Statistical Analysis Plan J2A-MC-GZGM

A Phase 1, Open-label, Drug Interaction Study to Investigate the Effect of Multiple Doses of Clarithromycin on the Pharmacokinetics of LY3502970 in Healthy Participants

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STATISTICAL ANALYSIS PLAN

A Phase 1, Open-label, Drug Interaction Study to Investigate the Effect of Multiple Doses of Clarithromycin on the Pharmacokinetics of LY3502970 in Healthy Participants

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1. TABLE OF CONTENTS

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-∞)	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
BQL	Below lower limit of the quantification
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
C_{min}	Minimum observed drug concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
ECG	Electrocardiogram
ICH	International Conference on Harmonisation
LLOQ	Lower limit of quantification
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
OATP	Organic anion-transporting polypeptides
PK	Pharmacokinetic
Q12H	Every 12 hours
SAE	Serious adverse event
SAP	Statistical Analysis Plan

SD	Standard deviation
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
TEAE	Treatment-emergent adverse events
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
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 06 May 2022).

This SAP describes the planned analysis of the safety, tolerability, pharmacokinetic (PK) and biomarker 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 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. For open-label studies, this SAP must be signed off prior to first participant visit for this study. 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 clarithromycin on the PK of LY3502970 in healthy participants	• PK of LY3502970 (area under the concentration versus time curve [AUC] and maximum observed drug concentration [C_{max}])
Secondary	
• To evaluate the safety and tolerability of LY3502970 dosed alone and concomitantly with clarithromycin	• Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
Exploratory	
• Effect of clarithromycin on endogenous organic anion-transporting polypeptides (OATP) biomarker	• Concentrations of biomarker coproporphyrin 1

5. STUDY DESIGN

Study GZGM is a phase 1, open-label, 2-period, fixed sequence single-arm study in healthy participants that will investigate the effect of multiple doses of clarithromycin on the PK of LY3502970.

The schema below illustrates the study design.

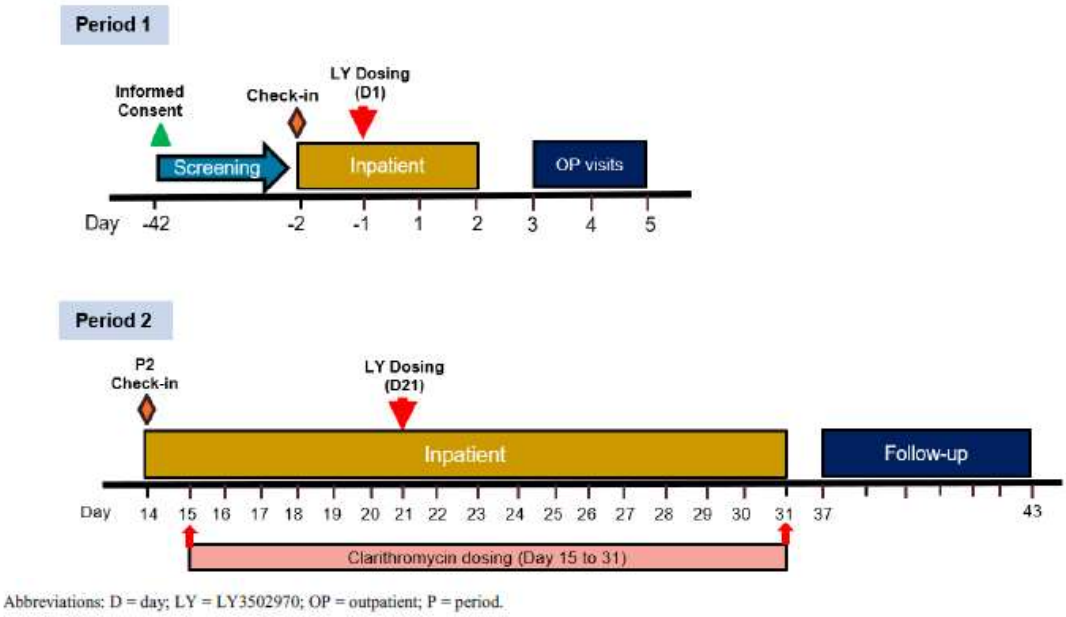

Figure 1: Study Schema for Study J2A-MC-GZGM

Screening

All participants will be screened for study inclusion within 42 days prior to enrollment (Day -2).

Treatment and Assessment Period

Participants will be admitted into the clinical research unit (CRU) on Day -2 and Day 14 for an inpatient treatment period. Approximately 24 participants will be enrolled to ensure that at least 20 evaluable participants complete the study.

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

Period 1:

On Day 1, LY3502970 will be administered orally as a single CCI mg dose with approximately 240 mL of water. Participants will be fasted overnight and remain fasted with no access to food for 4 hours after taking the study drug. Water is permitted ad libitum during the fasting period, except for 1 hour before and after dose administration.

Washout period:

Participants will be discharged from the CRU on Day 2 following the completion of study procedures. There will be a washout period of at least 14 days before period 2.

Period 2:

- Days 15 to 31: Clarithromycin will be administered orally as CCI-mg doses (CCI -mg tablet) every 12 hours (Q12H) with approximately 240 mL of water beginning on Day 15 to Day 31
- Day 21: LY3502970 will be administered orally as a CCI mg dose. Participants will be fasted overnight and remain fasted for 4 hours after taking the study drug. Clarithromycin should be administered 1 hour prior to LY3502970 dose administration.

Note: Clarithromycin should be taken at approximately the same times each day (Day 15 to 31) and may be taken with or without food, except for the morning dose on the day of LY3502970 dosing (Day 21) when it should be taken in the fasted state. Participants should remain fasted on this dosing day for 4 hours after the LY3502970 dose.

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

Participants will be discharged from the CRU on Day 31 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 from Day 37 to Day 43 after the final dose of study intervention. 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. TREATMENTS

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

Study Treatment Name	Treatment order in TFL
CCI mg LY3502970 (Day 1)	1
CCI mg clarithromycin Q12H (Days 15-20)	2
CCI mg clarithromycin Q12H + CCI mg LY3502970 (Day 21)	3

Q12H = every 12 hours

The following is a list of the study treatment names that will be used in the rest of the safety TFLs and the PK TFLs.

Study Treatment Name	Treatment order in TFL
CCI mg LY3502970 alone (Day 1)	1
CCI mg clarithromycin + CCI mg LY3502970 (Day 21)	2

Q12H = every 12 hours

7. SAMPLE SIZE JUSTIFICATION

Approximately 24 participants will be enrolled to ensure that at least 20 evaluable participants complete the study.

The sample size is calculated to quantify the clarithromycin's effect on each PK parameter of interest (AUC and C_{max}) of LY3502970. Assuming an intra-participant coefficient of variation (CV) of 28% and 20% for AUC and C_{max} respectively based upon the analyses in a previous study (GZGA), this sample size will provide approximately 90% chance to ensure no more than 2-fold increase on each LY3502970 PK parameter of interest induced by clarithromycin assuming up to 50% increase of a true effect.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Enrolled" population will consist of all participants assigned to study intervention (LY3502970), regardless of whether they take any doses.

The "Safety" population will consist of all participants who received at least one dose of study intervention (LY3502970), whether or not they completed all protocol requirements. Participants will be analyzed according to the intervention they actually received.

The "Pharmacokinetic" population will consist of all participants who received at least one dose of study intervention (LY3502970) and have evaluable PK data. Participants may be excluded from the PK summary statistics and statistical analysis if a participant has AE of vomiting that occurs at or before 2 times median time of maximum observed drug concentration (t_{max}).

The "Coproporphyrin Biomarker" population will consist of all participants who received at least 1 period of evaluable coproporphyrin 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.

9. STATISTICAL METHODOLOGY

9.1 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, min, max and n; for log-normal data (e.g. the PK parameters: AUCs and C_{max}) the geometric mean and geometric 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.

Mean change from baseline is the mean of all individual participants' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual participant's baseline value from the value at the timepoint. The individual participant's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

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

9.2 Demographics and Participant Disposition

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

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

The PK parameter estimates will be determined using non-compartmental methods in validated software program, Phoenix WinNonlin (Certara, Version 8.1.1 or later).

Plasma concentrations of LY3502970 on Day 1 and Day 21 and coproporphyrin 1 on baseline and Day 20 will be used to determine the following PK parameters, where possible:

Parameter	Units	Definition
AUC(0-∞)	ng.h/mL	Area under the concentration versus time curve from time zero to infinity (LY3502970 only)
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 (LY3502970 only)
C_{max}	ng/mL	Maximum observed drug concentration
t_{max}	h	Time of maximum observed drug concentration
$t_{1/2}$	h	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis (LY3502970 only)
CL/F	L/h	Apparent total body clearance of drug calculated after extra-vascular administration (LY3502970 only)
V_z/F	L	Apparent volume of distribution during the terminal phase after extra-vascular administration (LY3502970 only)

Additional PK parameters may be calculated, as appropriate.

The software and version used for the final analyses will be specified in the CSR. Any exceptions or special handling of data will be clearly documented within the final CSR.

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 pre-dose sampling times which will be set to zero.
- 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 ($t_{1/2}$) 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 $t_{1/2}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{1/2}$ 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 last predicted quantifiable drug concentration (C_{last}) 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.

- For multiple-dosing data, when pre-dose concentrations are missing, the value to be substituted will be minimum observed drug concentration (C_{min}) for the dosing interval.

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 CSR.
- 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 of ± 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 CSR.

Treatment of Outliers during PK 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 single dosing of non-endogenous compounds, the concentration in a pre-dose sample is quantifiable.
- For PK profiles during multiple dosing, the concentration of the pre-dose sample exceeds all measured concentrations for that individual in the subsequent post-dose samples.
- 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≥6, 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 ≥ 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 CSR. Approval of the final CSR will connote approval of the exclusion.

9.3.2 Pharmacokinetic Statistical Methodology

LY3502970 administered alone (Day 1) will represent the reference treatment, and LY3502970 administered with clarithromycin will represent the test treatment (Day 21) for this PK analysis.

The log-transformed PK parameters C_{max} and AUC(0-∞) for LY3502970 will be analysed using a linear mixed-effects model with treatment as a fixed effect and participant as a random effect. The least-square (LS) means for each treatment, the difference between the treatment LS means (test–reference), and the associated 90% confidence intervals (CIs) will be estimated from the model and back-transformed from the log scale to provide estimates of the geometric means for each treatment, geometric mean ratio between test and reference treatments, and corresponding 90% CIs.

A drug-drug interaction will be assessed by examining the 90% CIs for the geometric mean ratios of LY3502970 co-administered with clarithromycin relative to LY3502970 alone.

Example SAS code:

```
proc mixed data=test covtest alpha=0.1;
   class treatment participant;
   model log_pk=treatment / ddfm=kr2 alpha=0.1;
   random participant;
   lsmeans treatment / pdiff cl alpha=0.1;
   ods output lsmeans=lsmeans diffs=diffs covparms=cov;
run;
```

The t_{max} of LY3502970 for both treatments, test and reference, will be analyzed using a Wilcoxon signed-rank test. An estimate of the median difference and approximately 90% CI will be reported.

9.4 Coproporphyrin Biomarker Assessment

9.4.1 Coproporphyrin Biomarker Analysis

Plasma concentrations of coproporphyrin 1 will be listed and summarized, using standard descriptive statistics. Parameter estimates for coproporphyrin 1 will be calculated by standard noncompartmental methods as mentioned in Section 9.3.1. Parameters, including C_{max}, t_{max}, and AUC(0-t_{last}), will be summarized using descriptive statistics.

Additional analysis may be performed, if warranted, upon review of the data.

9.4.2 Coproporphyrin Biomarker Statistical Methodology

The log-transformed PK parameters C_{max} and AUC(0-t_{last}) for coproporphyrin (test, i.e. after clarithromycin treatment) with the C_{max} and AUC(0- t_{last}) for coproporphyrin (reference, i.e., prior to clarithromycin and LY treatment) will be compared using a linear mixed-effect model. The model will include treatment as a fixed effect and participant as a random effect. The LS means for each treatment, the difference between the treatment LS means (test–reference), and the associated 90% CIs will be estimated from the model and back-transformed from the log scale to provide estimates of the geometric means for each treatment, geometric mean ratio between test and reference treatments, and corresponding 90% CIs.

Similar SAS code will be used as in Section 9.3.2.

9.5 Safety and Tolerability Assessments

9.5.1 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 TEAE 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. The TEAEs 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 TEAEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 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 SAEs will be listed. AEs by day of onset will be presented.

Discontinuations due to AEs will be listed.

Any adverse events of special interest will be listed separately.

9.5.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version March 2022). Concomitant medication will be listed.

9.5.3 Clinical laboratory parameters

All clinical chemistry, hematology, and 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.

9.5.4 Vital signs

Vital signs data for individual participants will be listed.

9.5.5 Electrocardiograms

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.

9.5.6 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 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.

9.5.7 Hypersensitivity reactions

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

These data will be listed.

9.5.8 Other assessments

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

9.5.9 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

No interim statistical analyses are planned.

11. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

12. 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.

13. DATA PRESENTATION

13.1 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. N 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.

13.2 Missing Data

Missing data will not be displayed in listings.

13.3 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.”

14. 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