

The proportion of patients with COVID-19-related hospitalization or all-cause death through day 29 will be compared between each dose group and placebo using the stratified Cochran-Mantel-Haenszel (CMH) test with country as a stratification factor. P-values from the stratified CMH test and 95% confidence intervals for the risk ratio and relative risk reduction (1-risk ratio) using Farrington-Manning method will be presented. Exact method for p-values and confidence intervals

will be used if the expected frequencies in all cells are not at least 5. As key secondary analyses, the same analyses will be performed for the proportion of patients with COVID-19-related hospitalization or all-cause death through day 29 for patients with high baseline viral load (>10^6 copies/mL) in the mFAS and for seronegative mFAS, and for proportion of patients with a COVID-19-related hospitalization or all-cause death from day 4 through day 29 in the mFAS. The comparison of 1200 mg dose group to placebo will include only the subset of placebo patients concurrently randomized with 1200 mg dose group. Sensitivity analyses will be performed using FAS. Additional subgroup analysis will also be performed by baseline serostatus (negative, positive, other) and by baseline viral load categories (>10^4 copies/mL, >10^5 copies/mL, >10^6 copies/mL, >10^7 copies/mL).

5.7.2. Analysis of Secondary Efficacy Variables

Patient-reported symptoms endpoint

Cohort 1

Time to symptoms resolution of COVID-19 symptoms (Fever, Sore throat, Cough, Shortness of breath/difficulty breathing, Chills, Nausea, Diarrhea, Headache, Red/watery eyes, Body aches such as muscle pain, Loss of taste/smell, Fatigue, Loss of appetite, Dizziness, Pressure/tightness in chest, Chest pain, Stomach ache, Runny nose, Sputum/phlegm) will be analyzed using the stratified log-rank test with randomization strata as stratification factor. The analyses will be performed for mFAS. Estimates of median times and associated 95% confidence intervals using the Kaplan-Meier method will be reported. The hazard ratio and its 95% CI for time to symptoms resolution of COVID-19 symptoms endpoint will be estimated by the Cox regression model with terms for treatment group, randomization strata. P-value from the stratified log-rank test will be reported. Subgroup analyses may be performed among patients with more than one risk factor, with high baseline viral load, or who are seronegative at baseline.

Patients who do not experience resolution of symptoms will be censored at the last observation time point. Patients who died or had COVID-19-related hospitalization prior to day 29 will be censored at day 29. Patients with a baseline raw score ≤3 will be censored at day 0. Patients with missing baseline assessment will not be included in the analysis.

Clinical endpoints

Cohort 1

The proportion endpoints, such as proportions of patients with a COVID-19-related hospitalization/ER or all-cause death and proportion of patients with a COVID-related MAV or all-cause death, will be compared between each dose group and placebo using stratified Cochran-Mantel-Haenszel (CMH) test with country as a stratification factor. P-values from the stratified CMH test and 95% confidence intervals for risk ratio and relative risk reduction (1-risk ratio) using Farrington-Manning method will be presented. Exact method for p-values and confidence intervals will be used if the expected frequencies in all cells are not at least 5. The analyses will be performed based on observed data for the mFAS, seronegative mFAS, and FAS. Similar analysis will be performed for the proportion of patients with COVID-19-related hospitalization or ER or urgent care visits as well as proportions of patients with each type of COVID-19-related MAVs. Risk difference and its 95% confidence interval based on stratified Newcombe method for the

proportion endpoints between 1200 mg and 2400 mg dose groups will calculated based on patients concurrently randomized, i.e., under Amendment 6, 7 or 8, for the mFAS.

Analyses will be performed for the cumulative incidence of patients having a COVID-19-related hospitalization or all-cause death through day 29 based on the time to first COVID-19-related hospitalization or all-cause death using the stratified log-rank test with randomization strata (country) as stratification factor for mFAS. Estimates of cumulative event rate at different time points and associated 95% confidence intervals using the Kaplan-Meier method will be reported. The hazard ratio and its 95% CI for patients having event will be estimated by the Cox regression model with terms for treatment group (2400 mg dose groups versus placebo), and randomization strata. The p-value from the stratified log-rank test for risk of having events will be reported. Similar analysis will be performed comparing 1200 mg dose group to placebo including only the subset of patients concurrently randomized. A patient who has no COVID-19-related hospitalization will be censored at last known date of contact up to day 29. A patient who dies on or before day 29 will be considered as having an event at the date of death. A patient with multiple COVID-19 related hospitalization visits and/or who dies will be counted as having one event with time computed at the first event.

Similar secondary analyses will be performed for cumulative incidence of patients having a COVID-19-related hospitalization, ER visit, or all-cause death and cumulative incidence of patients having a COVID-19-related MAV or all cause death through day 29 for the mFAS.

Additional landmark analysis for time to event endpoint such as cumulative incidence of hospitalization or death may be performed if the proportional hazard assumption is considered not valid.

Sensitivity analyses will be performed using FAS.

Additional analyses will be performed to examine the relationship between viral load and COVID-19-related MAVs in patients who underwent an intensive sampling schedule. Viral load over time will be compared between patients with and without a COVID-19-related MAV.

Cohort 2 and 3

Proportion of patients with COVID-19-related hospitalization or ER or urgent care visits or all-cause death as well as proportions of patients with each type of MAVs for cohort 1 patients with no risk factor, cohort 2 and 3 will be descriptively summarized.

Virologic endpoints

Cohort 1

For phase 3, virologic analyses will be descriptive.

To 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 mFAS will be analyzed using a mixed-effect model for repeated measures (MMRM) with terms for baseline viral load, baseline serostatus, country, treatment, visit, treatment by baseline viral load interaction, baseline viral load 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 treatment arm and placebo will be provided along with the corresponding standard error, p-value, and associated 95% confidence interval. Subgroup analysis of the change from baseline in viral load at each visit will also be performed by baseline serostatus (negative, positive, other) and by baseline viral load categories (>10^4 copies/mL, >10^5 copies/mL, >10^6 copies/mL, >10^7 copies/mL).

The time-weighted average change from baseline in viral load (log10 copies/mL) from day 1 to post-baseline visit timepoints will be analyzed using the same method as the phase 2 primary virologic endpoint (see Phase 2 primary anlysis SAP) based on mFAS for seronegative patients and seropositive patients separately. This analysis will only be performed for patients randomized prior to amendment 6. The variable is analyzed using an Analysis of Covariance (ANCOVA) model with treatment group and country as fixed effects and baseline viral load and treatment by baseline viral load interaction as covariates. Similar analysis will be performed for mFAS with baseline serostatus as an additional term to the ANCOVA model. The least squares means estimates for the time-weighted average mean change from baseline in viral load for each treatment group, as well as the difference comparing each anti-spike mAb treatment arm versus placebo, will be presented along with the corresponding p-value, standard error, and associated 95% confidence interval. Subgroup analysis of the TWA change from baseline in viral load at each visit will also be performed by baseline viral load categories (>10^4 copies/mL, >10^5 copies/mL, >10^6 copies/mL, >10^7 copies/mL).

Proportion endpoints based on observed virologic data will be compared between groups using similar method as the proportion clinical endpoints based on mFAS.

Cohort 2 and 3

Virologic data for cohort 1 patients with no risk factor, cohort 2 and 3 will be summarized descriptively.

5.7.3. Adjustment for Multiple Comparisons

Cohort 1

The analysis of the primary endpoint (proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29) and key secondary endpoint (time to symptom resolution) will be conducted at the overall $\alpha = 0.05$. The endpoints will be tested hierarchically in the following order, adjusting for interim analysis.

Table 4: Hierarchical testing order

Hierarchy Number	Description
1	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS for REGN10933+REGN10987 2400 mg group versus placebo
2	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS for REGN10933+REGN10987 1200 mg group versus placebo
3	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS patients with baseline viral load $>10^6$ copies/mL for REGN10933+REGN10987 2400 mg group versus placebo
4	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS patients who are seronegative at baseline for REGN10933+REGN10987 2400 mg group versus placebo
5	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS patients with baseline viral load $>10^6$ copies/mL for REGN10933+REGN10987 1200 mg group versus placebo
6	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS patients who are seronegative at baseline for REGN10933+REGN10987 1200 mg group versus placebo
7	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death from day 4 through day 29 in the mFAS for REGN10933+REGN10987 2400 mg group versus placebo
8	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death from day 4 through day 29 in the mFAS for REGN10933+REGN10987 1200 mg group versus placebo
9	Time to COVID-19 symptoms resolution in the mFAS for REGN10933+REGN10987 2400 mg group versus placebo
10	Time to COVID-19 symptoms resolution in the mFAS for REGN10933+REGN10987 1200 mg group versus placebo

The final analysis of the primary efficacy endpoint, i.e., proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 for the 2400 mg group versus placebo comparison will be performed based on patients randomized on or before 17 January 2021 in the mFAS, at α level of 0.05.

If the 2400 mg group versus placebo comparison for the primary endpoint is positive, an interim analysis of the primary efficacy endpoint for the 1200 mg group versus placebo comparison (#2 in Table 4) will be performed at α level of 0.01 based on patients randomized on or before 17 January 2021 in the mFAS. If the comparison is positive, this analysis will be considered as the final analysis of the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 for the 1200 mg group versus placebo comparison. Final analysis of the primary and key endpoints for the comparisons 3 to 10 (Table 4) will be performed based on

patients randomized on or before 17 January 2021 in the mFAS in the hierarchical order above at α level of 0.05.

If the interim analysis of the primary efficacy endpoint for the 1200 mg group versus placebo comparison (#2 in Table 4) is negative at α level of 0.01, no tests will be performed for the primary and key endpoints for the comparisons 3 to 10 in Table 4 based on patients randomized on or before 17 January 2021. Final analysis of the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 for the 1200 mg group versus placebo comparison (#2 in Table 4) and other comparisons 3 to 10 will be performed based on all patients randomized on or before 24 February 2021 and tested hierarchically at an alpha level adjusted based on the information fraction at the interim analysis using Gamma family alpha spending function, e.g., at 0.047 level as illustrated in the example in Table 5. Additional details are provided in section 7.

Table 5 provides an example alpha spending boundary for the interim analysis and final analysis of the primary and key secondary endpoints. Under amendment 6 and 7, a total of 2524 patients were randomized to the 1200 mg, 2400 mg, and placebo groups on or before 17 January 2021 for the planned interim analysis, and 4056 patients were randomized on or before 24 February 2021 for the final analysis of 1200 mg versus placebo comparisons. With these sample sizes utilized in each analysis, the information fraction is approximately 62% (gamma=-4), assuming the proportions of RT-qPCR-positive patients in the FAS are the same at the interim and final analysis. The resulting overall alpha for the final analysis would then be 0.047 if the interim analysis is negative at 0.01 level.

Table 5: Example Alpha Spending Function for Analysis of Primary Endpoint

Information Time	Value	Overall α for Proportion Analysis = 0.05
62% of the mFAS patients completing day 29	α (2-sided)	0.01
Final analysis	α (2-sided)	0.047

Cohort 2 and 3

Analysis cohort 2 and cohort 3 will be descriptive. No multiplicity adjustment will be applied.

5.8. Analysis of Safety Data

The analysis of safety data will be performed on the SAF, as defined in Section 3.2.

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

Thresholds for Potential Clinically Significant Values (PCSV) in laboratory variables, vital signs and ECG are defined in Section 10.2.

The summary of safety results will be presented for each treatment group for each cohort.

5.8.1. Adverse Events

Definitions

For safety variables, 2 periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before study drug administration
- The observation period is defined as the time of study drug administration to the last study visit

Treatment-emergent SAEs and AESIs 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 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 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 hypersensitivity reactions (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 4.6.1), 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 (cohort 2 and cohort 3 <18 years only).

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

5.8.2. Clinical Laboratory Measurements

Laboratory measurements include clinical chemistry and hematology results, and will be converted to standard international units and US conventional units. Summaries of laboratory variables based on standard international units will include:

- Descriptive statistics of laboratory result and change from baseline to Day 29. Summary statistics will include the number of patients, mean, median, standard deviation, quartiles, minimum, and maximum.
- 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 parameters of interest.

Listing of all laboratory parameters normal range and abnormal flag by patient and visit will be provided.

5.8.3. Analysis of Vital Signs

Vital signs (including temperature, blood pressure, pulse, and respiration) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics. The graphs of mean (or median) value of some vital sign parameter vs. visit will also be plotted.

5.9. Analysis of Pharmacokinetics, Pharmacodynamics and Biomarker Data

5.9.1. Analysis of Drug Concentration Data

Cohort 1 PK Sub-study
The concentrations of REGN10933 and REGN10987 in serum over time will be summarized descriptively for each of the treatment groups.

Cohort 2 Pediatric Patients
The concentrations of REGN10933 and REGN10987 in serum over time will be summarized descriptively by body weight tier and treatment group.

Cohort 3 Pregnant Women
The concentrations of REGN10933 and REGN10987 in serum over time will be summarized descriptively for each of the treatment groups.

5.9.2. Analysis of Pharmacokinetics and Pharmacokinetics/Pharmacodynamics

Exposure-response analyses for virologic, other select efficacy and safety endpoints, and/or biomarkers may be performed, as appropriate.

5.10. Analysis of Immunogenicity Data

5.10.1. Analysis of ADA Data

Immunogenicity variables will be summarized using descriptive statistics.

Immunogenicity will be characterized by the ADA responses and titers observed in subjects in the ADA analysis set.

ADA response categories and titer categories are defined as follows:

ADA response categories:

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

Titer categories (Maximum titer values)

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

The following analysis will be provided:

- Number (n) and percent (%) of ADA-negative subjects (pre-existing immunoreactivity or negative in the ADA assays at all time points) by treatment arms

- Number (n) and percent (%) of treatment-emergent ADA positive subjects by treatment arms and ADA titer categories
  - Number (n) and percent (%) of persistent treatment-emergent ADA positive subjects
  - Number (n) and percent (%) of indeterminate treatment-emergent ADA positive subjects
  - Number (n) and percent (%) of transient treatment-emergent ADA positive subjects
- Number (n) and percent (%) of treatment-boosted ADA positive subjects by treatment arms and ADA titer categories

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

5.10.2. Analysis of NAb Data

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

5.11. Association of Immunogenicity with Exposure and Safety

5.11.1. 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, and titer on these profiles.

5.11.2. Immunogenicity and Safety

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

- Infusion reactions
- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylaxis (SMQ: Anaphylaxis [Narrow]).

6. DATA CONVENTIONS

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

6.1. Definition of Baseline for Efficacy/Safety Variables

Definitions of baseline for efficacy variables are defined in Section 4.5.

For safety variables, baseline will be the latest available valid measurement taken prior to the administration of study drug.

6.2. Data Handling Convention for Efficacy Variables

Not applicable.

6.3. Data Handling Convention for Missing Data

If pre-dose virologic results from the qualitative test are missing, then results from post-dose sample may be used to determine the qualitative PCR status at baseline, as long as the sample was collected 2 hours or less after starting study drug infusion.

For categorical variables, patients with missing data will be included in calculations of percentages. Number of patients with missing data will be presented.

Handling of Medications with missing/partial dates

To determine whether a medication is prior or concomitant medication, the missing medication start date is estimated as early as possible up to first dose date, and the missing medication end date is estimated as late as possible up to Day 29. If the medication start date is missing, the onset day will not be imputed in medication listings.

Handling of Adverse events Severity and Relatedness

If the intensity of a SAE, AESI and grade 3 or 4 AEs is missing, it will be classified as "Grade 3" in the frequency tables by CTC grade of SAE and AESIs. If the assessment of relationship of the investigational product is missing, it will be classified as related to the investigational product.

Date of infusions

Date of infusion is the non-missing administration date filled in the Study Drug Administration-IV CRF. If the first dose of study drug administration date is missing (even after site is queried), then the dosing date will be imputed with the randomization date. If any subsequent study drug administration date is missing, the date of dispensation of study drug from IRT will be used.

6.4. Visit Windows

Data analyzed by-visit-analysis will be summarized by the study scheduled visits described in Appendix 10.1, "Schedule of Event". The analysis visit windows will be exhaustive so that all available values obtained from unscheduled visits, early termination visit (ETV) and end of treatment (EOT)/end of study (EOS) have the potential to be summarized. No analysis visit windows will be applied for the study scheduled visits nor for drug concentration/immunogenicity data.

The following analysis visit windows will be used to map the unscheduled visits, ETV and EOT visits for NP Swab for SARS-CoV-2 RT-qPCR, based on the study day during the double blind period:

Table 6: Time Window for Summary of NP Swab for SARS-CoV-2 RT-qPCR (Cohort 1 Patients; Cohort 3 Patients ≥ 18 Years)

Visit Label	Targeted Study Day	Analysis Window in Study Day
Baseline	1	≤ 1
Day 7	7	[2, 10]
Day 15	15	[11, 22]
Day 29	29	[23, 32]

Table 7: Time Window for Summary of NP Swab for SARS-CoV-2 RT-qPCR (Cohort 2 Patients; Cohort 3 Patients < 18 Years)

Visit Label	Targeted Study Day	Analysis Window in Study Day
Baseline	1	≤ 1
Day 3	3	[2, 4]
Day 7	7	[5, 10]
Day 15	15	[11, 22]
Day 29	29	[23, 32]

The following analysis visit windows will be used to map the unscheduled visits, ETV and EOT visits for laboratory and biomarker variables based on the study day during the double blind period:

Table 8: Time Window for Summary of Laboratory and Biomarker Variables except Serum for Serology (Cohort 1 Patients; Cohort 3 Patients ≥ 18 Years)

Visit Label	Targeted Study Day	Analysis Window in Study Day
Baseline	1	≤ 1
Day 7	7	[2, 11]
Day 15	15	[12, 22]
Day 29	29	[23, 32]

Table 9: Time Window for Summary of Laboratory and Biomarker Variables except Serum for Serology (Cohort 2 Patients and Cohort 3 Patients <18 Years with Body Weight ≥ 10 kg)

Visit Label	Targeted Study Day	Analysis Window in Study Day
Baseline	1	≤ 1
Day 7	7	[2, 11]
Day 15	15	[12, 22]
Day 29	29	[23, 32]

Table 10: Time Window for Summary of Serum for Serology (Cohort 1 Patients; Cohort 3 Patients ≥ 18 Years; Cohort 2 patients and Cohort 3 Patients <18 Years with Body Weight ≥ 10 kg)

Visit Label	Targeted Study Day	Analysis Window in Study Day
Baseline	1	≤ 1
Day 29	29	[2, 32]

Table 11: Time Window for Summary of Laboratory and Biomarker Variables (Cohort 2 Patients with Body Weight < 10 kg)

Visit Label	Targeted Study Day	Analysis Window in Study Day
Baseline	1	≤ 1
Day 7	7	[2, 18]
Day 29	29	[19, 32]

In the event of multiple measurements of the same test in the same window, if the measurements are from different categories, the priority order is scheduled, early termination visit then unscheduled visit. For the measurements in the same category, the value measured nearest to the target day will be assigned to the window; if they are at the same distance to the target day, the latest one will be used. 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 listings, but not summaries except for the endpoint determination. If more than one laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

The determination of baselines and values at the end of treatment for both efficacy and safety variables will be based on scheduled available assessments and unscheduled available assessments.

6.5. Pooling of Centers for Statistical Analyses

Not applicable.

7. INTERIM ANALYSIS

Cohort 1

The final analysis of the primary efficacy endpoint, i.e., proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 for the 2400 mg group versus placebo comparison will be performed based on patients randomized on or before 17 January 2021. If the 2400 mg group versus placebo comparison is positive, an interim analysis of the primary endpoint for the 1200 mg group versus placebo comparison will be performed at α level of 0.01 based on patients randomized on or before 17 January 2021. If the interim analysis is positive for the 1200 mg group versus placebo comparison, this analysis will be considered as the final analysis and final analysis of the other key secondary analyses will be performed based on patients randomized on or before 17 January 2021. If the interim analysis is negative for the 1200 mg group versus placebo comparison, no further tests will be conducted for other key secondary endpoints at the interim analysis, and final analysis of the primary endpoint for the 1200 mg group versus placebo comparison and other key secondary analyses will be performed based on patients randomized on or before 24 February 2021.

The Gamma family alpha spending function (Hwang, Shih, DeCani 1990) based on the primary endpoint of proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 for the 1200 mg versus placebo comparison will be used to control for type I error for the planned interim analysis and the final analysis. The parameter for the Gamma family spending function will be calculated based on the information fraction of the interim analysis such that the alpha level at the interim analysis is equal to 0.01. If the interim analysis is not significant at 0.01 level for an endpoint, the remaining alpha level will be calculated based on the gamma parameter and information fraction. The information fraction will be determined based on the sample size in the mFAS at the interim analysis and final analysis of the primary endpoint for the 1200 mg group versus placebo comparison as follows: number of patients randomized to 1200 mg or placebo on or before 17 January 2021 in the mFAS divided by number of patients randomized to 1200 mg or placebo on or before 24 February 2021 (i.e., the day before the placebo treatment group was dropped per IDMC recommendation) in the mFAS.

Cohort 2 and 3

An interim descriptive analysis of phase 3 cohort 2 and 3 may be conducted for regulatory purposes when the phase 3 cohort 1 primary analysis is performed.

8. SOFTWARE

All analyses will be done using SAS Version 9.4.

9. REFERENCES

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10. APPENDIX

10.1. Schedule of Time and Events

Schedule of Events: Phase 3 (Cohort 1 Patients; Cohort 3 Patients ≥18 Years)

Day	Screening/Baseline Visit[1]				Follow Up[3]										EOS[3]
	-1 to 1				2	3	4	7	15	22	29	60	90	120	169
	Screen	Pre-Dose	Dose	Post-Dose											
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12
Window (Days)								±1	±3	±3	±3	±3	±3	±7[12,14]	±7[14]
Screening/Baseline Only															
Informed consent	X														
PGx sub-study consent (optional)[4]	X														
Immunoprofiling sub-study consent (optional)[4]	X														
Inclusion/exclusion	X														
Antigen or molecular diagnostic test for SARS-CoV-2[5]	X														
Demographics	X														
Medical history (including COVID-19 illness, risk factors)	X														
Weight and height	X														
Randomization (treatment assignment)		X													
Treatment															
Study drug administration			X												
Efficacy															
Query for COVID-19-related medically-attended visit details								X	X	X	X				
NP swab for SARS-CoV-2 RT-qPCR		X						X	X		X				
Safety															
Vital signs		X[6]		X[6]											
Treatment-emergent grade ≥2 IRRs[7,8]			X	X	← cont. mon. →										
TEAEs that led to ***any*** medically-attended visit[7,8]				X	← continuous monitoring →										
Treatment-emergent grade ≥2 hypersensitivity[7,8]			X	X	← continuous monitoring →										
Treatment-emergent SAEs[7,8,16]			X	X	← continuous monitoring →										
Targeted concomitant medications[7, 8]	X		X	X	← continuous monitoring →										
Concomitant procedures[7,8]	X		X	X	← continuous monitoring →										

Day	Screening/Baseline Visit[1]				Follow Up[3]										EOS[3]
	-1 to 1				2	3	4	7	15	22	29	60	90	120	169
	Screen	Pre-Dose	Dose	Post-Dose											
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12
Window (Days)								±1	±3	±3	±3	±3	±3	±7[12,14]	±7[14]
Vital status[16]														X	X
Pregnancy test (women of childbearing potential)[9]	X														
Pregnancy status[16]														X	X
Safety information (newborns of study participants)[16]														X	X
Central Laboratory Safety Testing															
Hematology (including differential)	X[10]							X	X		X				
Blood chemistry (including AST, ALT, CRP, LDH)	X[10]							X	X		X				
Coagulation tests (D-dimer, PT/INR, aPTT)	X[10]							X	X		X				
Central Laboratory Immunogenicity Testing (Not Enrolled in PK Sub-Study, Not Pregnant at Randomization)															
Serum for ADA[13]	X[13]										X				
Central Laboratory Drug Concentration and Immunogenicity Testing (Enrolled in PK Sub-Study, Not Pregnant at Randomization)															
Serum for drug concentration (PK)[12]	X[10,12]										X[12]			X[12]	
Serum for ADA[13]	X[13]										X[13]			X[13]	
Central Laboratory Drug Concentration and Immunogenicity Testing (Pregnant at Randomization)															
Serum for drug concentration (PK)[12]	X[10,12]			X[12]							X[12]			X[12]	
Serum for ADA[13]	X[13]										X[13]			X[13]	
Central Laboratory Biomarker Testing															
Serum for serology	X[10]										X				
Serum for research	X[10]							X	X		X				
Plasma for research	X[10]							X	X		X				
Exploratory Patient-reported Outcomes															
SE-C19[14]		X			Daily										
PGIS[14]		X			Daily										
PGIC[14]											X				
Item: return to usual health		X			Daily										
Item: return to usual activities		X			Daily										
EQ-5D-5L[14]		X			Daily							X[14]	X[14]	X[14]	X[14]
WPAI+CIQ								X	X	X	X				
Immunoprofiling (Optional Sub-Study)															
Blood for PBMCs		X									X				

Day	Screening/Baseline Visit[1]				Follow Up[3]										EOS[3]
	-1 to 1				2	3	4	7	15	22	29	60	90	120	169
	Screen	Pre-Dose	Dose	Post-Dose											
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12
Window (Days)								±1	±3	±3	±3	±3	±3	±7[12,14]	±7[14]
Pharmacogenomics (Optional Sub-Study)															
Blood for DNA[4]		X[4]													
Blood for RNA[4]	X[4]														

ADA, anti-drug antibodies; AE; adverse event; ALT, alanine transaminase; aPTT, activated partial thromboplastin time; AST, aspartate transaminase; CRP, c-reactive protein; EOS, end of study; INR, international normalized ratio; IRR, infusion-related reaction; LDH, lactate dehydrogenase; NP, nasopharyngeal; PBMC, peripheral blood mononuclear cells; PGx, pharmacogenomics; PK, pharmacokinetics; PT, prothrombin time; SAE, serious adverse event; RT-qPCR, quantitative reverse transcription polymerase chain reaction; TEAE, treatment-emergent adverse event.

Schedule of Events: Phase 3 (Cohort 2 Patients; Cohort 3 Patients <18 Years)

Day	Screening/Baseline Visit[1]				Follow Up[3]										EOS[3]
	-1 to 1				2	3	4	7	15	22	29	60	90	120	169
	Screen	Pre-Dose	Dose	Post-Dose											
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12
Window (Days)								±1	±3	±3	±3	±3	±3	±7[14]	±7[14]
Screening/Baseline Only															
Parental informed consent and informed assent	X														
Inclusion/exclusion	X														
Antigen or molecular diagnostic test for SARS-CoV-2[5]	X														
Demographics	X														
Medical history (including COVID-19 illness, risk factors)	X														
Weight and height	X														
Randomization (treatment assignment)		X													
Randomization (PK-ADA schedule assignment)[15]		X													
Treatment															
Study drug administration			X												
Efficacy															
Query for COVID-19-related medically-attended visit details		X						X	X	X	X				
NP swab for SARS-CoV-2 RT-qPCR		X				X		X	X		X				
Safety															
Vital signs (≥12 years)		X[6]		X[6]											
Vital signs (<12 years)		X[6]	X[6]	X[6]											
Treatment-emergent grade ≥2 IRRs[7, 8]			X	X[17]	← cont. mon. →										
TEAEs that led to ***any*** medically-attended visit[7, 8]				X[17]	← continuous monitoring →										
Treatment-emergent grade ≥2 hypersensitivity[7, 8]			X	X[17]	← continuous monitoring →										
Treatment-emergent grade 3 or 4 AEs[8]			X	X[17]	← continuous monitoring →										
Treatment-emergent SAEs[7, 8,16]			X	X[17]	`← continuous monitoring →										
Targeted concomitant medications[7,8]	X		X	X[17]	← continuous monitoring →										
Concomitant procedures[7,8]	X		X	X[17]	← continuous monitoring →										
Vital status[16]														X	X
Pregnancy test (women of childbearing potential)[9]	X														
Pregnancy status[16]														X	X

Day	Screening/Baseline Visit[1]				Follow Up[3]										EOS[3]
	-1 to 1				2	3	4	7	15	22	29	60	90	120	169
	Screen	Pre-Dose	Dose	Post-Dose											
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12
Window (Days)								±1	±3	±3	±3	±3	±3	±7[14]	±7[14]
Safety information (newborns of study participants)[16]														X	X
Central Laboratory Safety Testing and Central Laboratory Biomarker Testing, Body Weight ≥20 kg															
Hematology (including differential)	X[10]							X	X		X				
Blood chemistry (including AST, ALT, CRP, LDH)	X[10]							X	X		X				
Serum for serology	X[10]										X				
Serum for exploratory research	X[10]							X	X		X				
Plasma for exploratory research	X[10]							X	X		X				
Central Laboratory Safety Testing and Central Laboratory Biomarker Testing, Body Weight ≥10 kg to <20 kg															
Hematology (including differential)	X[10]							X	X		X				
Blood chemistry (including AST, ALT, CRP, LDH)	X[10]							X	X		X				
Serum for serology	X[10]										X				
Central Laboratory Safety Testing and Central Laboratory Biomarker Testing, Body Weight <10 kg															
Hematology (including differential)	X[10]							X			X				
Blood chemistry (including AST, ALT, CRP, LDH)	X[10]							X			X				
Serum for serology	X[10]														
Central Laboratory Drug Concentration and Immunogenicity Testing (All Body Weight Tiers)															
Serum for PK-ADA (Schedule A)[15]	X[10,12]		X[12]			X[12]					X[12]				
Serum for PK-ADA (Schedule B)[15]	X[10,12]		X[12]					X[12]			X[12]				
Serum for PK-ADA (Schedule C)[15]	X[10,12]		X[12]						X[12]		X[12]				
Serum for PK-ADA (Schedule D)[15]	X[10,12]		X[12]							X[12]	X[12]				
Exploratory Patient-reported Outcomes (Age ≥12 Years Only)[14]															
SE-C19[14]		X			Daily										
PGIS[14]		X			Daily										
PGIC[14]											X				
Item: return to usual health		X			Daily										
Item: return to usual activities		X			Daily										
EQ-5D-Y-5L[14]		X			Daily							X[14]	X[14]	X[14]	X[14]
WPAI+CIQ								X	X	X	X				

Day	Screening/Baseline Visit[1]				Follow Up[3]										EOS[3]
	-1 to 1				2	3	4	7	15	22	29	60	90	120	169
	Screen	Pre-Dose	Dose	Post-Dose											
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12
Window (Days)								±1	±3	±3	±3	±3	±3	±7[14]	±7[14]

ADA, anti-drug antibodies; AE; adverse event; ALT, alanine transaminase; aPTT, activated partial thromboplastin time; AST, aspartate transaminase; CRP, c-reactive protein; EOS, end of study; INR, international normalized ratio; IRR, infusion-related reaction; LDH, lactate dehydrogenase; NP, nasopharyngeal; PGx, pharmacogenomics; PK, pharmacokinetics; PT, prothrombin time; SAE, serious adverse event; RT-qPCR, quantitative reverse transcription polymerase chain reaction; TEAE, treatment-emergent adverse event.

1. Screening visit may occur on the same day as, or the day prior to, the baseline visit.
2. [Phase 1 footnote removed]
3. On visit days where in-person sample collections or assessments are not required, information may be collected by phone.
4. Patients (cohort 1; cohort 3 ≥18 years old) must provide separate consent to collect blood samples as part of the optional pharmacogenomics (PGx) sub-study. Blood sample for RNA may be collected at day -1 or day 1 (ie, screening or pre-dose) but must be collected prior to randomization. Blood sample for DNA should be collected at the day -1 or day 1 visit, but may be collected at any visit. Refer to Section 9.2.12 for more information about the PGx sub-study.

   Patients (cohort 1; cohort 3 ≥18 years old) must provide separate consent to collect blood samples as part of the optional peripheral blood mononuclear cell (PBMC) sub-study. Blood samples for PBMCs must be collected at the visits indicated. Refer to Section 9.2.11 for more information about this sub-study.
5. Refer to Section 9.2.1.2 for diagnostic test requirements during screening.
6. Vital signs, including temperature, blood pressure, heart rate, and SpO_2 will be collected as described in Section 9.2.4.1.

   For **patients in cohort 1 and patients ≥12 years in cohort 2 and cohort 3**, vital signs will be taken once before the infusion and once after the infusion is completed. After infusion of study drug, these patients will be observed for at least 1 hour.

   For patients in **patients <12 years in cohort 2 and cohort 3**, vital signs will be taken before infusion, approximately every 30 minutes during the infusion, after the infusion is completed, approximately 1 hour post-infusion, and approximately 2 hours post-infusion. After infusion of study drug, these patients will be observed for at least 2 hours.
7. Treatment-emergent AESIs (grade ≥2 IRRs, grade ≥2 hypersensitivity, and TEAEs associated with ***any*** medically-attended visit) and treatment-emergent SAEs will be recorded until day 29. From day 30 to day 169, only treatment-emergent SAEs will be recorded. **For patients in cohort 2 and patients <18 years in cohort 3**, treatment-emergent grade 3 or 4 AEs will also be recorded until day 29. Refer to Section 10 for more information on reporting and recording requirements.

Targeted concomitant medications and concomitant procedures will also be reviewed and recorded. Refer to Section 9.2.4.3 for more information.

8. Continuously-monitored events will be recorded when they occur during the corresponding time period marked on the schedule of events. Study visits (including phone calls) are not required solely to collect continuously-monitored assessments, if no other assessments are planned on that day.
9. Pregnancy testing will be performed in women of childbearing potential (WOCBP) only and regardless of pregnancy status. A negative test is **not required** prior to study drug administration. Serum or urine pregnancy test are both acceptable. Refer to Section 9.2.6 for more information, including a 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.
10. The indicated blood samples may be collected at the either day -1 or day 1 (ie, screening or pre-dose), but must be collected prior to randomization. For patients in phase 3 cohort 2, efforts should be made to collect all screening/pre-dose blood samples on the same study visit, when feasible.
11. [Footnote removed]
12. Actual dosing time and drug concentration sample collection times, as applicable, will be recorded.

    At the screening/baseline visit, blood for assessment of drug concentration in serum will be taken prior to dosing 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.

    In cohort 1 and cohort 3 (≥18 years old), patients will follow different blood sample collection schedules for drug concentration and immunogenicity depending on whether they enrolled in the PK sub-study (cohort 1), not enrolled in the PK sub-study (cohort 1), or are pregnant at randomization (cohort 3 patients ≥18 years old). For samples collected on day 120, the collection window is ±28 days. Refer to Section 9.2.8 for more information on the PK sub-study.
13. The window for predose ADA sample collection is as close to administration of study drug as is reasonable. Actual dosing time and ADA sample collection times, as applicable, will be recorded.
14. **Patients in cohort 1 and patients ≥12 years in cohort 2 and cohort 3** will self-report symptoms using electronic surveys. The order of completion is as follows: SE-C19, PGIS, PGIC, return to usual health, return to usual activities, EQ-5D-5L, WPAI+CIQ. On days when a survey/questionnaire is not required it will be skipped, but the overall order will remain the same. Note that the WPAI+CIQ, EQ-5D-5L, and EQ-5D-Y-5L will only be administered at sites when regionally available.

On days 60, 90, 120, and 169, the window for electronic survey/questionnaire assessment is ±3 days. Note that study visits are not required on days when only electronic survey data are collected.

15. In **cohort 2 (and patients <18 years in cohort 3)**, each patient will be assigned at randomization by IWRS to a blood sample collection schedule for drug concentration and immunogenicity analysis. Actual dosing time and PK-ADA sample collection times will be recorded. To conserve blood volume, a single blood draw for drug concentration and immunogenicity will be obtained.
16. Patients will be followed by phone at day 120 and day 169 for vital status, pregnancy status, targeted safety information, and additional safety information in newborns of study participants. Refer to Section 9.2.5 for more information on these follow-up assessments.
17. **For patients <12 years in cohort 2 and cohort 3**, follow-up by phone will be conducted within 6 to 8 hours of infusion to collect the information indicated.

10.2. Criteria for Potentially Clinically 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. * At least one level is required; multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
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. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
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.

Parameter	PCSV	Comments
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. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤1.5, >1.5 to ≤2.0 and > 2.0 category for baseline vs. post baseline may be provided
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. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤3, >3 to ≤10, and > 10 category for baseline vs. post baseline may be provided
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

Parameter	PCSV	Comments
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
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

Parameter	PCSV	Comments
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
Total Cholesterol	≥7.74 mmol/L or ≥ULN (if ULN≥7.74 mmol/L) and baseline < 7.74 mmol/L or <ULN (if ULN≥7.74 mmol/L)	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L or ≥ULN (if ULN≥4.6 mmol/L) and baseline < 4.6 mmol/L or <ULN (if ULN≥4.6 mmol/L)	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN and baseline < 3 ULN	
Amylasemia	≥3 ULN and baseline < 3 ULN	
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.
HbA1c	>8% and baseline ≤ 8%	
Albumin	≤25 g/L or ≤LLN (if LLN≤25 g/L) and baseline >25 g/L or >LLN (if LLN≤25 g/L)	
CRP	>2 ULN or >10 mg/L (if ULN not provided) and baseline ≤2 ULN or ≤10 mg/L (if ULN not provided)	FDA Sept 2005.

Parameter	PCSV	Comments
Hematology		
WBC	<3.0 Giga/L or <LLN (if LLN≤3.0 Giga/L) and baseline ≥3.0 Giga/L or ≥LLN (if LLN≤3.0 Giga/L) (Non-Black); <2.0 Giga/L or <LLN (if LLN≤2.0 Giga/L) and baseline ≥2.0 Giga/L or ≥LLN (if LLN≤2.0 Giga/L) (Black)* ≥16.0 Giga/L or ≥ULN (if ULN≥16.0 Giga/L) and baseline < 16 Giga/L or <ULN (if ULN≥16.0 Giga/L)	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 racce	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
Urinalysis		
pH	≤4.6 or ≤LLN (if LLN≤4.6) and baseline > 4.6 or >LLN (if LLN≤4.6) ≥8 or ≥ULN (if ULN≥8) and baseline < 8 or <ULN (if ULN≥8)	Two independent criteria
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
Weight	≥ 5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007

10.3. Symptom Evolution of COVID-19 (SE-C19)

Symptom Evolution of COVID-19 (SE-C19): The SE-C19 was developed based on the symptoms listed by the CDC, published literature and supported by interviews with patients with COVID-19. The symptom diary included a list of 23 symptoms (feverish, chills, sore throat, cough, shortness of breath or difficulty breathing, nausea, vomiting, diarrhea, headache, red or watery eyes, body aches, loss of taste or smell, fatigue, loss of appetite, confusion, dizziness, pressure or tight chest, chest pain, stomachache, rash, sneezing, sputum/phlegm, runny nose). On a daily basis, patients indicated which of the 23 symptoms they had experienced in the last 24 hours, and then rated each symptom selected at its worst moment in the last 24 hours on a scale of mild, moderate or severe. Each symptom on the SE-C19 was captured numerically as 0 (no symptom), 1 (mild symptom), 2 (moderate symptom), or 3 (severe symptom). For the purposes of analysis, 'no symptom' will be assigned a score of 0, 'mild symptom' and 'moderate symptom' will be assigned a score 1 (mild/moderate symptom), and 'severe symptom' will be assigned a score of 2 (ie, the mild and moderate symptom categories will be collapsed).

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