Statistical Analysis Plan I6T-MC-AMBV

Relative Bioavailability of a Mirikizumab Test Formulation Compared to the Reference Formulation in Healthy Subjects

NCT04548219

Approval Date: 18-Dec-2020

STATISTICAL ANALYSIS PLAN

Relative Bioavailability of a Mirikizumab Test Formulation Compared to the Reference Formulation in Healthy Subjects

Statistical Analysis Plan Status: Final
Statistical Analysis Plan Date: 05-June-2020

Study Drug: Mirikizumab (LY3074828)

Sponsor Reference: I6T-MC-AMBV
Covance CRU Study: 1000071-8418427

Clinical Phase I

Approval Date: 18-Dec-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
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
ECG	Electrocardiogram
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
PFS	Pre-filled syringe
PK	Pharmacokinetic
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
TE ADA	Treatment-emergent antidrug antibody
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, and Listings

t_{max}	Time of maximum observed drug concentration
ULN	Upper limit of normal
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
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 13 December 2019).

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 AND ENDPOINTS

Objectives	Endpoints
Primary • To evaluate the relative bioavailability of a single 200-mg subcutaneous (SC) dose (2 x 1-mL pre-filled syringe [PFS] injections) of Mirikizumab Test Formulation compared to the Reference Formulation	• Maximum observed drug concentration (C_{max}), area under the concentration versus time curve from time zero to infinity [AUC(0-∞)], and area under the concentration versus time curve from time zero to time t, where t is the last timepoint with a measurable concentration [AUC(0-t_{last})]
Secondary • To evaluate the safety and tolerability of a single 200-mg SC dose (2 x 1-mL PFS injections) of Mirikizumab Test Formulation compared to the Reference	• Treatment-emergent adverse events (TEAEs), and serious adverse events (SAEs)

Formulation	
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5. STUDY DESIGN

Study AMBV is a Phase 1, subject-blind, investigator-blind, 2-arm, randomized, single-dose, parallel-design study in healthy subjects.

All subjects will be screened within 28 days prior to enrollment. Eligible subjects will be admitted to the clinical research unit (CRU) on Day -1 and randomized

- 1:1 to 2 treatment formulations and
- within each treatment formulation, 1:1:1 to 3 injection sites (arm, thigh, or abdomen)

using a computer-generated allocation code. On Day 1, subjects will receive a 2 x 1-mL (200 mg mirikizumab) SC dose of 1 of the following treatments according to the randomization schedule:

- 200 mg Mirikizumab Reference Formulation (100 mg/mL), 2 x 1-mL PFS
- 200 mg Mirikizumab Test Formulation (100 mg/mL), 2 x 1-mL PFS

The maximum total dose of mirikizumab a subject will receive is 200 mg.

Subjects may be allowed to leave the CRU after completing the 4-hour safety assessments on Day 1, at the investigator's discretion, and will return for PK and immunogenicity sampling and safety assessments at predefined times up to 12 weeks postdose. Subjects will be monitored for safety between outpatient visits by way of telephone assessment. Subjects will participate in the study for up to 12 weeks after last dose.

Safety and tolerability will be assessed through clinical laboratory tests, vital sign measurements, recording of adverse events (AEs), physical examination, and immunogenicity. At prospectively defined time points, injection-related assessments will be made including a VAS pain score.

6. TREATMENTS

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

Study Treatment Name	Injection Site	Abbreviation	Treatment order in TFL
200 mg Mirikizumab Reference Formulation (100 mg/mL) 2 x 1-mL PFS	Arm	Reference (Arm)	1
	Thigh	Reference (Thigh)	2
	Abdomen	Reference (Abdomen)	3
200 mg Mirikizumab Test Formulation (100 mg/mL) 2 x 1-mL PFS	Arm	Test (Arm)	4
	Thigh	Test (Thigh)	5
	Abdomen	Test (Abdomen)	6

7. SAMPLE SIZE JUSTIFICATION

Up to 60 subjects may be enrolled to ensure that 48 subjects (24 subjects per treatment formulation with approximately 8 subjects per treatment formulation and injection site [arm, thigh, or abdomen]) complete the study.

Based on previous trials, it is expected that the coefficient of variation for area under the concentration versus time curve (AUC) and C_{max} to be approximately 40%. A sample size of 48 completed subjects (24 subjects per treatment formulation) will provide >90% probability that the limits of the 90% confidence interval (CI) for the ratio of geometric means will be within 24% of the estimate.

Subjects who are randomized but not administered any treatment formulation may be replaced to ensure that 48 subjects (24 per treatment formulation) complete the study.

8. DEFINITION OF ANALYSIS POPULATIONS

The “Safety” population will consist of all enrolled subjects who received at least one dose of mirikizumab, regardless of whether they complete all protocol requirements.

The “Pharmacokinetic” population will consist of all subjects who received at least one dose of mirikizumab and have evaluable PK data.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when subjects are assigned to analysis populations.

9. STATISTICAL METHODOLOGY

9.1 General

Data listings will be provided for all data that 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 coefficient of variation will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all subjects up to the point of withdrawal, with any subjects excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for subjects included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Mean change from baseline is the mean of all individual subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The individual subject's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

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

9.2 Demographics and Subject Disposition

Subject disposition will be listed. The demographic variables age, sex, race, ethnicity, country of enrolment, site ID, body weight, height and body mass index will be summarized by treatment formulation and injection site and listed. All other demographic variables will be listed only.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

PK parameter estimates will be determined using non-compartmental procedures in validated software program (Phoenix WinNonlin Version 8.1 or later).

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

Parameter	Units	Definition
AUC(0-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-∞)	day*µg/mL	area under the concentration versus time curve from time zero to infinity
%AUC(t_{last}-∞)	%	percentage of AUC(0-∞) extrapolated
C_{max}	µg/mL	maximum observed drug concentration
t_{max}	day	time of maximum observed drug concentration
$t_{1/2}$	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 may be calculated, as appropriate.

PK parameters may also be normalized by body weight in the event that there are differences in body weight between the cohorts.

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.

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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 the time of maximum observed drug concentration (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 subject will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in 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 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 below the quantifiable lower limit of the assay (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 subject or from a subsequent dose period following a suitable wash-out period.

    - The time points occur before the first quantifiable concentration.

- All other BQL concentrations that do not meet the above criteria will be set to missing.

- Also, where two or more consecutive concentrations are BQL towards the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

Individual Concentration vs. Time Profiles

- Individual concentrations will be plotted utilizing actual sampling times.

- The terminal point selections will be indicated on a semi-logarithmic plot.

Average Concentration vs. Time Profiles

- The average concentration profiles will be graphed using scheduled (nominal) sampling times.
- The average concentration profiles will be graphed using arithmetic average concentrations.
- The pre-dose average concentration for single-dose data from non-endogenous compounds will be set to zero. Otherwise, only quantifiable concentrations will be used to calculate average concentrations.
- Concentrations at a sampling time exceeding the sampling time window specified in the protocol, or ± 10%, will be excluded from the average concentration profiles.
- Concentrations excluded from the mean calculation will be documented in the final study report.
- A concentration average will be plotted for a given sampling time only if 2/3 of the individual data at the time point have quantifiable measurements that are within the sampling time window specified in the protocol or ± 10%. An average concentration estimated with less than 2/3 but more than 3 data points may be displayed on the mean concentration plot if determined to be appropriate and will be documented within the final study report.

Treatment of Outliers during Pharmacokinetic Analysis

Application of this procedure to all PK analyses is not a requirement. Rather, this procedure provides justification for exclusion of data when scientifically appropriate. This procedure describes the methodology for identifying an individual value as an outlier for potential exclusion but does not require that the value be excluded from analysis. The following methodology will not be used to exclude complete profiles from analysis.

<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 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.

<u>Data between Individual Profiles</u>

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 ≥ 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

PK parameters will be evaluated to estimate the relative bioavailability of the Test Formulation compared with the Reference Formulation. PK parameters will be summarized by treatment formulation and injection site.

Log-transformed C_{max}, AUC(0-t_{last}), and AUC(0-∞) parameters will be evaluated in a linear fixed-effects model with fixed effects for treatment formulation and injection-site location. The differences between the test and reference formulations will be back-transformed to present the ratios of geometric least squares means and the corresponding 90% CI.

Example SAS Code:

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

The t_{max} will be analyzed using a Wilcoxon rank sum test. Estimates of the median difference based on the observed medians, 90% CIs, and p-values from the Wilcoxon rank sum test will be calculated.

In addition, the following comparisons will be made:

- Test versus Reference separately at each injection site (injection site will be removed from the model above)
- Arm versus abdomen and thigh versus abdomen separately for each formulation (formulation will be removed from the model above)

Additional PK analyses may be conducted if deemed appropriate.

9.4 Safety and Tolerability Assessments

9.4.1 Adverse events

Where changes in severity are recorded in the case report form, each separate severity of the AE will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as an AE that starts before the subject has provided written informed consent and is ongoing at consent. A non-treatment emergent AE is defined as an AE which starts after informed consent but prior to dosing. A 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 formulation, injection site, severity and relationship to the study drug. The frequency (the number of AEs, the number of subjects experiencing an AE and the percentage of subjects experiencing an AE of TEAEs will be summarized by treatment formulation, 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 SAEs 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 MAR20B3). Concomitant medication will be listed.

9.4.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by parameter and treatment formulation, and listed. Urinalysis data will be listed. Changes from baseline, Day -1, will also be presented. Additionally, clinical chemistry, hematology and urinalysis data outside the reference ranges will be listed and flagged on individual subject data listings.

9.4.4 Vital signs

Vital signs data will be summarized by treatment formulation 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 formulation.

Values for individual subjects will be listed.

9.4.5 Body temperature

Body temperature data will be summarized by parameter and treatment formulation, with changes from baseline, Day -1, will be presented. The data will also be listed. Figures of mean body temperature will be presented by treatment formulation, over all timepoints.

9.4.6 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.

9.4.7 Hepatic Monitoring

If a subject experiences elevated alanine aminotransferase ≥3× upper limit of normal (ULN), alkaline phosphatase ≥2× ULN, or elevated total bilirubin ≥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 subjects' 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 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 formulation and listed. Alcohol and recreational drug use data will also be listed.

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

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[redacted]

[redacted]

CCI

[redacted]

CCI

[redacted]

9.4.11 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.

9.4.12 Other assessments

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

10. INTERIM ANALYSES

No formal interim statistical analyses are planned. However, review of the PK and safety data may be conducted during the conduct of this study to inform internal Chemistry, Manufacturing, and Control processes with regard to the test mirikizumab formulation development.

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

Unless otherwise stated, there are no plans to impute missing data. Missing data will not be displayed in listings.

13.3 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No serious adverse events occurred for this study.”

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Approver: PPD

Approval Date & Time: 18-Dec-2020 02:49:39 GMT

Signature meaning: Approved