
Statistical Analysis Plan Addendum

A Phase 1 Open-label, Randomized, Parallel-group Study to Assess the Relative Bioavailability of Rocatinlimab (AMG 451) Vial and Prefilled Syringe in Healthy Subjects

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Investigational Product: Rocatinlimab (AMG 451)

Protocol Reference: 20220015

Fortrea Study ID: 8524870

Sponsor: Amgen Inc.

Author:

PPD

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1. INTRODUCTION TO CHANGE DOCUMENTATION

Post database lock additions (e.g. sub-group analyses, sensitivity analyses, data driven inferential method changes, adding new tables/figures/listings) need to be documented here.

This document should not be used for tracking updates, corrections of typographical errors, modification of spelling, etc.

This document was prepared following final database lock 07NOV2024 and final SAP Version 1.0 dated 14FEB2024.

2. POST-SAP FINALIZATION CHANGES (POST DATABASE LOCK)

2.1. Changes to Analyses or Outputs

Changes to Pharmacokinetic Analyses or Outputs

The planned statistical analysis method was revised from a mixed model with actual treatment as a fixed effect and subject as a random effect to analysis of variance with actual treatment as a fixed effect to align with the study design. Within-subject CV was not calculated (this calculation could not be performed, due to the parallel group study design).

Sensitivity statistical analysis, summary tables, and descriptive statistics of PK data by

CCI

_____ were not included in the final PK tables, per the Amgen team's decision that these outputs were not needed.

Changes to Safety and Tolerability Analyses or Outputs

Treatment-emergent adverse events of interest were defined and summarized using the following search strategies below:

- Injection-related reaction (Injection-related reactions AMQ narrow AND onset within 72 hours post IP administration)
- Injection-site reactions (Injection site reactions AMQ narrow)
- Hypersensitivity (Hypersensitivity SMQ narrow)
- Anaphylactic reactions (Anaphylactic reactions SMQ narrow)
- Aphthous Ulcers (Stomatitis and ulceration AMQ narrow)

The frequency of subjects with each event of interest were summarized by severity, treatment, and by preferred term.

Time to onset and duration for adverse events of interest related to injection-related reactions (within 72 hours) were summarized.



Statistical Analysis Plan

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SAP Status: Final
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LIST OF ABBREVIATIONS

Abbreviations pertain to the statistical analysis plan (SAP) only (not the tables, figures, and listings [TFLs]).

%AUC _{extrap}	percentage of area under the concentration-time curve due to extrapolation from the last quantifiable concentration to infinity
ADaM	Analysis Data Model
CCI	
AE	adverse event
AUC _{inf}	area under the serum concentration-time curve from time zero extrapolated to infinity
AUC _{last}	area under the serum concentration-time curve from time zero to time of last quantifiable concentration
BLQ	below the limit of quantification
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CL/F	apparent total clearance
C _{max}	maximum observed serum concentration
CRU	clinical research unit
CSR	clinical study report
CV	coefficient of variation
DMP	data management plan
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
ICH	International Conference on Harmonisation
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
CCI	
PK	pharmacokinetic(s)
R ²	coefficient for determination of exponential fit
SAP	statistical analysis plan
SD	standard deviation
t _{1/2}	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
t _{last}	time of the last quantifiable serum concentration
t _{max}	time of the maximum observed serum concentration
V _z /F	apparent volume of distribution during the terminal phase
WHODrug	World Health Organization Drug Dictionary

λ_z apparent terminal elimination rate constant

1. INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Protocol, V1.0 dated 05 Dec 2023) and electronic case report form (eCRF).

This SAP describes the planned analysis of the pharmacokinetic (PK), safety, and tolerability data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shells document.

In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Amgen Inc. A limited amount of information about this study (eg, objectives, study design) is given to help the reader's interpretation.

This SAP must be finalized prior to the first subject enrollment (the point of enrollment occurs at the time of subject number allocation). Additionally, the SAP and TFL shells should be finalized prior to any programming activities commencing.

This SAP supersedes any statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified accordingly in the CSR. Any substantial deviations from this SAP will be agreed with Amgen Inc. and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E3 guideline *Structure and Content of Clinical Study Reports*, ICH E8 guideline *General Considerations for Clinical Trials*, ICH E9 guideline *Statistical Principles for Clinical Trials*.^{1,2,3}

The document history is presented in [Appendix 1](#).

2. STUDY OBJECTIVES

The primary objective of the study is:

- to evaluate the PK of rocatinlimab given as a single SC dose of CCI vial compared to prefilled syringe in healthy subjects.

The secondary objective of the study is:

- to evaluate the safety, tolerability, and immunogenicity of rocatinlimab after a single SC dose of rocatinlimab in healthy subjects.

3. STUDY ENDPOINTS

3.1. Primary Endpoints:

The primary endpoints of AMG 451 PK parameters are:

- maximum observed concentration (C_{max})
- area under the concentration time curve (AUC) from time zero to time of last quantifiable concentration (AUC_{last})
- AUC from time zero to infinity (AUC_{inf})

3.2. Secondary Endpoints:

The secondary endpoints of the study are:

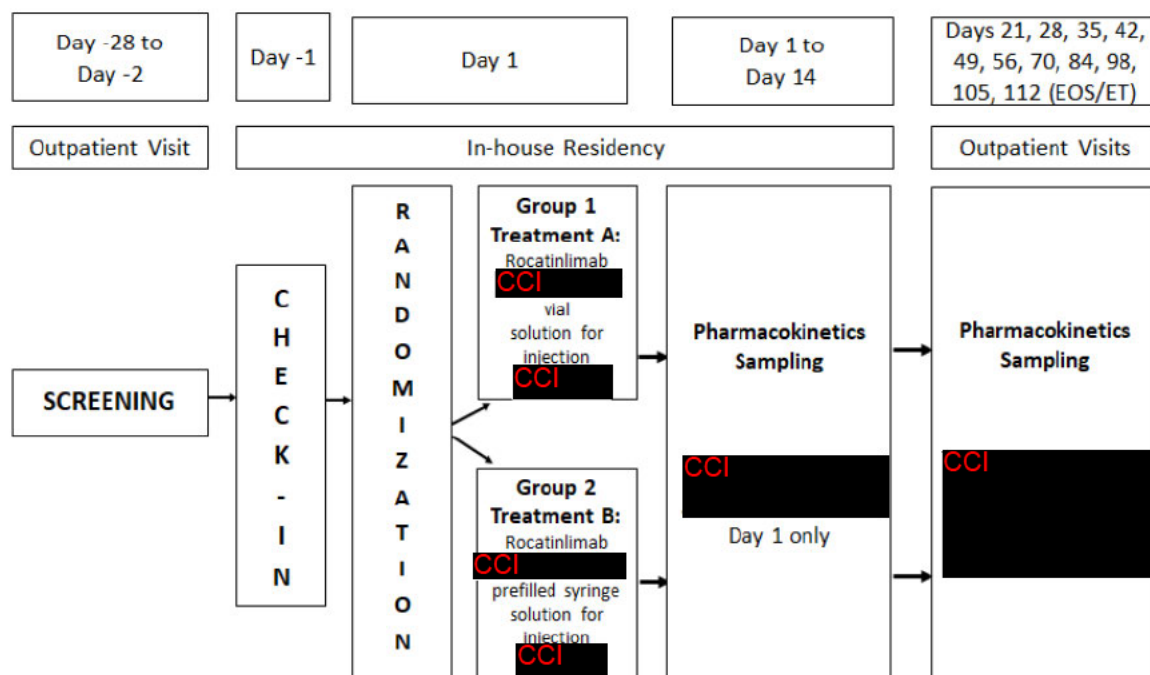
- treatment-emergent adverse events
- serious adverse events
- CCI [REDACTED]

4. STUDY DESIGN

This will be a Phase 1, multi-center, randomized, parallel-group study to investigate the relative bioavailability of rocatinlimab vials and prefilled syringes in healthy subjects. After informed consent is obtained, potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the dose administration. Subjects will be admitted into the Clinical Research Unit (CRU) on Day -1. On Day 1, subjects will be randomized to receive one of two treatments. Subjects will receive a single SC dose of rocatinlimab (Treatment A or Treatment B) on Day 1 and be confined to the CRU until discharge on Day 14. Subjects will return to the CRU for outpatient visits on Days CCI [REDACTED]

An overview of the study design is shown in [Figure 1](#).

Figure 1: Study Schematic



The estimated glomerular filtration rate will be determined by the Modification of Diet in Renal Disease (MDRD) formula⁴ and will be rounded and presented as the nearest whole number:

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The total duration of study participation for each subject (from Screening through EOS visit) is anticipated to be approximately 20 weeks.

The start of the study is defined as the date the first enrolled subject signs an Informed Consent Form (ICF). The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

5. SAMPLE SIZE JUSTIFICATION

Approximately CCI subjects will be randomized into 2 treatment groups CCI per group). Assuming CCI

. Assumin CCI

6. STUDY TREATMENTS

The study treatment names, abbreviations, and ordering to be used in the TFLs are presented in [Table 1](#).

Table 1: Presentation of Study Treatments in TFLs

	Study Treatment	Abbreviation	Order in TFLs
CCI	Rocatinlimab vial solution for injection	Treatment A	1
CCI	Rocatinlimab prefilled syringe solution for injection	Treatment B	2

All TFLs will be based on actual treatments (eg, if subject was assigned to receive Treatment A but was wrongfully dosed with Treatment B they would be summarized and listed under Treatment B).

7. DEFINITIONS OF POPULATIONS

Any protocol deviations and related restrictions will be considered prior to database lock for their importance and taken into consideration when assigning subjects to populations.

7.1. All Subjects Population

The all subjects population will include all randomized subjects who signed the ICF and had any study assessment recorded in the database per the protocol.

7.2. Safety Population

The safety population will include all subjects who received at least 1 dose of rocatinlimab and have at least 1 postdose safety assessment.

7.3. Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of rocatinlimab and have evaluable PK data.

8. STATISTICAL METHODOLOGY

8.1. General

Listings will be provided for all data captured in the database. Listings will include all subjects assigned to the ‘all subjects’ population and include data up to the point of study completion or discontinuation. Subjects are generally considered to have completed the study if they complete the scheduled End of Study visit. Any subject who discontinues the study will be identified accordingly in the listings. Summaries and statistical analyses will include the subjects assigned to the relevant population based on data type.

Data analysis will be performed using the

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Where reference is made to ‘valid’ data, this refers to non-missing data which meet the predetermined criteria (eg, are not flagged for exclusion).

Where reference is made to ‘all calculations’, this includes, but is not limited to, summary statistics, statistical analyses, baseline derivation, changes from baseline, and percentage changes from baseline.

All figures will be produced on CCI, as applicable, unless specifically stated otherwise.

All PK concentrations will be reported and analyzed with the same precision as the source data provided by the bioanalytical laboratory regardless of how many significant figures or decimals the data carry. Derived PK parameters will be rounded for reporting purposes in by-subject listings. Summary statistics and inferential analysis of derived PK parameters will be performed by using the unrounded values and the statistical results will be rounded for reporting purposes.

Derived PK parameters will be reported in 3 significant digits.

8.1.1. Calculation of the Summary Statistics

For continuous data, the following rules will be applied:

- Missing values will not be imputed, unless specifically stated otherwise.
- Unrounded data will be used in the calculation of summary statistics.
- Quantitative variables will be summarized using descriptive statistics, including n, mean, standard deviation (SD), coefficient of variation (CV), median, minimum, and maximum values. Geometric mean and geometric CV will be included for PK concentrations and parameters, where applicable.
- If the number of subjects with valid observations (n) < 3, summary statistics will not be calculated, with the exception of n, minimum, and maximum.

- In general, as early termination data are not associated with any scheduled timepoint, they will be excluded from all calculations of summary statistics and statistical analyses. Exceptions may be made where justified.

For categorical data the following rules will be applied:

- For ordered categorical data (eg, adverse event [AE] severity), all categories between the possible minimum and maximum categories will be included, even if $n = 0$ for a given category.
- For non-ordered categorical data (eg, race), only those categories for which there is at least 1 subject represented will be included; unless specifically stated otherwise.
- Missing values will not be imputed, unless specifically stated otherwise. A ‘missing’ category will be included for any parameter for which information is missing. This will ensure that the population size totals are consistent across different parameters.

8.1.2. Repeat and Unscheduled Readings

For vital signs and 12-lead electrocardiogram (ECG) data only, any predose value recorded in addition to the original value or a postdose value recorded within 15 minutes of the original value will be defined as a repeat value; any postdose value recorded more than 15 minutes after the original value will be defined as an unscheduled value. For all other data types (eg, laboratory parameters), any value recorded in addition to the original value will be defined as an unscheduled value.

The original value will be replaced by the last associated non-missing repeat value in all calculations.

As unscheduled values are not associated with any scheduled timepoint, they will be excluded from all calculations, with the exception of the baseline derivation (see [Section 8.1.3](#)).

8.1.3. Definitions of Baseline, Change from Baseline, and Percentage Change from Baseline

The baseline will be defined as the last non-missing value recorded prior to dosing. If the date/time of the value is incomplete or missing, it will be excluded from the baseline calculation, unless the incomplete date/time indicates the value was recorded prior to dosing.

Individual changes from baseline will be calculated by subtracting the individual subject’s baseline value from the value at the postdose timepoint.

Individual percentage changes from baseline will be calculated by subtracting the individual subject’s baseline value from the value at the postdose timepoint, then dividing this calculated value by the individual subject’s baseline value and multiplying by 100.

The summary statistics for change from baseline and percentage changes from baseline will be derived from individual subjects' values (eg, mean change from baseline will be the mean of the individual changes from baseline for all subjects, rather than difference between the mean value at the postdose timepoint and mean value at baseline).

See [Section 8.1.2](#) for more detail on handling repeat and unscheduled readings in the calculations.

8.2. Subject Disposition and Population Assignment

Subject disposition and population assignment will be listed, based on the all subjects population.

A summary table by treatment will be provided, based on the all subjects population.

8.3. Screening Demographics

The screening demographics including age, sex, race, ethnicity, height, body weight, and body mass index will be listed, based on the all subjects population.

A summary table by treatment will be provided, based on the safety population.

8.4. Prior and Concomitant Medication

Prior medication will be defined as medication that ends prior to dosing. Concomitant medication will be defined as medication that starts during or after dosing or starts but does not end prior to dosing.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) Global, Format B3, Version September 2023 (or later if a new version is issued during the study; see the data management plan [DMP] for more details). Prior and concomitant medications will be listed.

8.5. Pharmacokinetic Assessments

8.5.1. Pharmacokinetic Analysis

The following PK parameters will be determined on Day 1 to Day **CCI**, data permitting, from the serum concentrations of rocatinlimab using noncompartmental methods in a validated software program **CCI**):

Parameter	Units ^a	Definition
AUC _{last}	h*µg/mL	area under the serum concentration-time curve from time zero to time of last quantifiable concentration (t _{last}) ^b
AUC _{inf}	h*µg/mL	area under the serum concentration-time curve from time zero extrapolated to infinity ^c

%AUC _{extrap}	%	percentage of area under the serum concentration-time curve due to extrapolation from the last quantifiable concentration to infinity
C _{max}	µg/mL	maximum observed serum concentration
t _{max}	h	time of the maximum observed serum concentration
t _{last}	h	time of the last quantifiable serum concentration
t _{1/2}	h	apparent terminal elimination half-life
CL/F	L/h	apparent total clearance
V _z /F	L	apparent volume of distribution during the terminal phase

^a Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.

^b The AUCs will be calculated using the CCI

^c Based on the last observed quantifiable concentration.

Additional PK parameters may be determined where appropriate.

Pharmacokinetic analysis will be carried out where possible using actual dose administered (mg) and actual postdose blood sampling times (hr). If an actual time is missing, the sample concentration result will be treated as missing unless there is scientific justification to include the result using the nominal time.

The parameters C_{max}, t_{last}, and t_{max} will be obtained directly from the concentration-time profiles. If C_{max} occurs at more than 1 timepoint, t_{max} will be assigned to the first occurrence of C_{max}.

8.5.1.1. Criteria for the Calculation of Apparent Terminal Elimination Rate Constant and Half-life

The start of the terminal elimination phase for each subject CCI

The apparent terminal elimination rate CCI

The following regression-related diagnostic PK parameters will be determined, when possible:

Parameter	Units	Definition
λ _z	1/h	apparent terminal elimination rate constant
λ _z Upper	h	end of exponential fit

λ_z Lower	h	start of exponential fit
λ_z N	NA	number of data points included in the CCI
λ_z Span Ratio	NA	time period over which λ_z was determined as a ratio of $t_{1/2}$
R^2	NA	coefficient for determination of exponential fit

Abbreviation: NA = Not applicable

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8.5.1.2. Criteria for Calculation and Reporting of Area Under the Concentration-time Curve

The minimum requirement for the calculation of AUC will be the inclusion of at least CCI

If the CCI of the sponsor or pharmacokineticist.

If CCI may be used in the statistical analysis.

8.5.1.3. Criteria for Handling Concentration Below the Limit of Quantification or Missing Concentrations for Pharmacokinetic Analysis

Serum concentrations below the limit of quantification (BLQ) will be assigned CCI before the first quantifiable concentration and thereafter BLQ concentrations will be treated as missing. The following rules apply to the specific situations defined below:

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8.5.1.4. Treatment of Outliers in Pharmacokinetic Analysis

If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude the value from the PK analysis. However, the exclusion of any data must have strong justification and will be documented in the CSR.

Any quantifiable predose concentration value will be considered anomalous and set to missing for the PK analysis. This will be set to CCI [REDACTED].

8.5.2. Presentation of Pharmacokinetic Data

All PK concentrations and parameters will be listed.

Summary tables, arithmetic mean (+ standard deviation [SD]) figures, overlaying individual figures, and individual figures by treatment and time postdose will be provided for serum PK concentrations. All figures will be produced on both CCI [REDACTED] scales. The +SD bars will only be displayed on the CCI [REDACTED].

Summary tables by treatment will be provided for all PK parameters, with the exception of diagnostic regression-related PK parameters.

Summary tables and descriptive stats CCI [REDACTED] will be provided for all PK parameters.

If the actual time of sample collection deviates from the nominal time by more than $\pm 20\%$, the serum concentration will be flagged and excluded from the summary statistics. Individual concentrations deemed to be anomalous will be flagged in the listings and excluded from the summary statistics.

For serum concentration data the following rules will apply:

- CCI [REDACTED]

For PK parameters the following rule will apply:

- CCI [REDACTED]

8.5.3. Pharmacokinetic Statistical Methodology

A statistical analysis will be conducted to investigate the relative bioavailability of Treatment B (test treatment) to Treatment A (reference treatment).

CCI [REDACTED]

For each PK parameter separately, the CCI [REDACTED] for each treatment, CCI [REDACTED]

It will be concluded that the test treatment is bioequivalent to the reference treatment if, for all PK parameters, the 90% CI for the ratio of GLSMs is completely contained within the predefined interval of (0.8000, 1.2500).⁶ CCI [REDACTED]

Additionally, the pooled estimate (across treatments) of the within-subject coefficient of variation (CV) will be calculated, and residual plots will be produced to assess the adequacy of the model(s) fitted.

Sensitivity analysis will also be conducted to determine assess relative bioavailability of Treatment B (test treatment) to Treatment A (reference treatment) for subjects:

- with and without CCI [REDACTED]
- with and without CCI [REDACTED]

Examples of the SAS code that will be used are as follows:

CCI [REDACTED]

8.6. Safety and Tolerability Assessments

8.6.1. Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 26.1 (or higher if a new version is issued during the study; see the DMP for more details).

A treatment-emergent adverse event (TEAE) will be defined as an AE that starts during or after the dosing of study treatment and up to EOS.

A treatment related TEAE will be defined as a TEAE related to the study treatment, as determined by the investigator.

All AEs will be listed. In addition to the data recorded in the database, the listings will include derived onset time and duration. Onset time will be calculated from the time of dosing for each treatment for TEAEs only. Tables of fatal adverse events, serious adverse events, adverse events leading to discontinuation from investigational product(s), and/or noninvestigational product(s)/auxiliary medicinal product(s), and significant treatment-emergent adverse events will also be provided. Subject-level data may be provided instead of tables if the subject incidence is low.

The frequency of subjects with TEAEs and the number of TEAEs will be summarized for the following categories:

- TEAEs (overall, serious, leading to discontinuation, and leading to death) by treatment
- TEAEs by severity and treatment
- Treatment-related TEAEs (overall, serious, leading to discontinuation, and leading to death) by treatment
- Treatment-related TEAEs by severity and treatment

The frequency of subjects will be summarized separately for TEAEs and treatment-related TEAEs by the following:

- System organ class, preferred term, severity and treatment
- Preferred term, severity and treatment

For the AE data the following rules will apply:

- For the derivation of TEAE status: If the start date/time of an AE is incomplete or missing, an AE will be assumed to be a TEAE, unless the incomplete start date/time or the end date/time indicates an AE started prior to the dosing.
- For the derivation of treatment-related TEAE status: If the study treatment relationship for a TEAE is missing, a TEAE will be assumed to be a treatment-related TEAE.
- For the derivation of onset time (applicable to TEAEs only): If the start date/time of a TEAE is missing, onset time will not be calculated. If the start date/time of a TEAE is incomplete, where possible, the minimum possible onset time will be calculated and presented in '≥DD:HH:MM' format (eg, if the date/time of dosing is

01MAY2019/08:00 and recorded start date/time of a TEAE is 03MAY2019, then the minimum possible onset time will be calculated by assuming a TEAE started at the first hour and minute of 03MAY2019 [03MAY2019/00:00], thus will be presented as onset time $\geq$ 01:16:00 in the listing). If the start date of a TEAE is the same as the date of the dosing but the start time of a TEAE is missing, an onset time will be presented as ' $\geq$ 00:00:01'. Any clock changes will be accounted for in the derivation.

- For the derivation of duration (applicable to all AEs): If the end date/time of an AE is missing, duration will not be calculated. If the start or end date/time of an AE is incomplete, where possible, the maximum possible duration will be calculated and presented in ' $\leq$ DD:HH:MM' format (eg, if the start of an AE date/time is 01MAY2019/08:00 and its recorded end date/time is 03MAY2019, then the maximum possible duration will be calculated by assuming an AE ended at the last hour and minute of 03MAY2019 [03MAY2019/23:59], thus will be presented as duration $\leq$ 02:15:59 in the listing). Any clock changes will be accounted for in the derivation.
- For the calculation of TEAE summary statistics: If the severity of a TEAE is missing, that TEAE will be counted under the 'missing' category.
- For the calculation of TEAE by severity summary statistics: If a subject experienced multiple treatment-emergent adverse events with the same preferred term for the same treatment, this will be counted as separate TEAEs for that treatment under each specific severity recorded.

8.6.2. Clinical Laboratory Parameters

All clinical laboratory parameters, their changes from baseline, and percentage changes from baseline will be listed, as applicable; any value outside the clinical reference range will be flagged. Separate listings will be provided for any parameter for which there is any individual subject value outside the respective clinical reference range.

Summary tables by scheduled timepoint will be provided for clinical chemistry, hematology, and urinalysis parameters, with changes from baseline and percentage changes from baseline, as applicable.

Values recorded as $<x$, $\leq x$, $>x$, or $\geq x$ will be displayed in the listings as recorded. For the derivation of listing flags and calculation of summary statistics, $<x$ and $\leq x$ values will be set to 0, whereas $>x$ and $\geq x$ values will be set to x .

8.6.3. Vital Signs Parameters

All vital signs parameters, their changes from baseline, and percentage changes from baseline, will be listed, as applicable; any value outside the clinical reference range will be flagged.

Summary tables by scheduled timepoint will be provided for all vital signs parameters, with changes from baseline and percentage changes from baseline, as applicable.

8.6.4. 12-lead Electrocardiogram Parameters

All 12-lead ECG parameters will be listed, as applicable; any value outside the clinical reference range will be flagged.

Summary tables by timepoint will be provided for all 12-lead ECG parameters.

See [Section 8.1.2](#) for more detail on handling repeat and unscheduled readings in the calculations.

8.6.5. Other Assessments

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All other safety and tolerability assessments not detailed in the above sections will be listed only.

8.6.6. Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

9. INTERIM ANALYSES

No formal interim analyses are planned for this study.

10. SIGNIFICANT CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSES

There were no significant changes from the protocol -specified analyses.

11. REFERENCES

1. ICH. ICH Harmonised Tripartite Guideline: Structure and content of clinical study reports (E3). 30 November 1995.
2. ICH. ICH Harmonised Tripartite Guideline: General considerations for clinical trials (E8). 17 July 1997.
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4. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. 2020. Guidance for industry: Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing.
5. Keene ON. The log transformation is special. *Stat Med*. 1995;14(8):811-819.
6. Brown H, Prescott R. *Applied Mixed Models in Medicine*. Chichester: John Wiley & Sons, 1999.
7. *Statistical Approaches to Establishing Bioequivalence*. Rockville, MD: US Dept of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER); January 2001.

12. APPENDICES

Appendix 1: Document History

Status and Version	Date of Change	Summary/Reason for Changes
Final Version 1.0	NA	NA; the first version.

NA = not applicable