STATISTICAL ANALYSIS PLAN

A Phase I, Open-Label Trial to Assess the Mass Balance and Pharmacokinetics of a Single Intravenous Administration of (^{14}C)-OPC-61815 to Healthy Male Japanese Subjects

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Statistical Analysis Plan

A Phase I, Open-Label Trial to Assess the Mass Balance and Pharmacokinetics of a Single Intravenous Administration of (^{14}C)-OPC-61815 to Healthy Male Japanese Subjects

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LIST OF ABBREVIATIONS

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

ADaM	analysis data model
AE	adverse event
AUC	area under the concentration-time curve
AUC_∞	area under the concentration-time curve from time 0 to infinity
AUC_t	area under the concentration-time curve calculated to the last observable concentration at time t
BLQ	below the limit of quantification
CDISC	Clinical Data Interchange Standards Consortium
CL	total body clearance
C_{max}	maximum peak concentration
CSR	clinical study report
CV%	coefficient of variation
ECG	electrocardiogram
ICF	informed consent form
ICH	International Council for/Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IV	intravenous
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NC	not calculated
NR	no result
NS	no sample
PK	pharmacokinetic(s)
PT	preferred term
R^2-adj	adjusted coefficient for determination of exponential fit
SAP	statistical analysis plan
SD	standard deviation
$t_{1/2,z}$	terminal–phase elimination half-life
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
t_{last}	time of last measurable (positive) concentration
t_{max}	time to maximum peak concentration
WHODrug	World Health Organization Drug Dictionary
λ_z	apparent terminal elimination rate constant
λ_z Lower	start of exponential fit
λ_z N	number of data points included in the log-linear regression

λ_z Span Ratio	time period over which λ_z was determined as a ratio of $t_{1/2,z}$
λ_z Upper	end of exponential fit
$\%AUC_{extrap}$	percentage of AUC that is due to extrapolation from the last measurable concentration to infinity

1. INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version 1.0 dated 17 June 2019 and Amendment 1.0 dated 14 November 2019) and electronic case report form.

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 Otsuka Pharmaceutical Co., Ltd. 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 lock of the clinical database for this study. When the SAP and TFL shells are approved, they will serve as the template for this study's CSR.

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 Otsuka Pharmaceutical Co., Ltd and identified in the CSR.

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

The document history is presented in Appendix 1.

2. STUDY OBJECTIVES

2.1. Primary Objectives

- To determine the mass balance of total radioactivity following a single intravenous (IV) infusion of (^{14}C)-OPC-61815.
- To determine routes and rates of elimination of total radioactivity following a single IV infusion of (^{14}C)-OPC-61815.
- To assess the PK of total radioactivity in plasma and whole blood following a single IV infusion of (^{14}C)-OPC-61815.
- To assess the PK of OPC-61815 free form and OPC-41061 in plasma following a single IV infusion of (^{14}C)-OPC-61815.
- To identify and characterize metabolites in plasma, urine, and feces following a single IV infusion of (^{14}C)-OPC-61815.

2.2. Secondary Objective

- To assess the safety and tolerability of a single IV infusion of (^{14}C)-OPC-61815.

3. STUDY ENDPOINTS

3.1. Primary Endpoints

The PK parameter endpoints for OPC-61815 free form and OPC-41061 in plasma, and total radioactivity in whole blood and plasma are:

- Area under the concentration-time curve (AUC) from time 0 to infinity (AUC_∞)
- AUC calculated to the last observable concentration at time t (AUC_t)
- maximum peak concentration (C_{max}),
- time to maximum peak concentration (t_{max})
- time of last measurable (positive) concentration (t_{last})
- terminal-phase elimination half-life ($t_{1/2,z}$)

The total body clearance (CL) will also be determined for OPC-61815 free form. In addition, AUC ratios of whole blood total radioactivity relative to plasma total radioactivity (ratios of Blood/Plasma Ratio for both AUC_∞ and AUC_t) will be calculated.

The following PK parameter endpoints for total radioactivity in urine (calculated and reported separately in the radioanalysis report "Analysis of Total Radioactivity in Blood, Plasma and Excreta" [Covance study: 8405603] by Covance Laboratories) are:

- amount excreted in urine per sampling interval ($Ae_{,u}$)
- cumulative $Ae_{,u}$,
- percentage of drug dose excreted in urine per sampling interval ($\%fe_{,u}$)
- cumulative $\%fe_{,u}$

The following PK parameter endpoints for total radioactivity in feces (calculated and reported separately in the radioanalysis report by Covance Laboratories) are:

- amount excreted in feces per sampling interval ($Ae_{,f}$)
- cumulative $Ae_{,f}$
- percentage of drug dose excreted in feces per sampling interval ($\%fe_{,f}$)
- cumulative $\%fe_{,f}$

Overall amount and percent of total radioactivity in excreta (combined urine and feces per sampling interval and cumulative; calculated and reported separately in the radioanalysis report by Covance Laboratories).

For the primary objective to identify and characterize metabolites in plasma, urine, and feces, the endpoint is the metabolic profile of (^{14}C)-OPC-61815 and identification of radiolabeled metabolites present at >10% of the total drug-related exposure (AUC) plasma (calculated and reported separately in the metabolite profiling report [Covance study: 8405604] by Covance Laboratories).

3.1. Secondary Endpoints

The secondary endpoints are adverse events (AEs), clinical laboratory evaluations, physical examination findings, vital signs (blood pressure, pulse rate), body weight, and 12-lead electrocardiogram (ECG) parameters.

4. STUDY DESIGN

This will be a Phase I, single-site, open-label, nonrandomized, single IV dose trial in healthy male Japanese subjects.

Potential subjects will be screened to assess their eligibility to enter the trial within 28 days prior to the dose administration. Subjects will be enrolled and admitted into the trial site on Day -1. On Day 1, all subjects will receive a single IV infusion of 16 mg (^{14}C)-OPC-61815, containing approximately 75.1 μCi (2.78 MBq), over 60 minutes (55 to 65 minutes, inclusive) in the fasted state.

It is planned for at least 8 subjects to be dosed to ensure that 6 subjects complete the IV infusion. Up to a maximum of 10 subjects will be dosed in total.

Subjects will be confined to the trial site until at least Day 9. Subjects will be discharged from the trial site on Day 9 if the following discharge criteria are met:

- ≥ 90% mass balance recovery, and/or
- < 1% of the total radioactive dose is recovered in combined excreta (urine and feces) in 2 consecutive 24-hour periods.

If these criteria are not met by Day 9, subjects will remain at the trial site until any one of the discharge criterion are met up to a maximum of Day 10 to continue 24-hour blood, urine, and feces collections for total radioactivity, unless otherwise agreed upon by the sponsor and investigator.

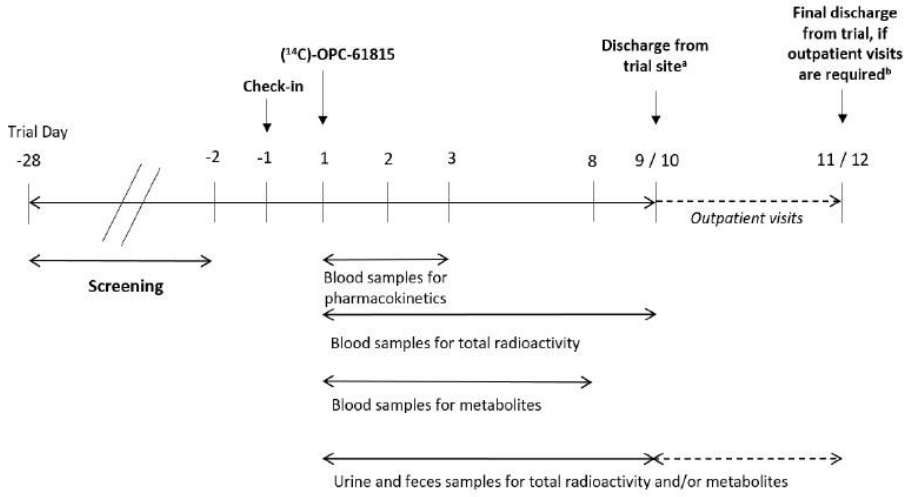
If criteria are not met by Day 10, subjects may be asked to collect 24-hour excreta samples on up to 2 further occasions on a nonresidential basis to allow extrapolation of urinary and fecal excretion. If needed, the 2 additional 24-hour nonresidential collections will start on Days 10 and 11 (to be brought to the trial site at the end of the collection interval on Days 11 and 12, respectively). If on the second occasion the subject has still not met the desired criterion, then the subject will be discharged from the trial, per investigator and sponsor decision.

Final Discharge from trial will be day of discharge from residential treatment period or the day of last outpatient visit if required to attend them based on the discharge criteria. The total duration of trial participation for each subject (from Screening through Final Discharge from trial) is anticipated to be a maximum of approximately 40 days.

The start of the trial 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 trial is defined as the last date of contact or the date of final contact attempt for the last subject completing or withdrawing from the trial.

A schematic of the study design is presented in Figure 1.

Figure 1: Study Design



[a] Subjects can be discharged on Day 9 if the following discharge criteria are met: ≥ 90% mass balance recovery and/or < 1% of the total radioactive dose is recovered in combined excreta (urine and feces) in 2 consecutive 24-hour periods. If the discharge criteria are not met, subjects will be asked to remain resident within at the trial site and additional 24-hour collection (blood, urine, and feces) for total radioactivity will continue until these criteria are met, up to a maximum of Day 10.
[b] Up to 2 additional 24-hour nonresidential collections (urine and feces) for total radioactivity may occur if discharge criteria have not been met by Day 10. Subjects will collect excreta samples at home for the 24-hour period prior to the clinic visit and deliver them to the trial site at the end of the collection interval, within 24 hours

5. SAMPLE SIZE JUSTIFICATION

No formal statistical assessment of sample size has been conducted. The sample size chosen for this trial is common in human radiolabeled studies and is considered sufficient to achieve the objectives of the trial. It is planned for at least 8 healthy male Japanese subjects to be dosed to ensure that 6 subjects complete the IV infusion. Up to a maximum of 10 subjects will be dosed in total.

6. STUDY TREATMENTS

The study treatment is (^{14}C)-OPC-61815.

7. DEFINITIONS OF POPULATIONS

Any protocol deviations 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 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 that received (^{14}C)-OPC-61815.

7.3. Pharmacokinetic Population

The PK population will include all subjects that received (^{14}C)-OPC-61815 (full dose within the time frame of 55 to 65 minutes, inclusive) and have evaluable PK data.

8. STATISTICAL METHODOLOGY

8.1. General

Listings will be provided for all data captured in the database, with the exception of medical history. Listings will include all subjects assigned to the all subjects population and include data up to the point of study completion or discontinuation. Any subject who discontinued the study will be identified accordingly in the listings. Summaries will include the subjects assigned to the relevant population based on data type.

Data analysis will be performed using the SAS® statistical software package Version 9.4 (or higher if upversioned during the study).

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1 (or higher if upversioned during the study) and CDISC ADaM Implementation Guide Version 1.1 (or higher if upversioned during the study). Pinnacle 21 Community Validator Version 2.2.0 (or higher if upversioned during the study) will be utilized to ensure compliance with CDISC standards.

Where reference is made to ‘all calculations’, this includes, but is not limited to, summary statistics.

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.
- If number of subjects with valid observations (n) <3, summary statistics will not be calculated, with the exception of n, minimum, and maximum.
- As Early Termination data is not associated with any scheduled timepoint, it will be excluded from all calculations of summary statistics.

For categorical data the following rules will be applied:

- If the categories of a parameter are ordered (eg, AE severity), all categories between the possible minimum and maximum categories will be included, even if n = 0 for a given category. If the categories are not ordered (eg, race), only those categories for which there is at least 1 subject represented will be included.

- Missing values will not be imputed, with the exception of AEs where the 'worst-case' approach will be taken (see Section 8.6.1), or 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 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 repeat value in all calculations.

As unscheduled values are not associated with any scheduled timepoint, they will be excluded from all calculations.

8.2. Subject Disposition and Population Assignment

Subject disposition and population assignment will be listed.

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

8.3. Screening Demographics

The screening demographics including age, sex, race, ethnicity, country, height, body weight, and body mass index will be listed.

A summary table 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 the start of the infusion. Concomitant medication will be defined as medication that starts after the start of the infusion or starts but does not end prior to the start of the infusion.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) Global, Format B2, Version September 2018 (or later if upversioned during the study). Prior and concomitant medications will be listed.

8.5. Pharmacokinetic Assessments

8.5.1. Pharmacokinetic Analysis

The following PK parameters will be determined where possible from the plasma concentrations of OPC-61815 free form and OPC-41061, and total radioactivity in whole blood and plasma using non compartmental methods performed using Phoenix WinNonlin (Certara USA Inc, Version 8.1 or higher):

Parameter	Definition
AUC_t	area under the concentration-time curve calculated to the last observable concentration at time t
AUC_∞	area under the concentration-time curve from time 0 to infinity
$\%AUC_{extrap}$	percentage of AUC that is due to extrapolation from the last measurable concentration to infinity
C_{max}	maximum peak concentration
t_{max}	time to maximum peak concentration
t_{last}	time of last measurable (positive) concentration
$t_{1/2,z}$	terminal–phase elimination half-life
CL	total body clearance (OPC-61815 free form only)
AUC_∞ Blood /Plasma Ratio	AUC_∞ of total radioactivity in whole blood relative to AUC_∞ of total radioactivity in plasma
AUC_t Blood/Plasma Ratio	AUC_t of total radioactivity in whole blood relative to AUC_t of total radioactivity in plasma

The parameters related to the regression analysis for the terminal elimination phase shown below will be presented in the listings only and not summarized:

Regression Parameter	Definition
λ_z Lower	start of exponential fit
λ_z Upper	end of exponential fit
λ_z N	number of data points included in the log-linear regression
R^2-adj	adjusted coefficient for determination of exponential fit
λ_z	apparent terminal elimination rate constant
λ_z Span Ratio	time period over which λ_z was determined as a ratio of $t_{1/2,z}$

Additional PK parameters may be determined where appropriate.

The PK analysis will be carried out using actual postdose times recorded in the raw data. If actual times are missing, nominal times will be used.

Concentrations will be used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory.

C_{max}, t_{max}, and t_{last} will be obtained directly from the concentration-time profiles.

When C_{max} occurs at more than 1 timepoint, t_{max} will be assigned to the first occurrence of C_{max}.

The urine and fecal PK parameters for total radioactivity in urine and feces will be calculated where possible and reported separately in the radioanalysis report by Covance Laboratories.

Identification of radiolabeled metabolites present at >10% of the total drug-related exposure (AUC) will be reported separately in the metabolite profiling report by Covance Laboratories.

8.5.1.1. Criteria for Handling Concentrations Below the Limit of Quantification

Predose concentration values that are below the level of quantification (BLQ) will be set to 0 and postdose concentration values that are BLQ will be set to missing for the purposes of PK analysis, with defined exceptions as follows;

- If there are late positive concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will be evaluated. If these values are considered to be anomalous, they will be set to missing.
- If an entire plasma/blood concentration-time profile is BLQ, the profile will be excluded from the PK analysis.
- If a predose plasma/blood concentration is missing, this value will be set to 0 by default.

8.5.1.2. Criteria for the Regression Analysis of the Terminal Elimination Phase

- At least 3 data points will be included in the regression analysis and preferably should not include C_{max}.
- When assessing terminal elimination phases, the adjusted coefficient of determination for exponential fit (R^2-adj) will be used as a measure of the goodness of fit of the data points to the determined line.
- The λ_z will not be assigned if the R^2-adj value of the regression line is <0.8. In cases where the λ_z is not assigned all regression based parameters (including R^2-adj) will not be calculated.
- Time period used for the estimation of $t_{1/2,z}$ will be calculated over a time period of at least 2 half-lives (λ_z Span Ratio >2), where possible. Where λ_z Span Ratio <2 the robustness of $t_{1/2,z}$ will be discussed in the CSR.

8.5.1.3. Calculation of Area Under the Concentration-time Curve

- The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive concentrations above the lower limit of quantification (LLOQ), with at least 1 of these concentrations following C_{max}.
- AUCs will be calculated using the Linear Trapezoidal Linear/Log Interpolation method.

8.5.1.4. Anomalous Values

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

8.5.2. Presentation of Pharmacokinetic Data

8.5.2.1. Presentation Pharmacokinetic Concentration Data

- The following rules will be applied if there are values that are BLQ or if there are missing values (eg, no result [NR] or No Sample [NS]) in a concentration data series to be summarized:
    - For the calculation of summary statistics, predose BLQ values will be set to zero and postdose BLQ values will be set to missing.
    - If an embedded BLQ value is considered anomalous within the concentration-time profile, this value will be excluded from the summary statistics.
    - Where there is NR or NS, these will be set to missing.
    - If there are less than 3 non-missing values in the data series, only the min, max and n will be presented. The other summary statistics will be denoted as not calculated (NC).

Where there is a PK blood sampling time deviation from the nominal sampling time occurring outside the PK sampling time windows specified in the protocol, the concentration will be excluded from the summary statistics and summary concentration-time figures and flagged in the concentration listings.

8.5.2.2. Presentation Pharmacokinetic Parameters

Individual PK parameters will be presented to 3 significant figures with the exception of t_{max}, t_{last}, λ_z Lower and λ_z Upper which will be presented to 2 decimal places.

For the calculation of summary statistics of PK parameters, all NR and NC values in a data series will be set to missing.

The AUC values will be set to NC if they have been calculated using fewer than 3 concentrations, and/or 3 concentrations if the last is C_{max}.

8.5.3. Pharmacokinetic Statistical Methodology

All PK concentrations and parameters will be listed.

Summary tables, mean (+ SD) figures, overlaying individual figures, and individual figures by time postdose will be provided for plasma PK concentrations. All figures will be produced

on both linear and semi-logarithmic scales. The +SD bars will be only displayed on the linear scale.

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

No inferential statistical analyses are planned.

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 22.1 (or higher if upversioned during the study).

A treatment-emergent adverse event (TEAE) will be defined as an AE that starts during or after the start of the infusion, or starts prior to the start of the infusion and increases in severity after the start of the infusion.

A treatment-related TEAE will be defined as a TEAE with a relationship of 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 the start of the infusion for TEAEs only.

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

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

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

- System organ class, and preferred term (PT)
- PT

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, a AE will be assumed to be a TEAE, unless the incomplete start date/time or the end date/time indicates a AE started prior to the start of the infusion.

- 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: If the start date/time of an AE is missing, onset time will not be calculated. If the start date/time of an AE 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 the start of the infusion is 01MAY2019/08:00 and recorded start date/time of an AE is 03MAY2019, then the minimum possible onset time will be calculated by assuming the AE started at the first hour and minute of 03MAY2019 [03MAY2019/00:00], thus will be presented as onset time ≥01:16:00 in the listing).

- For the derivation of duration: 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 '≤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 the AE ended at the last hour and minute of 03MAY2019 [03MAY2019/23:59], thus will be presented as duration ≤02:15:59 in the listing).

- For the calculation of summary statistics: If the severity of a TEAE is missing, a TEAE will be counted under the maximum severity possible.

- For the calculation of summary statistics: If a subject experienced multiple TEAEs with the same PT for the same treatment, this will be counted as 1 TEAE for that treatment under the maximum severity recorded.

8.6.2. Clinical Laboratory Parameters

All clinical laboratory parameters will be listed; 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 and boxplots by timepoint will be provided for serum chemistry and hematology parameters.

Values recorded as <x, ≤x, >x, or ≥x will be displayed in the listings as recorded. For the derivation of listing flags, calculation of summary statistics, and presentation in the figures, <x and ≤x values will be set to 0, whereas >x and ≥x values will be set to x.

8.6.3. Vital Signs Parameters

All vital signs parameters will be listed; any value outside the clinical reference range will be flagged.

Summary tables and boxplots by timepoint will be provided for all vital signs parameters.

8.6.4. Body Weight

The body weight will be listed.

A summary table by timepoint will be provided.

8.6.5. 12-lead Electrocardiogram Parameters

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

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

8.6.6. Other Assessments

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

Medical history will be listed.

8.6.7. Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

9. INTERIM ANALYSES

No interim analysis or adaptive design is applicable.

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: Statistical principles for clinical trials (E9). 5 February 1998.

2. ICH. ICH Harmonised Tripartite Guideline: Structure and content of clinical study reports (E3). 30 November 1995.

12. APPENDICES

Appendix 1: Document History

Version, Status	Date of Change	Summary/Reason for Changes
Version 1, Final	NA	NA; the first version

NA = not applicable