REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN
VERSION: FINAL

Clinical Study Protocol Title: A PHASE 2A, OPEN-LABEL STUDY ASSESSING PHARMACOKINETICS, SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF SINGLE-DOSE SUBCUTANEOUS ANTI-SPIKE (S) SARS-COV-2 MONOCLONAL ANTIBODIES (CASIRIVIMAB AND IMDEVIMAB) IN HIGH-RISK PEDIATRIC PARTICIPANTS UNDER 12 YEARS OF AGE

Compound:	R10933-10987
Protocol Number:	R10933-10987-COV-2121
Clinical Phase:	Phase 2a
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatistician:	[redacted]
Clinical Trial Manager:	[redacted]
Study Medical Director:	[redacted]
Version/Date:	Original Statistical Analysis Plan 23-JUN-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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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
Casirivimab+imdevimab	REGN10933 and REGN10987; also referred to by the proprietary name conditionally accepted by the FDA (REGEN-COV™) and by the EMA (RONPAPREVE®)
COVID-19	Coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
eCRF	Electronic case report form
FDA	U.S. Food and Drug Administration
ICF	Informed consent form
ICH	International Council for Harmonisation
MIS-C	Multisystem inflammatory syndrome in children
NAb	Neutralizing antibody
PK	Pharmacokinetic
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
SC	Subcutaneous
SOC	System organ class
TEAE	Treatment-emergent adverse event

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 statistical methods to be used in the analysis of data for R10933-10987-COV-2121 study.

The study was paused for new enrollment on December 28, 2021 due to the increasing prevalence of Omicron and the lack of neutralization of REGEN-COV to the Omicron variant. The participants who had been enrolled prior to the pause date were followed in the study according to the protocol.

1.1. Background/Rationale

This study assess the pharmacokinetics (PK), safety, tolerability and immunogenicity, of casirivimab and imdevimab in children under 12 years old who are uninfected but at high risk to develop severe COVID-19 if they become infected.

1.2. Study Objectives

1.2.1. Primary Objectives

The primary objective of this study is to characterize the concentrations of casirivimab and imdevimab serum over time after a single subcutaneous (SC) administration.

1.2.2. Secondary Objectives

The secondary objectives of the study are:

- To assess the safety and tolerability of SC single administration of casirivimab and imdevimab
- To assess the occurrence of grade ≥3 injection site reactions and grade ≥3 hypersensitivity reactions in participants treated with SC doses of casrivimab and imdevimab
- To assess the immunogenicity of casirivimab and imdevimab

1.2.3. Modifications from the Statistical Section in the Final Protocol

The NAb analysis specified in section 11.4.5.2 in protocol will not be performed.

1.2.4. Revision History for SAP Amendments

There is no revision history – this is original version of the SAP document.

2. INVESTIGATION PLAN

2.1. Study Design

This is a Phase 2a open label study with no placebo control to assess the PK, safety, tolerability, and immunogenicity of casrivimab and imdevimab in participants <12 years old who are not infected with SARS-CoV-2 but are at high risk to develop severe COVID-19 if they were to become infected. In this study, participants will be evaluated separately in two groups with each group defined according to body weight (≥10 kg and <40 kg vs ≥3 kg to <10 kg). In each group, dosing will be adjusted by weight (Protocol Table 2). After a single SC dose of casrivimab and imdevimab, a total of 28 participants will be followed for approximately 24 weeks (6 months) for assessment of drug concentrations, safety, and immunogenicity.

2.2. Sample Size and Power Considerations

There are no formal hypotheses in this study. The sample size was chosen based on PK considerations and is consistent with early phase studies to assess PK.

At least 12 participants are needed to enroll in each weight group (Group A: ≥10 kg to <40 kg, and Group B: ≥3 kg to <10 kg) to assess drug concentration. The study plans to enroll approximately 28 participants in total.

The sample size may be adjusted if planned SC dosing of casirivimab+imdevimab does not achieve concentrations in serum similar to, or higher than, that observed in adults (≥18 years of age) after casirivimab+imdevimab 1200 mg (600 mg per mAb) SC administration. PK will be evaluated on an ongoing basis to determine if dose adjustments are needed and whether more participants are needed for analysis.

2.3. Study Plan

The schedule of events is presented within Section 9.1 of the study protocol.

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. Safety Analysis Set

The Safety Analysis Set (SAF) includes all participants who received any study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

3.2. Pharmacokinetic Analysis Set

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

3.3. Immunogenicity Analysis Sets

The_ADA analysis sets (AAS) is defined for each study drug separately and includes all treated participants who received any amount of study drug [safety data set] and had at least one non-missing ADA result from the respective ADA assay following the first dose of the respective study drug.

Neutralizing antibody (NAb) analysis will not be performed.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic variables will be summarized:

- Age at screening (year)
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White and Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Baseline Weight
- Baseline Height
- Baseline Body mass index (BMI) calculated from weight and height

Baseline measure is the last available value obtained prior to drug administration.

4.2. Medical History

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. Pre-Treatment / Concomitant Medication

Medications/Procedures will be recorded from the day of informed consent until the end-of-study (EOS) visit. 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. Procedures will be coded to a Preferred Term (PT) and associated Primary System Organ Class (SOC) associated to the latest available version of MedDRA®.

Pre-treatment 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.

For medications/procedures started prior to the administration of study drug, the study day onset is defined as (date of start - date of the drug administration); for medications/procedures started on or after treatment, the study day onset is defined as (date of start - date of the drug administration) + 1.

Any positive SARS-COV-2 test conducted during an unscheduled visit will be recorded as lab assessment: SARS-CoV2-Test Local Lab and associated with the COVID-19 AE.

4.4. Rescue Medication/or Prohibited Medication During Study if Applicable

Prohibited medications are defined as any non-permitted medication as outlined within Section 8.7 of the protocol.

4.5. Efficacy Variable

4.5.1. Primary Efficacy Variable (s)

Not applicable.

4.5.2. Secondary Efficacy Variable(s)

Not applicable.

4.6. Safety Variables

4.6.1. Adverse Events and Serious Adverse Events

Adverse events and serious adverse events diagnosed by the investigators will be collected from the time of informed consent signature and then at each visit until the end of the study. All adverse events are to be coded to a "Preferred Term (PT)" and associated primary "System Organ Class (SOC)" according to the Medical Dictionary for Regulatory Activities (MedDRA).

A Serious Adverse Event is an adverse event (AE) that is classified as serious according to the criteria specified in section 10.2.2 of the protocol.

Laboratory results, vital signs, or ECG abnormalities are to be recorded as AEs if they are medically relevant: symptomatic, requiring corrective therapy, leading to treatment discontinuation and/or fulfilling a seriousness criterion.

4.6.2. Adverse Events of Special Interest

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

- Grade≥3 injection-site reactions
- Grade≥3 hypersensitivity reactions
- Multisystem inflammatory syndrome in children (MIS-C)

These AESI variables are defined in protocol section 10.1.3 and recorded via eCRF specific tick box on AE page. In addition, hypersensitivity will also be summaried by SMQ hypersensitivity (narrow) and PTs.

4.6.3. Laboratory Safety Variables

The following laboratory tests will be collected and summarized:

Blood Chemistry

Sodium	Total protein, serum
Potassium	Creatinine
Chloride	Blood urea nitrogen (BUN)
Carbon dioxide	Aspartate aminotransferase (AST)
Calcium	Alanine aminotransferase (ALT)
Glucose	Total bilirubin
Albumin	

Hematology

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

4.6.4. Vital Signs

The following vital signs parameters will be recorded and summarized:

- Body temperature
- Blood pressure
- Pulse rate
- Respiration rate

4.6.5. 12-Lead Electrocardiography (ECG)

12-Lead ECG parameters are not collected in this study.

4.6.6. Physical Examination Variables

Physical examination will be conducted at the protocol scheduled visits. If any abnormal findings during the screening period, they will be recorded in medical history eCRF form and AE eCRF form for any new or worsening abnormal findings during post-screening period.

4.6.7. Other Safety Variables

Not applicable.

4.7. Pharmacokinetic Variables

The PK variables are concentrations of casirivimab and imdevimab in serum and sampling time. The sampling time points are specified in Table 3 in the protocol.

The analysis of PK will be documented in a separate document.

4.8. Immunogenicity Variables

The immunogenicity variables include ADA status and titer at nominal sampling time/visit. Serum samples for ADA will be collected at the clinic visits specified in the protocol SOE. Samples positive in the ADA assay will be further characterized for ADA titers.

5. STATISTICAL METHODS

Unless otherwise stated, the following conventions will be applied when presenting summary level statistics for data.

Continuous variables will be summarized within each body weight group by presenting the following summary statistics: number of participants with an available value of the variable (n), mean, standard deviation, median, minimum, maximum, 1st quartile and 3rd quartile.

Categorical data will be summarized within each body weight group by presenting the frequency (i.e. total number of participants within each level of the categorical variable in a given body weight group). All levels of the categorical variable will be included. Percentages will also be calculated for each level of the categorical variables with respect to the total sample size of the respective treatment arm.

In general, summaries will display grouping by weight group, and by all participants combined. Weight groups are defined according to protocol section 8.1. Weight group A: ≥10 kg to <40 kg, and weight group B: ≥3 kg to <10 kg. Within each weight group, sub groups are further defined in the SAP according to weight based dosing categories: weight group A1: ≥20 kg to <40 kg, weight group A2: ≥10 kg to <20 kg; weight group B1: ≥5 kg to <10 kg, and weight group B2: ≥3 kg to <5 kg.

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized via descriptive statistics based on SAF population. A participant listing will be provided.

5.2. Medical History

Medical history will be summarized by SOC then PT. A participant listing will be provided.

5.3. Prior/concomitant Illnesses and Medications

Medications and procedures will be summarized based on SAF using descriptive statistics.

Prior/concomitant medications will be summarized by ATC level 2 and ATC level 4.

Prior/concomitant procedures will be summarized by SOC and PT.

Listings will also be provided.

Participants who received COVID 19 vaccine and their time to first COVID 19 vaccine (days) from the study treatment administration including the following categories: ≤90 days and >90 days, will be summarized using descriptive statistics.

5.4. Prohibited Medications

Prohibited medications is defined as any non-permitted medication as outlined within Section 8.7.1 of the protocol. They will be reviewed and identified by the study clinician and reported in protocol deviations.

5.5. Participant Disposition

Enrolled participants are defined as those who signed an informed consent form. Screen-failed participants are collected from participants screening status and eligibility eCRF form and summarized. Listing of participant discposition will be provided.

Participant counts of those screened, enrolled, the completion status for the study (along with reason for any study withdrawal) will be summarized.

5.6. Extent of Study Treatment Exposure and Compliance

Exposure data will be summarized based on SAF using descriptive statistics. Listings will also be provided. Participants with a complete or delayed dose administration (completed SC dose administered) will be summarized.

5.6.1. Measurement of Compliance

Treatment compliance is not applicable as this is a single-dose study.

5.6.2. Study Observation Duration

Study observation duration (days) will be summarized and is defined as:

Study observation duration = (date of the last study visit - date of study treatment administration) + 1

5.7. Analyses of Efficacy Variables

5.7.1. Analysis of Primary Efficacy Variable(s)

Not applicable

5.7.2. Analysis of Secondary Efficacy Variables

Not applicable.

5.8. Analysis of Safety Data

For safety variables, two observation periods are defined:

- Pre-treatment period is defined as the time from signing the Informed Consent Form (ICF) to the time before administration of study drug
- On-treatment period is defined as the time after administration of study drug until the end of study.

Safety data will be summarized for all participants based on SAF using descriptive statistics unless noted otherwise.

5.8.1. Adverse Events

All AEs reported in this study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The verbatim text, the PT, and the primary SOC will be listed in participant listings.

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

The focus of adverse event reporting in the clinical study report will be on TEAEs. A listing will be provided for COVID-19 Signs and Symptoms.

For details on handling missing data and partial dates, see Section 6.

Summaries of all TEAEs will include:

- Overview of TEAEs
- The number (n) and percentage (%) of participants with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlines in protocol section 10.2.4), presented by SOC and PT
- Treatment-related TEAEs presented by SOC and PT
- Treatment-emergent AESIs by SOC and PT
- Treatment-emergent hypersensitivity events by SMQ hypersensitivity (narrow) and PT

5.8.2. Analysis of Adverse Events of Special Interest

Hypersensitivity events will be presented by SMQ hypersensitivity (narrow) and PT, as well as SOC and PT according to eCRF, respectively. Other treatment-emergent AESIs will be presented by SOC and PT. The summaries will be sorted by decreasing incidence of PT within each SOC/SMQ based on all participants combined column.

5.8.3. Clinical Laboratory Measurements

Individual participant laboratory parameter measurements will be evaluated by PCSV criteria (See Appendix 10.1), specifically identifying participants with at least one post-baseline measurement that meets the PCSV criteria. These laboratory parameters will be presented by the biological functions (e.g. red blood cells and platelets, white blood cells, and liver function, etc.). The incidence of PCSVs at any time including data from unscheduled visits during the study period will be summarized.

Listings of laboratory measurements at all timepoints for the participants that meet PCSV criteria will be provided. Listings of all local laboratory measurements will also be provided.

A listing of all women of childbearing potential with a confirmed serum pregnancy test during the study will be provided.

5.8.4. Analysis of Vital Signs

Individual participant laboratory parameter measurements will be evaluated by PCSV criteria (See Appendix 10.1), specifically identifying participants with at least one post-baseline measurement that meets the PCSV criteria.

Listings of vital sign measurements at all timepoints for the participants that meet PCSV criteria will be provided. Listings of vital signs for all participants will also be provided.

5.8.5. Analysis of 12-Lead ECG

There are no ECG data collected in this study.

5.8.6. Physical Exams

There is no specific physical exams data collected in this study. Any abnormal findings will be included in either medical history or TEAE summary depending on the timing of the abnormal findings.

5.9. Analysis of Pharmacokinetic Data

5.9.1. Analysis of Pharmacokinetic Data

Analysis will be performed according to two groups:

- Group A: body weight ≥10 kg to <40 kg
- Group B: body weight ≥3 kg to <10 kg

The concentrations of total casirivimab and total imdevimab over time will be summarized by descriptive statistics for each weight group.

Participants who test positive for SARS-CoV-2 infection during the treatment period may be analyzed separately from the PK analysis population.

Stratification of the analysis may be performed if participants receive a treatment that has the potential to impact the pharmacokinetics of casirivimab+imdevimab (eg, IVIG)

No formal statistical hypothesis testing will be performed.

5.10. Analysis of Immunogenicity Data

5.10.1. Analysis of ADA Data

The immunogenicity variables described in Section 4.8 will be summarized using descriptive statistics. Immunogenicity will be characterized per drug molecule by ADA status, ADA category and maximum titer observed in participants in the ADA analysis sets. For samples confirmed as drug specific ADA positive, but found negative at the lowest titer dilution, the lowest dilution in the titer assay is imputed.

The ADA status of each participant may be classified as one of the following:

Positive

Pre-existing - If the baseline sample is positive and all post baseline ADA titers are reported as less than 9-fold the baseline titer value

Negative - If all samples are found to be negative in the ADA assay.

The ADA category of each positive participant is classified as:

Treatment-boosted - A positive result at baseline in the ADA assay with at least one post baseline titer result ≥ 9-fold the baseline titer value

Treatment-emergent - A negative result or missing result at baseline with at least one positive post baseline result in the ADA assay.

The maximum titer category of each participant is classified as:

Low (titer <1,000)

Moderate (1,000 ≤ titer ≤ 10,000)

High (titer >10,000)

The following will be summarized by treatment group and ADA titer level:

- Number (n) and percent (%) of ADA-negative participants
- Number (n) and percent (%) of pre-existing participants
- Number (n) and percent (%) of treatment-emergent ADA positive participants
  - Number (n) and percent (%) of persistent treatment-emergent ADA positive participants
  - Number (n) and percent (%) of indeterminate treatment-emergent ADA positive participants
  - Number (n) and percent (%) of transient treatment-emergent ADA positive participants
- Number (n) and percent (%) of treatment-boosted ADA positive participants

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

5.11. Association of Immunogenicity with Exposure and Safety

5.11.1. Immunogenicity and Exposure Data

Potential association between immunogenicity variables and systemic exposure to casirivimab and imdevimab may be explored by treatment groups. Plots of individual casirivimab and imdevimab concentration time profiles may be provided to examine the potential impact of ADA category and maximum titer category and NAb status on these profiles.

5.11.2. Immunogenicity and Safety

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

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

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 study drug.

6.2. Data Handling Convention for Efficacy Variables

Not applicable as clinical efficacy variables are not collected within this study.

6.3. Data Handling Convention for Missing Data

Missing data will not be imputed in listings. This section includes the methods for missing data imputation for some summary analyses, if necessary.

For categorical variables, participants with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of participants with missing data is presented.

Adverse event

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

Medication/Procedure

If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly or stopped prior to the first study treatment administration, it will be considered as concomitant medication/procedure by imputing the start date on the date of first study treatment administration.

Potentially Clinically Significant Value (PCSV)

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

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

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

6.4. Out of window visits

Analysis will be based on nominal visits; analysis windows will not be defined.

6.5. Unscheduled Assessments

Extra assessments (e.g. laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing AEs) will be included in listings and PCSV summaries. For by visit summaries, only scheduled visit values will be included. Both scheduled and unscheduled measurements will be considered for determining abnormal values from laboratory data, vital sign, as well as the baseline values.

6.6. Pooling of Centers for Statistical Analyses

No plan of pooling of centers for analysis.

7. INTERIM ANALYSIS

No interim analysis is planned.

8. SOFTWARE

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

9. REFERENCES

1. ICH. (1996, July 30). ICH Harmonized tripartite guideline: Structure and content of clinical study reports (E3). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
2. ICH. (1997, July 17). ICH Harmonized tripartite guideline: General considerations for clinical trials (E8). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
3. ICH. (1998, February 5). ICH Harmonized tripartite guideline: Statistical principles for clinical trials (E9). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

10. APPENDIX

10.1. Criteria for Potentially Clinically Significant Values (PCSV)

If baseline is missing, only post-baseline criteria will be considered.

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. Each category is calculated independently.
AST	>3 and ≤5 ULN and baseline ≤3 ULN >5 and ≤10 ULN and baseline ≤5 ULN >10 and ≤20 ULN and baseline ≤10 ULN >20 ULN and baseline ≤20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Each category is calculated independently.
Alkaline Phosphatase	>1.5 ULN and baseline ≤1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L.
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.
Conjugated bilirubin	>35% Total Bilirubin and TBILI >1.5 ULN, and baseline Total Bilirubin ≤35% or TBILI ≤1.5 ULN	Conjugated bilirubin dosed 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	

Parameter	PCSV	Comments
CPK	>3 and ≤10 ULN and baseline ≤3ULN >10 ULN and baseline ≤10ULN	
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	3 independent criteria
Creatinine Clearance (Cockcroft's formula)	<15 ml/min and baseline ≥15 ml/min (end stage renal impairment) ≥15 to <30 ml/min and baseline ≥30 ml/min (severe renal impairment) ≥30 to < 60 ml/min and baseline ≥60 ml/min (moderate renal impairment) ≥60 to < 90 ml/min and baseline ≥90 ml/min (mild renal impairment)	Four independent criteria
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)	Two independent criteria
Blood Urea Nitrogen	≥17 mmol/L or ≥ULN (if ULN ≥17 mmol/L) and baseline <17 mmol/L or <ULN (if ULN≥17 mmol/L)	Two independent criteria
Chloride Hypochloremia: Hyperchloremia:	<80 mmol/L or <LLN (if LLN ≤80 mmol/L) and baseline ≥80 mmol/L or ≥LLN (if LLN ≤80 mmol/L) >115 mmol/L or >ULN (if ULN ≥115 mmol/L) and baseline ≤115 mmol/L or ≤ULN (if ULN ≥115 mmol/L)	Two independent criteria

Parameter	PCSV	Comments
Sodium Hyponatremia: Hypernatremia:	 ≤129 mmol/L or ≤LLN (if LLN ≤129 mmol/L) and baseline >129 mmol/L or >LLN (if LLN ≤129 mmol/L) ≥160 mmol/L or ≥ULN (if ULN ≥160 mmol/L) and baseline <160 mmol/L or <ULN (if ULN ≥160 mmol/L)	Two independent criteria
Potassium Hypokalemia Hyperkalemia	 <3 mmol/L or <LLN (if LLN ≤3 mmol/L) and baseline ≥3 mmol/L or ≥LLN (if LLN ≤3 mmol/L) ≥5.5 mmol/L or ≥ULN (if ULN ≥5.5 mmol/L) and baseline <5.5 mmol/L or <ULN (if ULN ≥5.5 mmol/L)	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
Glucose Hypoglycemia Hyperglycemia	 ≤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)	
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)	
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)	
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) 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)	
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)	

Parameter	PCSV	Comments
Hemoglobin	≤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) 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.
Hematocrit	≤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 ≤0.32 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
RBC	≥6 Tera/L or ≥ULN (if ULN ≥6 Tera/L) and baseline < 6 Tera/L or <ULN (if ULN ≥6 Tera/L)	
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)	Two independent criteria

Parameter	PCSV	Comments
Vital signs		
HR	<45 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
SBP	≤95 mmHg and decrease from baseline ≥20 mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	

Footnote: Only data collected in this study will be applied to these criteria.

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