Statistical Analysis Plan H8H-MC-LAHD

Effect of Lasmiditan on Heart Rate and Blood Pressure in Healthy Subjects Receiving Oral Doses of Propranolol

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STATISTICAL ANALYSIS PLAN

Effect of Lasmiditan on Heart Rate and Blood Pressure in Healthy Subjects Receiving Oral Doses of Propranolol

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Study Drug: LY573144 (Lasmiditan)

Sponsor Reference: H8H-MC-LAHD
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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
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
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
%AUC(t_{last}-∞)	Percentage of AUC(0-∞) extrapolated
AUC_{τ}	Area under the concentration versus time curve during one dosing interval
bid	Twice daily
bpm	Beats per minute
BQL	Below the quantifiable lower limit of the assay
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
CSR	Clinical Study Report
CRU	Clinical Research Unit
CV	Coefficient of variation
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
HR	Heart rate
ICH	International Council on Harmonisation
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities

MRE	Magnetic resonance elastography
NA	Not applicable
PK	Pharmacokinetic
SAP	Statistical Analysis Plan
SD	Standard deviation
SOP	Standard Operating Procedure
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 normla
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 27 June 2017) and Protocol Amendment (a) (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

The primary objective of this study is to evaluate the effects of propranolol alone and in combination with lasmiditan on heart rate (HR).

4.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the effects of propranolol alone and in combination with lasmiditan on blood pressure and PR interval.
- To explore the tolerability of a single dose of lasmiditan alone or in combination with propranolol.
- To evaluate the PK of lasmiditan alone and in combination with propranolol.
- To evaluate the PK of propranolol alone and in combination with lasmiditan.

4.3 Exploratory Objectives

The exploratory objectives of this study are:

- To evaluate the effects of lasmiditan alone and in combination with propranolol on orthostatic changes in blood pressure and pulse rate.

- To evaluate the PK of the metabolites M8, M7, and M18 in healthy subjects following a single 200-mg oral dose of lasmiditan alone and in combination with propranolol.

5. STUDY DESIGN

This is an open-label, fixed-sequence study in healthy subjects to assess the cardiovascular effects of coadministration of lasmiditan with propranolol.

Screening Period:

All subjects will participate in a screening visit up to 28 days prior to the first lasmiditan dose.

Dosing Period:

Subjects will be admitted to the clinical research unit (CRU) on Day -2. On Day 1, subjects will receive a single dose of 200 mg lasmiditan, then receive propranolol (immediate release formulation; half-life approximately 3 to 6 hours) 80 mg twice daily (bid) on Days 4 through 10 and a single dose of 200 mg lasmiditan coadministered with propranolol on Day 9. Subjects will reside in the CRU from Day -2 until Day 11 when they may be discharged from the CRU following completion of all study procedures, at the investigator's discretion.

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

Blood samples will be collected predose and up to 48 hours postdose on Days 1 and 9 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 8 and 9 for the measurement of plasma concentrations of propranolol.

Safety assessments performed during the study will include adverse events (AEs), clinical laboratory evaluations, vital signs measurements, 12-lead ECGs, and physical examinations.

Cardiovascular effects will be assessed by Holter ambulatory monitoring and replicate measurements of blood pressure at predose, and for 12 hours postdose on Days -1, 1, 8, and 9.

Follow-up Period

Subjects will attend a follow-up visit approximately 7 days after the last dose.

Figure 1 illustrates the study design.

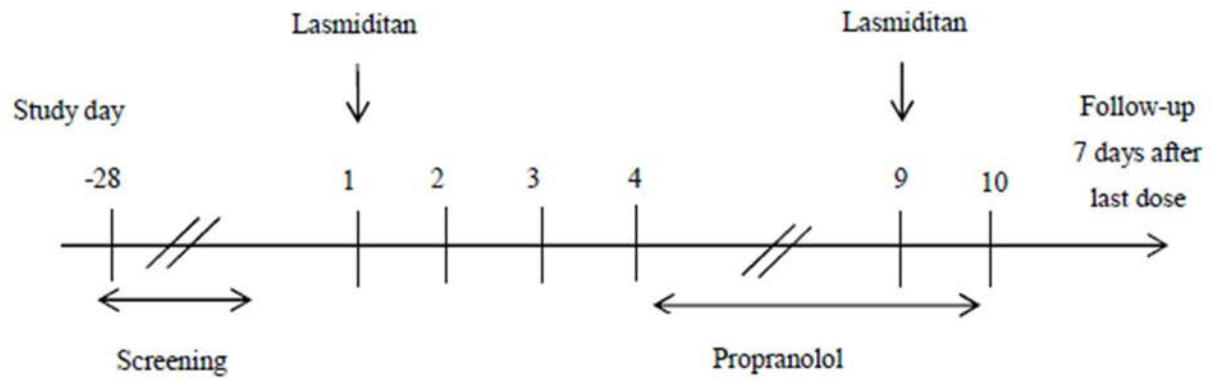

Figure 1. Illustration of study design for Protocol H8H-MC-LAHD

6. TREATMENTS

The treatment sequence to be administered to all subjects is: 200 mg lasmiditan (Day 1); 80 mg propranolol bid (Day 4 to Day 10); 200 mg lasmiditan + 80 mg propranolol (Day 9).

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

Study Treatment Name	Treatment order in TFL
200 mg lasmiditan	1
80 mg propranolol bid	2
80 mg propranolol bid + 200 mg lasmiditan	3

7. SAMPLE SIZE JUSTIFICATION

Up to 44 subjects may be enrolled to ensure 36 subjects complete the study. Assuming a standard deviation for the change in HR of 10.9 (based on previous studies [H8H-MC-CD-LAHO and H8H-CD-LAHJ]), this will result in a 90% probability that the half-width of the 90% confidence interval (CI) about the mean within-subject change is no larger than 5 beats per minute (bpm). Subjects who are randomized but do not complete the study 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 “Pharmacokinetic” population will consist of all subjects who received at least one dose of lasmiditan or propranolol and have evaluable PK data.

The "Cardiovascular" population will consist of all subjects who had the relevant test and reference treatment measurements.

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 are 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 9.4 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

Pharmacokinetic 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 propranolol 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 clinical study report. Any exceptions or special handling of data will be clearly documented within the final study report.

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

General PK Parameter Rules

- Actual sampling times will be used in the final analyses of individual PK parameters, except for non-bolus predose sampling times which will be set to zero. For non-bolus, multiple dose profiles, the predose 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 predose 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 pharmacokinetic 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.

<u>Data within an Individual Profile</u>

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

- For pharmacokinetic 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 pharmacokinetic 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≥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 report. Approval of the final report will connote approval of the exclusion.

9.3.2 Pharmacokinetic Statistical Methodology

Pharmacokinetic parameters will be evaluated to determine the impact of propranolol coadministration on the PK of a single dose of lasmiditan and its metabolites. Log-transformed $C_{max,}$ AUC(0-∞), and AUC(0-tlast) parameters will be evaluated in a linear mixed-effects model with a fixed effect for treatment (lasmiditan coadministered with propranolol [Day 9; test treatment] versus lasmiditan alone [Day 1; reference 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% CI.

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.

The t_{max} will be analyzed using a 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.

A similar analysis will be performed to determine the impact of coadministration of a single dose of lasmiditan on the steady-state PK of propranolol. The model will include the following treatments: propranolol coadministered with lasmiditan (Day 9; test treatment) versus propranolol alone (Day 8; reference treatment).

Additional analyses may be performed, as warranted.

9.4 Cardiovascular Assessment

9.4.1 Cardiovascular Analysis

The primary parameters for the cardiovascular analyses will be mean hourly HR, mean hourly HR nadirs, and HR. Mean hourly HR from 1 hour predose to 12 hours postdose will be calculated on Days -1, 1, 8, and 9 from the Holter monitoring data. Negative chronotropic effects will be evaluated using nadir (1–6 h), nadir (>6 h–12 h), and nadir (1–12 h), which are defined as the lowest mean hourly HR during each postdose time period on each day. The parameters HR and PR interval will also be determined on Days -1, 1, 8, and 9 from the 10-second Holter traces extracted at the time points listed in Section 2 of the protocol. Orthostatic changes in blood pressure and pulse rate will be determined at the time points listed in Section 2 of the protocol.

9.4.2 Cardiovascular Statistical Methodology

Cardiovascular parameters will be evaluated to determine the impact of coadministration of propranolol with lasmiditan on HR, PR interval, and blood pressure compared to propranolol alone. Primary cardiovascular parameters (mean hourly HR, mean hourly HR nadirs, and HR) will be evaluated in a linear mixed-effects model with a fixed effect for treatment (lasmiditan coadministered with propranolol [Day 9; test treatment] versus propranolol alone [Day 8; reference treatment]), and a random effect for subject. Least squares means will be calculated for the test and reference treatments. Mean treatment differences will be presented, along with the corresponding 90% CI.

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

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

where cardio is the cardiovascular primary parameter.

Primary cardiovascular parameters may be log-transformed prior to the statistical analysis if a review of the data indicates that the assumption of normality is violated.

A similar analysis will be performed to determine the impact of coadministration of lasmiditan with propranolol on HR, PR interval, and blood pressure compared to lasmiditan alone. The model will include the following treatments: propranolol coadministered with lasmiditan (Day 9; test treatment) versus lasmiditan alone (Day 1; reference treatment). The impact of coadministration of propranolol with lasmiditan on orthostatic blood pressure and pulse rate will be evaluated using descriptive statistics as appropriate.

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 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. Adverse events by day of onset will be presented.

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 adverse events, the number of subjects experiencing an adverse event and the percentage of subjects experiencing an adverse event) of treatment-emergent adverse events will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 system organ class and preferred term. The summary and frequency adverse event tables will be presented for all causalities and those considered related to the study drug. Any serious adverse events will be tabulated.

9.5.2 Concomitant medication

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

9.5.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be listed, as well as summarized together with changes from baseline, where baseline is defined as the last assessment prior to Day 1 dosing.

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 Hepatic Monitoring

If a subject experiences elevated alanine aminotransferase (ALT) ≥ 3 × upper limit of normal (ULN), alkaline phosphatase (ALP) ≥ 2 × ULN, or elevated total bilirubin (TBL) ≥ 2 × 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 a magnetic resonance elastography (MRE) scan and 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.

9.5.5 Vital signs

The means of the triplicate supine blood pressure and pulse rates values 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 changes 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 of each treatment period for supine vital signs, and the last measurement on Day 1 predose of each treatment period for standing and orthostatic vital signs. Figures of mean vital signs and mean changes from baseline profiles will be presented over time. Furthermore, values for individual subjects will be listed.

9.5.6 Electrocardiogram (ECG)

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

9.5.7 Holter Ambulatory Monitoring

Continuous 12-lead Holter recordings over 12 hours will be performed. Mean hourly HR and mean hourly HR nadirs will be calculated. Data will be summarized by treatment together with changes from baseline, and listed. For ECG extractions baseline is defined as the mean of the last triplicate extractions taken predose. For the mean hourly HR, baseline is defined as the hourly mean of the one hour predose time point.

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 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.”