Protocol Addendum I6T-MC-AMAN (5)

A Phase 1, Open-Label, Drug Interaction Study to Investigate the Effect of Single Dose Selpercatinib on the Pharmacokinetics of Rosuvastatin in Healthy Participants

NCT05906836

Approval Date: 24-May-2023

STATISTICAL ANALYSIS PLAN

A Phase 1, Open-Label, Drug Interaction Study to Investigate the Effect of Single Dose Selpercatinib on the Pharmacokinetics of Rosuvastatin in Healthy Participants

Statistical Analysis Plan Status: Final
Statistical Analysis Plan Version: 1.0
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Investigational Medicinal Product: LY3527723 (selpercatinib)

Protocol Reference: J2G-MC-JZPB
Labcorp Drug Development Study: 8513406

Clinical Phase I

Approved on 24 May 2023 GMT

1. TABLE OF CONTENTS

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2. ABBREVIATIONS

Abbreviations pertain to the Statistical Analysis Plan (SAP) only (not the tables, figures and listings [TFLs]).

%AUC(t_{last}-∞)	Percentage of AUC(0-∞) extrapolated
AE	Adverse event
AUC	Area under the concentration versus time curve
AUC(0-24)	Area under the concentration versus time curve from time zero to 24 hours postdose
AUC(0-∞)	Area under the concentration versus time curve from time zero to infinity
AUC(0-t_{last})	Area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
BCRP	Breast Cancer Resistance Protein
BQL	Below the quantifiable lower limit of the assay
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
C_{last}	Last quantifiable drug concentration
C_{max}	Maximum observed drug concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
DMP	Data Management Plan
ECG	Electrocardiogram
ICF	Informed consent form
ICH	International Conference on Harmonisation
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
PK	Pharmacokinetic
SAP	Statistical Analysis Plan
SD	Standard deviation

$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
OATP1B1	organic anion transporting polypeptide 1B1
V_{ss}/F	Apparent volume of distribution at steady state after extravascular administration
V_z/F	Apparent volume of distribution during the terminal phase after extra-vascular administration
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 03 April 2023).

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

The intent of this document is to provide guidance for the statistical and PK analyses of data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Eli Lilly and Company. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. This SAP must be finalized prior to first participant visit. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the 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 in the CSR. Any substantial deviations from this SAP will be agreed upon with Eli Lilly and Company and identified in the CSR. Any minor deviations from the TFLs may not be documented in the CSR.

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

4. STUDY OBJECTIVES AND ENDPOINTS

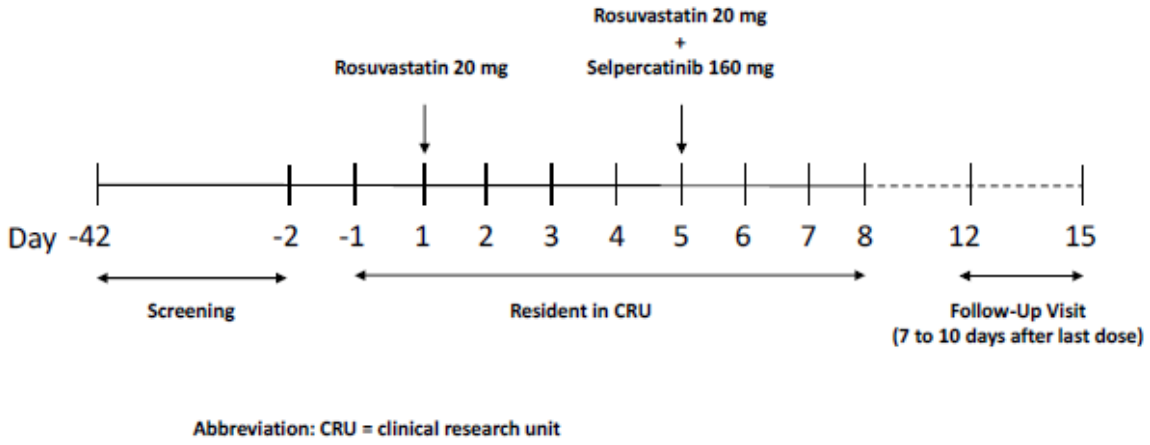
Objectives	Endpoints
Primary	
• To evaluate the effect of a single dose of selpercatinib on breast cancer resistance protein (BCRP) activity in healthy participants	• Maximum observed drug concentration (C_{max}) and area under the concentration versus time curve from time zero to infinity (AUC[0-∞]) of rosuvastatin
Secondary	
• To describe the safety and tolerability of rosuvastatin in combination with selpercatinib in healthy participants	• Incidence of treatment-emergent adverse event (TEAEs) and serious adverse events (SAEs)

Exploratory	
• To assess the exploratory measurement of plasma coproporphyrin I as biomarker of transporter organic anion transporting polypeptide 1B1 (OATP1B1) and organic anion transporting polypeptide 1B3 (OATP1B3) inhibition in healthy participants to further inform degree of transporter inhibition risk	• Plasma concentrations of biomarker coproporphyrin I: C_{max} and area under the concentration versus time curve from time zero to 24 hours postdose (AUC[0-24])

5. STUDY DESIGN

Study J2G-MC-JZPB is a Phase 1, open-label, fixed-sequence, drug interaction study to investigate the effect of a single dose of selpercatinib on the PK of rosuvastatin in healthy participants. Figure 1 shows the study schema.

Figure 1: J2G-MC-JZPB Study Schema



Abbreviation: CRU = clinical research unit

Screening

All participants will be screened for study inclusion within 42 days prior to enrollment (Day 1). Screening should not occur less than 14 days prior to enrollment (Day 1) in order to allow sufficient time to receive genotyping results.

Treatment and Assessment Period

Participants will check in to the clinical research unit (CRU) on Day -1 and remain resident until discharge on Day 8.

While resident at the CRU, all participants will receive study intervention as follows:

- Day 1: 20 mg rosuvastatin alone
- Day 5: 20 mg rosuvastatin coadministered simultaneously with 160 mg selpercatinib

Pharmacokinetic blood sampling and safety assessments, including vital signs measurements, physical examinations, clinical laboratory tests, electrocardiograms (ECGs), and adverse events (AE) recording, will be performed.

Participants will be discharged from the CRU on Day 8 following completion of study procedures, provided they are deemed medically fit by the investigator or designee.

Follow-up

Participants will attend an outpatient follow-up visit 7 to 10 days (Days 12 to 15) after the final dose of rosuvastatin coadministered with a single dose of selpercatinib. If participants are not able to attend the CRU for this visit, the CRU should contact the participant via phone call to conduct AE and concomitant medication review.

6. BLINDING

This is a non-randomized, open-label study.

The Labcorp biometrics and Eli Lilly study teams will be unblinded throughout the study.

7. TREATMENTS

The following is a list of the study treatment abbreviations that will be used in the TFLs.

Study Treatment Name	Treatment order in TFL
20 mg rosuvastatin	1
20 mg rosuvastatin + 160 mg selpercatinib	2

8. SAMPLE SIZE JUSTIFICATION

Approximately 28 participants will be enrolled to ensure that at least 20 evaluable participants complete the study.

A total of 20 evaluable participants will provide at least 90% coverage probability to ensure the half-width of the 90% confidence interval (CI) for the area under the concentration time curve (AUC) ratio of rosuvastatin falls within 25% of the true ratio ([rosuvastatin + selpercatinib] / rosuvastatin).

Participants are evaluable if adequate PK data are obtained sufficient for inclusion of the participant in this analysis of AUC ratio. This sample size of at least 20 evaluable participants (out of 28 treated) assumes unknown selpercatinib effect on rosuvastatin PK and intra-participant coefficient of variation of 33% for the PK parameter of interest for each treatment (precision method) based on internal data.

9. DEFINITION OF ANALYSIS POPULATIONS

The "Entered" population will consist of all participants who sign the informed consent form (ICF).

The "Safety" population will consist of all participants who receive at least 1 dose of rosuvastatin.

The "Pharmacokinetic" population will consist of all participants who receive at least 1 dose of rosuvastatin and have evaluable PK data.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when participants are assigned to analysis populations.

10. STATISTICAL METHODOLOGY

10.1 General

Data listings will be provided for all data that is databased. Summary statistics and statistical analysis will only be presented for data where detailed in this SAP. For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation (SD), median, minimum, maximum and number of observations; for log-normal data (e.g. the PK parameters: AUCs and C_{max}) the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all participants up to the point of withdrawal, with any participants excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for participants included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

For change from baseline summary statistics, each individual change from baseline will be calculated by subtracting the individual participant's baseline value from the value at that time point. The individual participants' change from baseline values will be used to calculate the summary statistics (arithmetic mean, arithmetic SD, median, minimum, maximum and number of observations) using a SAS procedure such as Proc Univariate.

Data analysis will be performed using SAS® Version 9.4 or greater.

10.2 Demographics and Participant Disposition

Participant disposition will be listed. The demographic variables age, sex, race, ethnicity, country of enrolment, site ID, height and body mass index will be summarized and listed. All other demographic variables will be listed only.

10.3 Pharmacokinetic Assessment

10.3.1 Pharmacokinetic Analysis

Non-compartmental methods applied with a validated software program Phoenix WinNonlin v8.3.5 or later will be used to determine PK parameter estimates.

The plasma concentrations of rosuvastatin will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
AUC(0-∞)	ng.h/mL	area under the concentration versus time curve from time zero to infinity
AUC(0-t_{last})	ng.h/mL	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
%AUC(t_{last}-∞)	%	percentage of AUC(0-∞) extrapolated
$t_{1/2}$	h	half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
CL/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration
V_z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration
Vss/F	L	apparent volume of distribution at steady state after extra-vascular administration

The plasma concentrations of selpercatinib will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration

The plasma concentrations of coproporphyrin 1 will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-24)	pg.h/mL	area under the concentration versus time curve from time zero to 24 hours postdose
C_{max}	pg/mL	maximum observed Coproporphyrin 1 concentration
t_{max}	h	time of maximum observed Coproporphyrin 1 concentration

If a participant has an AE of vomiting that occurs at or before 2 times median t_{max} of selpercatinib and rosuvastatin, the impacted period of this participant will be excluded from the summary statistics and statistical analysis.

Additional PK parameters may be calculated, as appropriate. The software and version used for the final analyses will be specified in the clinical study report. Any exceptions or special handling of data will be clearly documented within the final study report.

Formatting of tables, figures and abbreviations will follow the Eli Lilly Global PK/PD/TS Tool: NON-COMPARTMENTAL PHARMACOKINETIC STYLE GUIDE. The version of the tool effective at the time of PK analysis will be followed.

General PK Parameter Rules

- Actual sampling times will be used in the final analyses of individual PK parameters, except for non-bolus pre-dose sampling times which will be set to zero. For non-bolus, multiple dose profiles, the pre-dose time will be set to zero unless a time deviation falls outside of the protocol blood collection time window which is considered to impact PK parameter derivation.

- C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than one time point, t_{max} will be assigned to the first occurrence of C_{max}.

- AUC parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}. AUC(0-∞) values where the percentage of the total area extrapolated is more than 20% will be flagged. Any AUC(0-∞) value excluded from summary statistics will be noted in the footnote of the summary table.

- Half-life ($t_{½}$) will be calculated, when appropriate, based on the apparent terminal log-linear portion of the concentration-time curve. The start of the terminal elimination phase for each participant will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in plasma concentrations. Half-life will only be calculated when a reliable estimate for this parameter can be obtained comprising of at least 3 data points. If $t_{½}$ is estimated over a

time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{½}$ value excluded from summary statistics will be documented in the footnote of the summary table.

- A uniform weighting scheme will be used in the regression analysis of the terminal log-linear portion of the concentration-time curve.

- The parameters based on predicted last quantifiable drug concentration (C_{last}) will be reported (except in bioequivalence and bioavailability studies, where only the observed parameters will be reported).

Individual PK Parameter Rules

- Only quantifiable concentrations will be used to calculate PK Parameters with the exception of special handling of certain concentrations reported below the lower limit of quantitation (BQL). Plasma concentrations reported as BQL will be set to a value of zero when all of the following conditions are met:

    - The compound is non-endogenous.

    - The samples are from the initial dose period for a participant or from a subsequent dose period following a suitable wash-out period.

    - The time points occur before the first quantifiable concentration.

- All other BQL concentrations that do not meet the above criteria will be set to missing.

- Also, where two or more consecutive concentrations are BQL towards the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

Individual Concentration vs. Time Profiles

- Individual concentrations will be plotted utilizing actual sampling times.

- The terminal point selections will be indicated on a semi-logarithmic plot.

Average Concentration vs. Time Profiles

- The average concentration profiles will be graphed using scheduled (nominal) sampling times.

- The average concentration profiles will be graphed using arithmetic average concentrations.

- The pre-dose average concentration for single-dose data from non-endogenous compounds will be set to zero. Otherwise, only quantifiable concentrations will be used to calculate average concentrations.

- Concentrations at a sampling time exceeding the sampling time window specified in the protocol, or ± 10%, will be excluded from the average concentration profiles.

- Concentrations excluded from the mean calculation will be documented in the final study report.

- A concentration average will be plotted for a given sampling time only if 2/3 of the individual data at the time point have quantifiable measurements that are within the sampling time window specified in the protocol or ± 10%. An average concentration estimated with less than 2/3 but more than 3 data points may be displayed on the mean concentration plot if determined to be appropriate and will be documented within the final study report.

Treatment of Outliers during Pharmacokinetic Analysis

Application of this procedure to all PK analyses is not a requirement. Rather, this procedure provides justification for exclusion of data when scientifically appropriate. This procedure describes the methodology for identifying an individual value as an outlier for potential exclusion, but does not require that the value be excluded from analysis. The following methodology will not be used to exclude complete profiles from analysis.

Data within an Individual Profile

A value within an individual profile may be excluded from analysis if any of the following criteria are met:

- For PK profiles during multiple dosing, the concentration of the pre-dose sample exceeds all measured concentrations for that individual in the subsequent postdose samples.

- For PK profiles during single dosing of non-endogenous compounds, the concentration in a pre-dose sample is quantifiable.

- For any questionable datum that does not satisfy the above criteria, the profile will be evaluated and results reported with and without the suspected datum.

Data between Individual Profiles

1. If $n<6$, then the dataset is too small to conduct a reliable range test. Data will be analyzed with and without the atypical value, and both sets of results will be reported.

2. If $n\geq6$, then an objective outlier test will be used to compare the atypical value to other values included in that calculation:

    a. Transform all values in the calculation to the logarithmic domain.

b. Find the most extreme value from the arithmetic mean of the log transformed values and exclude that value from the dataset.

c. Calculate the lower and upper bounds of the range defined by the arithmetic mean ±3*SD of the remaining log-transformed values.

d. If the extreme value is within the range of arithmetic mean ±3*SD, then it is not an outlier and will be retained in the dataset.

e. If the extreme value is outside the range of arithmetic mean ±3*SD, then it is an outlier and will be excluded from analysis.

If the remaining dataset contains another atypical datum suspected to be an outlier and $n \geq 6$ following the exclusion, then repeat step 2 above. This evaluation may be repeated as many times as necessary, excluding only one suspected outlier in each iteration, until all data remaining in the dataset fall within the range of arithmetic mean ±3*SD of the log-transformed values.

Reporting of Excluded Values

Individual values excluded as outliers will be documented in the final report. Approval of the final report will connote approval of the exclusion.

10.3.2 Pharmacokinetic Statistical Methodology

Rosuvastatin

Log-transformed C_{max} and AUC(0-∞) of rosuvastatin will be evaluated in a linear mixed-effects model with fixed effects for treatment and a random effect for participant. The treatment differences will be back-transformed to present the ratios of geometric least squares means and the corresponding 90% CIs. The test treatment is rosuvastatin in the presence of selpercatinib, and reference treatment is rosuvastatin alone.

The parameter t_{max} of rosuvastatin will be analyzed non-parametrically. Estimates of the median for each treatment, median of the within-participant differences, approximate 90% CI for the difference, and p-value from the Wilcoxon signed-rank test will be calculated.

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

Mixed Model Analysis

CCI

Signed rank test (tmax)

CCI

Coproporphyrin 1

The effect of a single dose of selpercatinib (Day 5) on plasma coproporphyrin I, a biomarker of OATP inhibition in healthy participants, will be explored.

Log-transformed C_{max} and AUC(0-24) of coproporphyrin I will be evaluated in a linear mixed-effects model with fixed effects for treatment and a random effect for participant. The treatment differences will be back-transformed to present the ratios of geometric least squares means and the corresponding 90% CIs. The test treatment is coproporphyrin I in the presence of rosuvastatin and selpercatinib (Day 5), and reference treatment is coproporphyrin I in the presence of rosuvastatin (Day 1).

The SAS code will be similar to that above.

Selpercatinib

The PK parameters of selpercatinib will be summarized and listed. No inferential statistical analyses are planned.

10.4 Safety and Tolerability Assessments

10.4.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the AE will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as a condition that starts before the participant has provided written informed consent and is ongoing at consent. A non-treatment emergent AE is defined as an AE which starts after informed consent but prior to dosing. A treatment-emergent AE is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose.

All AEs will be listed. Treatment-emergent AEs will be summarized by treatment, severity and relationship to the study drug. The frequency (the number of AEs, the number of participants experiencing an AE and the percentage of participants experiencing an AE) of treatment-emergent AEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) (version is documented in the Data Management Plan [DMP]) system organ class and preferred term. The summary and frequency AE tables will be presented for all

causalities and those considered related to the study drug by the investigator. Any serious AEs will be listed.

Discontinuations due to AEs will be listed.

Adverse events of special interest include hypersensitivity, liver injury, QT prolongation, and hypertension. Any adverse events of special interest will be listed.

10.4.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (version is documented in the DMP). Concomitant medication will be listed.

10.4.3 Clinical laboratory parameters

All clinical chemistry and hematology data and their changes from baseline will be summarized by time point, where baseline is defined as Day -1, and listed. Urinalysis data will be listed. Additionally, clinical chemistry, hematology and urinalysis data outside the reference ranges will be listed and flagged on individual participant data listings.

Values recorded as $<x$, $\leq x$, $>x$, or $\geq x$ will be displayed in the listings as recorded. For the calculation of summary statistics, $<x$ and $\leq x$ values will be set to $0.5 \times x$, whereas $>x$ and $\geq x$ values will be set to $1.1 \times x$.

10.4.4 Vital signs

Vital signs data will be summarized by time point together with changes from baseline, where baseline is defined as the Day 1 predose assessment. Figures of mean vital signs and mean changes from baseline will be presented over time.

Values for individual participants will be listed.

10.4.5 Electrocardiogram (ECG)

ECGs will be performed for safety monitoring purposes only and will not be presented. Any clinically significant findings from ECGs will be reported as an AE.

10.4.6 Hepatic Monitoring

If a participant experiences elevated laboratory parameters, as detailed in Section 8.2.6.1 of the protocol, additional tests will be performed to confirm the abnormality. Additional safety data may be collected if required, as defined in the protocol. Where applicable, the following will be presented.

The participants' liver disease history and associated person liver disease history data will be listed. Use of acetaminophen during the study, which has potential for hepatotoxicity, will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography (MRE) scan, and biopsy assessments will be listed, if performed.

Hepatic risk factor assessment data will be listed. Liver related signs and symptoms data will be summarized by treatment, if deemed appropriate, and listed. Alcohol and recreational drug use data will also be listed.

All hepatic chemistry, hematology, coagulation, and serology data will be listed. Values outside the reference ranges will be flagged on the individual participant data listings.

10.4.7 Hypersensitivity reactions

For all drug hypersensitivity reactions that occur, additional follow-up data will be collected to assess the participant's medical history, alternative causes, and symptoms.

These data will be listed.

10.4.8 Other assessments

All other safety assessments not detailed in this section will be listed but not summarized or statistically analyzed.

10.4.9 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

11. INTERIM ANALYSES

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the protocol must be amended.

12. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

13. REFERENCES

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

14. DATA PRESENTATION

14.1 Derived Parameters

Individual derived parameters (e.g. PK parameters) and appropriate summary statistics will be reported to three significant figures. Observed concentration data, e.g. C_{max}, should be reported as received. Observed time data, e.g. t_{max}, should be reported as received. Number of

observations and percentage values should be reported as whole numbers. Median values should be treated as an observed parameter and reported to the same number of decimal places as minimum and maximum values.

14.2 Missing Data

Missing data will not be displayed in listings.

14.3 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of participants or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No serious adverse events occurred for this study.”

15. 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

Signature Page for VV-CLIN-115921 v1.0

Approval	PPD Mx 22-May-2023 09:08:55 GMT+0000

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