Statistical Analysis Plan Version 2.0 I6T-MC-AMBY

A Bioequivalence Study of Subcutaneous Injections of Mirikizumab Reference Solution Using Investigational 1-mL and 2-mL Prefilled Syringes and Mirikizumab Test Solution Formulation Using Investigational 1-mL and 2-mL Prefilled Syringes in Healthy Participants

NCT05644353

Approval Date: 07-MAR-2023

STATISTICAL ANALYSIS PLAN

A Bioequivalence Study of Subcutaneous Injections of Mirikizumab Solution using Investigational 1-mL and 2-mL Prefilled Syringes and Mirikizumab Citrate-free Solution Formulation using Investigational 1-mL and 2-mL Prefilled Syringes in Healthy Participants

Statistical Analysis Plan Status: Final
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Investigational Medicinal Product: Mirikizumab (LY3074828)

Protocol Reference: I6T-MC-AMBY
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Clinical Phase I

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
ADA	Anti-drug antibody
AE	Adverse event
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 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 quantifiable drug concentration
C_{max}	Maximum observed drug concentration
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
DMP	Data Management Plan
ECG	Electrocardiogram
ICH	International Conference on Harmonisation
IWRS	Interactive web response system
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
PC	Product complaints
PFS	Prefilled syringe
PK	Pharmacokinetic
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation

SOP	Standard Operating Procedure
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
TEAE	Treatment emergent adverse event
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
VAS	Visual analog scale
V_{ss}/F	Apparent volume of distribution at steady state after extravascular administration
V_z/F	Apparent volume of distribution during the terminal phase after extra-vascular administration

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 01 February 2023).

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 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 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 AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the bioequivalence of a single 300-mg subcutaneous (SC) dose of mirikizumab in a citrate-free solution formulation using a 1-mL and 2-mL prefilled syringe (PFS) (test) compared to the mirikizumab solution formulation using a 1-mL and 2-mL PFS (reference)	• Maximum observed drug concentration (C_{max}), area under the concentration versus time curve (AUC) from time zero to infinity (AUC[0-∞]), and AUC from time zero to time t, where t is the last time point with a measurable concentration (AUC[0-t_{last}])
Secondary	
• To describe the safety and tolerability of a single 300-mg SC dose of mirikizumab in a citrate-free solution formulation using a 1-mL and 2-mL PFS (test) compared to the mirikizumab solution formulation using a 1-mL and 2-mL PFS (reference)	• Treatment-emergent adverse events (TEAEs) and serious adverse event (SAEs)
Exploratory	
• To evaluate the effect of mirikizumab citrate-free solution formulation using a 1-mL and 2-mL PFS and of mirikizumab solution formulation using a 1-mL and 2-mL PFS on immunogenicity	• Treatment-emergent antidrug antibody [TE-ADA]
• To evaluate the impact of injection-site location (arm, thigh, or abdomen) on PK	• C_{max}, AUC(0-∞), and AUC(0-t_{last})

5. STUDY DESIGN

Study I6T-MC-AMBY (AMBY) is a Phase 1, participant-blind, randomized, 2-arm, 2-formulation, parallel-design, single-dose, multi-center study 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 also be randomized in a 1:1 ratio to either mirikizumab solution (reference) or citrate-free solution (test) with a computer-generated allocation code using an Interactive Web Response Systems (IWRS). Injection site location (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 368 completers. Approximately 220 participants will be randomized to the test arm and approximately 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 70 participants in each weight category should complete the study.

On Day 1, participants will receive 1×1-mL and 1 × 2-mL SC dose of 100 mg/mL mirikizumab (total dose: 300 mg mirikizumab).

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 and immunogenicity sampling and safety assessments at predefined times up to approximately 12 weeks postdose. Participants will be monitored for safety between outpatient visits by way of telephone assessment.

Safety and tolerability will be assessed through clinical laboratory tests, vital signs measurements, recording of AEs and product complaints (PCs), physical examination, and immunogenicity.

6. BLINDING

This is a randomized participant-blind study. Only the participants will be blinded to treatment assignment.

The Labcorp biometrics and Eli Lilly study teams will be unblinded throughout the study.

7. TREATMENTS

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

Study Treatment Name	Injection Site	Abbreviation	Treatment order in TFL
1 × 1-mL (100 mg) and 1 × 2-mL (200 mg) Mirikizumab Solution SC PFS (Reference)	Abdomen	Solution PFS (Reference) (Abdomen)	1
	Arm	Solution PFS (Reference) (Arm)	2
	Thigh	Solution PFS (Reference) (Thigh)	3
1 × 1-mL (100 mg) and 1 × 2-mL (200 mg) Mirikizumab Citrate-free Solution SC PFS (Test)	Abdomen	CF Solution PFS (Test) (Abdomen)	4
	Arm	CF Solution PFS (Test) (Arm)	5
	Thigh	CF Solution PFS (Test) (Thigh)	6

Abbreviations: CF = citrate-free; PFS = prefilled syringe; SC = subcutaneous

8. SAMPLE SIZE JUSTIFICATION

Approximately 410 (approximately 205 participants in the mirikizumab solution [reference] group and approximately 205 participants in the mirikizumab citrate-free solution [test] group) participants may be enrolled. This is to ensure that approximately 368 participants (184 participants in the mirikizumab solution [reference] group and 184 participants in the mirikizumab citrate-free solution [test] 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 68 participants per injection site for the reference and test arms).

A sample size of 184 participants per treatment group will provide approximately 90% power that the 90% confidence interval (CI) of the geometric mean ratio of C_{max} and AUC between groups will fall within the equivalence range of 0.8 to 1.25. This sample size calculation was based on the assumptions that the PK parameters have log-normal distribution, the % coefficient of variation (CV) of C_{max} and AUC are approximately 44% (based on the PFS arm of Study I6T-MC-AMBX), the expected ratio of geometric means is 0.91 (based on the results of Study I6T-MC-AMBV), and the %CV is the same for participants from each treatment group.

9. DEFINITION OF ANALYSIS POPULATIONS

The “Enrolled” population will consist of all participants randomly assigned to mirikizumab.

The “Safety” population will consist of all participants who are exposed to mirikizumab. Participants will be analyzed according to the mirikizumab they actually received.

The “Pharmacokinetic” population will consist of all enrolled participants who receive a dose of mirikizumab and have evaluable PK data.

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

- a device malfunction,
- administration of only 1 of the 2 PFS doses, or
- administration of an incorrect dose, incomplete dose or incorrect use of procedure instructions.

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.

10. STATISTICAL METHODOLOGY

10.1 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, minimum, maximum and number of observations; 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.

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 time point. The individual participants' 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.

10.2 Demographics and Participant Disposition

Participant disposition will be listed. The demographic variables age, sex, race, ethnicity, country of enrolment, site ID, body weight, body weight category, height, and body mass index will be summarized by treatment, injection site, and overall (overall for each treatment arm and overall), and listed. All other demographic variables will be listed only.

10.3 Pharmacokinetic Assessment

10.3.1 Pharmacokinetic Analysis

PK parameter estimates will be determined using non-compartmental procedures in validated software program (Phoenix WinNonlin Version 8.1.1 or later).

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

Parameter	Units	Definition
$AUC(0\text{-}t_{last})$	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
$AUC(0\text{-}\infty)$	day*µg/mL	area under the concentration versus time curve from time zero to infinity
$\%AUC(t_{last}\text{-}\infty)$	%	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.

- 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 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 ($t_{1/2}$) 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 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 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 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 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.Insert from PKAP (note PKAP should detail WinNonlin version)

10.3.2 Pharmacokinetic Statistical Methodology

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

The C_{max}, AUC(0-∞), and AUC(0-t_{last}) will be log-transformed and analyzed using a linear fixed-effects model. The model will include mirikizumab solution formulation, injection site location, and weight category stratification as fixed effects. The least squares (LS) mean differences between citrate-free solution PFS (Test) and solution PFS (Reference) administrations (across all locations) will be back-transformed to present the ratios of geometric LS means and the corresponding 90% CI.

Example SAS Code:

```
proc mixed data=xxx;
by parameter;
class formulation location strat_weight;
model log_pk = formulation location strat_weight / residual;
lsmeans formulation / alpha=0.1 cl pdiff;
lsmeans location / alpha=0.1 cl pdiff;
ods output lsmeans=lsmeans diffs=diffs;
run;
```

The 2 solution formulations will be considered bioequivalent if the 90% CIs of the ratio of geometric LS means fall within 0.800 to 1.250.

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

- The 2 solution formulations compared separately at each injection location (injection location will be removed from the model above)
- The 3 injection locations (arm versus abdomen and thigh versus abdomen) separately for each solution formulations (solution formulations will be removed from the model above)

In addition, the t_{max} of mirikizumab between the solution formulations will be analyzed using a Wilcoxon rank-sum test. Estimates of the median, the median difference, 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 formulation;
  var pk;
  exact wilcoxon hl;
  ods output wilcoxontest = Wilcoxon;
  ods output HodgesLehmann=hl;
run;
```

Additional PK analyses may be conducted if deemed appropriate.

10.4 Safety and Tolerability Assessments

10.4.1 Adverse events

Where changes in severity are recorded in the Case Report Form, 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 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 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. TEAEs will be summarized by treatment, injection site location, 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, injection site location, Medical Dictionary for Regulatory Activities (MedDRA) (version is documented in the Data Management Plan [DMP]) 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 SAEs and PCs will be listed. Adverse events of special intrest (protocol section 8.3.3) will be listed.

Discontinuations due to AEs will be listed.

10.4.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (version is documented in the DMP). Concomitant medication will be listed.

10.4.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by parameter, treatment overall, treatment subset by injection location, and overall and timepoint together with changes from baseline, where baseline is defined as the Day 1 predose assessment. All clinical chemistry, hematology and 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.

10.4.4 Vital signs

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

Values for individual participants will be listed.

10.4.5 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.

10.4.6 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. 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 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.

10.4.7 Immunogenicity Assessments

Immunogenicity data will be listed and frequency tables will be presented if analysed. The frequency and percentage of participants with pre-existing antidrug antibody (ADA) and with TE-ADAs will be presented. TE-ADAs are those that are boosted or induced by exposure to study drug, with a 4-fold increase in titer compared to baseline if ADAs were detected at baseline or a titer 2-fold greater than the minimum required dilution (1:10) if no ADAs were detected at baseline, where baseline is defined as Day 1 predose. For the TE-ADA+ participants, the distribution of maximum titers may be described.

The frequency and percentage of participants with neutralizing antibodies, if measured, may also be tabulated for participants with TE ADA.

The relationship between the presence of antibodies and PK parameters of mirikizumab may be assessed if deemed appropriate.

10.4.8 Visual Analog Scale (VAS) 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 VAS.

Injection-site assessments should be conducted at the next planned visit following the reporting of an injection-related AE.

The participants' maximum post-dose pain scores will be summarized by treatment and injection site location. Participants who do not report paint 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).

All data collected will be listed.

10.4.9 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, categorical pain, pruritus, and edema) will be listed and summarized by treatment overall, treatment subset by injection location, and overall in frequency tables.

10.4.10 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 will be listed.

10.4.11 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.

10.4.12 Other assessments

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

10.4.13 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

11. 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.

12. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

13. 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.

14. DATA PRESENTATION

14.1 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. 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.

14.2 Missing Data

Missing data will not be displayed in listings.

14.3 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.”

15. APPENDICES

Appendix 1: Document History

Status and Version	Date of Change	Summary/Reason for Changes
Final Version 1.0	NA	NA; the first version.
Final Version 2.0	05 March 2023	Incorporated Protocol amendment (b) dated 01 Feb 2023

NA = not applicable

Signature Page for VV-CLIN-089798 v1.0

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