Statistical Analysis Plan I6T-MC-AMAB (1)

A Bioequivalence Study of Subcutaneous Injections of Citrate-Free Mirikizumab Solution using a 1-mL Autoinjector and an Investigational 2-mL Autoinjector in Healthy Participants

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Title Page

Protocol Title: A Bioequivalence Study of Subcutaneous Injections of Citrate-Free Mirikizumab Solution using a 1-mL Autoinjector and an Investigational 2-mL Autoinjector in Healthy Participants

Protocol Number: I6T-MC-AMCB

Compound Number: Mirikizumab (LY3074828)

Short Title: A Bioequivalence Study of Subcutaneous Injections of Citrate-Free Mirikizumab Solution Using a 1-mL Autoinjector and Investigational 2-mL Autoinjector in Healthy Participants

Acronym: AMCB

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Version history

This statistical analysis plan (SAP) for Study I6T-MC-AMCB (AMCB) is based on the protocol dated 21 March 2024.

SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	See date on Page 1	Not Applicable	Original version

1. Introduction

This SAP has been developed after review of the clinical study protocol (final version dated 2 1 March 2024).

This SAP describes the planned analysis of the safety and pharmacokinetic (PK) data from this study. A detailed description of the planned tables, figures, and listings (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. A limited amount of information concerning this study (for example, objectives, study design) is given to help the reader's interpretation.

This SAP must be finalized prior to first participant visit. 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 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" (ICH 1998) and the International Conference on Harmonisation E3 Guideline entitled "Guidance for Industry: Structure and Content of Clinical Study Reports" (ICH 1995).

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1.1. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
• To evaluate the bioequivalence of a 200-mg SC dose of 100 mg/mL citrate-free mirikizumab solution using a 1 × 2-mL AI (test) compared to using 2 × 1-mL AI (reference)	• C_{max}, $AUC_{(0-\infty)}$, and $AUC_{(0-tlast)}$
Secondary	
• To describe the safety of a 200-mg SC dose of 100 mg/mL citrate-free mirikizumab solution using a 1 × 2 mL AI (test) compared to using 2 × 1 mL AI (reference)	• TEAEs and SAEs
Exploratory	
• To evaluate the impact of injection site location on PK	• C_{max}, $AUC_{(0-\infty)}$, and $AUC_{(0-tlast)}$

Abbreviations: AI = autoinjector; $AUC_{(0-\infty)}$ = 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; C_{max} = maximum observed drug concentration; PK = pharmacokinetics; SAE = serious adverse event; SC = subcutaneous; TEAE = treatment emergent adverse event.

1.2. Study Design

Study AMCB is a Phase 1, open-label, randomized, 2-arm, parallel-design, single-dose multi-center study of citrate-free mirikizumab administered via autoinjector (AI) in healthy participants.

Screening

All participants will be screened within 35 days prior to Day 1.

Treatment and assessment period

Eligible participants will be admitted to the clinical research unit (CRU) on Day -1. Participants will be stratified by 1 of 3 weight categories based on their weight assessment measured on Day -1:

- less than 75.0 kg
- 75.0 to 85.0 kg
- more than 85.0 kg

Participants will be stratified by weight category and randomized in 1:1 to either 1 × 2-mL subcutaneous (SC) injection of 100 mg/mL citrate-free mirikizumab (test) or 2 × 1-mL SC injections of 100 mg/mL citrate-free mirikizumab (reference) with a computer-generated allocation code using an interactive web-response system (IWRS). Injection site location, either arm, thigh, or abdomen, will be assigned in an approximately equal distribution within each study arm using an IWRS.

Approximately 440 participants will be enrolled to ensure 400 completers. Approximately 220 participants will be randomized to the test arm, and 220 participants will be randomized to the reference arm, with approximately 73 participants for each injection site in each study arm.

A minimum of approximately 73 participants overall in each weight category should complete the study.

On Day 1, participants will receive assigned study intervention. Participants may be allowed to leave the CRU after completing the 4-hour safety assessments on Day 1, or later at the investigator's discretion, and will return for PK sampling and safety assessments at predefined times up to 10 weeks postdose. Participants will be monitored for safety between outpatient visits by way of telephone assessment.

Safety will be assessed through clinical chemistry, hematology, urinalysis testing, vital signs measurements, recording of adverse events (AEs) and product complaints (PC), and physical examination.

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2. Statistical Hypotheses

The primary objective of this study is to evaluate the bioequivalence of a single 2-mL SC dose of citrate-free mirikizumab solution in AI compared to 2 × 1-mL SC dose of citrate-free mirikizumab solution in AI.

3. Analysis Sets

The following analysis sets are defined:

Participant Analysis Set	Description
Enrolled	All participants randomly assigned to study intervention.
Safety analysis set	All participants who are exposed to study intervention. Participants will be analyzed according to the intervention they actually received.
PK analysis set	All enrolled participants who receive a full dose of study intervention and have evaluable PK data according to the study intervention actually received. Note: The full dose will be determined only when the CRF data for full dose information is available.

Abbreviations: CRF = case report form; PK = pharmacokinetics.

Participants may be excluded from the PK analysis set in the event of

- a device malfunction
- administration of only 1 of the 2 × 1-mL AI doses, or
- administration of an incorrect or incomplete dose.

3.1. Treatments

Study Treatment Name	Injection Site	Abbreviation	Treatment order in TFL	
2 × 1-mL SC injections of 100 mg/mL citrate-free mirikizumab (Reference)	Abdomen	CF Solution AI (Reference) (Abdomen)	1	3
	Arm	CF Solution AI (Reference) (Arm)		4
	Thigh	CF Solution AI (Reference) (Thigh)		5
1 × 2-mL SC injections of 100 mg/mL citrate-free mirikizumab (Test)	Abdomen	CF Solution AI (Test) (Abdomen)	2	6
	Arm	CF Solution AI (Test) (Arm)		7
	Thigh	CF Solution AI (Test) (Thigh)		8

Abbreviations: AI = autoinjector; CF = citrate-free; SC = subcutaneous; TFL = table, figure, and listing.

Note: A TFL with only treatment arms order will be 1 and 2, while a TFL with treatment by injection site order will be 3, 4, 5, 6, 7, and 8, as shown in the above table.

4. Statistical Analyses

4.1. General Considerations

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, minimum, maximum, and number of observations; for log-normal data (for example, the PK parameters: areas 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 participants up to the point of withdrawal, including both scheduled or unscheduled visit results, 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 at scheduled visits only. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

For change from baseline summary statistics, each individual change from baseline will be calculated by subtracting the individual participant's baseline value from the value at that timepoint, where baseline is defined as the last non-missing data up to the first dose. The individual participant's change from baseline values will be used to calculate the summary statistics (arithmetic mean, arithmetic SD, median, minimum, maximum, and number of observations) using a SAS procedure such as Proc Univariate.

Data analysis will be performed using SAS® Version 9.4 or greater.

4.2. Demography and Participant Dispositions

Participant disposition will be listed. The demographic variables age, sex, race, ethnicity, country of enrolment, site ID, body weight, weight category, height, and body mass index will be summarized by treatment, and overall; the data will also be listed. All other demographic variables will be listed only.

4.3. Primary Endpoint(s) Analysis

4.3.1. Pharmacokinetic Analysis

PK parameter estimates will be determined using non-compartmental procedures in the validated software program (Phoenix WinNonlin Version 8.3.5).

Serum concentrations of mirikizumab will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
$AUC_{(0\text{-}tlast)}$	day*µg/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
t_{last}	Day	the last time point with a measurable concentration
$AUC_{(0\text{-}\infty)}$	day*µg/mL	area under the concentration versus time curve from time zero to infinity
$\%AUC_{(tlast\text{-}\infty)}$	%	percentage of $AUC_{(0\text{-}\infty)}$ extrapolated
C_{max}	µg/mL	maximum observed drug concentration
t_{max}	day	time of maximum observed drug concentration
$t_{½}$	day	half-life associated with the terminal rate constant (λz) in non-compartmental analysis
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

Additional PK parameters such as weight-normalized PK parameter estimates 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 CSR.

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

General PK parameter rules

- Actual sampling times will be used in the final analyses of individual PK parameters, except for non-bolus pre-dose sampling times, which will be set to zero. For non-bolus, multiple dose profiles, the pre-dose time will be set to zero unless a time deviation falls outside of the protocol blood collection time window which is considered to impact PK parameter derivation.
- C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than one time point, t_{max} will be assigned to the first occurrence of C_{max}.
- AUC parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max}, and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive concentrations above the lower limit of quantification, with at least one

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of these concentrations following C_{max}. $AUC_{(0-\infty)}$ values where the percentage of the total area extrapolated is more than 20% will be flagged. Any $AUC_{(0-\infty)}$ value excluded from summary statistics will be noted in the footnote of the summary table.

- Half-life ($t_{1/2}$) 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 $t_{1/2}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{1/2}$ 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 observed last quantifiable 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). 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 versus 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 versus 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 CSR.
- 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 CSR.

Treatment of outliers during PK 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 $n \geq 6$, 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 CSR. Approval of the final CSR will connote approval of the exclusion.

4.3.2. Primary Analysis for the Primary Endpoint

Pharmacokinetic parameter estimates for mirikizumab will be calculated using standard noncompartmental methods of analysis.

The primary parameters for analysis will be the C_{max}, $AUC_{(0-\infty)}$, and $AUC_{(0-tlast)}$ of mirikizumab. The secondary parameter for analysis will be the t_{max} of mirikizumab.

The PK parameters will be summarized by treatment and listed. Additionally, the PK parameters will also be summarized by treatment and injection site location.

4.3.2.1. Pharmacokinetic Statistical Methodology

The C_{max}, $AUC_{(0-\infty)}$, and $AUC_{(0-tlast)}$ will be log-transformed and analyzed using a linear fixed-effects model. The model will include mirikizumab administration method (2 × 1 mL as reference, 1 × 2 mL as test), injection site location, and weight category stratification as fixed effects. The least squares (LS) mean differences between mirikizumab administration method administrations (across all locations) will be back transformed to present the ratios of geometric LS means and the corresponding 90% confidence interval (CI). Comparisons will be made between the 2 administration methods.

Example SAS Code:

```
proc mixed data=xxx;

by parameter;

class administration location strat_weight;

model log_pk = administration location strat_weight / residual;

lsmeans administration / alpha=0.1 cl pdiff;
```

```
lsmeans location / alpha=0.1 cl pdiff;

ods output lsmeans=lsmeans diffs=diffs;

run;
```

The two administration methods will be considered bioequivalent if the 90% CIs of the ratio of geometric LS means fall within 0.800 to 1.250.

In addition, the t_{max} of mirikizumab between the two administration methods will be analyzed using a Wilcoxon rank-sum test. Estimates of the median, the median difference, approximately 90% CIs, and p-values from the Wilcoxon rank-sum test will be reported.

Example SAS code:

```
proc npar1way data = xxx hl(refclass="xx") alpha = 0.1;

by parameter;

class administration;

var pk;

exact wilcoxon hl;

ods output wilcoxontest = Wilcoxon;

ods output HodgesLehmann=hl;

run;
```

Using the same model, the following exploratory comparisons will also be made:

- The 2 administration methods (2 × 1 mL [Reference] versus 1 × 2 mL [Test]) compared separately at each injection location (injection location will be removed from the model above)
- The 3 injection locations (arm [Test] versus abdomen [Reference] and thigh [Test] versus abdomen [Reference]) separately for each administration method (2 × 1 mL [Reference] versus 1 × 2 mL [Test]) (administration methods will be removed from the model above)

There is no intention for formal statistical analysis in these comparisons but rather to explore potential heterogeneity; therefore, bioequivalence will not be determined based on this exploratory purpose.

Additional PK analyses may be conducted if deemed appropriate.

4.4. Safety Analyses

4.4.1. Adverse Events

Where changes in severity are recorded in the Case Report Form, only the most severe adverse event will be used in the summary tables. A pre-existing condition is defined as a condition 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 that starts after informed consent but prior to dosing. A treatment emergent AE (TEAE) is defined as an AE that occurs postdose or that is present prior to dosing and the severity worsens postdose.

TEAEs will be summarized by treatment, severity, and relationship to the study drug, including the frequency (the number of TEAEs, the number of participants experiencing a TEAE, and the percentage of participants experiencing a TEAE), based on Medical Dictionary for Regulatory Activities (MedDRA) 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 (SAEs) and PCs will be listed. Adverse events of special interest (Protocol section 8.3.3) may be listed if data warrant.

AEs of special interest for this study include:

- infection and
- systemic allergic/hypersensitivity reactions.

4.4.2. Protocol Deviation

Important protocol deviations that occur during Study AMCB will be listed if data is available.

4.4.3. Concomitant Medication

Concomitant medication will be coded using the WHO drug dictionary.

4.4.4. Clinical Laboratory Parameters

All clinical chemistry and hematology data will be summarized by parameter, treatment, and scheduled timepoint together with changes from baseline, where baseline is defined as the Day 1 predose assessment. Additionally, clinical chemistry, hematology, and urinalysis data outside the reference ranges will be listed and flagged.

4.4.5. Vital Signs

Vital signs data will be summarized by parameter, treatment, and scheduled time point, together with changes from baseline, where baseline is defined as the Day 1 predose assessment.

4.4.6. Electrocardiogram

Electrocardiograms (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, and no formal statistical analysis will be conducted on ECG parameters for this study.

4.4.7. Hepatic Monitoring

If a participant experiences elevated hepatic laboratory parameters, as detailed in Section 8.2.6.1 of the protocol, additional 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 if data warrants. Use of acetaminophen during the study, which has potential for hepatotoxicity, will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography scan, and biopsy assessments will be listed, if performed.

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

Hepatic chemistry, hematology, coagulation, and serology values outside the reference ranges will be flagged on the individual participant data listings as part of the listing mentioned in Section 4.4.4.

4.4.8. Visual Analog Scale Pain Scores

If injection-site pain is reported at any time during the study, the intensity of pain will be quantified using the 100-mm validated pain visual analog scale (VAS).

The participants' maximum post-dose pain scores will be summarized by treatment and injection site location. Participants who do not report pain will be included with a score of 0. Additionally, maximum post-dose pain score will also be summarized by category, treatment, and injection site location. The pain categories of VAS for presentation in the TFLs will be no pain (VAS pain score = 0), mild pain (VAS pain score > 0 and ≤ 30), moderate pain (VAS pain score > 30 and ≤ 70), and severe pain (VAS pain score > 70). Also, VAS scores will be summarized by treatment and injection site location using mean, SD, median minimum and maximum.

4.4.9. Injection Site Reactions

Although no prospective collection, spontaneously reported, will be captured as an AE of Injection-site reaction and additional info will be recorded.

Injection-site reaction data (erythema, induration, pain, pruritus, and edema) may be listed and summarized by treatment and overall, where treatment is subset by injection location, and overall (within the treatment arm) in frequency tables or alternative visual form.

4.4.10. Hypersensitivity Reactions

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

4.4.11. Bleeding and Bruising Assessment

The presence of visible bleeding/bruising at the injection site will be recorded as an AE if judged to be more severe than expected with a typical SC administration.

If available, any bleeding/bruising data will be listed.

4.4.12. Other Assessments

All other safety assessments not detailed in this section may be listed, if data warrants, but not summarized or statistically analyzed.

4.4.13. Safety Statistical Methodology

No inferential statistical analyses are planned.

4.5. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the protocol must be amended.

4.6. Changes from the Protocol-Specified Statistical Analyses

There were no changes from the protocol-specified statistical analyses.

5. Sample Size Determination

Approximately 440 participants, 220 participants in each treatment arm, may be enrolled so that approximately 400 participants, 200 in each test and reference group, complete the study.

Within each weight category, participants will be assigned to an SC injection site of either the arm, thigh, or abdomen, approximately 73 participants per injection site for the reference and test arms.

A sample size of 200 participants per treatment group will provide approximately 90% probability that the 90% CI of the geometric mean ratio of C_{max} and area under the concentration versus time curve between groups will fall within the equivalence boundary of 0.80 to 1.25. This sample size calculation was based on the assumptions that the coefficient of variation of PK parameters is up to 41.8% for each treatment group and the expected ratio of geometric means is between 0.9 and 1.1.

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6. Data Presentation

6.1. Derived Parameters

Individual derived parameters (for example, PK parameters) and appropriate summary statistics will be reported to three significant figures. Observed concentration data, for example, C_{max}, should be reported as received. Observed time data, for example, t_{max}, should be reported as received. Number of observations 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.

6.2. Missing Data

Missing data will not be displayed in listings.

6.3. 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.”

7. References

[ICH] International Conference on Harmonisation. Statistical principles for clinical trials E9. ICH harmonised tripartite guideline. February 05, 1998. Accessed March 25, 2024. https://database.ich.org/sites/default/files/E9_Guideline.pdf

[ICH] International Conference on Harmonisation. Structure and content of clinical study reports E3. ICH harmonised tripartite guideline. November 30, 1995. Accessed March 25, 2024. https://database.ich.org/sites/default/files/E3_Guideline.pdf

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