Statistical Analysis Plan H8H-MC-LAIG

A Study to Investigate the Cardiovascular Effects of Lasmiditan in Healthy Elderly Subjects

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STATISTICAL ANALYSIS PLAN

A Study to Investigate the Cardiovascular Effects of Lasmiditan in Healthy Elderly Subjects

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2. ABBREVIATIONS

Abbreviations pertain to the Statistical Analysis Plan (SAP) only (not the tables, figures and listings [TFLs]).

ABPM	Ambulatory blood pressure monitoring
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-tlast)	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(tlast-∞)	Percentage of AUC(0-∞) extrapolated
BQL	Below the quantifiable lower limit of the assay
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
C_{last}	Last measurable drug concentration
C_{max}	Maximum observed drug concentration
CRF	Case Report Form
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
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
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
PD	Pharmacodynamic

PK	Pharmacokinetic
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
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 19 December 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 test whether each oral dose of lasmiditan (100 and 200 mg) is non-inferior to placebo with regard to increasing blood pressure in healthy elderly subjects (≥65 years of age).

4.2 Secondary Objectives

- To determine the PK of lasmiditan in healthy elderly subjects (≥65 years of age) following single 100 and 200 mg oral doses of lasmiditan.

- To assess the safety and tolerability of 100 and 200 mg oral doses of lasmiditan in healthy elderly subjects.

5. STUDY DESIGN

This is a randomized, subject- and investigator-blind, crossover study with 3 treatment periods in healthy elderly subjects.

The treatments are as follows:

- Treatment A: Lasmiditan 200 mg
- Treatment B: Lasmiditan 100 mg
- Treatment C: Placebo

Each subject will be randomized to 1 of 6 treatment sequences in a Williams design, as outlined in Table 1.

Table 1. Sequences in Study LAIG

Sequence	Period 1	Period 2	Period 3
1	Lasmiditan 200 mg	Lasmiditan 100 mg	Placebo
2	Lasmiditan 100 mg	Placebo	Lasmiditan 200 mg
3	Placebo	Lasmiditan 200 mg	Lasmiditan 100 mg
4	Placebo	Lasmiditan 100 mg	Lasmiditan 200 mg
5	Lasmiditan 200 mg	Placebo	Lasmiditan 100 mg
6	Lasmiditan 100 mg	Lasmiditan 200 mg	Placebo

Screening Period
All subjects will participate in a screening visit up to 28 days prior to study drug dosing.

Dosing Period
Subjects will participate in 1 inpatient period involving 3 treatment periods. Subjects will be admitted on Day -1 and will be randomized to 1 of 6 treatment sequences to receive lasmiditan or placebo on Days 1, 3, and 5. There will be a washout period of approximately 48 hours between each dosing day. Subjects may be discharged on Day 7 based on investigators' discretion.

All subjects will be discharged from the study approximately 2 days after their final dose of lasmiditan or placebo.

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
100 mg Lasmiditan	1
200 mg Lasmiditan	2
Placebo	3

7. SAMPLE SIZE JUSTIFICATION

Up to 36 subjects may be enrolled to ensure 30 subjects complete the study. Assuming a 1-sided significance level of 0.05, a standard deviation (SD) for the within-subject change in systolic blood pressure (SBP) of 6.0 mmHg (a slightly larger estimate than that seen in Study LAHA), and a non-inferiority margin of 10 mmHg, this sample size will result in at least 90% power to

detect a true increase of 5 mmHg in the mean within-subject change for lasmiditan 200 mg compared with placebo.

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 study drug 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 drug concentration (t_{max}).

Cardiovascular analyses will be conducted on data from subjects who complete at least 1 dosing period.

PK/pharmacodynamics (PD) analyses will be conducted on data from subjects who have evaluable data in both PK and cardiovascular datasets.

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 SD, median, min, max and N; for log-normal data (e.g. the PK parameters: are 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

PK parameter estimates will be determined using non-compartmental procedures in validated software program (Phoenix WinNonlin Version 6.4 or later). For the calculation of the PK parameter estimates, the samples collected at predose of Days 3 and 5 will also be used as 48 h postdose samples of the Day 1 and 3 PK profiles, respectively.

Plasma concentrations of lasmiditan (LY573144) 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
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

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.

- 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 last measurable 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 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

The PK parameters will be listed, and summarized using standard descriptive statistics, including estimates of intra-subject variability as appropriate. Arithmetic mean (+/- 1 SD) plasma

concentration profiles, as well as individual subject profiles, will be presented graphically by treatment over time.

9.4 Cardiovascular Assessment

9.4.1 Cardiovascular Analysis

The primary parameter for the cardiovascular analyses will be peak hourly mean values of SBP, and will be determined using ambulatory blood pressure monitoring (ABPM). For each subject, the mean SBP value will be calculated for each hour within the dosing period. The highest mean value across the 24 calculated means will be considered the peak hourly mean value. Baseline value will be defined as the mean value during the 2 hours pre-dose for each period.

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

9.4.2 Cardiovascular Statistical Methodology

Observed values, as well as change from baseline, for all cardiovascular parameters (including peak hourly mean SBP and mean hourly SBP values), will be listed and summarized by treatment using descriptive statistics. Mean hourly SBP values will be plotted over time, together with changes from baseline. In addition, mean hourly SBP and peak hourly mean SBP values will be plotted against plasma concentrations of lasmiditan to explore the relationship between PK and cardiovascular effects.

As a primary analysis, changes from baseline in peak hourly mean values of SBP will be analyzed to test whether each dose of lasmiditan (100 mg, 200 mg) is non-inferior to placebo, assuming a non-inferiority margin of 10 mmHg. Specifically, these changes from baseline will be analyzed to test the null hypothesis that the difference in mean baseline change between lasmiditan at each dose and placebo is at least 10 mmHg versus the alternative hypothesis that this difference is less than 10 mmHg.

A linear mixed-effects model with baseline as a covariate, fixed effects for treatment, period (1, 2, or 3), and treatment sequence, and a random effect for subject will be used to test the hypotheses at a 1-sided significance level of 0.05. Least squares (LS) means and treatment differences (lasmiditan 200 mg – placebo, lasmiditan 100 mg – placebo) will be calculated and presented with their corresponding 95% confidence intervals (CIs).

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

```
proc mixed data=xxx;
    class trtmnt period sequence subject;
    model cardiochg = baseline trtmnt period sequence / alpha=0.05 cl ddfm=kr;
    random subject;
    lsmeans trtmnt;
    lsestimate trtmnt 'Ltn100 - Placebo' 1 0 -1 / lower testvalue=10 cl alpha=0.05;
    lsestimate trtmnt 'Ltn200 - Placebo' 0 1 -1 / lower testvalue=10 cl alpha=0.05;
run;
```

where cardiochg is the change from baseline in peak hourly mean values of SBP, trtmnt is the treatment, and seq is the treatment sequence.

The following gatekeeping procedure will be used to adjust for multiplicity when conducting the hypothesis tests. The null hypothesis that the difference in mean baseline change between lasmiditan 100 mg and placebo is at least 10 mmHg will first be tested against the alternative hypothesis that this difference is less than 10 mmHg. If the p-value for this test is less than 0.05, then there is significant evidence that lasmiditan 100 mg is non-inferior to placebo and these hypotheses will be re-tested using lasmiditan 200 mg. Otherwise, if the p-value is at least 0.05, then there is no significant evidence that lasmiditan 100 mg is non-inferior to placebo, in which case the null and alternative hypotheses will not be re-tested using lasmiditan 200 mg.

A sensitivity analysis will be performed on subjects who complete all 3 dosing periods. In addition, sensitivity analyses will be conducted where baseline value is the mean SBP value during the 1 hour pre-dose for each period. These analyses will be performed separately on subjects who complete at least 1 dosing period and on subjects who complete all 3 dosing periods. The same mixed-effects model as that was used in the primary analysis will be implemented.

A repeated measures analysis will also be conducted in which changes from baseline in hourly mean values of SBP will be analyzed to test whether each dose of lasmiditan (100 mg, 200 mg) is non-inferior to placebo at each time point (hour), assuming a non-inferiority margin of 10 mmHg. A repeated measures linear mixed-effects model with baseline as a covariate, fixed effects for time point, treatment, period, treatment sequence, and the treatment by time point interaction, and a random effect for subject will be used to conduct the tests at a 1-sided significance level of 0.05. An unstructured covariance structure will be applied. If the model fails to converge, alternative structures shall be examined using Akaike's criteria. At each time point, LS means and treatment differences (lasmiditan 200 mg – placebo, lasmiditan 100 mg - placebo) will be calculated and presented with their corresponding 95% CIs, from which non-inferiority of lasmiditan (100 mg, 200 mg) to placebo will be determined if the upper confidence limit is less than 10 mmHg.

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

```
proc mixed data=xxx;
    class trtmnt time period seq subject;
    model cardiochg = base time trtmnt period seq trtmnt*time / alpha=0.05 cl ddfm=kr;
    repeated time / type=un subject=subject;
    random subject;
    lsmeans trtmnt*time / alpha=0.05 cl pdiff=controll('reftrt');
run;
```

where cardiochg is the change from baseline in hourly mean values of SBP, trtmnt is the treatment, seq is the treatment sequence, and reftrt is the reference treatment of the comparison.

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.

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.

9.5.2 Concomitant medication

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

9.5.3 Clinical laboratory parameters

All clinical chemistry, hematology and urinalysis data will be listed. Additionally clinical chemistry, hematology and urinalysis data outside the reference ranges will be listed.

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

Supine vital signs data will be summarized by treatment together with changes from baseline, where baseline is defined as predose of each period. Figures of supine 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)

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

9.5.6 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 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. 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.

9.5.7 Columbia Suicide Severity Rating Scale (C-SSRS)

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

9.5.8 Other assessments

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

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.”

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