I7X-MC-LLCE

Relative Bioavailability and Food Effect Study in Healthy Subjects Administered Two Different Formulations of LY3202626

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STATISTICAL ANALYSIS PLAN

Relative Bioavailability and Food Effect Study in Healthy Subjects Administered Two Different Formulations of LY3202626

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Study Drug: LY3202626

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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]).

AE	Adverse event
AUC	Area under the concentration versus time curve
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
AUC(0-∞)	Area under the concentration versus time curve from zero to infinity
%AUC(t_{last}-∞)	Percentage of AUC(0-∞) extrapolated
BQL	Below the quantifiable lower limit of the assay
C_{max}	Maximum observed drug concentration
CI	Confidence interval
C_{last}	Last quantifiable drug concentration
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
C_{nadir}	Nadir concentration
CRF	Case Report Form
CSR	Clinical Study Report
CRU	Clinical Research Unit
CV	Coefficient of variation
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
FDA	Food and Drug Administration
ICH	International Council on Harmonisation
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic
PK	Pharmacokinetic
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula

SAP	Statistical Analysis Plan
SD	Standard deviation
SOP	Standard Operating Procedure
TFLs	Tables, Figures, and Listings
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
t_{nadir}	Time to reach nadir concentration
t_{max}	Time of maximum observed drug concentration
V_{ss}/F	Apparent volume of distribution at steady state after extra vascular 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 10 September 2016).

This SAP describes the planned analysis of the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) 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 , PD, and PK analyses of data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement between Eli Lilly and Company and Covance Early Clinical (EC) Biometrics. 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 signed off prior to first subject administration 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 between Eli Lilly and Company and Covance EC Biometrics 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 out lined in the International Council 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

4.1 Primary Objective

- To evaluate the relative bioavailability of a single 12 mg dose of LY3202626 as a tablet formulation (test formulation [T1-12]) compared to the capsule formulation (reference formulation [R]).

4.2 Secondary Objectives

- To evaluate the effect of a high-fat meal on the bioavailability of LY3202626 when administered as a single 12 mg dose of the test tablet formulation (T1-12).
- To assess the tolerability of LY3202626 when administered as a single 12 mg dose to healthy subjects.

4.3 Exploratory Objective

- To evaluate plasma Aβ1-40 and Aβ1-42 after a single 12 mg dose of LY3202626 as a tablet formulation (test formulation [T1-12]) and capsule formulation (reference formulation [R]).

5. STUDY DESIGN

This is a single-center, open-label, single-dose, randomized, 6-sequence, 3-period, crossover study in healthy subjects.

Screening will occur up to 28 days prior to the first dose of LY3202626.

Subjects will be admitted to the clinical research unit (CRU) on Day -1 of each period. In each period, subjects will be fasted overnight for at least 10 hours, and a single dose of 12 mg LY3202626, as either tablet (T1-12) in a fed state or fasted state or capsule (R) in a fasted state according to the randomization schedule, will be administered on the morning of Day 1. Blood sampling for assessment of LY3202626 PK and for PD assessments of Aβ1-40 and Aβ1-42 will be performed up to 168 hours postdose (Day 8). Subjects may be discharged from the CRU following completion of all 24-hour or 36-hour procedures on Day 2. If discharged after 24-hour procedures, subject will return to the CRU as an outpatient visit for the 36-hour PK sample collection. Subjects will return to the CRU daily for outpatient visits for PK sample collections Days 3 through 8. The washout period between dosing in 2 consecutive periods will be at least 10 days. A follow-up telephone call will be performed approximately 5 to 8 days after Period 3, Day 8.

Tolerability will be explored by clinical laboratory tests, vital sign measurements, 12-lead electrocardiograms (ECGs), and recording of adverse events (AEs).

The 3 dose administrations received by each subject will be:

- A = Reference (R): 12 mg LY3202626 capsule; administered in a fasted state
- B = Test (T1-12): 12 mg LY3202626 tablet; administered in a fasted state
- C = Test (T1-12): 12 mg LY3202626 tablet; administered in a fed state (Food and Drug Administration [FDA] high-fat meal)

Subjects will be randomized to 1 of 6 dose administration sequences (Table 1).

Table 1. Dose Administration Sequences

Sequence	Period 1	Period 2	Period 3
ABC	R fasted	T1-12 fasted	T1-12 fed
BCA	T1-12 fasted	T1-12 fed	R fasted
CAB	T1-12 fed	R fasted	T1-12 fasted
CBA	T1-12 fed	T1-12 fasted	R fasted
ACB	R fasted	T1-12 fed	T1-12 fasted
BAC	T1-12 fasted	R fasted	T1-12 fed

Abbreviations: R = reference (capsule formulation); T1-12 = test (tablet formulation)

Figure 1 illustrates the study design.

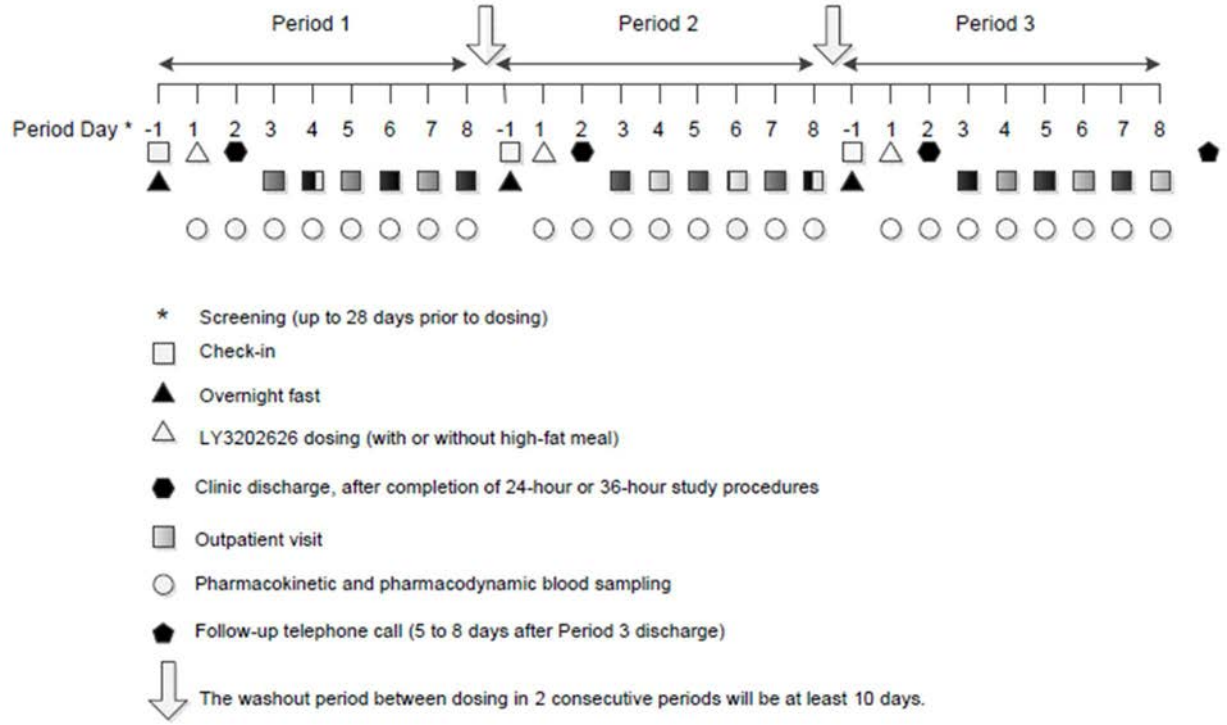

Figure 1. Illustration of Study Design for Protocol I7X-MC-LLCE

6. TREATMENTS

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

Study Treatment Name	Abbreviation	Treatment order in TFL
12 mg LY3202626 capsule (fasted)	R fasted	1
12 mg LY3202626 tablet (fasted)	T1-12 fasted	2
12 mg LY3202626 tablet (fed)	T1-12 fed	3

7. SAMPLE SIZE JUSTIFICATION

Up to approximately 24 healthy subjects may be enrolled to ensure that at least 20 subjects complete the study. This sample size is based on a calculation of precision of the estimated ratio of area under the concentration versus time curve (AUCs).

CCI [redacted]

CCI [redacted]

At the discretion of the investigator and sponsor, if multiple subjects who are randomized withdraw before study end, an additional 6 subjects (up to a total enrollment of 30 subjects) may be enrolled to ensure completion of 20 subjects. The replacement subject will be assigned the same dose administration sequence as the withdrawn subject's dose administration sequence (receiving each dose administration allocated).

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all enrolled subjects, whether or not they completed all protocol requirements.

The PK analyses will be conducted on the full analysis set. This set includes all data from all subjects who received at least one dose of LY3202626.

The "Pharmacodynamic" population will consist of all subjects who received at least one dose of study drug and have evaluable PD data.

All protocol deviations that occur during the study wil l 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, min, max and N; for log-normal data (e.g. the PK parameters: AUCs and maximum observed drug concentration [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 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 r elevant 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 base line 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 9.3 or greater.

9.2 Demographics and Subject Disposition

Subject 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.

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 6.4.1 or later).

Plasma concentrations of LY3202626 will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
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(0-∞)	ng.h/mL	area under the concentration versus time curve from zero to infinity
%AUC(t_{last}-∞)	%	percentage of AUC(0-∞) extrapolated
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 (λz) 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
V_{ss}/F	L	apparent volume of distribution at steady state after extra-vascular administration

An alternative AUC measure, such as AUC to a common time point, may be calculated if AUC(0-∞) cannot be reliably calculated.

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 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 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 $t_{½}$ 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 observed last 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 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 multiple dosing, the concentration of the pre-dose sample exceeds all measured concentrations for that individual in the subsequent post-dose 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.

9.3.2 Pharmacokinetic Parameter Estimation

The primary parameters for analysis, C_{max}, AUC(0-∞), AUC(0-t_{last}), and t_{max} of LY3202626,will be evaluated to delineate relative bioavailability and food effects.

The following comparisons will be interests of statistical analysis of PK parameters:

- relative bioavailability: LY3202626 T1-12 fasted (test) versus LY3202626 R fasted (reference)
- food effect: LY3202626 T1-12 fed (test) versus LY3202626 T1-12 fasted (reference).

Log-transformed C_{max} and AUC estimates will be evaluated in a linear mixed-effects model with fixed effects for dose administration and period and a random effect for subject. The ratio of geometric least squares means and corresponding 90% CI will be presented for LY3202626 T1-12 versus LY3202626 R for analysis of relative bioavailability, and LY3202626 T1-12 administered with a high-fat meal versus LY3202626 T1-12 administered fasted for the analysis of the food effect. One model will be used for the assessment of relative bioavailability and the effect of food.

The t_{max} will be analyzed non-parametrically for the same comparisons stated above. Median of differences and approximate 90% CI for the median of differences will be calculated. P-values will also be calculated using a Wilcoxon signed rank test.

Additional analyses may be performed if deemed necessary.

Example SAS code:

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

9.4 Pharmacodynamic Assessment

Plasma concentrations of $A\beta_{1-40}$ and $A\beta_{1-42}$ will be summarized by timepoint and treatment together with changes from baseline, where baseline is defined as Day 1 predose of the respective period, and listed. Additionally, percent changes from baseline will also be summarised and listed. Figures of mean profiles, mean changes from baseline, and mean percent changes from baseline will be presented by treatment.

9.4.1 Pharmacodynamic Parameter Estimation

Plasma concentrations of $A\beta_{1-40}$ and $A\beta_{1-42}$ will be used to derive baseline predose concentration ($C_{predose}$, defined as the Day 1 predose concentration of each respective treatment period), the nadir concentration (C_{nadir}), time to reach C_{nadir} (t_{nadir}), and the 0-24-hour average percent change from baseline values. C_{nadir} is defined as the lowest observed $A\beta_{1-40}$ or $A\beta_{1-42}$ concentration following study drug administration. The percent change from baseline (predose) at C_{nadir} will be reported, as will the 0-24-hour average change from baseline, which will be derived as

$$\%\text{Time Average Change From Baseline} = \frac{\frac{AUC_{0-24}}{24} - C_{predose}}{C_{predose}} \cdot 100.$$

The PD parameters will be summarized by treatment and listed.

9.4.2 Pharmacodynamic Statistical Inference

No formal statistical testing will be conducted.

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 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 the first dose. 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 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 19.1 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. Any serious AEs will be tabulated.

9.5.2 Concomitant medication

Concomitant medication will be coded using the World Health Organization (WHO) drug dictionary (Version September 2016). Concomitant medication will be listed.

9.5.3 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.

Values for any clinical chemistry, hematology and urinalysis values outside the reference ranges will be flagged on the individual subject data listings.

9.5.4 Vital signs

Vital signs data will be summarized by treatment together with changes from baseline, where baseline is defined as Day 1 predose of the respective period. Figures of mean vital signs and mean changes from baseline profiles by treatment will be presented by treatment. Furthermore, values for individual subjects will be listed.

9.5.5 Electrocardiogram (ECG)

ECGs will be performed for safety monitoring purposes only and will not be presented.

9.5.6 Other assessments

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

9.5.7 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 centre of the table, such as, “No serious adverse events occurred for this study.”

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