REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN
FINAL ANALYSIS OF PHASES 1, 2 AND 3 OF THE STUDY COV-2066 FOR ALL COHORTS
VERSION: FINAL 1.0

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

Compound:	REGN10933+REGN10987 (REGEN-COV; REGN-COV2)
Protocol Number:	R10933-10987-COV-2066
Clinical Phase:	Phases 1/2/3
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatisticians:	[redacted]
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Version/Date:	Original (Version 1.0) / 07 JULY 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.

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Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
aPTT	Activated partial thromboplastin time
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
CSR	Clinical study report
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
EUA	Emergency Use Authorization
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
FiO_2	Fraction inspired oxygen
ICH	International Council for Harmonisation
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IWRS	Interactive Web Response System
IV	Intravenous
IVIG	Intravenous immunoglobulin
mFAS	Modified Full Analysis Set
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
NCA	Non-compartmental analyses of Pharmacokinetic parameters
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NLR	Neutrophil-lymphocyte ratio
NP	Nasopharyngeal
PCSV	Potentially Clinically Significant Value
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred Term
RBC	Red Blood Cell
RNA	Ribonucleic Acid
Regeneron	Regeneron Pharmaceuticals, Inc.
REGN-COV2 (R10933+R10987)	Co-administered REGN10933 and REGN10987 combination therapy
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
SOC	System organ class
SpO_2	Peripheral capillary oxygen saturation
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. OVERVIEW

1.1. Background/Rationale

R10933-10987-COV-2066 (referred to as study "COV-2066" hereafter) is an adaptive phase 1/2/3, randomized, double-blinded, placebo-controlled master protocol to evaluate the efficacy and safety of co-administered REGN10933+REGN10987 combination therapy ("REGN10933+REGN10987") in hospitalized adult patients with COVID-19.

The purpose of this 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 the final database lock. This final version of the SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of final data from all phases (phase 1, phase 2, and phase 3) and all cohorts (cohort 1A, cohort 1, cohort 2, and cohort 3), based on Protocol Amendment 7 (dated 07 July 2021).

Summary of Study Conduct and Patient Enrollment

In this study, patients were enrolled in one of the following 4 cohorts based on disease severity at randomization:

- **Cohort 1A (Room Air):** Patients with COVID-19 symptoms but not requiring supplemental oxygen
- **Cohort 1 (Low Flow Oxygen):** Patients with O_2 saturation >93% on low-flow oxygen via nasal cannula, simple face mask, or other similar device
- **Cohort 2 (High-Intensity Oxygen):** Patients on high-intensity oxygen therapy* but not on mechanical ventilation

  **High-intensity oxygen therapy is defined as the use of non-rebreather mask with an oxygen flow rate of at least 10 L/min; use of a high flow device with at least 50% FiO_2, or use of non-invasive ventilation to treat hypoxemia*
- **Cohort 3 (Mechanical Ventilation):** Patients on mechanical ventilation

In the first-in-human (FIH) phase 1 portion of the study, patients were enrolled into cohort 1 only. Subsequently, in phase 2, patients were enrolled into all 4 cohorts.

On 30 October 2020, an Independent Data Monitoring Committee (IDMC) recommended pausing enrollment into cohort 2 and cohort 3 based on a potential safety imbalance, while proceeding with enrollment in cohort 1A and cohort 1. All cohort 2 and 3 patients enrolled at the time of the recommendation continued in the study and were followed up through the end of study visit as per the protocol. This IDMC recommendation on enrollment was maintained for the duration of the study.

An unblinded phase 1/2 analysis was performed on the patients who were randomized through 01 December 2020 in phase 1 (cohort 1 only) and phase 2 (cohorts 1, 2, and 3) using a data cutoff date of 09 December 2020, based on a database lock on 22 December 2020 (refer to the phase 1/2 SAP dated 21 December 2020 for details). Phase 2 cohort 1A was not included in the analysis. All patients enrolled into cohort 1 after 01 December 2020 were considered to be part of phase 3.

On 09 April 2021, the Sponsor made a business decision to terminate patient enrollment in this study due to extremely low recruitment over several months. This decision was not based on any safety concerns. Accordingly, phase 3 cohort 1 and phase 2 cohort 1A enrollment was prematurely terminated. Until this time, only cohort 1 patients were enrolled into the phase 3 portion of the study. All ongoing subjects were followed up through their end of study visit as per the protocol.

Cohort 1 reached its phase 2 enrollment goal first, and phase 3 cohort 1 started enrollment after 01 December 2020. As cohort 1A never reached its predetermined phase 2 enrollment goal of 1000 patients, phase 2 cohort 1A and cohort 1 enrolled concurrently. Phase 2 cohort 1A data were handled and overseen similar to phase 3 cohort 1 data.

Given much smaller sample size than anticipated as a result of early termination of enrollment, the Sponsor has elected to pool phase 2 cohort 1A and phase 3 cohort 1 and combine the REGN10933+REGN10987 2.4g and 8.0g dose groups for the primary analyses.

Overall, approximately 2252 subjects were randomized in study COV-2066:

Phase 1

- Cohort 1: 60 patients

Phase 2

- Cohort 1A: 609 patients
- Cohort 1: 629 patients
- Cohort 2: 164 patients
- Cohort 3: 35 patients

Prematurely Terminated phase 3

- Cohort 1 (ie, subjects randomized after 01 Decemeber 2020 in cohort 1): 755 patients

This final SAP outlines the strategy and statistical methods to be used in the final analysis of data from all phases and all cohorts in the prematurely terminated study COV-2066, as below:

Efficacy Analysis

The efficacy analysis will be performed for the modified full analysis set (mFAS, defined in Section 3.1) of the following pooled cohort of patients and individual subsidiary cohorts, representing the totality of patients in this prematurely terminated study who were not unblinded in the database lock on 22 December 2020. In this document, the prematurely terminated phase 3 cohort 1 is referred as phase 3 cohort 1 and prematurely terminated phase 2 cohort 1A as phase 2 cohort 1A.

- Pooled phase 3 cohort 1 and phase 2 cohort 1A
- Phase 3 cohort 1
- Phase 2 cohort 1A

In each of these data sets (ie, the 2 terminated cohorts and the pooled cohort), the analyses will be conducted in the mFAS for the following patient populations. The mFAS is defined as patients that have a positive central-lab confirmed SARS-CoV-2 RT-qPCR result from an NP

swab sample and the efficacy analysis was conducted in the mFAS to ensure detectable virus was present at baseline.

- Seronegative mFAS
- High Viral Load mFAS, where high viral load is defined as $>10^6$ copies/mL at baseline
- Overall mFAS

The **primary** virologic endpoint is time-weighted average change from baseline viral load in nasopharyngeal (NP) samples through Day 7. The primary analysis will be performed in the Seronegative mFAS population that is combined across the 2.4 g and 8g doses and pooled across phase 3 cohort 1 and phase 2 cohort 1A.

The **primary** clinical endpoint is death or mechanical ventilation. It will be estimated based on the proportion of patients who died or went on mechanical ventilation from Day 6 through Day 29, where events occurring during the first 5 days will excluded because of the notion that clinical impact would occur only after achieving several days of viral suppression. This observation was noted in the analysis of data from phase 1/2 portion of this study. In addition, the endpoint of death or mechanical ventilation from Day 1 through Day 29 will also be evaluated. The primary analysis will be performed for the High Viral Load mFAS, Seronegative mFAS, and the Overall mFAS in the pooled phase 3 cohort 1 and phase 2 cohort 1A and combined across the 2.4 g and 8 g doses of REGN10933+REGN10987. To control alpha at a strict 0.05 level, the two primary endpoints will be tested hierarchically, with the virologic endpoint tested first.

Safety Analysis

The safety analysis will be performed for the following cohorts, separately. Patients in phase 1/2 cohort 1, phase 2 cohort 2 and cohort 3 are included into the analysis because more safety data were collected for the patients after the database lock on 22 December 2020.

- Phase 2 cohort 1A
- Phase 2 cohort 2
- Phase 2 cohort 3
- Phase 1/2/3 cohort 1 combined

Pharmacokinetics (PK) and Immunogenicity Analysis

The PK and ADA analysis will be performed for phase 1/2/3 cohort 1 combined, phase 2 cohort 1A, phase 2 cohort 2, and phase 2 cohort 3, separately. The NAb analysis will be performed for phase 2/3 patients.

1.2. Study Objectives

1.2.1. Primary Objectives

Pooled Phase 3 Cohort 1 and Phase 2 Cohort 1A

The primary objectives include:

- To evaluate the virologic efficacy of REGN10933+REGN10987 compared to placebo in reducing viral load of SARS-CoV-2
- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo, as measured by death or mechanical ventilation

Phase 2 (Cohort 1A)

There is no primary objective for phase 2 cohort 1A as enrollment was prematurely terminated.

Phase 2 (Cohort 2 and Cohort 3)

There is no primary objective for cohort 2 and cohort 3 in phase 2 as enrollment was put on hold. All safety and efficacy analyses are exploratory.

Phase 3 (Cohort 1).

There is no primary objective for phase 3 cohort 1 as enrollment was prematurely terminated.

1.2.2. Secondary Objectives

Pooled Phase 3 Cohort 1 and Phase 2 Cohort 1A

The secondary objectives are:

- To evaluate additional indicators of clinical efficacy of REGN10933+REGN10987 compared to placebo
- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo

Phase 2 (Cohort 1A)

The secondary objectives are:

- To evaluate the virologic efficacy of REGN10933+REGN10987 compared to placebo in reducing viral load of SARS-CoV-2
- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo, as measured by death or mechanical ventilation
- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo
- To characterize the concentrations of REGN10933 and REGN10987 in serum over time
- To assess the immunogenicity of REGN10933 and REGN10987

Phase 2 (Cohort 2 and Cohort 3)

The secondary objectives are:

- To characterize the concentrations of REGN10933 and REGN10987 in serum over time
- To assess the immunogenicity of REGN10933 and REGN10987

Phase 3 (Cohort 1)

The secondary objectives are:

- To evaluate the virologic efficacy of REGN10933+REGN10987 compared to placebo in reducing viral load of SARS-CoV-2
- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo, as measured by death or mechanical ventilation
- To evaluate additional indicators of clinical efficacy of REGN10933+REGN10987 compared to placebo
- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo

Phase 1/2/3 (Cohort 1)

The secondary objectives are:

- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo
- 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 in all phases of the study are:

- To assess viral genetic variation in patients with a positive SARS-CoV-2 RT-qPCR
- 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 understand 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

For phase 2 (cohort 2 and cohort 3), the exploratory objectives include:

- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo, as measured by death or mechanical ventilation (as applicable based on the cohort)
- To evaluate additional indicators of clinical efficacy of REGN10933+REGN10987 compared to placebo
- To evaluate the virologic efficacy of REGN10933+REGN10987 compared to placebo in reducing viral load of SARS-CoV-2
- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo

1.2.4. Modifications from the Statistical Section in the Final Protocol

There is no modification from the statistical section in protocol amendment 7.

1.2.5. Revision History for SAP Amendments

Analyses described in this SAP supersede analyses described in any prior SAPs for this study. Analyses of phase 1 and phase 2 data not specified in this phase 1/2/3 SAP were based on phase 1 SAP version 1.0 approved on 23 Jun 2020 and phase 1/ 2 SAP version 1.0 approved on 21 Dec 2020.

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

COV-2066 study followed an adaptive, phase 1/2/3, randomized, double-blinded, placebo-controlled master protocol design to evaluate the efficacy, safety, and tolerability of REGN10933+REGN10987 in hospitalized adult patients with COVID-19.

There is some evidence that suggests baseline clinical disease severity influences progression and outcomes of COVID-19. In order to evaluate potential differential treatment effects across the spectrum of hospitalized COVID-19 patients, eligible patients who have been hospitalized for ≤72 hours at screening were enrolled in one of the 4 cohorts of patients with COVID-19 based on disease severity at randomization (see Table 1).

Table 1: Cohorts of Hospitalized Patients in Study R10933-10987-COV-2066

Study Cohort	Phase	Brief Name	Cohort Description
Cohort 1A	Phase 2 (Prematurely Terminated)	Room Air	Patients with COVID-19 symptoms but not requiring supplemental oxygen
Cohort 1	Phase 1 (Completed) Phase 2 (Completed) Phase 3 (Prematurely Terminated)	Low Flow Oxygen	Patients with O_2 saturation >93% on low-flow oxygen via nasal cannula, simple face mask, or other similar device
Cohort 2	Phase 2 (Prematurely Terminated)	High-Intensity Oxygen	Patients on high-intensity oxygen therapy* but not on mechanical ventilation
Cohort 3	Phase 2 (Prematurely Terminated)	Mechanical Ventilation	Patients on mechanical ventilation

* High-intensity oxygen therapy is defined as the use of non-rebreather mask with an oxygen flow rate of at least 10 L/min; use of a high flow device with at least 50% FiO2, or use of non-invasive ventilation to treat hypoxemia.

Patients were randomized in a stratified manner according to a central randomization scheme using an interactive web response system (IWRS).

Phase 1

In phase 1, 60 patients from Cohort 1 were randomized in a 1:1:1 allocation ratio to one of the following treatment groups:

- Co-administered REGN10933+REGN10987 combination therapy, 2.4 g (1.2 g each of REGN10933 and REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy, 8.0 g (4.0 g each of REGN10933 and REGN10987) IV single dose
- Placebo IV single dose

Randomization in phase 1 were stratified by type of background standard-of-care being administered for COVID-19 at randomization as follows:

- Antiviral therapies (remdesivir or other)
- Other therapies (immune-based therapies, both antiviral and immune-based therapies, or no COVID-19-specific treatment)

Phase 2/3

In phase 2/3, patients were randomized in a 1:1:1 allocation ratio to one of the following treatment groups:

- Co-administered REGN10933+REGN10987 combination therapy 2.4 g (1.2 g of REGN10933 plus 1.2 g of REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy 8.0 g (4.0 g of REGN10933 plus 4.0 g of REGN10987) IV single dose
- Placebo IV single dose

Randomization in phase 2/3 was stratified by country and type of background standard-of-care being administered for COVID-19 at randomization as follows:

- Antiviral therapies (remdesivir or other)
- Non-antiviral therapies (immune-based therapies, both antiviral and immune-based therapies, or no COVID-19-specific treatment)

The enrollment into Cohorts 2 and 3 were paused based on a recommendation from the IDMC (initial IDMC recommendation on 30 October 2020).

Most of the patients in the study were enrolled in the United States. Other countries where patients were enrolled in the study include Romania, Brazil, Chile, Mexico, and Moldova.

2.2. Statistical Hypothesis

The statistical hypotheses tested in terms of the primary virologic and clinical efficacy endpoints are listed in Table 2. Multiplicity will be controlled using a hierarchical testing strategy as represented in Section 5.6.3. The mFAS, Seronegative mFAS, and High Viral Load mFAS are defined in Section 3.1.

Table 2: Statistical hypotheses

Type	Null Hypothesis
Primary virologic endpoint	There is no difference in the time weighted average change from baseline viral load in NP sample through day 7 between the REGN10933+REGN10987 2.4g and 8.0g **combined** dose group and placebo in the **Seronegative mFAS population** in the pooled phase 3 cohort 1 and phase 2 cohort 1A
Primary clinical endpoint	There is no risk reduction in the REGN10933+REGN10987 2.4g and 8.0g **combined** dose groups versus placebo in terms of cumulative incidence of death or mechanical ventilation **from day 6 to day 29** in the **High Viral Load mFAS population** in the pooled phase 3 cohort 1 and phase 2 cohort 1A

Type	Null Hypothesis
	There is no risk reduction in the REGN10933+REGN10987 2.4g and 8.0g **combined** dose groups versus placebo in terms of cumulative incidence of death or mechanical ventilation **from day 6 to day 29** in the **Seronegative mFAS population** in the pooled phase 3 cohort 1 and phase 2 cohort 1A
	There is no risk reduction in the REGN10933+REGN10987 2.4g and 8.0g **combined** dose groups versus placebo in terms of cumulative incidence of death or mechanical ventilation **from day 6 to day 29** in the **overall mFAS population** in the pooled phase 3 cohort 1 and phase 2 cohort 1A
	There is no risk reduction in the REGN10933+REGN10987 2.4g and 8.0g **combined** dose groups versus placebo in terms of cumulative incidence of death or mechanical ventilation **from day 1 to day 29** in the **High Viral Load mFAS population** in the pooled phase 3 cohort 1 and phase 2 cohort 1A
	There is no risk reduction in the REGN10933+REGN10987 2.4g and 8.0g **combined** dose groups versus placebo in terms of cumulative incidence of death or mechanical ventilation **from day 1 to day 29** in the **Seronegative mFAS population** in the pooled phase 3 cohort 1 and phase 2 cohort 1A
	There is no risk reduction in the REGN10933+REGN10987 2.4g and 8.0g **combined** dose groups versus placebo in terms of cumulative incidence of death or mechanical ventilation **from day 1 to day 29** in the **overall mFAS population** in the pooled phase 3 cohort 1 and phase 2 cohort 1A

2.3. Sample Size and Power Considerations

The initial sample size for this adaptive study, COV-2066, was estimated separately for phase 1 and phase 2 and was based on the original primary virologic endpoint of time-weighted average change from baseline to day 7 in viral load.

In phase 1, a sample size of a total of 60 patients in Cohort 1 as the sentinel safety group was planned per discussions with regulatory authorities, i.e., 20 patients per arm in each of the 3 treatment arms. Since the goal was to assess safety and tolerability of REGN10933+REGN10987, this sample size would allow preliminary estimation of the incidences of SAEs and AESIs.

Cohorts 1A, 2 and 3 were to be enrolled after phase 1, beginning with the phase 2 portion of the study.

For phase 2 portion of the study, an initial sample size of 390 patients per cohort (i.e., 130 patients per arm) in each of cohorts 1A, 1, 2, and 3, for a total of 1560 patients was planned. This sample size was based on 80% power to detect a treatment difference of 0.84 log10 copies/mL for the primary virologic endpoint assuming a standard deviation of 2.1 log10 copies/mL and 23% dropout rate.

Per Protocol Amendment 6, an interim database lock for analysis of phase 1/2 combined data was planned and accordingly phase 2 sample size for Cohort 1 (low flow oxygen) was adapted to reflect the planned futility analysis using the primary clinical endpoint of death or mechanical ventilation. A total of 43 events of death or mechanical ventilation in seronegative modified Full Analysis Set (seronegative mFAS) patients in Cohort 1 was estimated to achieve 80% power to detect a risk reduction of 50% (HR=0.5) between any REGN10933+REGN10987 dose groups (2.4g IV or 8.0g IV) versus placebo at α=0.1 (one-sided) level of significance. This translated to a total sample size

of 250 randomized and treated patients across 3 arms, assuming patients would be followed through day 29, accrual takes 90 days, and 30% of FAS (randomized and treated) patients are in the seronegative mFAS.

The sample size of phase 2 cohort 1A was adjusted to approximate 1000 patients based on clinical judgement without statistical justification. However, this target was not reached because the enrollment was prematurely terminated.

Per IDMC recommendation received on 30 October, 18 November, 10 December 2020, patient enrollment in cohort 2 and cohort 3 has been placed on hold based on a potential safety signal.

Phase 3 Sample Size

Details for sample size calculations are provided in the protocol.

Finalization of the sample size and patient population for phase 3 was planned to be subject to change and would be determined after review of phase 2 data. However, enrollment of patients into the study was terminated prematurely by the Sponsor on 09APR2021 because of extremely slow enrollment in the months preceding the decision. The sample size of phase 3 was not re-estimated.

Approximately 2252 patients were randomized in the study, which includes 60 patients in phase 1 Cohort 1, 629 in phase 2 Cohort 1, 755 in planned phase 3 Cohort 1, 609 in phase 2 Cohort 1A, 164 in phase 2 Cohort 2 and 35 in phase 2 Cohort 3.

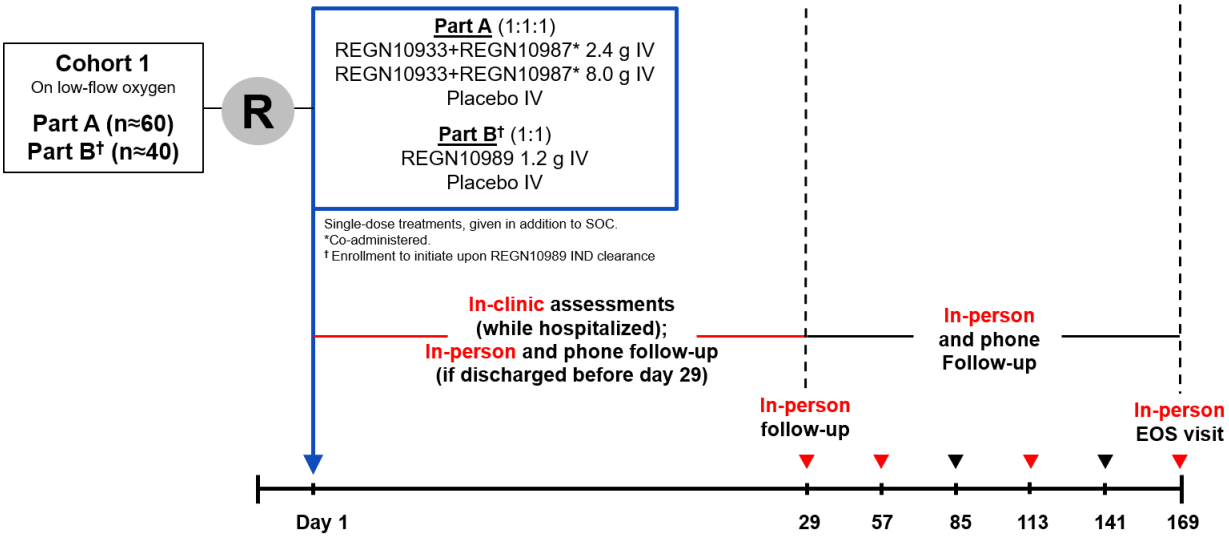
Assuming the proportion of patients who died or went on machenical ventilation from day 1 to day 29 in placebo group is 13.1% which is same as the blinded proportion in the Seronegative mFAS patients of the pooled phase 3 cohort 1 and phase 2 cohort 1A and alpha is 0.05 2-sided, the minimal significant difference in relative risk reduction between the the REGN10933+REGN10987 2.4g and 8.0g combined dose group and placebo group is 29.0%, 41.2%, and 36.6% for overall mFAS, Seronegative mFAS, and High Viral Load mFAS patients, respectively.

2.4. Study Plan

The Study event table of phase 1 is presented in Section 10.1. The Study event table of phase 2 is presented in Section 10.2.

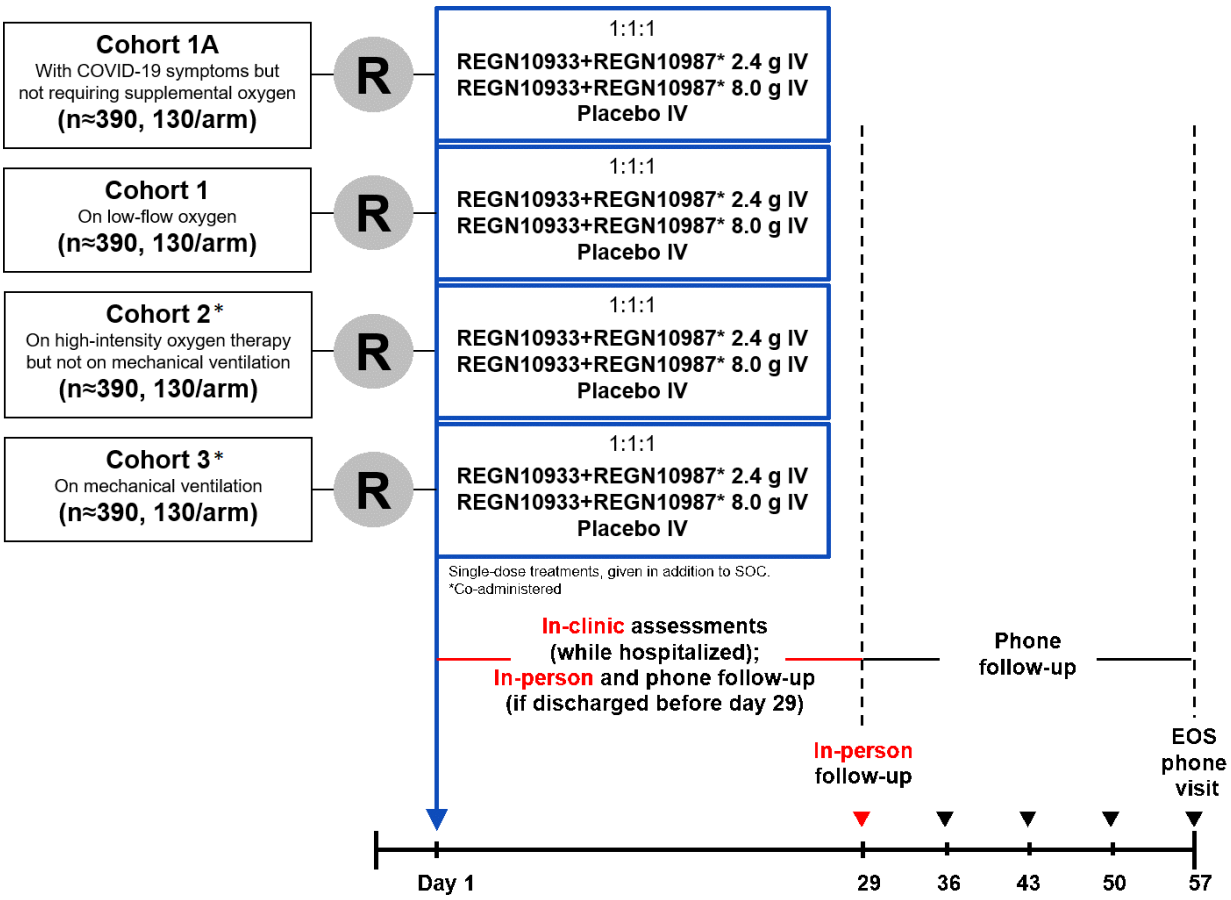
Study flow diagrams for phase 1 and phase 2 are showin in Figure 1 and Figure 2, respectively.

Figure 1: Phase 1 – Study Flow Diagram



At the time of the finalization of this SAP version, REGN10989 was not studied in the clinical trials.

Figure 2: Phase 2 – Study Flow Diagram



Phase 3

In phase 3, patients will be assessed daily up to day 29 for clinical improvement. After day 29, patients will be followed-up via intermittent phone calls until EOS on day 57.

2.4.1. Definition of Study Completion

For individual patients, study completion is defined as collection of vital status information on their projected EOS date. All measures will be taken to obtain vital status information on the projected EOS date, and all patients with recorded vital status information at projected EOS date will be considered study completers. The end of study is considered day 169 (for phase 1) or day 57 (for phase 2 and phase 3) (refer to Section 10 Schedule of Events).

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Council 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 analysis sets will be used for all statistical analyses in the study.

3.1. Efficacy Analysis Sets

Full Analysis Set (FAS): The full analysis set (FAS) includes all randomized patients who received at least one dose (full or partial) of the study drug. Analysis of the FAS population will be done according to the treatment allocated (as randomized).

Modified Full Analysis Set (mFAS): The modified full analysis set (mFAS) includes all FAS patients with a positive SARS-CoV-2 RT-qPCR conducted in the central laboratory in NP swab samples at randomization and analysis is based on the treatment allocated (as randomized).

Seronegative mFAS: The seronegative mFAS is defined as all patients in mFAS with documented seronegative status at the baseline.

High Viral Load mFAS: The High Viral Load mFAS is defined as all patients in mFAS with baseline viral load $>10^6$ copies/mL.

Both FAS and mFAS will be used for the summaries of demographic and baseline characteristics and analysis of clinical/biomarker endpoints. The mFAS will be used for the analysis of all efficacy endpoints, based on the principle that an anti-viral agent would only be anticipated to provide efficacy in patients with measurable virus at baseline. The seronegative mFAS as well as the high viral load mFAS will be used for the primary analysis and descriptive analysis of certain virologic endpoints and clinical endpoints. Additional analyses will be performed in the seropositive mFAS, as needed.

3.2. Safety Analysis Set (SAF)

The safety analysis set (SAF) includes all randomized patients who received a dose (full or partial) of the study drug. Analysis of the SAF will be done according to the treatment received (as treated). Determination of “as treated” will be based on the actual study drug received on day 1. Since the treatment of “as treated” is same as “as randomized” in this study, the FAS is equivalent to the SAF. Therefore, the treatment administration and all clinical safety variables will be analyzed using the FAS.

3.3. Pharmacokinetics Analysis Set

The pharmacokinetics (PK) analysis population includes all patients who received any study drug of REGN10933 and REGN10987 and who had at least 1 non-missing drug concentration measurement following the first dose of study drug as indicated in the Schedule of Events table (please refer to Section 10.2). Patients will be analyzed based on actual treatment received.

3.4. Immunogenicity Analysis Set

The anti-drug antibody (ADA) analysis set (AAS) includes all subjects who received any study drug (active or placebo) and at least one non-missing ADA result from the ADA assay after a first dose of the study drug or placebo.

The NAb analysis set (NAS) includes all treated subjects who received any study drug (active or placebo), have at least one non-missing anti-drug antibody result following the first dose of study drug (active or placebo), and either tested negative at all ADA sampling times or tested positive for ADA with at least one non-missing NAb result after first dose of the study drug (active or placebo). Subjects who are ADA negative are set to negative in the NAb analysis set.

Subjects will be analyzed according to the treatment actually received.

4. ANALYSIS VARIABLES

4.1. Demographics and Baseline Characteristics

Demographic and baseline characteristic variables include the following for each Cohort (1A, 1, 2 and 3):

- Age at screening (years)
- Age group (18-<40, 40-<65, >=65, >=75, >=85 years)
- Sex (Male, Female)
- Race (White, Black/African American, American Indian or Alaska Native, Native Hawaiian/Other Pacific Islander, Not Reported, Other)
- Ethnicity (Hispanic or Latino, Not-Hispanic or Latino, Not Reported, Unknown)
- Baseline Weight (kg)
- Baseline Height (cm)
- Baseline Body mass index (BMI) (kg/m^2) calculated from weight and height
- Obesity (BMI < 30 kg/m^2, ≥30 kg/m^2, Missing)
- Woman of child bearing potential (WOCB) (Yes; No)
  - If "No", then Post-menopausal, Surgically Sterile, Other
- Baseline SARS-CoV-2 Viral Load from central lab in Nasopharyngeal Swab (excluding assessments at screening visit if any) (log_{10} copies/mL)
- Baseline SARS-CoV-2 Viral Load based on RT-qPCR result in Nasopharyngeal Swab (copies/mL)
- Baseline SARS-CoV-2 Viral Load categories ($\leq 10^4$ vs $>10^4$, $\leq 10^5$ vs $>10^5$, $\leq 10^6$ vs $>10^6$, $\leq 10^7$ vs $>10^7$ copies/mL)
- Baseline SARS-CoV-2 Qualitative PCR results (central lab result; positive, negative, Other [not done, borderline])

  [Positive result is ≥ lower limit of detection (LOD) and negative is <LOD]
- Baseline SARS-CoV-2 Serology status (negative, positive, other [i.e., borderline, not determined])

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.

- Presence of neutralizing antibodies at baseline for seropositive subjects (Yes; No; Borderline; Unknown/Missing/indeterminate)
- Baseline C-Reactive Protein (mg/L)
- Baseline Neutrophils-Lymphocyte Ratio (NLR)

- Immunocompromised (Yes; No)

  Immunocompromised patients include those with immunological diseases, are immunosuppressed or have immunodeficiencies. Examples of medical history for this category include rheumatoid arthritis and cancer.

- Background Standard of Care (per IRT) (Antiviral therapies; Non-antiviral therapies)

Other baseline disease characteristic variables for this study population are as follows.

Vital Signs at baseline – (selected from Vital Signs – At Baseline CRF)

- Oxygen source (Supplemental Oxygen; Room Air)
- Temperature degrees in centigrade (C)
- Location for Temperature (oral cavity, axillary, rectal, ear, temple)
- Respiratory Rate (breaths/min)
- Oxygen Saturation, SpO_2 % (range is 0% to 100%)
- Oxygen Flow rate (L/min), (if not mechanically ventilated)
- FiO_2 (fraction of inspired oxygen) (range is 0.0 to 1.0), (if mechanically ventilated)

COVID-19 Pneumonia status at baseline – (selected from Pneumonia Status at Baseline CRF, unless specified otherwise)

- Duration of pneumonia (including any COVID-19 symptoms) prior to baseline (calculated as onset date for symptoms of pneumonia to first dose date. If date of onset of symptoms of pneumonia is missing, then date is not imputed.)
- Duration of COVID-19 illness (symptoms) prior to baseline (based on Medical History CRF)
- Patients using long-term oxygen therapy prior to admission for COVID-19 (e.g., use of Oxygen at home for COPD) (Yes/No)
- Usual Oxygen flow rate for patients using long-term oxygen therapy prior to admission for COVID-19 (L/min)
- Oxygen flow frequency for patients using long-term oxygen therapy prior to admission for COVID-19
- Oxygen flow route for patients using long-term oxygen therapy prior to admission for COVID-19

Clinical and Oxygen Status at randomization and pre-dose – (selected from Clinical and Oyxgen Status – At Randomization as well as Pre-dose CRFs)

- Use of supplemental oxygen (Yes; No; Missing)
- If no, subject requiring ongoing medical care (COVID-19 related or otherwise)? (Yes; No; Missing)

- If yes, Type of Oxygen delivery device/ventilation used
  - Supplemental oxygen (not requiring high flow oxygen devices)
  - Non-invasive ventilation or high-flow oxygen devices
  - Invasive mechanical ventilation
  - Extracorporeal Membrane Oxygen ventilation (ECMO)
- Clinical Status using Ordinal Scale
  - 1 = Death
  - 2 = Hospitalized, requiring invasive mechanical ventilation or ECMO
  - 3 = Hospitalized, requiring non-invasive ventilation or high flow oxygen devices
  - 4 = Hospitalized, requiring supplemental oxygen
  - 5 = Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise)
  - 6 = Hospitalized, nor requiring supplemental oxygen – no longer requires ongoing medical care
  - 7 = Not hospitalized

Hospital or ICU stay – (selected from Hospital – ICU Admission and Discharge CRF)

- Length of hospital stay including ICU prior to the first dose date (days)
- Admitted into ICU during hospital stay prior to the first dose date (yes/no)
- Length of ICU stay prior to the first dose date (days)

4.2. Medical History

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

Medical history will include the following:

- Prior and current symptoms related to COVID-19
- Child-bearing potential/Menopausal history in women

4.3. Prior / Concomitant Medications or Procedures

Medications/Procedures will be recorded from the day of informed consent until the final study visit. Medications will be coded using the WHO Drug Dictionary (WHODD). 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 visit. This includes medications that were started before the study and are ongoing during the study

A targeted list of following medications are expected to be recorded by the sites in the CRFs.

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

Prior/Concomitant medications of interest for COVID-19: medications will be adjudicated in blinded manner by medical directors before database lock.

4.4. Rescue Medication/or Prohibited Medication During Study

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

Patients are not permitted to receive any medication specified in the exclusion criteria for study enrollment. Patients may otherwise continue their normal regimen of medications and procedures.

SARS-CoV-2 Vaccination. Current CDC guidance recommends deferral of SARS-CoV-2 vaccination for at least 90 days after administration of passive antibody treatment (eg, REGN10933+REGN10987) (CDC, 2020):

> *Based on the estimated half-life of such therapies as well as evidence suggesting that reinfection is uncommon in the 90 days after initial infection, vaccination should be deferred for at least 90 days, as a precautionary measure until additional information becomes available, to avoid interference of the antibody treatment with vaccine-induced immune responses.*

4.5. Efficacy Endpoints

4.5.1. Primary Endpoints

4.5.1.1. Primary Virologic Efficacy Endpoint

The **primary** virologic endpoint is time-weighted average change from baseline viral load in NP sample through day 7, as measured by quantitative reverse transcription polymerase chain reaction (RT-qPCR) in nasopharyngeal (NP) swab sample. The primary analysis will be performed for the Seronegative mFAS.

Time-weighted average of change from baseline in viral load in the NP swab samples will be calculated for each patient using the 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 (e.g., time interval will be 6 days for the observation period day 1 through day 7, or 10 days for observation period day 1 through day 11, etc.). This endpoint represents the reduction in average (mean) daily viral load from baseline.

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

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

Where

- k refers to the number of post-baseline assessments (e.g., k=3 for 3 post-baseline assessments through day 7, i.e., day 3, day 5, and day 7)
- D_i is the change from baseline in viral load value ($\log_{10}$ 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, for i = 1 to 3 where the postbaseline assessment is taken
- If the D_i is missing due to failed test or other reasons, only the time points with non-missing values will be included in the calculation. For example, we will calculate the TWA till day 7. 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

$$TWA_{[0-3]} = [(t_1 - t_0) * (D_1 + D_0)/2 \ + (t_3 - t_1) * (D_3 + D_1)/2]/(t_3 - t_0)$$

Time-weighted average (TWA) change from baseline in viral load in any sample (nasopharyngeal, nasal or saliva) from day 1 through post-baseline day X is as described above. It represents the reduction in average (mean) daily viral load for the observation period of day 1 through day X.

Baseline is defined as the last non-missing viral load value (copies/mL) prior to the study drug infusion, unless specified otherwise. Patients with a missing baseline value will be excluded from the analysis.

Since viral load values (copies/mL) are expected to be highly skewed, these raw values will be transformed on $\log_{10}$ scale to achieve symmetric distribution that can be approximated with normal distribution.

Viral load below the lower limit of detection (LLOD) of the assay (i.e., 299 copies/mL) will be imputed with 1 copy/mL, i.e., 0 $\log_{10}$ copies/mL. Viral load values below the lower limit of quantification (LLOQ) of the assay (i.e., 714 copies/mL) but have positive results on the qualitative assay will be imputed as LLOQ/2 = 357 copies/mL. The upper limit of quantification of assay (ULOQ) is 71 million copies/mL (i.e., ~7.85 $\log_{10}$ copies/mL). Original assay test results above the upper limit of quantification (>ULOQ) of the assay will be replaced by results based on the diluted and reflexed testing results, when available. Otherwise, the ULOQ will be used in the analysis.

Change from baseline at day X in viral load in any sample is the post-baseline viral load at day X minus viral load at day 1. Change from baseline and TWA change from baseline will be derived based on $\log_{10}$ copies/mL.

Percent change from baseline is the change from baseline divided by day 1 viral load. Percent change from baseline will be derived based on raw copies/mL.

4.5.1.2. Primary Clinical Efficacy Endpoint

The **primary** clinical endpoint is death or mechanical ventilation. It will be estimated by the proportion of patients who died or went on mechanical ventilation from day 6 through day 29 and from day 1 through day 29. The endpoint and populations are listed in Table 3.

The proportion from day 6 to day X = (Total number of patients who died between day 6 to day X [days inclusive], or ever had ordinal scale = 2 (mechanical ventilation/ECMO) at any timepoint on or after day 6 through day X)/(Total number in the treatment group), where the following patients will be excluded from both numerator and denominator.

- Patients who died before day 6 or
- Patients who went on mechanical ventilation before day 6 or
- Patients who dropped out from study before day 6

The proportion from day 1 to day X = (Total number of patients who died on or before day X, or ever had ordinal scale = 2 (mechanical ventilation/ECMO) at any timepoint through day X)/(Total number in the treatment group)

Table 3: Primary Clinical Efficacy Endpoints and Populations

Endpoint	Timepoint	Population
Proportion of patients who died or went on mechanical ventilation (for cohort 1 and cohort 1A)	day 6 to day 29	1. High Viral Load mFAS 2. Seronegative mFAS, 3. mFAS
	day 1 to day 29	1. High Viral Load mFAS 2. Seronegative mFAS, 3. mFAS

Definitions of death or mechanical ventilation:

Death or mechanical ventilation is derived based on the patient vital status and the mechanical ventilation use recorded on Clinical status using an Ordinal Scale eCRF which is described in the following paragraphs. The patients who went on mechanical ventilation are those whose ordinal scale was 2.

Clinical status using Ordinal Scale: The ordinal scale provides an assessment of the clinical status of a patient (Peterson, 2017 [1]). The 7-point ordinal scale is as follows:

1 = Death

2 = Hospitalized, requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)

3 = Hospitalized, requiring non-invasive ventilation or high flow oxygen devices

4 = Hospitalized, requiring supplemental oxygen

5 = Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19-related or otherwise)

6 = Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care

7 = Not hospitalized

Clinical and oxygen status, vital status and hospitalization status will be collected and recorded on the CRFs as follows.

- *Clinical and Oxygen Status – At Randomization* CRF; *Clinical and Oxygen Status – Pre-dose* CRF; and *Clincal and Oxygen Status* – Post-dose visits CRF:
  - Use of supplemental oxygen: Yes/No
  - Type of Oxygen delivery device/ventilation, if using supplemental oxygen: Supplemental oxygen (not requiring high flow oxygen devices), Non-invasive ventilation or high flow oxygen devices,

Invasive mechanical ventilation, Extracorporeal membrane oxygenation (ECMO)

- Vital status: Record vital status (dead or alive) of the day
- Hospitalization Status: Starting on day 2, record daily whether patient is hospitalized without requiring medical care or discharged.

- *Hospital – ICU Admission and Discharge* CRF: Record hospital discharge (if applicable) on the day of discharge
- *Death Details* CRF: Record any death (if applicable) on the day of death.

An ordinal scale score will be generated in the electronic database based on the records on clinical and oxygen status.

4.5.2. Secondary Endpoints

4.5.2.1. Secondary Virologic Efficacy Endpoints

The virologic efficacy endpoints are listed in Table 4. Definitions of the endpoints are described in subsections below.

Table 4: Secondary Virologic Efficacy Endpoints and Populations

Endpoint	Timepoint	Population
Time-weighted average change from baseline viral load in NP sample	Through day 7	mFAS
Time-weighted average change from baseline viral load in NP sample	Through day 7	Baseline Viral load categories ($>10^5$, $>10^6$ copies/mL) mFAS
Time-weighted average change from baseline viral load in NP sample	Through day 11	Seronegative mFAS
Time-weighted average change from baseline viral load in NP sample	Through day 11	mFAS
Time-weighted average change from baseline viral load in NP sample	Through day 11	Baseline Viral load categories ($>10^5$, $>10^6$ copies/mL) mFAS
Time-weighted average change from baseline, change from baseline, and percent change from baseline in viral load in NP sample	Through each post-baseline timepoint until day 29	1. Seronegative mFAS, 2. Baseline Viral load categories ($>10^5$, $>10^6$copies/mL) mFAS, 3. mFAS

The time-weighted average change from baseline, change from baseline, and percent change from baseline in viral load in NP sample are defined in Section 4.5.1.1.

4.5.2.2. Secondary Clinical Efficacy Endpoint

The secondary clinical efficacy endpoints and populations are defined in Table 5. All clinical outcomes derived from the ordinal scale (Section 4.5.1.2) will be based on data until day 29.

Definition of readmission

Readmission to hospital will also be based on what investigators report on *Hospital – ICU Admission and Discharge* CRF.

Table 5: Secondary Clinical Efficacy Endpoints and Populations

Endpoint	Timepoint	Population
Proportion of patients who went on mechanical ventilation (for cohort 1 and cohort 1A)	By day 29	1.High viral load mFAS, 2.Seronegative mFAS, 3. mFAS;
Proportion of patients who died	• day 6 to day 29 • day 1 to day 29	
Proportion of patients who were discharged	By day 29	
Proportion of patients who died or were readmitted	All available follow-up data	
Cumulative incidence of Death (i.e. Overall Survival)	All available follow-up data	
Cumulative incidence of Mechanical Ventilation (for cohort 1 and cohort 1A)	All available follow-up data up to day 29	
Cumulative incidence of Death or Mechanical Ventilation (for cohort 1 and cohort 1A)	All available follow-up data up to day 29	
Time to Discharge	All available follow-up data	

4.5.2.3. Clinical Endpoints based on Proportions

Clinical endpoints based on proportions will be computed as numerator over denominator as given in Table 6.

Table 6: Secondary Clinical Endpoints based on Proportions of Patients with Outcome

Number	Endpoint	Timepoint	Numerator	Denominator
1.	Died	day 6 to day X	Total number of patients who died after day 5 and on or before day X (death data will captured from any CRF in the study)	Number of patients in the treatment group excluding patients who died or dropped out before day 6

		day 1 to day X	Total number of patients who died on or before day X (death data will captured from any CRF in the study)	Number of patients in the treatment group
2.	Went on Mechanical Ventilation	Through day X	Number of patients who ever went on mechanical ventilation or ECMO (ordinal scale =2) through day X	Number of patients in the treatment group
3.	Discharge	Through day X	Number of patients who discharged through day X	Number of patients in the treatment group
4	Death or readmission	Through end of study	Number of patients who died or readmitted into hospital during the study	Number of patients in the treatment group

4.5.2.4. Clinical Endpoints based on Time and Events

Definitions of cumulative incidence of event efficacy endpoints and censoring rules are given in Table 7.

Table 7: Cumulative Incidence of Event Endpoints - Definitions of Events and Censoring Rules

Endpoint	Event and Time	Censor and Time	Observation Period
Cumulative Incidence of Death	Event = patient died Time is days since first dose date, i.e., (Date of death – Date of first dose)	Censor = patient is alive Time is days alive = (last follow-up date – Date of first dose)	day 1 through day 169 (Phase 1 patients only) day 1 through day 57 (Phase 2/3 patients)
Cumulative Incidence of Mechanical Ventilation	Event = patient ever went on mechanical ventilation Time is days since first dose date until first event of ventilation, i.e., (Date of first mechanical ventilation – Date of first dose)	Censor otherwise (even if never ventilated and died) Time is days since first dose until last follow-up = (last follow-up date – Date of first dose)	day 1 through day 29
Cumulative Incidence of Death or Mechanical Ventilation	Event = patient died or patient ever went on mechanical ventilation Time is days since first dose date until the death date or the earliest date of the ordinal scale reaching 2, whichever is earlier, i.e. (min (Death Date, Date of first mechanical ventilation) – Date of first dose))	Censor otherwise The censor date is the last follow-up date. Time is days since first dose until last follow-up = (last follow-up date – Date of first dose)	day 1 through day 29

Endpoint	Event and Time	Censor and Time	Observation Period
Time to Discharge	Event = First discharge and alive Time is days since first dose date until first discharge, i.e., (Date of first discharge – Date of first dose)	Censor otherwise If alive, then Time = (End of study date – Date of first dose) If died, then Time = 168 days for Phase 1 patients or 56 days for Phase 2/3 patients	day 1 through day 169 (Phase 1 patients) day 1 through day 57 (Phase 2/3 patients)

4.5.3. Exploratory Endpoints

The exploratory endpoints include:

- Proportion of patients with treatment failure having mutations in the gene encoding the SARS-CoV-2 S protein through day 29
- Change and percentage change in neutrophil-lymphocyte ratio (NLR) at each visit through day 29
- Change and percentage change in D-dimer at each visit through day 29
- Change and percentage change in ferritin at each visit through day 29
- Change and percentage change in C-reactive protein (CRP) at each visit through day 29
- Change and percentage change in lactate dehydrogenase (LDH) at each visit through day 29

4.6. Safety Variables

4.6.1. Adverse Events and Serious Adverse Events

Treatment-emergent adverse events (AEs) (grade 3 or 4; for phase 1 only), treatment-emergent serious adverse events (SAEs) and treatment-emergent adverse events of special interest (AESIs) will be collected according to the Schedule of Events (Appendix 10.1 and Appendix 10.2). All adverse events are to be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

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

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

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

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 AEs, treatment-emergent SAEs, or treatment-emergent AESIs not listed in the NCI-CTCAE will be graded according to the scale in Table 8.

Table 8: 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 done.

In this study, the AESIs are listed below:

- Grade ≥2 infusion related reactions
  - selected from Adverse Events CRF
- Grade ≥2 hypersensitivity reactions
  - selected from Adverse Events CRF

4.6.3. Laboratory Safety Variables

Blood Chemistry

Samples for laboratory testing will be collected at visits according to the schedule of events in Section 10.2.

Tests will include:

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

Hematology

Hematology, urinalysis, and pregnancy testing samples will be analyzed by the local laboratory.

Tests will include:

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

Other Laboratory Tests

Coagulation tests: D-dimer, prothrombin time (PT/INR), activated partial thromboplastin time (aPTT).

Laboratory results, vital signs, and other diagnostic results or findings that are appraised by the investigator and determined by investigator to fulfil the criteria of TEAEs (grade 3 or 4), treatment-emergent SAEs, or treatment-emergent AESIs will be reported.

4.6.4. Vital Signs

Vital signs, including temperature, blood pressure, pulse, pulse oximetry and respiratory rate are recorded according to Schedule of Events table (See Section 10.2).

Body weight and height are recorded according to Schedule of Events table (See Section 10.2).

Supplemental oxygen/FiO_2 use will be measured at baseline to monitor the patient's status regarding gas exchange. As applicable, the following will be recorded:

- Oxygen flow rate in L/min (if not mechanically ventilated)
- FiO_2 (if mechanically ventilated)
- Resting SpO_2 (in %)

4.7. Pharmacokinetic Variables

The PK variable is the concentration of REGN10933 and REGN10987 antibodies in serum and sampling time that a sample was collected as specified in the Schedule of Events table (See Section 10.2).

4.8. Immunogenicity Variables

The immunogenicity variables are ADA and (in phase 2 and phase 3 only) NAb status, titer, and time-point/visit. Serum samples for ADA will be collected at the visits as specified in Section 10.2. Samples positive in the ADA assay will be further characterized for ADA titers and for the presence of NAb.

5. STATISTICAL METHODS

For continuous variables, descriptive statistics will include the following: the number of patients reflected in the calculation (n), mean, Q1, median, Q3, standard deviation (sd), 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 by treatment group, and all groups combined. These will be analyzed for FAS and mFAS populations. Similar analysis will be performed by baseline serostatus and baseline viral load categories ($\leq 10^6$ copies/mL and $>10^6$ copies/mL) for mFAS population.

5.2. Medical History

Medical history will be summarized by SOC (system organ class) and PT (preferred term) and by treatment group and all groups combined in the mFAS and FAS population.

5.3. Prior / Concomitant Medications or Procedures

Prior or concomitant medications/procedures will be summarized by treatment groups. 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) in the FAS and mFAS populations.

Number and proportion of patients undergoing a prior/concomitant procedure(s) will be summarized, sorted by decreasing frequency of SOC and PT based on the incidence in the overall group incidence (or high dose group incidence in tables where the overall is not presented). Patients will be counted only once for each SOC and PT linked to the procedure.

Prior or concomitant medications/procedures of interest for COVID-19 will be summarized similarly.

5.4. Subject Disposition

The following summaries will be provided for both mFAS and FAS populations.

- The total number of randomized patients: received a randomization number
- The total number of randomized patients who were not treated by study drug
- The total number of randomized patients who discontinued the study, and the reasons for discontinuation
- A summary of analysis sets including FAS, mFAS, SAF, PK, immunogenicity (ADA), and NAb analysis set (NAS) (Section 3).

5.5. Extent of Study Treatment Exposure

5.5.1. 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 (ie, patients completed the full dose but had infusion interruptions)
- Number of patients with infusion discontinuation (ie, patients didn't completed the full dose infusion)

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

5.6. Analyses of Efficacy Endpoints

The efficacy analyses will be performed for the following subjects on all efficacy endpoints, separately. The comparisons in all efficacy endpoints will be performed between the the REGN10933+REGN10987 2.4g and 8.0g combined dose group and placebo group as well as between each treatment group and placebo group.

- Pooled phase 3 Cohort 1 and phase 2 cohort 1A subjects
- Phase 3 Cohort 1 subjects (ie, subjects randomized after 01DEC2020 in Cohort 1)
- Phase 2 cohort 1A subjects

5.6.1. Analysis of Primary Efficacy Endpoints

5.6.1.1. Analysis of Primary Virologic Efficacy Endpoint

The primary analysis on the comparison between the the REGN10933+REGN10987 2.4g and 8.0g combined dose group and placebo with respect to the virologic endpoint of time-weighted average daily change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7 and other post-baseline visit timepoint will be performed in the Seronegative mFAS in the pooled phase 3 cohort 1 and phase 2 cohort 1A patients. The estimand for the analysis is the difference in means between the the REGN10933+REGN10987 2.4g and 8.0g combined dose group and placebo in the pooled phase 3 cohort 1 and phase 2 cohort 1A patients. Data collected after use of convalescent plasma therapy or other antispike monoclonals will be excluded from efficacy analysis. All other available data will be used in the analysis regardless of intercurrent events such as rescue medication or discontinuation, i.e., treatment policy approach.

The analysis will be based on the observed data with no imputation for missing data except as defined in Section 4.5.1.1 for viral load values that are below lower limit of detection (<LLOD), below lower limit of quantification (<LLOQ) or above upper limit of quantification (>ULOQ) of the assay.

The variable will be analyzed using the Analysis of Covariance (ANCOVA) model with treatment group and the type of background standard-of-care as fixed effects, and baseline viral load and treatment by baseline interaction as covariates.

The least squares means estimates for time-weighted average daily change from baseline in viral load for each treatment group, as well as the difference between the REGN10933+REGN10987 2.4g and 8.0g combined doses and placebo as well as between each individual dose treatment group and placebo, will be provided along with the corresponding two-sided p-value, standard error, and associated 95% confidence interval.

5.6.1.2. Analysis of Primary Clinical Efficacy Endpoints

The primary efficacy analysis will be the comparison between the the REGN10933+REGN10987 2.4g and 8.0g combined dose group and placebo in the pooled phase 3 cohort 1 and phase 2 cohort 1A patients. The primary clinical endpoint defined in Section 4.5.1.2 will be analyzed using the landmark analysis approach for day 6 through day 29, as well as analyzed for day 1 through day 29 in the order specified in Section 5.6.3.

The proportion of patients who died or went on mechanical ventilation will be analyzed using either the exact method for binomial distribution or asymptotic normal approximation method. If the number of events is small (e.g., $np \leq 5$ or $n(1-p) \leq 5$ in any treatment group, where n is the number of patients in the treatment group and p is the proportion of events), then the Fisher's exact test will be applied. Otherwise, stratified Cochran-Mantel Haenszel (CMH) test, stratified by the type of background standard-of-care (antiviral therapies and non-antiviral therapies), will be applied. Relative risk and relative risk reduction and corresponding 95% confidence intervals compared to placebo group will be estimated by Farrington-Manning method. Missing data will be considered as non-events.

The analysis will be performed for the High Viral Load mFAS, the Seronegative mFAS, and the overall mFAS.

5.6.2. Descriptive Analysis of Secondary Efficacy Endpoints

All analyses for the secondary efficacy endpoints are descriptive and all p-values are nominal.

5.6.2.1. Descriptive Analysis of Secondary Virologic Efficacy Endpoints

The time-weighted average daily change from baseline in viral load (log_{10} copies/mL) from day 1 to all post-baseline visit timepoints will be descriptively analyzed similar to primary virologic analysis for patients by serostatus in mFAS, by baseline viral load ($\leq 10^5$ vs $>10^5$ copies/mL and $\leq 10^6$ vs $>10^6$ copies/mL) (with serostatus added to the ANCOVA model as a factor) in the mFAS, and overall mFAS (with serostatus added to the ANCOVA model as a factor).

To assess the time course of treatment effect in viral load, the change from baseline in viral load (log10 copies/mL) at each visit for seronegative mFAS and overall mFAS will be analyzed using

a mixed-effect model for repeated measures (MMRM) with terms for baseline viral load, type of background standard-of-care, treatment, visit, treatment by baseline interaction, baseline by visit interaction, and treatment-by-visit interaction. Within-patient errors will be modeled with an unstructured covariance matrix. The least squares means estimates for the mean at each visit and mean change from baseline to each visit as well as the difference of these estimates between each anti-S mAb treatment arm and placebo will be provided along with the corresponding standard error, p-value, and associated 95% confidence interval. The percentage change from baseline in viral load in raw scale at each visit will be back-transformed from the $\log_{10}$-transformed viral load and presented along with the change from baseline in viral load (log10 copies/mL). The analysis will be performed for patients by serostatus in the mFAS, by baseline viral load ($\leq 10^5$ vs $>10^5$ copies/mL and $\leq 10^6$ vs $>10^6$ copies/mL) (with serostatus added to the MMRM model as a factor) in the mFAS, and in overall mFAS (with serostatus added to the MMRM model as a factor).

5.6.2.2. Descriptive Analysis of Secondary Clinical Efficacy Endpoints

All clinical endpoints based on proportions (defined in Section 4.5.2.3) will be analyzed using similar methods as for the primary clinical efficacy endpoint described in Section 5.6.1.2. The analysis will be performed for patients by baseline viral load ($\leq 10^6$ vs $>10^6$ copies/mL) in the mFAS, by serostatus in the mFAS, and in overall mFAS.

All clinical endpoints based on time-to-event (defined in Section 4.5.2.4) will be estimated using the Kaplan-Meier method and comparisons between treatment groups will be made using the stratified log-rank test with the type of background standard-of-care as stratification factor. P-values will be compared with 0.05 (two-sided).

The log-rank "observed minus expected" statistic (and its variance) will be used to calculate the one-step estimate of the event rate ratio and confidence interval for each pairwise comparison versus placebo group (Peto 1977) [2].

As sensitivity analysis, the hazard ratio and its 95% CI will be estimated by the Cox proportional-hazards regression model with terms for treatment group, and type of background standard-of-care. P values from the stratified log-rank test will be reported. Hazard ratio (HR) < 1 will imply reduction of hazard of REGN10933+REGN10987 versus placebo. Estimates of median times along with 25^{th} and 75^{th} percentiles (if median and quartiles are reached) and associated two-sided 95% CI will be reported using the Kaplan-Meier method.

Landmark analysis starting from day 6 will be performed using similar Cox proportional-hazard model on the cumulative incidence of death or mechanical ventilation and cumulative incidence of death. The patients with corresponding events occurring before day 6 and patients who drop out early from study before day 6 will be excluded from the analysis (Dafni, U. 2011) [3].The analysis will be performed for patients by baseline viral load ($\leq 10^6$ vs $>10^6$ copies/mL) in mFAS (with baseline serostatus added to the stratified log-rank test and the Cox model as a factor), by serostatus in mFAS, and overall mFAS (with baseline serostatus added to the stratified log-rank test and the Cox model as a factor).

5.6.3. Adjustment for Multiple Comparisons

Multiplicity Considerations

The following multiplicity adjustment approach, a hierarchical procedure, will be used to control the overall Type-1 error rate at 0.05 for the primary virologic and clinical outcome endpoints in comparison between the combined doses of REGN10933+REGN10987 treatment group and placebo group in the pooled phase 3 cohort 1 and phase 2 cohort 1A patients. Each hypothesis will be formally tested only if the preceding one is significant at the 2-sided 0.05 significance level. The hierarchical testing order is shown in Table 9.

Table 9: Hierarchical testing order

Type	Description	Testing Order
Primary virologic outcome	Time-weighted average change from baseline viral load in NP sample through day 7 **in seronegative mFAS** for comparing the combined doses of REGN10933+REGN10987 versus placebo	1
Primary clinical outcome	Proportion of patients who died or went on machenical ventilation **from day 6 to day 29 in High Viral Load mFAS** for comparing the combined doses of REGN10933+REGN10987 versus placebo	2
	Proportion of patients who died or went on machenical ventilation **from day 6 to day 29 in Seronegative mFAS** for comparing the combined doses of REGN10933+REGN10987 versus placebo	3
	Proportion of patients who died or went on machenical ventilation **from day 6 to day 29 in overall mFAS** for comparing the combined doses of REGN10933+REGN10987 versus placebo	4
	Proportion of patients who died or went on machenical ventilation **from day 1 to day 29 in High Viral Load mFAS** for comparing the combined doses of REGN10933+REGN10987 versus placebo	5
	Proportion of patients who died or went on machenical ventilation **from day 1 to day 29 in Seronegative mFAS** for comparing the combined doses of REGN10933+REGN10987 versus placebo	6
	Proportion of patients who died or went on machenical ventilation **from day 1 to day 29 in overall mFAS** for comparing the combined doses of REGN10933+REGN10987 versus placebo	7

All other analyses for virologic and clincal endpoints will be reported descriptively for each individual cohort and for pairwise comparison of each REGN10933+REGN10987 dose group (2.4 g IV or 8.0 g IV) versus placebo.

5.6.4. Analysis of Exploratory Endpoints

The change and percentage change in NLR, D-dimer, ferritin, CRP, and LDH will be summarized at each visit through day 29 using descriptive statistics for mFAS and FAS.

The proportion of patients with treatment failure having mutations in the gene encoding the SARS-CoV-2 S protein through day 29 will be analyzed in separate report.

5.7. Analysis of Safety Data

The analysis of safety data will be performed for cohort 1 in combined phases 1, 2 and 3, phase 2 cohorts 1A, 2 and 3, separately in the FAS population.

In this study, only targeted treatment-emergent adverse events will be recorded:

- All phases: Treatment-emergent adverse events of special interest (AESIs)
  - Grade ≥2 hypersensitivity
  - Grade ≥2 infusion-related reactions
- All phases: Treatment-emergent serious adverse events (SAEs)
- All phases: TEAEs (Grade 3 or Grade 4 only)

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 and vital signs are defined in Section 10.3.

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

5.7.1. Adverse Events

Summaries that include frequencies and proportions of patients reporting AEs will include the PTs and the SOCs.

An overview of adverse events will be provided by treatment group and for combined dose groups of R10933+R10987, including:

- Total number of TEAEs, SAEs, Total number of AESIs, Serious AESIs, Grade 3 or 4 TEAEs, as well as
- The number and percentage of patients with
  - any TEAE, any SAE, any AESI, any serious AESI, any grade 3 or grade 4 TEAE, any fatal TEAEs, any TEAEs leading to withdrawal from the study, any TEAEs leading to study infusion discontinuation, and any TEAEs leading to study infusion interruption.

Summaries of SAEs and AESIs by treatment group and for combined R10933+R10987 doses will include number (n) and percentage (%) of patients with at least :

- Treatment-emergent AE by SOC and PT
- Treatment-emergent AE by SOC and PT and CTCAE grade

- Treatment-emergent AE related to study treatment by SOC and PT
- Treatment-emergent SAE by SOC and PT
- Treatment-emergent AESIs presented by SOC and PT
- Treatment-emergent grade 3 or 4 AEs presented by SOC and PT

Counts will be provided according to treatment group for each PT within each SOC. Percentages will be calculated using the number of patients from the FAS in each treatment group.

Primary SOCs will be sorted according to decreasing order of frequency in combined treatment group. Within each primary SOC, PTs will be sorted by decreasing frequency in combined treatment group.

5.7.2. Clinical Laboratory Measurements

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

A treatment-emergent Potential Clinically Significant abnormal value (PCSV) is a laboratory value that was normal at Screening and Baseline but abnormal after treatment with study drug. See Appendix 10.3 for the criteria of PCSV values.

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

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

5.7.3. Analysis of Vital Signs

Vital signs (temperature, pulse, blood pressure, SpO_2, FiO_2, and respiration rate) will be summarized using descriptive statistics. Number and percentage of patients with a potentially clinically significant value (PCSV) at any post-randomization time point will be summarized.

5.8. Analysis of Pharmacokinetics, Pharmacodynamics and Biomarker Data

5.8.1. Analysis of Drug Concentration Data

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

Phase 1 (Dense Sampling)

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

- C_{max}
- C_{max}/Dose
- t_{max}
- AUC_{last}
- AUC_{inf}
- AUC_{inf}/Dose
- $t_{1/2}$
- CL
- V_{SS}
- MRT

Selected PK parameters will be summarized by descriptive statistics by treatment group. All parameters will be summarized (mean, SD, %CV, range, median, and number of samples).

5.8.2. Analysis of Pharmacokinetics and Pharmacokinetics/Pharmacodynamics

At a minimum the viral-exposure response analysis will be performed.

5.9. Analysis of Immunogenicity Data

5.9.1. 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 (only applicable to phase 1) – 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 groups and ADA titer categories

- 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.

5.9.2. 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.

5.10. Association of Immunogenicity with Exposure, Safety, and Efficacy

5.10.1. 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.

5.10.2. Immunogenicity and Safety and Efficacy

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

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

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

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

- ADA positive subjects: Subjects with treatment-emergent or treatment-boosted response.
- Maximum post-baseline titer.
- NAb positive

6. DATA CONVENTIONS

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

6.1. Definition of Baseline for Efficacy/Safety Variables

Definitions of baseline for efficacy variables are defined in Section 4.5.1.1. Baseline viral load value will be the latest available valid measurement before the administration of study drug or the measurement taken within 2 hours after the administration of study drug if the pre-treatment measurement is missing.

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

The virologic endpoint analysis will be based on the observed data with no imputation for missing data except as defined in Section 4.5.1.1 for viral load values that are below lower limit of detection (<LLOD), below lower limit of quantification (<LLOQ) or above upper limit of quantification (>ULOQ) of the assay.

In the analysis for the clinical endpoints based on proportions of patients with the event, the missing data will be considered as non-events.

6.3. Data Handling Convention for Missing Data

For categorical variables, patients with missing data will be included in calculation 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 AE Missing and Partial Start Dates

Every effort will be made to collect the start dates of all AEs. However, in the case the start date of an AE is incomplete or missing, it will be assumed to have occurred on or after the first dose of study medication, except if an incomplete date (e.g., month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the first dose of study medication date, then the start date of the first dose will be imputed, otherwise, the missing day or month by the first day or the first month will be imputed.

Handling of Adverse events Severity and Relatedness

If the intensity of an SAE or AESI is missing, it will be classified as “Grade 3” in the frequency tables by CTC grade of SAE or AESIs. If the assessment of relationship of the investigational product is missing, it will be classified as related to the investigational product.

Date of infusion

Date of infusion is the non-missing administration date filled in the Drug Administration–Infusion CRF. If the first dose of study drug administration date is missing (even after site is queried), then the dosing date is 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 the "Schedule of Events" Appendices 10.1 and 10.2. 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 and discharge visit.

The following analysis visit windows will be used to map the unscheduled visits, ETV and EOT visits for Nasopharyngeal swab, saliva and nasal samples for SARS-CoV-2 RT-qPCR, based on the study day during the study:

Table 10: Time Window for Summary of Swab Samples for SARS-CoV-RT-qPCR

Visit Label	Targeted Study Day	Analysis Window in Study Day
Baseline	1	≤ 1
Day 3	3	[2, 3]
Day 5	5	[4, 5]
Day 7	7	[6, 7]
Day 9	9	[8, 9]
Day 11	11	[10, 11]
Day 13	13	[12, 13]
Day 15	15	[14, 18]
Day 22	22	[19, 25]
Day 29	29	[26, 32]

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

Table 11: Time Window for Summary of Laboratory Variables and Biomarkers

Visit Label	Targeted Study Day	Analysis Window in Study Day
Baseline	1	≤ 1
Day 7	7	For phase 1 [2, 18] For phase 2/3 [2, 11]
Day 15	15	For phase 2/3 only [12, 22]
Day 29	29	For phase 1 [19, 32] For phase 2/3 [23, 32]
Day 57	57	For phase 1 only [33,71]

6.5. Pooling of Centers for Statistical Analyses

Data from countries (US and non-US) will be pooled in the phase 1/2/3 analysis.

7. INTERIM ANALYSIS

This SAP is for the final analysis of the study. No interim analyses were planned or conducted for Phase 3 portion of the study.

8. SOFTWARE

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

9. REFERENCES

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2. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Peto J and Smith PG. Design and analysis of randomized clinical trials requiring prolonged observation of each patient - II Analysis and Examples. British Journal of Cancer 1977; 35, 1.
3. Dafni, U. (2011). Landmark analysis at the 25-year landmark point. Circulation: Cardiovascular Quality and Outcomes, 4(3), 363-371.

10. APPENDIX

10.1. Schedule of Events for Phase 1 (Cohort 1)

Day	Screening/Baseline[1]				Hospitalization/Post-Discharge Period[2]																						EOS
	-1 to 1				Discharge Before Day 29	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16, 17, 18, 19, 20, 21	22	23, 24, 25, 26, 27, 28	29	57	85	113	141	169
	Screen	Pre-Dose	Dose	Post-Dose																							
Week Number	1					1	1	1	1	1	1	2	2	2	2	2	2	2	3	3	4	4	5	9	13	17	21	25
Visit Number	1					2	3	4	5	6	7	8	9	10	11	12	13	14	15	16-21	22	23-28	29	30	31	32	33	34
Window (Days)					±1								±1		±1		±1		±1		±3		±3	±7	±7	±7	±7	±7
Screening/Baseline Only																												
Informed consent	X																											
PGx sub-study consent (optional)[3]	X																											
Inclusion/exclusion	X																											
Antigen or molecular diagnostic test for SARS-CoV-2 (local)[4]	X																											
Demographics	X																											
Medical history[5]	X																											
Weight and height	X																											
Randomization		X																										
Treatment																												
Study drug administration			X																									
Safety Assessments																												
Vital signs[6]	X	X	X																									
Treatment-emergent grade ≥2 infusion-related reactions[7,8]			← Continuous monitoring →																									
Treatment-emergent grade ≥2 hypersensitivity reactions[7,8]			← Continuous monitoring →																									
Treatment-emergent SAEs[7,8]			← Continuous monitoring →																									
Grade 3 or 4 TEAEs[7,8]			← Continuous monitoring →																									
Targeted concomitant medications[8,9]	X	X	← Continuous monitoring →																									
Post-discharge phone follow-up[8]												X							X		X		X	X	X	X	X	X

Day	Screening/Baseline[1]				Hospitalization/Post-Discharge Period[2]																						EOS
	-1 to 1				Discharge Before Day 29	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16, 17, 18, 19, 20, 21	22	23, 24, 25, 26, 27, 28	29	57	85	113	141	169
	Screen	Pre-Dose	Dose	Post-Dose																							
Week Number	1					1	1	1	1	1	1	2	2	2	2	2	2	2	3	3	4	4	5	9	13	17	21	25
Visit Number	1					2	3	4	5	6	7	8	9	10	11	12	13	14	15	16-21	22	23-28	29	30	31	32	33	34
Window (Days)					±1								±1		±1		±1		±1		±3		±3	±7	±7	±7	±7	±7
Pregnancy test (WOCBP)[10]	X																										X
Local Laboratory Testing																											
Hematology (including differential)[11]	X				X						X												X	X				
Blood chemistry (including AST, ALT, CRP, ferritin, LDH)[11]	X				X						X												X	X				
Coagulation tests (D-dimer, PT/INR, aPTT)[11]	X				X						X												X	X				
Efficacy Assessments (Virologic)																											
Saliva for SARS-CoV-2 RT-qPCR		X			X		X		X		X		X		X		X		X		X		X					
Nasal swab for SARS-CoV-2 RT-qPCR		X			X		X		X		X		X		X		X		X		X		X					
NP swab for SARS-CoV-2 RT-qPCR		X			X		X		X		X		X		X		X		X		X		X					
Efficacy Assessments (Clinical/Oxygen Status)																											
Oxygen delivery device status[12]		X[12]	X[12]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Vital status[12]		X[12]	X[12]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Hospitalization status[12]		X[12]	X[12]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Pharmacokinetics/Immunogenicity																											
Serum for PK[13]		X[14]		X[14]	X		X		X		X								X				X	X		X		X
Serum for ADA[15]		X[15]			X																		X	X				X
Pharmacodynamic/Biomarkers																											
Serum for serology		X																					X					X
Pharmacogenomics Sub-Study (Optional)																											
Blood for RNA[3]		X[3]																									
Blood for DNA[3]		X[3]																									

10.1.1. Footnotes for Schedule of Events (Phase 1)

1. Every effort should be made to perform all screening and baseline activities on the same day. Randomization within the Interactive Response Technology (IRT) system and administration of study drug should occur on the same day (day 1). All samples will be collected before study drug administration at the baseline visit except post-infusion PK samples.
2. For a given day, the visit may occur in clinic, as a home-based visit (defined as visits by home health care staff, at mobile units, and/or testing centers), or by phone. All samples will be collected as indicated whether the patient is hospitalized or has been discharged.
3. Patients must provide separate consent to collect blood samples as part of the optional pharmacogenomics (PGx) sub-study. Blood sample for RNA must be collected pre-dose on day 1. Blood sample for DNA should be collected at the screening/baseline visit but may be collected at any visit.
4. Refer to protocol Section 9.2.1.2 for diagnostic test requirements during screening.
5. Medical history should include collecting onset of pneumonia symptoms.
6. Vital signs (including respiratory rate, temperature, blood pressure, heart rate, and SpO_2) will be taken as described in protocol Section 9.2.3.1.

   For patients in the phase 1 sentinel safety group only (protocol Section 3.1.1.1), vital signs will be taken once before the infusion, every 15 minutes during the infusion, every 30 minutes for the first 2 hours after the infusion is completed, and then once per hour for the following 4 hours. **For all other patients**, vital signs will be taken once before the infusion and once after the infusion is completed.
7. Only TEAEs (grade 3 or 4), treatment-emergent SAEs, and treatment-emergent AESIs will be recorded in the eCRF.
8. Patients discharged from the hospital may receive phone follow-up for TEAEs (grade 3 or 4), treatment-emergent SAEs, treatment-emergent AESIs, and/or targeted concomitant medications as indicated in the protocol table 1 (post-discharge phone follow-up). These visits may occur in addition to any in-person visit listed for the given day. Phone visits will have a window of ±1 day.
9. Medications will be reviewed and recorded. Only the targeted medications listed in protocol Section 9.2.3.3 will be recorded in the eCRF.
10. Pregnancy testing will be performed locally in women of childbearing potential (WOCBP) only. Negative pregnancy test must be confirmed prior to study drug administration. Serum or urine pregnancy test are both acceptable. Refer to protocol Section 9.2.3.4 for more information on pregnancy testing and contraceptive measures.

11. Hematology, blood chemistry, and coagulation tests will be collected at the visits indicated and results will be entered in the eCRF. Hematology, blood chemistry, and coagulation tests must be collected prior to randomization. Testing will be performed locally, and standard-of-care labs are acceptable.
12. Clinical and oxygen status will be collected 3 times during the screening/baseline visit period: prior to randomization, just prior to dosing, and post-dose. Clinical and oxygen status will be collected and recorded in the eCRF as described in protocol Section 9.2.5.2.
13. Actual dosing time and PK sample collection times will be recorded.
14. At the baseline visit, blood samples for PK assessment will be taken predose 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.
15. The window for predose ADA sample collection is as close to administration of study drug as is reasonable. Actual dosing times and ADA sample collection times will be recorded.

10.2. Schedule of Events for Phase 2/3 (Cohort 1A, Cohort 1, Cohort 2, Cohort 3)

Day	Screening/Baseline[1]				Hospitalization/Post-Discharge Period[2]																				Follow-up Period			EOS
	-1 to 1				Discharge Before Day 29	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16, 17, 18, 19, 20, 21	22	23, 24, 25, 26, 27, 28	29	36	43	50	57
	Screen	Pre-Dose	Dose	Post-Dose																							
Week Number	1					1	1	1	1	1	1	2	2	2	2	2	2	2	3	3	4	4	5	6	7	8	9
Visit Number	1					2	3	4	5	6	7	8	9	10	11	12	13	14	15	16-21	22	23-28	29	30	31	32	33
Window (Days)					±1								±1		±1		±1		±1		±3		±3	±3	±3	±3	±3
Screening/Baseline Only																											
Informed consent	X																										
PGx sub-study consent (optional)[3]	X																										
Inclusion/exclusion	X																										
Antigen or molecular diagnostic test for SARS-CoV-2 (local)[4]	X																										
Pregnancy test (WOCBP)[5]	X																										
Demographics	X																										
Medical history[6]	X																										
Weight and height	X																										
Randomization		X																									
Treatment																											
Study drug administration			X																								
Efficacy Assessments (Virologic)																											
NP swab for SARS-CoV-2 RT-qPCR		X			X		X		X		X		X		X		X		X		X		X				
Efficacy Assessments (Clinical/Oxygen Status)																											
Oxygen delivery device status[7]		X[7]	X[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Vital status[7]		X[7]	X[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Hospitalization status[7]		X[7]	X[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Safety Assessments																											
Vital signs[8]		X		X																							
Treatment-emergent grade ≥2 infusion-related reactions[9,10]			← Continuous monitoring →																								
Treatment-emergent grade ≥2 hypersensitivity reactions[9,10]			← Continuous monitoring →																								
Treatment-emergent SAEs[9,10]			← Continuous monitoring →																								

Day	Screening/Baseline[1]				Hospitalization/Post-Discharge Period[2]																			Follow-up Period			EOS
	-1 to 1				Discharge Before Day 29	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16, 17, 18, 19, 20, 21	22	23, 24, 25, 26, 27, 28	29	36	43	50	57
	Screen	Pre-Dose	Dose	Post-Dose																							
Week Number	1					1	1	1	1	1	1	2	2	2	2	2	2	2	3	3	4	4	5	6	7	8	9
Visit Number	1					2	3	4	5	6	7	8	9	10	11	12	13	14	15	16-21	22	23-28	29	30	31	32	33
Window (Days)					±1								±1		±1		±1		±1		±3		±3	±3	±3	±3	±3
Targeted concomitant medications[10,11]	X	X	← Continuous monitoring →																								
Post-discharge phone follow-up[10]												X							X		X		X	X	X	X	X
Pregnancy follow-up																											X
Local Laboratory Testing																											
Hematology (including differential)[12]	X				X						X								X				X				
Blood chemistry (including AST, ALT, CRP, ferritin, LDH)[12]	X				X						X								X				X				
Coagulation tests (D-dimer, PT/INR, aPTT)[12]	X				X						X								X				X				
Pharmacokinetics/Immunogenicity																											
Serum for PK[13]		X[14]		X[14]	X														X				X				
Serum for ADA[15]		X[15]			X																		X				
Pharmacodynamic/Biomarkers																											
Serum for serology		X			X																		X				
Serum for cytokines and CK-MB		X			X						X								X				X				
Serum for research and cardiac biomarkers		X			X						X								X				X				
Plasma for research and cardiac biomarkers		X			X						X								X				X				
Plasma for hsTroponin-T		X			X						X								X				X				
Pharmacogenomics Sub-Study (Optional)																											
Blood for RNA[3]		X[3]																									
Blood for DNA[3]		X[3]																									

10.2.1. Footnotes for Schedule of Events (Phase 2)

1. Every effort should be made to perform all screening and baseline activities on the same day. Randomization within the IRT system and administration of study drug should occur on the same day (day 1). All samples will be collected before study drug administration at baseline visit except post-infusion PK samples.
2. For a given day, the visit may occur in clinic, as a home-based visit (defined as visits by home health care staff, at mobile units, and/or testing centers), or by phone. All samples will be collected as indicated whether the patient is hospitalized or has been discharged.
3. Patients must provide separate consent to collect blood samples as part of the optional PGx sub-study. Blood sample for RNA must be collected pre-dose on day 1. Blood sample for DNA should be collected at the screening/baseline visit but may be collected at any visit.
4. Refer to protocol Section 9.2.1.2 for diagnostic test requirements during screening.
5. Pregnancy testing will be performed locally in women of childbearing potential (WOCBP) only. Negative pregnancy test must be confirmed prior to study drug administration. Serum or urine pregnancy test are both acceptable. Refer to protocol Section 9.2.3.4 for more information on pregnancy testing and contraceptive measures.
6. Medical history should include collecting onset of pneumonia symptoms.
7. Clinical and oxygen status will be collected 3 times during the screening/baseline visit period: prior to randomization, just prior to dosing, and post-dose. Clinical and oxygen status will be collected and recorded in the eCRF as described in protocol Section 9.2.5.2.
8. Vital signs (including temperature, blood pressure, heart rate, and SpO_2) will be collected pre-dose and post-dose, as described in protocol Section 9.2.3.1.
9. Only treatment-emergent SAEs and AESIs will be recorded in the eCRF.
10. Patients discharged from the hospital may receive phone follow-up for treatment-emergent SAEs, treatment-emergent AESIs, and/or targeted concomitant medications as indicated in protocol Table 2 (post-discharge phone follow-up). These visits may occur in addition to any in-person visit listed for the given day. Phone visits will have a window of ±1 day.
11. Medications will be reviewed and recorded. Only the targeted medications listed in protocol Section 9.2.3.3 will be recorded in the eCRF.
12. Hematology, blood chemistry, and coagulation tests will be collected at the visits indicated and results will be entered in the eCRF. Hematology, blood chemistry, and coagulation tests must be collected prior to dosing. Testing will be performed locally, and standard-of-care labs are acceptable.
13. Actual dosing time and PK sample collection times will be recorded.
14. At the baseline visit, blood samples for PK assessment will be taken predose 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.

15. The window for predose ADA sample collection is as close to administration of study drug as is reasonable. Actual dosing times and ADA sample collection times will be recorded.

10.3. 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.
Hematology		

Parameter	PCSV	Comments
WBC	<3.0 Giga/L or <LLN (if LLN≤3.0 Giga/L) and baseline ≥3.0 Giga/L or ≥LLN (if LLN≤3.0 Giga/L) (Non-Black); <2.0 Giga/L or <LLN (if LLN≤2.0 Giga/L) and baseline ≥2.0 Giga/L or ≥LLN (if LLN≤2.0 Giga/L) (Black)* ≥16.0 Giga/L or ≥ULN (if ULN≥16.0 Giga/L) and baseline < 16 Giga/L or <ULN (if ULN≥16.0 Giga/L)	Increase in WBC: not relevant. *The default criteria. Summary by race (black and Non-black) are optional. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L or >ULN (if ULN≥4.0 Giga/L) and baseline ≤ 4.0 Giga/L or ≤ULN (if ULN≥4.0 Giga/L)	
Neutrophils	<1.5 Giga/L or <LLN (if LLN≤1.5 Giga/L) for Non-Black or <1.0 Giga/L or <LLN (if LLN≤1.0 Giga/L) for Black and baseline ≥1.5 Giga/L or ≥LLN (if LLN≤1.5 Giga/L) for Non-Black or ≥1.0 Giga/L or ≥LLN (if LLN≤1.0 Giga/L) for Black* <1.5 Giga/L or <LLN (if LLN≤1.5 Giga/L) and baseline ≥1.5 Giga/L or ≥LLN (if LLN≤1.5 Giga/L) (Non-Black); <1.0 Giga/L or <LLN (if LLN≤1.0 Giga/L) and baseline ≥1.0 Giga/L or ≥LLN (if LLN≤1.0 Giga/L) (Black) <0.5 Giga/L regardless of baseline value or 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 r >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
Coagulation Parameters		
INR	>2.5	

Parameter	**PCSV**	**Comments**
PT	>2.5 x ULN	
aPTT	>2.5 x ULN	
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

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