STATISTICAL ANALYSIS PLAN
VERSION: FINAL V1.0

A PHASE 1/2/3 ADAPTIVE STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF REGN14256+IMDEVIMAB FOR THE TREATMENT OF COVID-19 PATIENTS WITHOUT RISK FACTORS FOR PROGRESSION TO SEVERE DISEASE

Compound:	REGN14256+Imdevimab
Protocol Number:	R14256-COV-2149
Clinical Phase:	Phase 1/2/3
Sponsor:	Regeneron Pharmaceuticals, Inc.
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Version/Date:	Original Statistical Analysis Plan (Version 1.0) / June 30, 2022

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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ACE2	Angiotensin-converting enzyme 2
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ALP	Alkaline phosphatase
CDC	US Centers for Disease Control and Prevention
C_{max}	Maximum concentration
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
EOS	End of study
EQ-5D-5L	European Quality of Life Five Dimension-5 Level
EQ-5D-Y	European Quality of Life Five Dimension-Youth
ER	Emergency room
EUA	Emergency Use Authorization
FAS	Full analysis set
FDA	US Food and Drug Administration
FIH	First-in-human
GCP	Good clinical practice
IRB	Institutional Review Board
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive care unit
IDMC	Independent data monitoring committee
ISR	Injection-site reaction
IWRS	Interactive web response system
IV	Intravenous
IVIG	Intravenous immunoglobulin
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MAV	Medically-attended visit
mFAS	Modified full analysis set
NCI	National Cancer Institute
NLR	Neutrophil-lymphocyte ratio
NP	Nasopharyngeal
NT-proBNP	N-terminal pro B-type natriuretic peptide
OP	Oropharyngeal
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic
PRO	Patient-reported outcome

PT	Preferred term
RBD	Receptor binding domain
Regeneron	Regeneron Pharmaceuticals, Inc.
RT-qPCR	Quantitative reverse transcription polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SE-C19	Symptom Evolution of COVID-19
SE-LC19	Symptom Evolution of Long COVID-19
SF-36	Short Form-36
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TWA	Time-weighted average
VBM	Variants Being Monitored
VOC	Variant of Concern
VOHC	Variant of High Consequence
VOI	Variant of Interest
VUI	Variant Under Investigation
VUS	Variants under surveillance
WHO	World Health Organization
WOCBP	Women of childbearing potential
WPAI+CIQ	Work Productivity and Activity Impairment and Classroom Impairment Questions

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to database lock. The SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of data for study R14256-COV-2149 (hereafter referred to as COV-2149) of monoclonal antibodies (mAbs) for the treatment of non-hospitalized patients with COVID-19 who are at low risk of progressing to severe disease. The SAP is based on the Protocol Amendment 1 (dated 26-AUG-2021) of COV-2149.

To address the COVID-19 pandemic and the predominant SARS-CoV-2 variants at the time (e.g., the Delta variant), the Sponsor (Regeneron) designed and implemented this phase 1/2/3 adaptive COV-2149 study to evaluate the safety, virologic efficacy, and clinical efficacy of a new mAb R14256 alone or in combination with a previously evaluated mAb, imdevimab. Enrollment was subsequently prematurely closed on 16 December 2021 based on the reduced activity of R14256 and imdevimab against the newly emerging Omicron variant that had become the predominant circulating lineage variants in the US, and not due to any safety concerns.

Therefore, enrollment was stopped during the phase 1 portion of the first-in-human (FIH) COV-2149 study, and the phase 2/3 portions were never opened. Accordingly, the focus of this SAP is on the data collected in phase 1.

All analyses will be descriptive in nature and will mainly pertain to the primary objectives of the phase 1 portion of the study, including:

- Safety and tolerability (as measured by treatment-emergent adverse events, injection-site reactions, and hypersensitivity reactions), and
- Virologic efficacy (as measured by time-weighted average (TWA) change from baseline in viral load through day 7)

Additional data pertaining to secondary objectives of the phase 1 will also be descriptively analyzed and selective exploratory outcome data will be provided in a brief clinical study report(CSR).

This is the final statistical plan, and the SAP will be issued prior to data lock. In case of any unexpected issues prior to the data lock, any revisions to the SAP will be issued before code breaking of the blinded data.

1.1. Background/Rationale

COV-2149 was designed as a phase 1/2/3 randomized, placebo-controlled, adaptive study to evaluate the safety, tolerability, virologic efficacy, and clinical efficacy of REGN14256+imdevimab compared to placebo in non-hospitalized patients with COVID-19 who are at low risk of progressing to severe disease. Casrivimab+imdevimab, the mAb combination previously authorized for treatment of COVID-19 in non-hospitalized patients, was included as a calibrator arm.

For more information regarding the rationale for the study design and dose selection, refer to Section 3.2 of the Protocol Amendment 1. Additional background information on

REGN14256+imdevimab and the overall development program can be found in the Investigator's Brochure.

1.2. Study Objectives

1.2.1. Primary Objectives

The primary objectives of the phase 1 are to:

- Evaluate the safety and tolerability of REGN14256+imdevimab and REGN14256 monotherapy, as measured by treatment-emergent adverse events (TEAEs), injection-site reactions (ISRs), and hypersensitivity reactions
- Evaluate the virologic efficacy of REGN14256+imdevimab and REGN14256 monotherapy compared to placebo, as measured by time-weighted average (TWA) change from baseline in viral load through day 7
- Evaluate the clinical efficacy of REGN14256+imdevimab compared to placebo, as measured by COVID-19 symptoms resolution

1.2.2. Secondary Objectives

The secondary objectives of the phase 1 are to:

- Evaluate the safety and tolerability of REGN14256+imdevimab and REGN14256 monotherapy, as measured by treatment-emergent serious adverse events (SAEs)
- Evaluate additional indicators of virologic efficacy of REGN14256+imdevimab and REGN14256 monotherapy
- Characterize the concentration-time profile of REGN14256 administered in combination with imdevimab or alone as a monotherapy
- Assess the immunogenicity of REGN14256 administered in combination with imdevimab or alone as a monotherapy

1.2.3. Exploratory Objectives

The exploratory objectives are to:

- Evaluate the clinical efficacy of REGN14256 in combination with imdevimab, compared to placebo
- Evaluate the impact of REGN14256+imdevimab treatment, given during acute SARS-CoV-2 infection, on long COVID symptoms, compared to placebo
- Explore relationships between REGN14256 alone (as applicable) and in combination with imdevimab exposure and selected efficacy endpoints, safety endpoints, and/or biomarkers
- Characterize the concentrations of casirivimab and imdevimab in serum over time

1.2.4. Modifications from the Statistical Section in the Final Protocol

Because enrollment was stopped prematurely during the phase 1 portion of Study COV-2149, the target sample size that the originally planned inferential analyses were based on would not be achieved. Therefore, due to a lack of sufficient statistical power to detect significant treatment differences, the inferential analyses planned in the final protocol will not be conducted. Instead, this study will descriptively analyze the endpoints mainly for phase 1 with no formal hypothesis testing to be performed.

1.2.5. Revision History for SAP Amendments

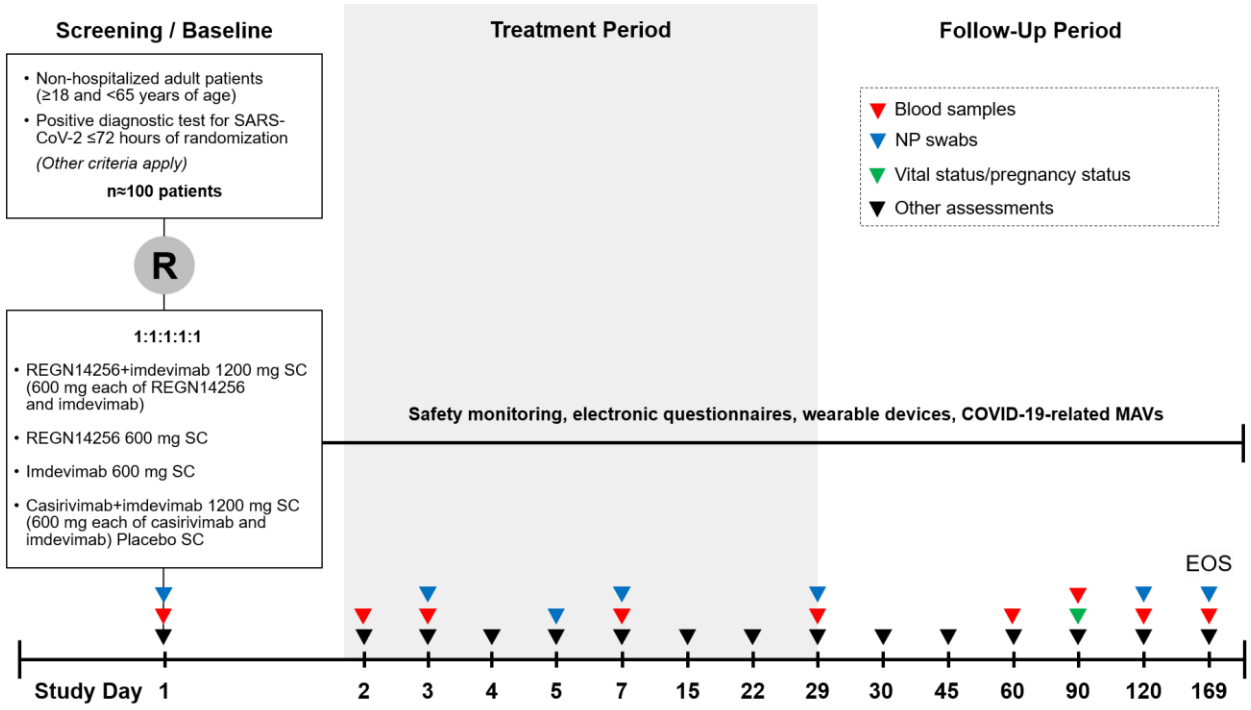
Not applicable

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This is a phase 1/2/3, randomized, double-blind, placebo-controlled adaptive study to assess the safety, tolerability, virologic and clinical efficacy of REGN14256+imdevimab, compared to placebo, in non-hospitalized adults (≥18 years of age) with COVID-19. Phase 1 of the study consists of 3 periods: a screening/baseline period, a treatment period, and a follow-up period. Refer to the phase 1 study flow diagram (Figure 1) for more details. The Schedule of Events is provided in Section 10.1.

Figure 1: Study Flow Diagram for Phase 1



2.2. Sample Size and Power Considerations

Power calculations are not applicable as the enrollment was stopped at Phase 1.

2.3. Study Plan

The Study event table is presented in Section 10.1.

3. ANALYSIS POPULATIONS

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

3.1. Efficacy Analysis Set

The **full analysis set (FAS)** includes all randomized patients and is based on the treatment allocated (as randomized).

The **modified full analysis set (mFAS)** includes all randomized patients with a positive central lab determined SARS-CoV-2 RT-qPCR result from nasopharyngeal (NP) swab samples at randomization and is based on the treatment received (as treated).

3.2. The Safety Analysis Set (SAF)

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

3.3. The Pharmacokinetic Analysis Set (PKAS)

The pharmacokinetic (PK) analysis set is defined for each analyte separately. Each PK Analysis set includes all participants who received any study drug (SAF) and who had at least 1 non-missing result of respective analyte following the first dose of study drug. Subjects will be analyzed based on the actual treatment received.

3.4. The Anti-drug Antibody (ADA) Analysis Set

Not applicable as anti-drug antibody (ADA) analysis will not be performed due to early study discontinuation.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic variables will be summarized:

- Age at screening (years)
- Age range (quantitative and qualitative variable: 18 – 44, 45 – 64 years)
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White and Other)
- Ethnicity (Hispanic/Latino, Not Hispanic/Latino)
- Baseline Weight (kg)
- Baseline Height (cm)
- Baseline Body mass index (BMI) (kg/m^2) calculated from weight and height
- Baseline Obesity (BMI < 30 kg/m^2, BMI ≥ 30 kg/m^2)
- Baseline Viral Load in nasopharyngeal swab samples (copies/mL, log10 copies/mL)
- Baseline Viral Load Category (Below the Lower Detection Limit, <= 10^4 copies/mL, >10^4 copies/mL, >10^5 copies/mL, >10^6 copies/mL, >10^7 copies/mL)
- Baseline SARS-CoV-2 diagnostic test result (Positive, Negative)
- Baseline anti-SARS-CoV-2 serostatus (Negative, Positive, Other)
- Baseline SARS-CoV-2 Spike Protein Antibody (U/mL)

Additional baseline characteristics will be included if needed.

4.2. Medical History

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

- COVID-19 with start date as the date of onset of first symptoms related to COVID-19
- Menopausal history
- Pregnancy or breastfeeding status, if applicable

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

4.3. Prior / Concomitant Medications or Procedures

Any treatment or procedure administered from the first dose of study drug to the final study visit will be considered a concomitant medication or procedure. Medications will be coded to the ATC level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup),

according to the latest available version of WHO Drug Dictionary (WHODD). Patients will be counted once in all ATC categories linked to the medication.

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

Concomitant medications / procedures: medications taken or procedures performed following the dose of study drug through the EOS visit.

4.4. Rescue Medication/or Prohibited Medication During Study

4.4.1. Rescue Treatment

There will be no specific protocol-defined rescue therapy. Patients with signs or symptoms suggestive of progression to severe COVID-19 may be treated according to local standard of care as per the discretion of the investigator or treating physician. Any rescue medication use should be captured in the concomitant medication eCRF.

4.4.2. Prohibited Medications and Procedures

Patients are not permitted to receive any medication specified in the exclusion criteria for study enrollment (Section 7.2.2 of the Protocol Amendment 1) unless medically indicated. Patients may otherwise continue their normal regimen of medications and procedures.

Based on CDC guidance and per protocol, the use of any authorized or approved COVID-19 vaccine should be deferred for at least 90 days after dosing to reduce potential interference of the study drug with vaccine-induced immune responses. Refer to the latest CDC guidance (CDC, 2021a).

Other than the prohibited medications and vaccines listed above, treatment with concomitant medications is permitted during the study. Any medications used by the study subject should be captured in the concomitant medication eCRF.

4.5. Efficacy Variable

4.5.1. Primary Efficacy Variable (s)

Virologic

- Time-weighted average (TWA) daily change from baseline in viral load (log10 copies/mL) from day 1 to day 7, as measured by SARS-CoV-2 quantitative reverse transcription polymerase chain reaction (RT-qPCR) in nasopharyngeal (NP) swab samples.

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

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

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

Where

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

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

Baseline is defined as the last non-missing values prior to the study drug administration. Patients with missing baseline will be excluded from the analysis.

4.5.2. Secondary Efficacy Variable(s)

Virologic

- Time-weighted average change from baseline in viral load at each timepoint, as measured by RT-qPCR in NP samples
- Change from baseline in viral load at each timepoint through day 7, as measured by RT-qPCR in NP samples
- Proportion of patients with viral loads below the limit of detection at each visit

4.5.3. Exploratory Efficacy Variable(s)

Virologic

- Change from baseline in viral load through day 29 as measured by RT-qPCR in NP swab samples

Clinical

- Proportion of patients with COVID-19-related medically attended visits (MAVs) or all-cause mortality through day 29 and day 169

  Note: A COVID-19-related medically-attended visit will be defined as follows: hospitalization, emergency room (ER) visit, urgent care visit, physician's office visit, or telemedicine visit, with the primary reason for the visit being COVID-19. Refer to Section 9.2.9 of the Protocol Amendment 1 for more information.

Drug Concentration

- Concentrations of REGN14256, casirivimab and imdevimab in serum over time

4.6. Safety Variables

4.6.1. Adverse Events and Serious Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. All adverse events are to be coded to a "Preferred Term" and associated primary "System Organ Class (SOC)" according to the latest available version of Medical Dictionary for Regulatory Activities (MedDRA®).

Treatment-emergent adverse events are defined as the AEs that are not present at baseline or represent the exacerbation of a pre-existing condition during the on-treatment period. A Serious Adverse Event is an AE that is classified as serious according to the criteria specified in Section 10.2.2 of the Protocol Amendment 1. All TEAEs and SAEs will be collected through the end of study.

4.6.2. Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical interest specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the Sponsor can be appropriate. Adverse events of special interest for this study include the following:

- Grade ≥3 injection-site reactions (ISRs) through study day 4
- Grade ≥3 hypersensitivity reactions through study day 29

All the adverse events define above in Section 4.6.1 and Section 4.6.2 must be reported with investigator's assessment of the event's seriousness, severity, and causality to the blinded study drug.

The severity of adverse events (including test findings classified as AEs) will be graded using the current version of the NCI-CTCAE v5.0. Treatment-emergent AEs, SAEs, or AESIs not listed in the NCI-CTCAE will be graded according to the scale in Table 6 of the Protocol Amendment 1. The grading systems for anaphylaxis, allergic reaction (hypersensitivity), and injection-site reaction are provided in Table 7 of the Protocol Amendment 1.

The investigator must provide causality assessment as whether there is a reasonable possibility that the drug caused the adverse event, based on evidence or facts, his/her clinical judgment, and the following definitions. For more information regarding the causality assessment, refer to Section 10.2.5 of the Protocol Amendment 1.

Laboratory results, vital signs, and other diagnostic results or findings (e.g., positive pregnancy test) should be appraised by the Investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or other diagnostic findings (i.e., not part of a reported diagnosis) should be reported as AEs if they are symptomatic, require corrective

treatment, or constitute an AE in the investigator's clinical judgement. More details on the reporting of adverse events can be found in Section 10.1.1 of the Protocol Amendment 1.

4.6.3. Laboratory Safety Variables

Hematology, chemistry, and serum β-HCG pregnancy testing samples will be analyzed by a central laboratory. The laboratory tests listed below will only be performed based on samples that are collected according to the corresponding Schedules of Events (Section 10.1). Tests will include:

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin
Potassium	Creatinine	Total cholesterol
Chloride	Blood urea nitrogen (BUN)	Triglycerides
Carbon dioxide	Aspartate aminotransferase (AST)	Uric acid
Calcium	Alanine aminotransferase (ALT)	Creatine phosphokinase (CPK)
Glucose	Alkaline phosphatase	
Albumin	Lactate dehydrogenase (LDH)	

Hematology

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

Other Test(s)

β-HCG pregnancy testing (serum)

4.6.4. Vital Signs

The following vital signs parameters will be recorded at multiple time points according to Schedule of Time and Event Table (Section 10.1):

- Respiratory rate (bpm)
- Heart rate (bpm)
- Systolic and diastolic blood pressures (mmHg)
- SpO_2 (%)
- Body temperature (°C)

4.7. Pharmacokinetic Variables

The PK variables are the concentrations of REGN14256, casirivimab and imdevimab in serum at each timepoint. These sampling timepoints are specified in the corresponding Schedule of Events (Section 10.1).

4.8. Exploratory Variables

Exploratory variables include, but not limited to, the patient-reported COVID-19 symptoms and outcomes assessed by electronic questionnaires (e.g., SE-C19), the exploratory parameters (e.g., physical activities) measured using wearable devices, and the parameters collected from viral sequencing tests, viral infectivity assays, serological immunoassays for Anti-SARS-CoV-2 Antibodies, and serum and plasma samples for exploratory research. Refer to section 9.2.8 of the Protocol Amendment 1 for more information. These results may be reported outside of the clinical study report (CSR).

5. STATISTICAL METHODS

For continuous variables, descriptive statistics will include the following: the number of patients reflected in the calculation (n), mean, median, standard deviation, 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 will be summarized descriptively by treatment group, and by all groups combined using FAS, mFAS, and SAF. The corresponding subgroup summaries by baseline anti-SARS-CoV-2 serostatus will also be provided.

5.2. Medical History

Medical history will be summarized by primary SOC and PT by treatment group and all groups combined using SAF. The table will be sorted by decreasing frequency of SOC followed by PT based on the overall incidence across treated groups.

5.3. Prior/concomitant Medications and Procedures

Prior or concomitant medications/procedures will be summarized by treatment groups using SAF. 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.

5.4. Prohibited Medications

Prohibited medications will be summarized using SAF in a similar way as described above for concomitant medications.

5.5. Subject Disposition

The following summaries will be provided using FAS:

- The total number of screened patients/subjects who have signed ICF
- The total number of randomized patients: received a randomization number
- The total number of screening phase discontinuation, and the reasons for discontinuation
- The total number of patients randomized, patients randomized and treated, patients randomized but not treated, and patients treated but not randomized
- The total number of patients who discontinued the study, and the reasons for discontinuation
- A summary of analysis sets including FAS, mFAS, SAF, and PKAS.

5.6. Extent of Study Treatment Exposure and Compliance

5.6.1. Measurement of Compliance

Treatment compliance is not applicable for this study since the study drug is administered once at the site.

5.6.2. Exposure to Investigational Product

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

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

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

5.7. Analyses of Efficacy Variables

5.7.1. Analysis of Primary Efficacy Variable(s)

Virology

The primary virologic efficacy variable is time-weighted average (TWA) change from baseline in viral load from day 1 to day 7, as measured by RT-qPCR in NP swab samples. The primary virologic efficacy variable will be analyzed descriptively by treatment group, and by all groups combined in the mFAS population. The corresponding subgroup analyses by baseline anti-SARS-CoV-2 serostatus will also be performed.

The analyses will be based on the observed data with no imputation for missing data except the following cases: uncertain viral load values with less than the lower limit of quantification of the PCR assay but with positive qualitative results are imputed with half of lower limit of quantification of the PCR assay; uncertain values with negative RNA are imputed with 0 log10 copies/mL if the reason for the uncertain values is not a failed test. The primary efficacy variable will be calculated using trapezoidal rule, i.e., area under the curve for change from baseline at each time point from day 1 to last observation divided by the number of days from day 1 to day of last observation.

5.7.2. Analysis of Secondary Efficacy Variables

Virology

Time-weighted average change from baseline in viral load at each timepoint, as measured by RT-qPCR in NP samples, will be analyzed descriptively in a similar way as described above for the primary virologic efficacy variable.

To assess the time course of treatment effect in viral load, change from baseline in viral load at each timepoint through day 7, as measured by RT-qPCR in NP samples, will be analyzed descriptively in the mFAS population. The viral load at each visit up to day 7 along with the change from baseline in viral load (log10 copies/mL) will be summarized by treatment group with descriptive statistics. The line plot of mean (+/-se) viral load change from baseline in log10 scale at each visit and the line plot of mean (+/-se) viral load in log10 scale at each visit will also be presented.

Proportion of patients with viral loads below the limit of detection at each visit through day 29 will be presented by treatment group. The percentage at each visit is derived using the number of patients with NP swab samples at the visit as the denominator.

The corresponding subgroup analyses/graphs by baseline anti-SARS-CoV-2 serostatus will be performed for all the secondary virologic efficacy analyses.

5.7.3. Analysis of Exploratory Variables

Virology

The analysis of change from baseline in viral load through day 29, as measured by RT-qPCR in NP swab samples, will be conducted referring to the previously detailed analysis of change from baseline in viral load at each timepoint through day 7.

Clinical Outcomes

The proportions of patients with medically attended visits (MAVs) due to COVID-19 or all-cause death through Day 29 and Day 169 will be summarized with descriptive statistics. The analyses will be performed based on the observed data from the mFAS patients. Listings of COVID-19-related MAVs during the study will also be summarized and presented.

5.7.4. Adjustment for Multiple Comparison

There is no issue with multiplicity for the primary efficacy variable.

5.8. Analysis of Safety Data

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

The safety analysis will be based on the reported AEs 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 10.2.

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

5.8.1. Adverse Events

Definitions

For safety variables, 2 periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before study drug administration.

- The observation period is defined as the time of study drug administration to the last study visit. Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the on-treatment period.

Analysis

All AEs reported in this study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®).

Summaries of TEAEs by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE through day 29 and day 169 by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 10.2.4 of the Protocol Amendment 1), presented by SOC and PT
- The number (n) and percentage (%) of patients with at least 1 TEAE related to study treatment through day 29 and day 169 by SOC and PT

Summaries of SAEs and AESIs by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 treatment-emergent SAE through day 169 by SOC, PT, and severity
- The number (n) and percentage (%) of patients with at least 1 treatment-emergent SAE through day 169 by SOC, PT, and relationship to study drug
- The number (n) and percentage (%) of patients with at least 1 AESI through day 29 (defined with a PT or a prespecified grouping)

Listings of deaths, SAEs, AESIs, and TEAEs leading to study discontinuation will be summarized and presented by treatment group.

5.8.2. Clinical Laboratory Measurements

Laboratory measurements include blood chemistry and hematology results and will be converted to standard international units and US conventional units. Patients with at least one post-baseline lab test result outside the normal range and patients with lab value status change from baseline to postbaseline will be summarized by each clinical laboratory test.

Listings of patients with a potentially clinically significant value (PCSV) at any post-randomization time point will be summarized and presented.

5.8.3. Analysis of Vital Signs

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

Listings of patients with a potentially clinically significant value (PCSV) at any post-randomization time point will be summarized and presented.

5.8.4. Analysis of Drug Concentration Data

Concentrations of REGN14256, casirivimab and imdevimab in serum over time will be measured and summarized descriptively in the PKAS population for each of the treatment cohorts.

A non-compartmental analysis (NCA) will be performed on the concentration in serum and actual time data for REGN14256, casirivimab and imdevimab to obtain pharmacokinetic parameters, which may include but are not limited to the following:

- AUClast – area under the curve (AUC) computed from time zero to the time of the last positive concentration
- AUCinf - AUC from time zero extrapolated to infinity
- Cmax – peak concentration
- Tmax – time of peak concentration
- Tlast - time of the last positive (quantifiable) concentration

PK parameters will be summarized by standard descriptive statistics. No formal statistical hypothesis testing will be performed.

6. DATA CONVENTIONS

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

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the Baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of investigational product.

6.2. Data Handling Convention for Efficacy Variables

Not applicable.

6.3. Data Handling Convention for Missing Data

Rules for handling missing data for primary and secondary efficacy variables are described in Section 5.7.1.

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

Medication missing/partial dates

To determine whether a medication is prior, concomitant or post-treatment medication, the missing medication start date is estimated as early as possible up to randomization 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.

Adverse event

If the severity of a SAE, AESI and grade 3 or 4 AEs is missing, it will be classified as “missing” in the frequency tables by CTC grade of SAE and AESIs. If the assessment of relationship of the investigational product is missing, it will be classified as “not reported” or “missing”.

Date of injection

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

6.4. Visit Windows

Data analyzed by-visit-analysis will be summarized by the study scheduled visits described in Section 10.1, “Schedule of Events”. The analysis visit windows will be exhaustive so that all available values obtained from unscheduled visits, early termination visit (ETV) and end of study (EOS) have the potential to be summarized. No analysis visit windows will be applied for the study scheduled visits.

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

Table 1: Time Window for Summary of NP Swab for SARS-CoV-2 RT-qPCR (central lab)

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, 18]
Day 29	29	[19, 32]
Day 120	120	[114, 144]
Day 169	169	[145, 176]

In the event of multiple measurements of the same test in the same window, if the measurements are from different categories, the priority order is scheduled, early termination visit then unscheduled visit. For the measurements in the same category, the value measured nearest to the target day will be assigned to the window; if they are at the same distance to the target day, the latest one will be used. Extra assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing adverse events) will be included in listings, but not summaries except for the endpoint determination. If more than one laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

6.5. Unscheduled Assessments

The determination of baselines and values at the end of treatment will be based on scheduled available assessments and unscheduled available assessments.

For by visit summary, unscheduled visit will not be summarized unless otherwise specified.

6.6. Pooling of Centers for Statistical Analyses

Not applicable.

7. INTERIM ANALYSIS

No interim analysis is planned for this study.

8. SOFTWARE

All analyses will be done using SAS Version 9.4.

9. REFERENCES

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4. CDC. Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States.Centers for Disease Control and Prevention. https://www.cdc.gov/vaccines/covid19/info-by-product/pfizer/clinical-considerations.html. Published 2021a. Updated 05 Mar 2021. Accessed 21 Mar 2021 2021.
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7. WHO. Update on Clinical long-term effects of COVID-19. https://www.who.int/docs/default-source/coronaviruse/risk-comms-updates/update54_clinical_long_term_effects.pdf?sfvrsn=3e63eee5_8. Published 2021b. Accessed 28 Jun 2021.

10. APPENDIX

10.1. Schedule of Time and Events

Day	*Screening/Baseline*[1]				*Treatment Period*[3]								*Follow-Up Period*[3]							
	Day -1 to 1				2	3	4	5	7	15	22	29	30	45	60	90	114–119	120[8]	163–168	169[8] EOS
	Screen	Pre-dose	Dose	Post-Dose																
Window (Day)										±1	±3	±3	±3	±3	±3	±3		+7 or ±7[4]		+7 or ±7[4]
Screening/Baseline																				
Inclusion/Exclusion	X																			
Informed Consent	X																			
PGx sub-study consent (optional)[5]	X																			
Antigen or molecular diagnostic test for SARS-CoV-2[6]	X																			
Serology for serostatus (central lab)[16]	X																			
Medical history (including COVID-19 symptoms)	X																			
Demographics	X																			
Weight and height	X																			
Randomization		X																		
Treatment																				
Study drug administration[7]			X																	
Virologic Outcomes																				
Nasopharyngeal swab for SARS-CoV-2 RT-qPCR (central lab)	X					X		X	X			X						X		X
Electronic Survey for Patient-Reported Symptoms																				
SE-C19[8]	X				Daily															
Electronic Surveys for Exploratory Patient-Reported Outcomes																				
SE-LC19[8]													Daily	X	X	X[8]	X[8]	X[8]	X[8]	
PGIS[8]	X				Daily									X	X	X[8]	X[8]	X[8]	X[8]	
PGIC[8]												X								X
Return to usual health[8]	X				Daily									X	X	X[8]	X[8]	X[8]	X[8]	
Return to usual activities[8]	X				Daily									X	X	X[8]	X[8]	X[8]	X[8]	
SF-36[8]													X	X	X	X		X		X
WPAI+CIQ[8]	X								X	X	X	X			X	X		X		X
EQ-5D-5L[8]	X								X	X	X	X			X	X		X		X
Safety																				
Vital Signs[2]	X	X		X																
Treatment-emergent AEs[10]				← Continuous monitoring →																
Treatment-emergent SAEs [10]				← Continuous monitoring →																
Treatment-emergent grade ≥3 ISRs[10]				←Continuous monitoring→																

Day	*Screening/Baseline*[1]				*Treatment Period*[3]								*Follow-Up Period*[3]								
	Day -1 to 1				2	3	4	5	7	15	22	29	30	45	60	90	114–119	120[8]	163–168	169[8] EOS
	Screen	Pre-dose	Dose	Post-Dose																
Window (Day)										±1	±3	±3	±3	±3	±3	±3		+7 or ±7[4]		+7 or ±7[4]
Treatment-emergent grade ≥3 hypersensitivity reactions[10]				← Continuous monitoring →																
Concomitant medications and procedures[11]	X			← Continuous monitoring →																
Pregnancy test (WOCBP)[12]	X																	X		X
Vital status																X				
Pregnancy status[12]																X				
Safety information (newborns of study participants)[12]																				X
Central Laboratory Safety Testing																				
Hematology (including differential)	X[13]								X											
Blood Chemistry	X[13]								X											
Pharmacokinetics and Immunogenicity Sampling																				
Serum for drug concentration (PK)[14]	X			X[15]	X	X			X			X			X	X		X		
Serum for immunogenicity (ADA)[16]	X											X						X		
Central Laboratory Biomarker Testing																				
Serum for exploratory research[17]	X											X						X		X
Plasma for exploratory research[17]	X											X						X		X
Exploratory Patients Outcomes Assessments																				
COVID-19-related MAV details[18]	X				← Continuous monitoring →															
Wearable device[19]	X	← Continuous monitoring →																		
Pharmacogenomics (Optional Sub-Study)																				
Blood for DNA[5]	X																			

1. Screening visit may occur on the same day as the baseline visit (day 1), or the day prior to the baseline visit (day -1).
2. In **phase 1**, on day 1, vital signs (as described in Section 9.2.5.1 of the Protocol Amendment 1) will be measured at pre-dose, approximately every 30 minutes during the first 2 hours after dose, at hour 3, and at hour 4.
3. On visit days when sample collection is not required (e.g., when only patient-reported questionnaires are collected), the information indicated in the Schedule of Events may be collected by phone without an in-person visit.

4. For all day 120 and day 169 questionnaires, a visit window of +7 days will be applied. For all other day 120 and day 169 assessments and sample collections, a visit window of ±7 days will be applied.
5. Patients must provide separate consent to collect blood samples as part of the optional pharmacogenomics (PGx) sub-study. Blood sample for DNA should be collected at the day -1 or day 1 visit but may be collected at any visit.
6. The investigator or sub-investigator will verify that the patient has tested positive for SARS-CoV-2, either at screening **or** by historical record of a positive antigen or molecular diagnostic test (by validated SARS-CoV-2 antigen, RT-PCR, or other molecular diagnostic assay, using an appropriate sample such as nasopharyngeal [NP], nasal, oropharyngeal [OP], or saliva) collected ≤72 hours prior to randomization. For local tests performed at screening, the local testing result, specimen type, assay type, and date of the test will be recorded in the eCRF.
7. Refer to Section 9.2.2 of the Protocol Amendment 1 for study drug administration instructions.
8. On visit days when other assessments or sample collections are required, the site will verify that questionnaires have been completed prior to all other assessments or collections. The questionnaires should be completed in the order listed. On days when a certain questionnaire is not required, it will be skipped while the overall order of the other required questionnaires remains the same. Note that questionnaires will only be administered to patients in study sites if regionally available, and will only be administered to patients who are able to complete the questionnaires in the language available at their study site. Refer to Section 9.2.4 of the Protocol Amendment 1 for additional information regarding these questionnaires.
8. Long-COVID electronic surveys (i.e., SE-LC19, PGIS, return to usual health, return to usual activities) must be completed as indicated in the Schedule of Events, then daily during the week leading up to day 120 visit, and daily during the week leading up to EOS visit on day 169.
9. On day 1, vital signs (as described in Section 9.2.5.1 of the Protocol Amendment 1) will be collected once before study drug administration and once after study drug administration is completed.
10. Refer to Section 10 of the Protocol Amendment 1 for more information on safety reporting and recording requirements for.
11. Concomitant medications and concomitant procedures will also be reviewed and recorded. Refer to Section 9.2.5.3 of the Protocol Amendment 1 for more information.
12. Pregnancy testing will be performed in women of childbearing potential (WOCBP) only. For WOCBP, negative pregnancy must be confirmed prior to study drug administration. Serum or urine pregnancy test are both acceptable. Note that a paper pregnancy report form must be completed for each patient who becomes pregnant and safety information in newborns of study participants will be collected.

13. The indicated blood samples may be collected at either day -1 or day 1 (screening or pre-dose) but must be collected prior to randomization.
14. Actual dosing time and drug concentration (PK) sample collection times will be recorded. At the screening/baseline visit, blood for assessment of drug concentration in serum will be taken prior to dosing (either at day -1 or day 1).
9. The post-dose blood collection on day 1, if indicated, should occur at least 1 hour after study drug administration.
15. In **phase 1** patients, the post-dose blood collection on day 1 should occur at least 5 hours after study drug administration.
16. The window for pre-dose ADA sample collection is as close to administration of study drug as is reasonable. Actual dosing time and ADA sample collection times will be recorded.
17. Baseline serum SARS-CoV-2 serology assays will be performed centrally to determine serostatus retrospectively. Other serologic and plasma-based exploratory assays will be performed centrally post-treatment.
18. COVID-19-related MAVs (defined as hospitalization, ER visit, urgent care visit, physician's office visit, or telemedicine visit, with the primary reason for the visit being COVID-19) will be recorded in the eCRF. At minimum, details listed in Section 9.2.9 of the Protocol Amendment 1 will be included.
19. Wearable devices will be worn continuously, starting at least 15 minutes before study drug administration (preferably starting at screening). Refer to Section 9.2.10 of the Protocol Amendment 1 for more information on the wearable device.

10.2. Criteria for Potentially Clinically Significant Values (PCSV)

Parameter	PCSV	Comments
Clinical Chemistry		
ALT*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required; multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided

AST*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
Alkaline Phosphatase	>1.5 ULN and baseline ≤ 1.5 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007.
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
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

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		
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.
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).

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

Urinalysis		
pH	≤4.6 or ≤LLN (if LLN≤4.6) and baseline > 4.6 or >LLN (if LLN≤4.6) ≥8 or ≥ULN (if ULN≥8) and baseline < 8 or <ULN (if ULN≥8)	Two independent criteria
Vital signs		
HR	<45 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions except STANDING
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions except STANDING
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions except STANDING
Weight	³ 5% increase from baseline ³5% decrease from baseline	FDA Feb 2007

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