Statistical Analysis Plan (v1): J2Z-MC-PGAB

A Randomized, Placebo-Controlled, Participant- and Investigator-Blind, Phase 1 Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of LY3832479 Administered Subcutaneously to Healthy Participants

NCT04611789

Approval Date: 16-Oct-2020

STATISTICAL ANALYSIS PLAN

A Randomized, Placebo-Controlled, Participant- and Investigator-Blind, Phase 1 Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of LY3832479 Administered Subcutaneously to Healthy Participants

Statistical Analysis Plan Status: Final v1
Statistical Analysis Plan Date: 13-October-2020

Study Drug: LY3832479

Sponsor Reference: J2Z-MC-PGAB
Covance CRU Study: 1000071 - 8454070

Clinical Phase I

Approval Date: 16-Oct-2020 GMT

1. TABLE OF CONTENTS

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
ADA	Anti-drug antibody
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
BQL	Below the lower limit of quantitation
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
CV	Coefficient of variation
ECG	Electrocardiogram
ICF	Informed consent form
ICH	International Conference on Harmonisation
ISR	Injection Site Reaction
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

SC	Subcutaneous
SD	Standard deviation
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
TBL	Total bilirubin
TEADA	Treatment-emergent antidrug antibodies
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, and Listings
t_{last}	Time of the last observed drug concentration
t_{max}	Time of maximum observed drug concentration
ULN	Upper limit of normal
VAS	Visual analog scale
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 30 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. 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 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 determine the PK of single subcutaneous (SC) doses of LY3832479 in healthy participants.

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

4.2 Secondary Objective

The secondary objective of the study is to describe safety and tolerability following single SC doses of LY3832479 in healthy participants.

The secondary endpoints of the study are:

- Incidence of spontaneously reported adverse events (AEs), treatment-emergent adverse events (TEAEs), and serious adverse events (SAEs)

- vital signs
- clinical laboratory results.

4.3 Exploratory Objectives

The exploratory objectives and endpoints of the study are:

- To assess injection site reactions (ISRs) following single SC doses of LY3832479 in healthy participants
    - Characterization and measurement of incidence and severity of ISRs (including injection site pain) using data collected from the ISR assessment, as well as the exploratory tool (Scarletred)
- To determine the immunogenicity of LY3832479 following single SC doses in healthy participants.
    - Incidence of treatment-emergent antidrug antibodies (TEADA)

5. STUDY DESIGN

This is a single-site study in healthy participants who will receive a single SC dose of LY3832479. The study will be participant- and investigator-blinded, randomized, and placebo controlled.

Up to 2 cohorts may be enrolled with at least 9 participants per cohort (7 LY3832479 : 2 placebo), with the intention that at least 6 participants randomized to LY3832479 have sufficient evaluable data in each cohort.

Participants will be screened within 14 days prior to Day 1 of dosing for each cohort. Participants will be admitted to the clinical research unit (CRU) as part of an inpatient visit on Day -1 and will be sequentially enrolled and then randomized to treatment.

Participants will be admitted to the study site on Day -1. They will remain inpatient until discharge on Day 7 after study procedures are complete.

Dosing will occur on Day 1. Intended doses of LY3832479 are as follows:

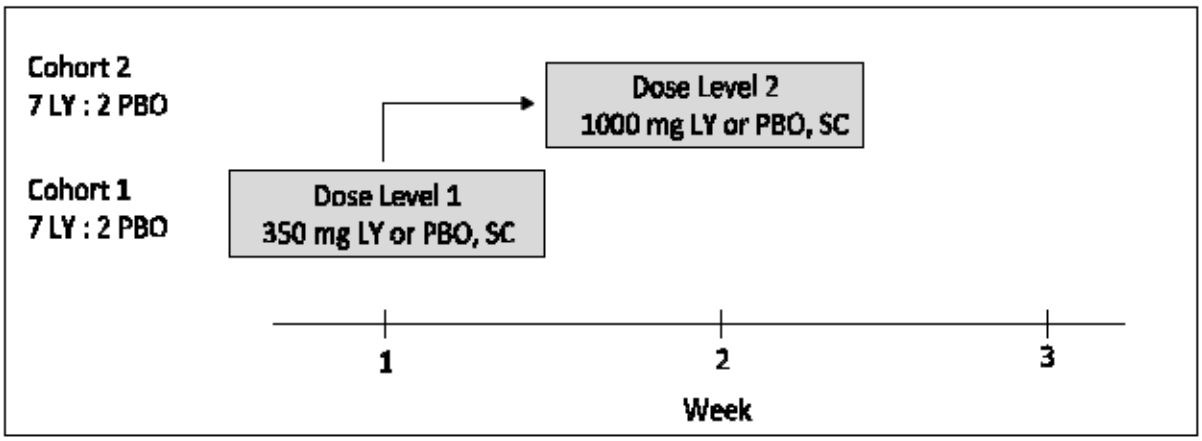
- Cohort 1: 350 mg
- Cohort 2: 1000 mg

Participants will undergo PK sampling and safety assessment after dosing.

For Cohort 1, a safety review will be conducted to determine whether it is appropriate to proceed with dosing of the next cohort. This safety review will be conducted based on data from at least 5 participants, after at least 4 days after dosing.

On Days 1 through 7, participants will undergo PK sampling and safety assessment.

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



Abbreviations: LY = LY3832479; PBO = placebo.

Figure 1 – General schema for PGAB

6. TREATMENTS

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

Cohort	Study Treatment Name	Treatment order in TFL
All	Placebo SC	1
1	350 mg LY3832479 SC	2
2	1000 mg LY3832479 SC	3

7. SAMPLE SIZE JUSTIFICATION

A maximum of 22 participants will be enrolled to study intervention with the intention that at least 6 participants randomized to LY3832479 have sufficient evaluable data in each cohort.

The sample size is not powered on the basis of statistical hypothesis testing. However, based on an assumption of 40% coefficient of variation (CV%) for between subject variability in a PK parameter of interest, 6 participants on active treatment per cohort may provide approximately 70% chance to ensure that a PK parameter's 90% confidence interval (CI) falls within (0.7, 1.43) over the corresponding geometric mean, such as AUC (0-∞).

8. DEFINITION OF ANALYSIS POPULATIONS

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

The "Enrolled / Intent-to-Treat" population will consist of all participants assigned to treatment, regardless of whether they received study treatment, or if they took the correct treatment. Participants will be analyzed according to the treatment group to which they were assigned.

The "Safety" population will consist of all participants randomly assigned to study intervention and who received study intervention. Participants will be analyzed according to the intervention they actually received.

The "Pharmacokinetic" population will consist of all treated participants who received a full dose of study intervention and have sufficient evaluable PK samples. Participants who did not receive a full dose (fewer injections than planned) would still have their PK analyzed, but the results will be reported separately and not included in the main analyses.

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, Phoenix WinNonlin (Certara, Version 8.1 or later) to the serum concentrations of LY3832479 will be used to determine the following PK parameters, when possible:

Parameter	Units [a]	Definition
AUC(0-∞)	µg*day/mL	Area under the concentration versus time curve from time zero to infinity
%AUC(t_{last}-∞)	%	Percentage of AUC(0-∞) extrapolated
AUC(0-t_{last})	µg*day/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
C_{max}	µg/mL	Maximum observed drug concentration
$t_{½}$	day	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
t_{last}	day	Time of the last observed drug concentration
t_{max}	day	Time of maximum observed drug concentration
CL/F	L/day	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

[a] Units of source LY3832479 serum concentration data will be ng/mL, to one decimal place.

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. When reporting unit-transformed individual C_{max} values (and the corresponding minimun, median, and maximum values) the original significance will be maintained (eg 12345.6 ng/mL becomes 123.456 µg/mL; other summary statistics will be rounded to 3 significant digits). 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 serum 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 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 serum 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 quantification (BQL). Serum 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 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.

<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 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≥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 $n \geq 6$ 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

All PK parameters will be summarized by treatment. Plots of the primary PK parameters ($AUC[0\text{-}\infty]$, $AUC[0\text{-}t_{last}]$, and C_{max}) by treatment will also be provided. Additionally, serum concentrations will be graphically presented by treatment over time.

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 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 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 participants experiencing an AE and the percentage of participants experiencing an AE) of treatment-emergent AEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 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 by the investigator. Any serious AEs will be listed.

Discontinuations due to AEs will be listed.

9.4.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version Global B3 March 2020). 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 and flagged on individual participant data listings.

9.4.4 Vital signs

Vital signs data will be summarized by treatment together with changes from baseline, where baseline is defined as the Day 1 predose assessment. 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 increases in alanine aminotransferase (ALT), alkaline phosphatase (ALP), or elevated total bilirubin (TBL), above predetermined specific thresholds, additional investigations will be performed to confirm the abnormality and/or search for possible causes as indicated in Section 8.2.5 of 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 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 Immunogenicity Assessments

The frequency and percentage of participants with pre-existing antidrug antibody (ADA) and with treatment-emergent ADAs (TE ADA) to LY3832479 will be tabulated and listed.

For participants who are ADA negative at baseline (Day 1 predose), TE ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution of the assay (1:10). For participants who are ADA positive at baseline, TE ADAs are defined as those with a 4-fold (2 dilution) increase in titer compared to baseline. The frequency and percentage of participants with cross-reactive and neutralizing antibodies, if measured, may also be tabulated for participants with TE ADA.

9.4.8 Hypersensitivity reactions

For all drug hypersensitivity reactions that occur, additional follow-up data will be collected to assess the patient's medical history, alternative causes, and symptoms.

These data will be listed.

9.4.9 Injection-Site Reactions

Injection site assessments using the ISR CRF, visual analog scale (VAS) if required, and an exploratory tool (Scarletred) will be performed.

The VAS is a well-validated tool (Williamson and Hoggart 2005) to assess injection site pain; it is presented as a 100-mm line anchored by verbal descriptors, usually "no pain" and "worst imaginable pain." The participant will be asked to rate any pain at the injection site on a scale of 0 to 100 on the line, as soon as possible following each injection.

In addition, the exploratory tool (Scarletred) will be used to acquire exploratory ISR data at each of the time points where the ISR data is being collected by administration of the ISR CRF.

Pain VAS data will be summarized, together with changes from baseline, by treatment and listed. Baseline is defined as the assessment collected on Day 1 predose. If pain VAS was not collected at baseline, the baseline value will be set to 0. Plots of both observed and change from baseline pain VAS data will be provided by treatment over time. The rest of the injection-site reaction data (including erythema, induration, pain, pruritus, and edema) will be summarized by treatment in frequency tables, and listed.

9.4.10 Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection

Data from SARS-CoV-2 clinical screening, serology, and point-of-care test will be listed, if available.

9.4.11 Other assessments

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

9.4.12 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.

3. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. J Clin Nurs. 2005;14(7):798-804

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."

Leo Document ID = 74ded06e-3522-4f9c-83e9-4c902d845d8b

Approver: PPD

Approval Date & Time: 15-Oct-2020 17:44:56 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 15-Oct-2020 20:52:02 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 16-Oct-2020 09:35:32 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 16-Oct-2020 15:38:18 GMT

Signature meaning: Approved