Statistical Analysis Plan J2A-MC-GZGF (Final)

Disposition of [^{14}C]-LY3502970 Following Oral Administration in Healthy Male Participants

NCT04680767

Approval Date: 28-Sep-2020

STATISTICAL ANALYSIS PLAN

Disposition of [^{14}C]-LY3502970 Following Oral Administration in Healthy Male Participants

Statistical Analysis Plan Status: Final
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Study Drug: LY3502970

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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-∞) Blood/Plasma Ratio	AUC(0-∞) of whole blood total radioactivity to AUC(0-∞) of plasma total radioactivity
AUC(0-∞) Plasma LY3502970/Total Radioactivity Ratio	AUC(0-∞) of plasma LY3502970 relative to AUC(0-∞) of plasma total radioactivity
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 the lower limit of quantitation
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration (LY3502970 only)
C_{max}	Maximum observed drug concentration
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
ECG	Electrocardiogram
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
PG	Plasma glucose
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

ULN	Upper limit of normal
V_Z/F	Apparent volume of distribution during the terminal phase after extra-vascular administration (LY3502970 only)
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 31 July 2020).

This SAP describes the planned analysis of the safety, tolerability and pharmacokinetic (PK) 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 subject 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

4.1 Primary Study Objective and Endpoint

Objective	Endpoint
• To determine the disposition of radioactivity in healthy male participants following administration of a single oral dose of CCI (approximately 200 µCi) [^{14}C]-LY3502970	• Urinary and fecal excretion of total radioactivity over time expressed as a percentage of the total radioactive dose.

4.2 Secondary Study Objectives and Endpoints

Objectives	Endpoints
• To determine the PK of LY3502970 in plasma and total radioactivity in plasma and whole blood.	• Area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration ($AUC(0\text{-}t_{last})$), area under the concentration versus time curve from time zero to infinity ($AUC(0\text{-}\infty)$), and maximum observed drug concentration (C_{max}) for LY3502970 in plasma and radioactivity in plasma and whole blood.
• To assess the mass balance of LY3502970 by quantifying radioactivity recovered in urine, feces, and expired air (if applicable).	• Total radioactivity recovered in urine, feces, and expired air (if applicable).
• To assess the metabolism of LY3502970 in plasma, urine, and feces (if applicable).	• Identity and the total number of metabolites of LY3502970.
• To assess the safety and tolerability of a single dose of LY3502970 in healthy male participants.	• Incidence of adverse events (AEs).

5. STUDY DESIGN

This is a Phase 1, open-label, single-center study in healthy male participants following a single oral dose of CCI LY3502970 containing approximately 200 µCi of [^{14}C]-LY3502970.

Participants will participate in a screening visit, a single study period, and a follow-up telephone assessment. Participants will be screened for SARS-CoV-2 (the virus that causes Coronavirus Disease 2019 [COVID-19]) in accordance with the clinical research unit (CRU) COVID-19 generic screening protocol and provided with a COVID-19 specific informed consent form.

Participants will be admitted to the CRU prior to dosing on Day -1 and will receive a single oral dose of [^{14}C]-LY3502970 on Day 1.

Participants will remain resident in the CRU for a minimum of 6 days postdose (Day 7), after which time each participant may be discharged if both the following release criteria have been met:

- ≥90% of the administered radioactivity (based on the actual dose) has been recovered,

AND

- 24-hour urine and fecal samples from 3 consecutive collections (where both collections have occurred) where each combined urine and feces collection has a radioactivity level <1.0% of the total administered radioactivity.

Participants may remain in the CRU up to a maximum of 16 days postdose (Day 17), at which time they will be discharged.

A follow-up assessment will be conducted by telephone and will include recording of AEs and concomitant medication. The follow-up assessment will be performed 7 ± 2 days after each participant has been discharged from the study or following early discontinuation from the study.

Sequential blood samples will be obtained predose and after dose administration to quantify the PK of the total radioactivity in whole blood and plasma, and LY3502970 in plasma. Separate blood samples will also be taken at selected time points for metabolite profiling.

Sequential urine and fecal samples will be obtained to determine the mass balance of LY3502970 by quantification of radioactivity and to identify metabolites. Samples of expired air will also be collected for the analysis of $^{14}CO_2$ at selected time points. If a significant amount of administered radioactivity is present in expired air samples, these data will be extrapolated to estimate the radioactive dose recovery. The percent of the dose eliminated in excreta will be estimated by measuring the amount of radioactivity in the urine and/or feces for each collection period.

Safety evaluations will include recording of AEs, clinical laboratory tests, glucose monitoring, vital sign measurements, 12-lead electrocardiograms (ECGs), and physical examinations.

Figure 1 illustrates the study design.

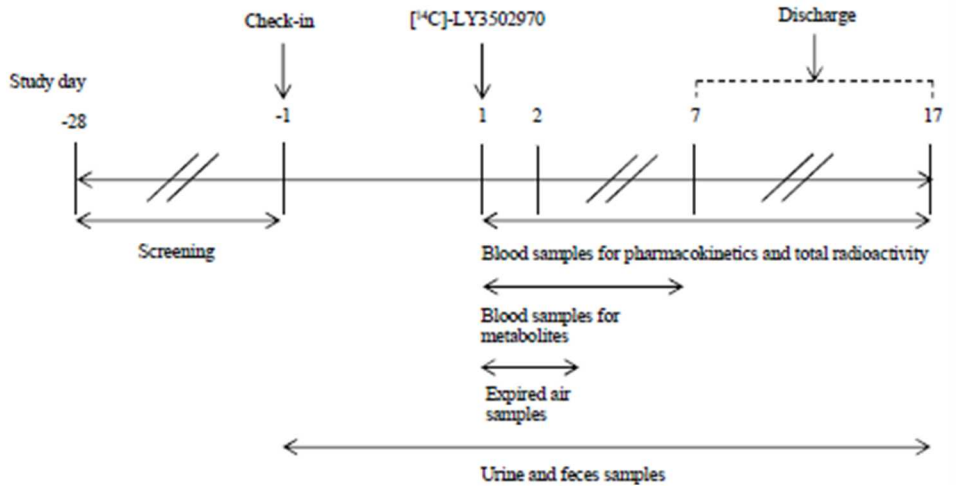

Figure 1: Study Schema

6. TREATMENT

The following is the study treatment abbreviation that will be used in the TFLs.

Study Treatment Name	Abbreviation
CCI LY3502970 containing approximately 200µCi of [^{14}C]-LY3502970	CCI [^{14}C]-LY3502970

7. SAMPLE SIZE JUSTIFICATION

Up to 8 participants may be enrolled. It is planned that up to 6 participants will be dosed initially and 2 additional participants may be dosed if needed, in order that a minimum of 4 participants complete the study. The sample size is customary for [^{14}C]-disposition studies and is chosen to provide adequate PK data while limiting the number of participants exposed to radiopharmaceuticals in non-therapeutic research.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all subjects enrolled in the study who received the study intervention.

The "Pharmacokinetic" population will consist of all subjects who received the study intervention and have evaluable PK samples. Subjects may be excluded from the PK summary statistics and statistical analysis if a subject has an AE of vomiting that occurs at or before 2 times median time of maximum observed drug concentration (t_{max}).

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when subjects 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, minimum, maximum and N; for log-normal data (e.g. the PK parameters: area under the concentration versus time curve (AUCs) and C_{max}) the geometric mean and geometric coefficient of variation will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all subjects up to the point of withdrawal, with any subjects excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for subjects 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 subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The individual subject'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 Subject Disposition

Subject disposition will be listed. The demographic variables age, sex, race, ethnicity, 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

PK parameter estimates will be determined using non-compartmental procedures in validated software program (Phoenix WinNonlin Version 8.1 or later).

Plasma concentrations of LY3502970 and plasma and whole blood concentrations of total radioactivity will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-t_{last})	Xg.h/mL or Xg equiv.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(0-∞)	Xg.h/mL or Xg equiv.h/mL	Area under the concentration versus time curve from time zero to infinity
%AUC(t_{last}-∞)	%	Percentage of AUC(0-∞) extrapolated
C_{max}	Xg/mL or Xg equiv/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
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)
AUC(0-∞) Plasma LY3502970/Total Radioactivity Ratio	NA	AUC(0-∞) of plasma LY3502970 relative to AUC(0-∞) of plasma total radioactivity
AUC(0-∞) Blood/Plasma Ratio	NA	AUC(0-∞) of whole blood total radioactivity to AUC(0-∞) of plasma total radioactivity

Additional PK parameters may be calculated, as appropriate.

The ratio of total radioactivity in whole blood : plasma will be calculated for each time point.

The ratio of plasma LY3502970 : plasma total radioactivity will be calculated for each time point.

The percentage and cumulative percentage of radiolabeled dose excreted in expired air may also be presented, if applicable.

The primary PK endpoints to determine urinary and fecal excretion of total radioactivity over time expressed as a percentage of the total radioactive dose and the PK endpoints to determine the mass balance derived from total radioactivity recovered in urine, feces, and expired air (if applicable) will be calculated by Covance Laboratories and reported separately in a radio analysis report.

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 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.

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

- Where concentration data are supplied in ng equiv/g, a matrix density of 1g/mL will be used for pharmacokinetic calculation.

- 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 concentrations above the lower limit of quantification, 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. An alternative AUC measure, such as AUC to a common time point, may be calculated if AUC(0-∞) cannot be reliably calculated.

- 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 subject 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 predicted last quantifiable drug concentration 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 and blood 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 subject 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 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.

9.3.2 Pharmacokinetic Statistical Methodology

PK parameters will be summarized using descriptive methodology. No formal statistical analysis will be performed.

9.4 Safety and Tolerability Assessments

9.4.1 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 an AE that starts before the subject 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 severity and relationship to the study drug. The frequency (the number of AEs, the number of subjects experiencing an AE and the percentage of subjects experiencing an AE) of treatment-emergent AEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 (or higher if upversioned during the course of the study) 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.

9.4.2 Glucose Monitoring and Hypoglycemia

During the study, blood glucose concentrations will be monitored for safety assessments. Glucose data will be listed and summarized by treatment together with changes from baseline, where baseline is defined as Day 1 predose.

Hypoglycemic events will be appropriately recorded in the CRF. In the case of a hypoglycemic event, the actual blood glucose value, if measured, will be recorded in the CRF, together with any treatments administered. Each category of hypoglycemic events (defined below) will be listed. Hypoglycemia is defined as follows:

- **Documented Glucose Alert Level (Level 1)**
  Plasma Glucose (PG) <70 mg/dL (3.9 mmol/L) and ≥54 mg/dL (3.0 mmol/L): Level 1 hypoglycemia can alert a person to take action such as treatment with fast-acting carbohydrates. Providers should continue to counsel participants to treat hypoglycemia at this glucose alert value.

- **Documented Clinically Significant Hypoglycemia (Level 2)**
  PG <54 mg/dL (3.0 mmol/L): This glucose threshold is clinically relevant regardless of the presence or absence of symptoms of hypoglycemia.

- **Severe Hypoglycemia (Level 3)**
  A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. For example, participants had altered mental status, and could not assist in their own care, or were semiconscious or unconscious, or experienced coma with or without seizures, and the assistance of another person was needed to actively administer carbohydrate, glucagon, or other resuscitative actions. Glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of glucose concentration to normal is considered sufficient evidence that the event was induced by a low glucose concentration.
    - The determination of a hypoglycemic event as an episode of severe hypoglycemia, as defined above, is made by the investigator based on the medical need of the participant to have required assistance and is not predicated on the report of a participant simply having received assistance.
    - If a hypoglycemic event meets the criteria of severe hypoglycemia, the investigator must record the event as serious on the AE CRF and report it to Lilly as an SAE.

Investigator review of glucose results clinically indicative of hypoglycemia will be required. If a hypoglycemic event meets the criteria of severe hypoglycemia, the investigator must record the event as serious on the AE CRF and report it to Lilly as an SAE.

9.4.3 Concomitant medication

Concomitant medication will be coded using the World Health Organization (WHO) drug dictionary (Version March 2020 or higher if upversioned during the course of the study). Concomitant medication will be listed.

9.4.4 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by parameter and treatment, 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 subject data listings.

9.4.5 Vital signs

Vital signs data will be summarized by treatment 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 profiles will be presented by treatment.

Values for individual subjects will be listed.

9.4.6 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.

9.4.7 Hepatic Monitoring

If a subject experiences elevated alanine aminotransferase ≥3× upper limit of normal (ULN), alkaline phosphatase ≥2× ULN, or elevated total bilirubin ≥2× ULN, liver tests will be performed to confirm the abnormality. Further diagnostic assessments will be recommended whenever lipase and/or amylase are confirmed to be ≥3x ULN at any timepoint post treatment even if the participant is asymptomatic. Additional safety data may be collected if required, as defined in the protocol. Where applicable, the following will be presented.

The subjects' liver disease history and associated person liver disease history data will be listed. Any concomitant medications that have potential for hepatotoxicity, including acetaminophen will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography 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 subject data listings.

9.4.8 Other assessments

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

9.4.9 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 subjects 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.”

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