Statistical Analysis Plan H8H-MC-LAHT

Safety, Tolerability, and Pharmacokinetics of Lasmiditan when Co-administered with Topiramate in Healthy Subjects

NCT03308669

Approval Date: 01-Nov-2017

STATISTICAL ANALYSIS PLAN

Safety, Tolerability, and Pharmacokinetics of Lasmiditan when Co-administered with Topiramate in Healthy Subjects

Statistical Analysis Plan Status: Final
Statistical Analysis Plan Date: 30-October-2017

Study Drug: LY573144 (Lasmiditan)

Sponsor Reference: H8H-MC-LAHT
Covance CRU Study: 1000071-8370359

Clinical Phase I

Approval Date: 01-Nov-2017 GMT

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
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AUC	Area under the concentration versus time curve
AUC_{τ}	Area under the concentration versus time curve during one dosing interval
$AUC(0\text{-}t_{last})$	Area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
$AUC(0\text{-}\infty)$	Area under the concentration versus time curve from time zero to infinity
$\%AUC(t_{last}\text{-}\infty)$	Percentage of $AUC(0\text{-}\infty)$ extrapolated
bid	Twice daily
BQL	Below the lower limit of quantification
CI	Confidence interval
C_{max}	Maximum observed drug concentration
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
CRF	Case Report Form
CRU	Clinical research unit
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CRU	Clinical Research Unit
CV	Coefficient of variation
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
ICH	International Council on Harmonisation
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MR	Metabolic ratio
MRE	Magnetic resonance elastography

qd	Once daily
QTc	QT correction; QT interval corrected for heart rate
QTcB	QTc calculated using the Bazett correction
QTcF	QTc calculated using the Fridericia correction
PK	Pharmacokinetic
SAP	Statistical Analysis Plan
SD	Standard deviation
TBL	Total bilirubin
TFLs	Tables, Figures, and Listings
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
t_{max}	Time of maximum observed drug concentration
ULN	Upper limit of normal
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 03 August 2017 and Protocol Amendment (c) (final version dated 20 October 2017).

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 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 outlined 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 safety and tolerability of a single dose of lasmiditan in combination with topiramate in healthy subjects.

4.2 Secondary Objectives

- To evaluate the PK of lasmiditan alone and in combination with topiramate in healthy subjects.
- To evaluate the PK of topiramate alone and in combination with lasmiditan.

4.3 Exploratory Objectives

- To evaluate the PK of lasmiditan metabolites alone and in combination with topiramate in healthy subjects.

5. STUDY DESIGN

This is a Phase 1, parallel, placebo-controlled, fixed-sequence study with open-label administration of topiramate and investigator- and subject-blind administration of lasmiditan/placebo conducted in healthy subjects.

Subjects will be admitted to the Clinical Research Unit (CRU) on Day -1 and are expected to remain a resident until all assessments are completed on Day 16; however, subjects may be allowed to leave the CRU at the discretion of the investigator.

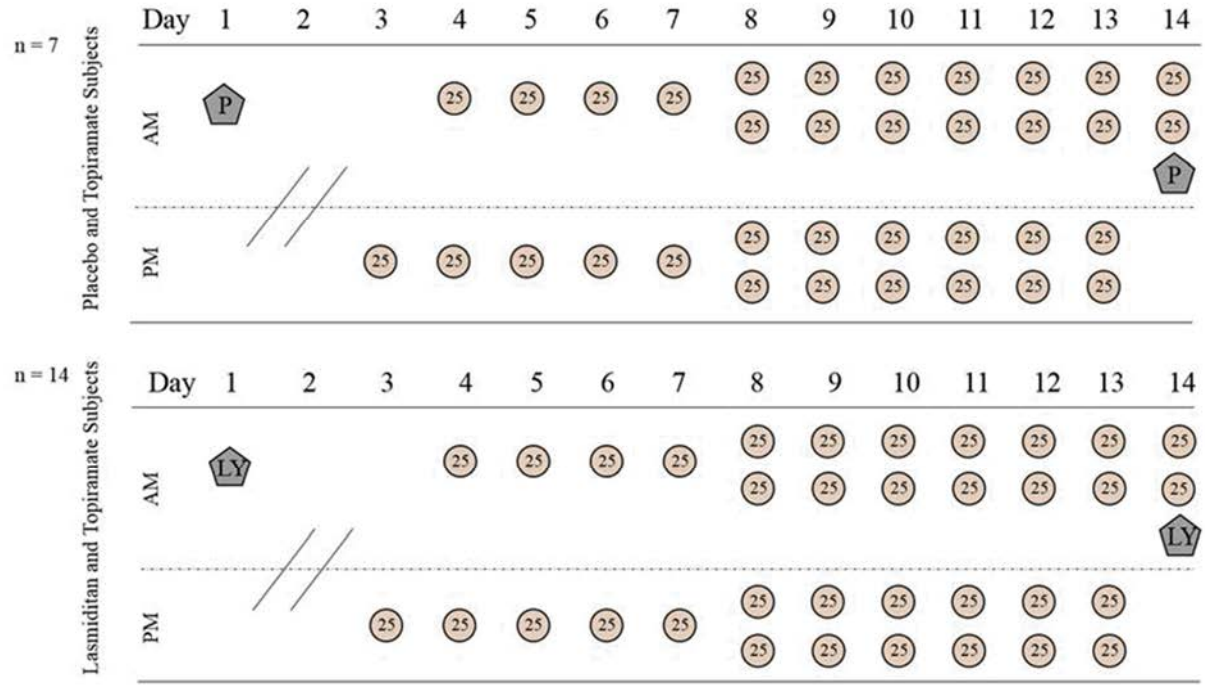
Study governance considerations are described in detail in Appendix 3 of the protocol.

Lasmiditan and topiramate doses will be administered at the CRU. Subjects will be randomly assigned in a 2:1 ratio to receive lasmiditan or placebo on both lasmiditan dosing days (Days 1 and 14). A single oral dose of study drug (200 mg lasmiditan or placebo) will be administered in the morning on Day 1. After lasmiditan wash-out, topiramate will be titrated up to 100 mg on Days 3 to 13. On Day 14, 1 oral dose of lasmiditan 200 mg or placebo will be co-administered with the final topiramate dose (50 mg) in the morning.

Blood sampling for PK assessment will be conducted predose and at time points up to 48 hours postdose on Days 1 and 14 for the measurement of plasma concentrations of lasmiditan and its metabolites. Blood samples will also be collected predose and up to 12 hours postdose on Days 13 and 14 for the measurement of plasma concentrations of topiramate.

A follow-up visit will take place at least 10 days following co-administration of lasmiditan and topiramate (Day 14).

Figure 1 illustrates the study design.



Abbreviations: LY = lasmiditan (200 mg); n = number of subjects in each group; P = placebo.
Symbols: "25" inside a circle = one 25 mg tablet of topiramate; gray pentagon = lasmiditan dose or placebo

Figure 1. Illustration of study design

6. 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**
Placebo	1
200 mg lasmiditan	2
25 mg topiramate QD	3
25 mg topiramate BID	4
50 mg topiramate BID	5
50 mg topiramate + placebo	6
50 mg topiramate + 200 mg lasmiditan	7

D = Day; QD = once daily; BID = twice daily

The following treatment sequences may be displayed across some outputs.

Sequence	Treatment Sequence Description
1	Placebo / 25 mg topiramate QD / 25 mg topiramate BID / 25 mg topiramate BID / 50 mg topiramate BID / 50 mg topiramate + placebo
2	200 mg lasmiditan / 25 mg topiramate QD / 25 mg topiramate BID / 25 mg topiramate BID / 50 mg topiramate BID / 50 mg topiramate + 200 mg lasmiditan

7. SAMPLE SIZE JUSTIFICATION

Approximately 30 subjects will be enrolled, so that at least 21 subjects complete the study. Subjects will be randomized in a 2:1 ratio of lasmiditan 200 mg : placebo. The sample size is customary for Phase 1 studies evaluating safety and tolerability, and is not powered on the basis of statistical hypothesis testing.

Subjects who are randomized but who do not complete Day 14 treatment may be replaced to ensure that enough subjects complete the study.

8. DEFINITION OF ANALYSIS POPULATIONS

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

The "PK" population will consist of all subjects who received at least one dose of lasmiditan or topiramate and have evaluable PK data. Subjects may be excluded from the PK summary statistics and statistical analysis if a subject has an adverse event (AE) of vomiting that occurs at or before 2 times median time of maximum observed 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, min, max and N; for log-normal data (e.g. the PK parameters: area under the concentration versus time curve [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 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 9.3 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 or later).

Plasma concentrations of lasmiditan (LY573144) and its metabolites 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
$t_{½}$	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 (LY573144 only)
V_z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration (LY573144 only)
V_{ss}/F	L	apparent volume of distribution at steady state after extra-vascular administration (LY573144 only)
MR		Metabolic ratio[a]

[a] no molar correction will be applied since the metabolites are very similar in molecular weight and within 5% of the molecular weight for lasmiditan.

Plasma concentrations of topiramate 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_{τ}	ng.h/mL	area under the concentration versus time curve during one dosing interval
CL/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration

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 predicted 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 ± X%. 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 Statistical Methodology

PK parameters will be evaluated to determine the impact of topiramate co-administration on the PK of a single dose of lasmiditan and its metabolites. Log-transformed C_{max}, AUC(0-∞), and AUC(0-t_{last}) parameters will be evaluated in a linear mixed-effects model with fixed effects for treatment and a random effect for subject. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% confidence interval (CI).The comparison of interest is:

Lasmiditan co-administered with topiramate (Day 14; test treatment) versus Lasmiditan alone (Day 1; reference treatment)

An example of the SAS code that will be used is as follows:

```
proc mixed data=xxx;
    class trtmnt subject;
    model l_pk = trtmnt / alpha=0.1;
    random subject;
    lsmeans trtmnt / pdiff;
run;
```

where l_pk is the log-transformed (base e) PK parameter.

A similar analysis will be performed to determine the impact of co-administration of a single dose of lasmiditan on the steady-state PK of topiramate. This analysis shall evaluate the log-transformed C_{max} and AUC_{τ} using a similar model to the one described above. The comparison of interest will be:

Topiramate co-administered with lasmiditan (Day 14; test treatment) versus Topiramate alone (Day 13; reference treatment)

The t_{max} will be analyzed using the Wilcoxon signed rank test. Estimates of the median difference based on the observed medians, 90% CIs and p-values from the Wilcoxon test will be calculated.

Additional analyses may be performed, as warranted.

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 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 20.0 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. Any serious AEs will be tabulated.

9.4.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version March 2017 Enhanced Dictionary B2 Format). Concomitant medication will be listed.

9.4.3 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.

9.4.4 Hepatic Monitoring

If a subject experiences elevated alanine aminotransferase (ALT) $\geq 3 \times$ upper limit of normal (ULN), alkaline phosphatase (ALP) $\geq 2 \times$ ULN, or elevated total bilirubin (TBL) $\geq 2 \times$ ULN, liver tests will be performed to confirm the abnormality.

The subjects' liver disease history and associated person liver disease history data will be listed. Any concomitant medication of acetaminophen/paracetamol will be listed. Results from any

hepatic monitoring procedures, such as a magnetic resonance elastography (MRE) scan and a biopsy assessment 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, if available.

All hepatic chemistry, hematology, coagulation, and serology data will be summarized by parameter and treatment, and listed. Values outside the reference ranges will be flagged on the individual subject data listings.

9.4.5 Vital signs

Where supine blood pressure and pulse rate are measured in triplicate, the mean value will be calculated and used in all subsequent calculations. When triplicate blood pressure or pulse rate measurements precede a standing measurement, the last supine blood pressure or pulse rate measurement will be used for orthostatic calculations. Orthostatic will be calculated as the standing value, minus the last supine value taken prior to the standing value.

Vital signs data will be summarized together with changes from baseline, where baseline is defined as the mean of the triplicate measurement on Day 1 predose for supine vital signs, and the last measurement on Day 1 predose for standing and orthostatic vital signs. Figures of mean vital signs and mean changes from baseline profiles will be presented by period over time. Furthermore, values for individual subjects will be listed.

9.4.6 Electrocardiogram (ECG)

For each subject, ECGs will be performed for safety purposes only, and will not be reported.

9.4.7 Columbia Suicide Severity Rating Scale (C-SSRS)

Data from the C-SSRS and self-harm questionnaire will be listed for individual subjects.

9.4.8 Neurological Examination

Data from the neurological examination questionnaire will be summarized in frequency tables and listed for individual subjects.

9.4.9 Other assessments

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

9.4.10 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 AE’s occurred for this study.”

Leo Document ID = 88462d58-9184-419b-9f38-0b09141455ae

Approver: PPD
Approval Date & Time: 31-Oct-2017 11:31:54 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 31-Oct-2017 13:07:43 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 01-Nov-2017 13:10:28 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 01-Nov-2017 16:46:40 GMT
Signature meaning: Approved