Statistical Analysis Plan Version 1 H8H-MC-LAIO (b)

An Open-Label, 2-Part Study to Investigate the Effect of Lasmiditan on the Pharmacokinetics of Dabigatran and Rosuvastatin in Healthy Volunteers

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STATISTICAL ANALYSIS PLAN

An Open-Label, 2-Part Study to Investigate the Effect of Lasmiditan on the Pharmacokinetics of Dabigatran and Rosuvastatin in Healthy Volunteers

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2. ABBREVIATIONS

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

%AUC(t_{last}-∞)	Percentage of AUC(0-∞) extrapolated
AE	Adverse event
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
BCRP	Breast cancer resistance protein
BQL	Below the lower limit of quantification
C_{last}	Last quantifiable drug concentration
C_{max}	Maximum observed drug concentration
CI	Confidence interval
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
CV	Coefficient of variation
DDI	Drug-drug interaction
ECG	Electrocardiogram
ICF	Informed consent form
ICH	International Conference on Harmonisation
LLOQ	Lower limit of quantification
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
P-gp	P-glycoprotein

PK	Pharmacokinetic
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SNP	Single nucleotide polymorphism
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
TOST	Two 1-sided t-tests
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 11 September 2020) and Protocol Amendment (a) (final version dated 16 September 2020).

This SAP describes the planned analysis of the safety, tolerability and pharmacokinetic (PK) data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical and PK analyses of data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Eli Lilly and Company. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. This SAP must be signed off prior to first participant visit for this study. When the SAP and TFL shells are agreed upon and finalized, they will serve as supporting material for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon with Eli Lilly and Company and identified in the CSR. Any minor deviations from the TFLs may not be documented in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials[1] and the ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports[2].

4. STUDY OBJECTIVES

4.1 Primary Objective

The primary objective of the study is to evaluate the effect of lasmiditan on P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) activity in healthy participants.

The primary endpoints of the study are maximum observed drug concentration (C_{max}) and area under the concentration (AUC) versus time curve from time zero to infinity (AUC [0-∞]) of dabigatran to assess P-gp activity and rosuvastatin to assess BCRP activity.

4.2 Secondary Objectives

The secondary objectives of the study are:

- To evaluate the safety and tolerability of dabigatran etexilate or rosuvastatin in combination with lasmiditan in healthy participants
- To evaluate the pharmacokinetics of lasmiditan and M8

The secondary endpoints of the study are:

- A summary of the number of treatment-emergent adverse events (TEAEs) and serious adverse events (SAE)
- C_{max} of lasmiditan and M8
- Time of maximum observed drug concentration (t_{max}) of lasmiditan and M8
- AUC (0-∞) of lasmiditan and M8

5. STUDY DESIGN

This is a Phase 1, two-part, two-period, open-label study in healthy participants. Part 1 will study dabigatran P-gp drug-drug interaction (DDI) with lasmiditan. Part 2 will study rosuvastatin BCRP DDI with lasmiditan. Parts 1 and 2 will have a similar design, i.e., dabigatran etexilate or rosuvastatin administration alone in Period 1 (Day 1) followed by a brief washout, then lasmiditan on Days 8, 9, and 10 (Period 2) with coadministration of dabigatran etexilate or rosuvastatin with lasmiditan on Day 10. Each part will consist of different participants and the 2 parts may run in parallel. Participants for both Part 1 and Part 2 will be consented with a single consent form, and both genotyping and coagulation tests will be performed for both parts during screening. Part 2 will be prioritized to complete first due to an anticipated screen fail rate of ~50% secondary to genotype criteria. Once Part 2 has achieved last participant dosed, no further genotyping will be needed for LAIO screening. Participants who failed Part 2 screening due to genotyping only and have a normal coagulation profile will automatically be eligible for Part 1.

A general schema for this study can be seen in Figure 1.

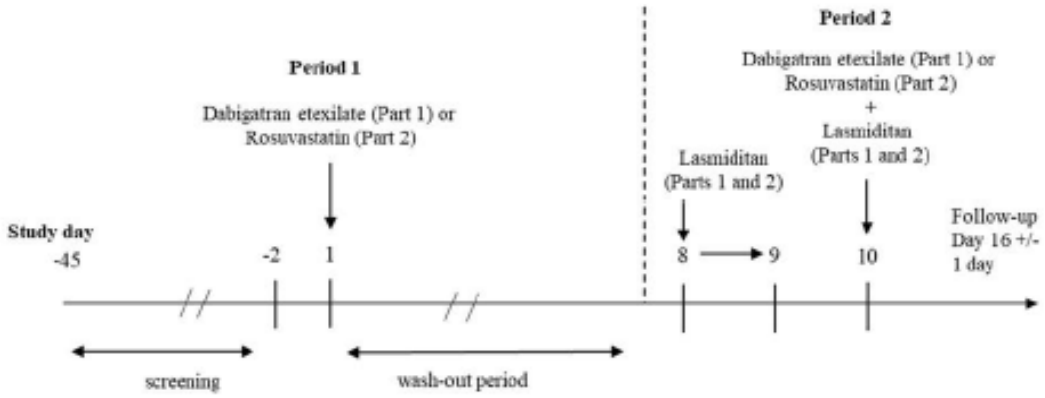

Figure 1 – General schema for LAIO

6. TREATMENTS

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

Part	Day	Study Treatment Name	Treatment order in TFL
1	1	150 mg dabigatran etexilate	1
	8-9	200 mg lasmiditan	2
	10	150 mg dabigatran etexilate + 200 mg lasmiditan	3
2	1	10 mg rosuvastatin	4
	8-9	200 mg lasmiditan	5
	10	10 mg rosuvastatin + 200 mg lasmiditan	6

7. SAMPLE SIZE JUSTIFICATION

Approximately 72 participants will be enrolled to Part 1 of the study to ensure that at least 62 evaluable participants complete that part. With 62 participants, we expect the two 1-sided t-tests (TOSTs) for equivalence applied to the log-normal mean ratio to have a power of at least 80% for the AUC (0-∞) and C_{max} tests in Part 1. This assumes a nominal expected mean ratio of 1.05, a coefficient of variation (CV) of 39.3%, and a significance level of 0.05 of each 1-sided test when testing against an upper limit of 1.25 and a lower limit of 0.80. The tests will be displayed in the form of 90% confidence intervals (CI), which are equivalent to the according TOST. The source of the CV is Boehringer Ingleheim bioequivalence study (EudraCT number 2007-005765-35), and the higher intrasubject CV observed in the second-generation dabigatran arm was chosen.

Approximately 32 participants will be enrolled to Part 2 to ensure that at least 28 evaluable participants complete that part. With 28 participants, we expect the TOSTs for equivalence applied to the lognormal mean ratio to have a power of at least 80% for the AUC(0-∞) and C_{max} tests in Part 2. This assumes a nominal expected mean ratio of 1.05, a CV of 25.1%, and significance level of 0.05 of each 1-sided test when testing against an upper limit of 1.25 and a lower limit of 0.80. The tests will be displayed in the form of 90% CI which are equivalent to the according TOST. The source of the CV is Study AZEB, and the higher of the rosuvastatin AUC(0-∞) and C_{max} intrasubject CVs was chosen.

8. DEFINITION OF ANALYSIS POPULATIONS

The “Entered” population will consist of all participants who signed the informed consent form (ICF).

The “Enrolled” population will consist of all participants assigned to treatment, regardless of whether they take any doses of study intervention, or if they took the correct treatment.

The “Safety” population will consist of all participants assigned to dabigatran etexilate or rosuvastatin and who take at least 1 dose of 1 of those products. Participants will be analyzed according to the product they actually received.

The "Pharmacokinetic" population will consist of all participants who receive at least 1 dose of dabigatran etexilate or rosuvastatin and have evaluable PK.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when participants 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 C_{max}) the geometric mean and geometric CV will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all participants up to the point of withdrawal, with any participants excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for participants 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 participants' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual participant's baseline value from the value at the timepoint. The individual participant'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 Participant Disposition

Participant disposition will be summarized and listed. The demographic variables age, sex, race, ethnicity, body weight, height and body mass index will be summarized and listed. All other demographic variables will be listed only.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

Noncompartmental methods applied with a validated software program (WinNonlin Phoenix v8.1 or later) to the plasma concentrations of dabigatran, rosuvastatin, lasmiditan and its metabolite M8 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 time 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 (λ_z) in non-compartmental analysis
CL/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration (not M8)
V_Z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration (not M8)
V_{SS}/F	L	apparent volume of distribution at steady state after extra-vascular administration (not M8)

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 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 (t½) 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 participant 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 t½ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any t½ 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 quantification (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 participant 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 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.

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 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 $n\geq6$, 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

Pharmacokinetic parameters will be evaluated to estimate drug interaction for dabigatran and rosuvastatin with lasmiditan. Log-transformed C_{max} and AUC(0-∞) parameters for dabigatran and rosuvastatin will be analyzed using a mixed effects linear model to compare dabigatran and rosuvastatin administered alone (reference), and dabigatran and rosuvastatin administered with lasmiditan (test). The model will include a fixed effect for treatment and a random effect for participant. The least squares (LS) means for each treatment, the difference between the treatment LS means ([dabigatran or rosuvastatin + lasmiditan] – dabigatran or rosuvastatin alone), and the associated 90% CIs will be estimated from the model and back-transformed from the log scale to provide estimates of the geometric means, geometric mean ratio, and corresponding 90% CIs.

Example of the SAS code for the analysis:

```
proc mixed data=xxx alpha=0.1;
  class treat subjid;
  model log_pk = treat / residual ddfm=kr;
  random subjid;
  lsmeans treat / cl pdiff alpha=0.1;
  ods output lsmeans=lsm01 diffs=estims01;
run;
```

The t_{max} will be analyzed non-parametrically using a Wilcoxon signed rank test. Estimates of the median difference, comparing dabigatran or rosuvastatin + lasmiditan (test) – dabigatran or rosuvastatin alone (reference), and the corresponding 90% CIs for the difference between treatments will be calculated and presented, alongside the p-value from the Wilcoxon signed-rank test.

Example SAS code to be used for the Wilcoxon signed-rank test:

```
proc univariate data = xxx cipctldf(alpha = 0.1);
  var ref test diff;
  ods output quantiles = quant01;
  ods output testsforlocation = out01;
run;
```

The effect of polymorphisms in genes coding for certain transporters (e.g., ABCG2, ABCB1, ABCC2, SLCO1B3, NTCP, and SLCO2B1) on the magnitude of the interaction between rosuvastatin and lasmiditan may be explored. For each participant, the ratio of rosuvastatin exposures with and without concomitant lasmiditan exposures will be calculated. A graphical

analysis of these ratios between participants with and without single nucleotide polymorphism (SNPs) of interest is intended.

Additional analyses may be conducted 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 adverse event (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 participant 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 TEAE 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. TEAEs will be summarized by treatment, severity and relationship to the study drug. The frequency (the number of AEs, the number of participants experiencing an AE and the percentage of participants experiencing an AE) of TEAEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1 system organ class and preferred term. The summary and frequency TEAE tables will be presented for all causalities and those considered related to the study drug by the investigator. Any serious AEs will be listed. AEs by day of onset will be presented.

Discontinuations due to AEs will be listed.

9.4.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version WHODD SEP20B3). Concomitant medication will be listed.

9.4.3 Clinical laboratory parameters

All clinical chemistry, hematology, and coagulation data will be summarized by part and parameter, and listed. Urinalysis data will be listed only. Additionally, clinical chemistry, hematology, coagulation, and urinalysis data outside the reference ranges will be listed and flagged on individual participant data listings.

9.4.4 Vital signs

Vital signs data will be summarized by part together with changes from baseline, where baseline is defined as the predose assessment of each dosing period (Day 1 for period 1 and Day 10 for Period 2). Figures of mean vital signs and mean changes from baseline profiles will be presented by treatment.

Values for individual participants will be listed.

9.4.5 Electrocardiogram (ECG)

ECGs will be performed for safety monitoring purposes only and will not be presented. Any clinically significant findings from ECGs will be reported as an AE.

9.4.6 Hepatic Monitoring

If a participant 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. Additional safety data may be collected if required, as defined in the protocol. Where applicable, the following will be presented.

The participants' liver disease history and associated person liver disease history data will be listed. Any concomitant medications that have potential for hepatotoxicity, including acetaminophen will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography (MRE) scan, and biopsy assessments will be listed, if performed.

Hepatic risk factor assessment data will be listed. Liver related signs and symptoms data will be summarized by treatment and listed. Alcohol and recreational drug use data will also be listed.

All hepatic chemistry, hematology, coagulation, and serology data will be listed. Values outside the reference ranges will be flagged on the individual participant data listings.

9.4.7 Columbia-Suicide Severity Rating Scale (C-SSRS) / Self-Harm Supplement

All C-SSRS and Self Harm Supplement data will be listed.

9.4.8 Other assessments

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

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 participants or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No serious adverse events occurred for this study.”

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