J2T-MC-KGBG SAP V2

A Phase 1, Open-Label, Single-Dose Bioequivalence Study of Injections of Lebrikizumab Using a 2-mL Pre-Filled Syringe with Needle Safety Device and an Investigational 2-mL Autoinjector in Healthy Participants

NCT04840901

Approval Date: 09-Mar-2022

STATISTICAL ANALYSIS PLAN

A Phase 1, Open-Label, Single-Dose Bioequivalence Study of Injections of Lebrikizumab Using a 2-mL Pre-Filled Syringe with Needle Safety Device and an Investigational 2-mL Autoinjector in Healthy Participants

Statistical Analysis Plan Status: Final V2
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Study Drug: Lebrikizumab (LY3650150)

Sponsor Reference: J2T-MC-KGBG
Covance CRU Study: 1000071-8462026

Clinical Phase I

Approved on 09 Mar 2022 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
AI	Autoinjector
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate 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
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
C_{max}	Maximum observed drug concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
ECG	Electrocardiogram
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
PFS-NSD	Pre-filled syringe with needle safety device
PK	Pharmacokinetic
SAE	Serious adverse events
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
TBL	Total bilirubin
TE-ADA	Treatment-emergent antidrug antibody
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, and Listings
t_{last}	Time of last observed drug concentration
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 extra-vascular administration
V_z/F	Apparent volume of distribution during the terminal phase after extra-vascular administration
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 04 March 2021).

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. For open-label studies, this SAP must be signed off prior to first participant visit for this study. When the SAP and TFL shells are agreed upon and finalized, they will serve as 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 evaluate the PK of lebrikizumab after subcutaneous (SC) administration of 250-mg dose using a 2-mL pre-filled syringe with needle safety device (PFS-NSD) and a 2-mL autoinjector (AI) in healthy participants.

The primary endpoints of the study are:

- Maximum observed drug concentration (C_{max}).
- Area under the concentration versus time curve (AUC) from time zero to infinity (AUC([0-∞]).
- AUC from time zero to time t, where t is the last timepoint with a measurable concentration (AUC[0-t_{last}]).

4.2 Secondary Objective

The secondary objective of the study is:

- To describe the safety and tolerability of lebrikizumab 250-mg dose through SC in healthy participants.

The secondary endpoints of the study are:

- Serious adverse events (SAEs).
- Treatment-emergent adverse events (TEAEs).

4.3 Tertiary/Exploratory Objectives

The exploratory objectives and endpoints of the study are:

- To evaluate the potential development of anti-lebrikizumab antibodies.
  - Treatment-emergent antidrug antibody (TE-ADA).
- To evaluate the impact of injection-site location on PK.
  - C_{max}.
  - AUC(0-∞).
  - AUC(0-t_{last}).

5. STUDY DESIGN

Study KGBG is a Phase 1, multi-site, randomized, parallel-design, open-label, 2-arm, single-dose study in healthy participants.

All participants will be screened within 28 days prior to enrollment. At screening, participants will be stratified into 1 of 3 weight categories.

- less than 70.0 kg,
- 70.0 to 80.0 kg, and
- more than 80.0 kg.

Approximately 240 participants will be randomly assigned according to Table 1, so that approximately 216 participants complete the study. If a participant needs to be replaced, a participant of the same weight category will be selected as their replacement.

Within the 3 weight categories, participants will be randomly assigned (Table 1) using a computer-generated allocation code:

- 1:1 to delivery device (either PFS-NSD [reference] or AI [test])
- within each delivery-device group 1:1:1 to injection site (arm, thigh, or abdomen)

On Day 1, participants will receive a 2-mL (total 250 mg lebrikizumab) SC dose, administered by the investigator or designee, and delivered via the device and in the location assigned by the randomization.

Participants may be allowed to leave the clinical research unit after completing the 3(±1)-hour safety assessments on Day 1, or later at the investigator's discretion. Participants will return for PK and immunogenicity sampling and safety assessments at predefined times up to 99 days 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 sign measurements, recording of adverse events (AEs), physical examination, and immunogenicity.

Weight Category (Desired Number of Participants)	Injection Device	Subcutaneous Injection Location	Desired Number of Participants
Low <70.0 kg (72 participants)	2-mL PFS-NSD (Reference)	Arm	12
	2-mL AI (Test)		12
	2-mL PFS-NSD (Reference)	Abdomen	12
	2-mL AI (Test)		12
	2-mL PFS-NSD (Reference)	Thigh	12
	2-mL AI (Test)		12
Medium 70.0 – 80.0 kg (72 participants)	2-mL PFS-NSD (Reference)	Arm	12
	2-mL AI (Test)		12
	2-mL PFS-NSD (Reference)	Abdomen	12
	2-mL AI (Test)		12
	2-mL PFS-NSD (Reference)	Thigh	12
	2-mL AI (Test)		12
High >80.0 kg (72 participants)	2-mL PFS-NSD (Reference)	Arm	12
	2-mL AI (Test)		12
	2-mL PFS-NSD (Reference)	Abdomen	12
	2-mL AI (Test)		12
	2-mL PFS-NSD (Reference)	Thigh	12
	2-mL AI (Test)		12

Abbreviations: AI = autoinjector; PFS-NSD = pre-filled syringe with needle safety device.

Table 1: Randomization allocation for KGBG

6. TREATMENTS

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

Study Treatment Name	Abbreviation	Treatment order in TFL
2 mL (125 mg/mL) lebrikizumab pre-filled syringe with needle safety device.	2-mL (125 mg/mL) lebrikizumab PFS-NSD	1
2 mL (125 mg/mL) lebrikizumab autoinjector	2-mL (125 mg/mL) lebrikizumab AI	2

7. SAMPLE SIZE JUSTIFICATION

Approximately 240 participants may be enrolled so that approximately 216 participants (108 in the lebrikizumab PFS-NSD [reference] group and 108 in the AI [test] group) complete the study.

A sample size of 108 participants per device 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 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 percent coefficients of variation (%CV) of C_{max} and AUC are less or equal to 30%, the expected ratio of geometric means is between 0.9 and 1.1, and the %CV are the same for participants from each device group. The 30% CV assumption is based on lebrikizumab PK data in several previous studies.

To properly evaluate AUC(0-∞), lebrikizumab concentrations must be collected through at least Day 71. To ensure that approximately 216 participants (108 in each group) provide evaluable PK data, approximately 240 participants will be enrolled and receive study drug, assuming up to 10% of the participants may not complete through at least Day 71. Participants who do not complete at least through Day 22 (a period sufficient to determine C_{max}) may be replaced. The replacement participants should be in the same weight category as the original participants.

8. DEFINITION OF ANALYSIS POPULATIONS

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

The "Pharmacokinetic" population will consist of all participants who received a full dose of study intervention and have evaluable PK sample.

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 listed. The demographic variables age, sex, race, ethnicity, country of enrolment, site ID, body weight, height, body mass index, weight category, and injection location will be summarized by treatment and listed, both by overall, and using subcategories of weight categories and injection site locations. 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 Version 8.1 or later) will be used.

Serum concentrations of lebrikizumab (LY3650150) will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-t_{last})	mg.day/L	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-∞)	mg.day/L	area under the concentration versus time curve from time zero to infinity
%AUC(t_{last}-∞)	%	percentage of AUC(0-∞) extrapolated
C_{max}	ug/mL	maximum observed drug concentration
t_{max}	day	time of maximum observed drug concentration
t_{last}	day	time of last 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. 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:

CCI [redacted]

CCI [redacted]

- CCI [redacted]

- CCI [redacted]
  - [redacted]
  - [redacted]
    - [redacted]
    - [redacted]
    - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

- CCI [redacted]

[redacted]

a. CCI [redacted]

CCI

The t_{max} will be analyzed between the two device groups using a Wilcoxon rank-sum test. The median for each device, Hodges-Lehmann estimate of the median difference between the test and reference device, corresponding 90% CI, and p-value will be calculated.

CCI

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 participant has provided written informed consent and is ongoing at consent. A non-treatment emergent AE is defined as an AE which starts after informed consent but prior to dosing. A TEAE is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose.

All AEs will be listed. 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 TEAEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 23.1 system organ class and preferred term. The summary and frequency 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. AEs of special interest, that is, conjunctivitis, herpes infection or zoster, and parasitic infection or an infection related to an intracellular pathogen, will be listed separately.

Discontinuations due to AEs will be listed.

9.4.2 Concomitant medication

Concomitant medication will be coded using the World Health Organization (WHO drug dictionary (Version September 2020 B3). Concomitant medication will be listed.

9.4.3 Clinical laboratory parameters

All clinical chemistry, hematology, and other chemistry data, along with their change from baseline, where baseline is defined as Day 1 predose, will be summarized by parameter and treatment, and listed. Urinalysis data will be listed. Additionally, clinical chemistry, hematology, other chemistry data and urinalysis data outside the reference ranges will be listed and flagged on individual participant data listings.

In cases where lab data are analyzed at multiple laboratories for the same date/time, then the central laboratory values will be used in the ADAM dataset and presented in the TFLs. All data will be retained in the SDTM datasets.

9.4.4 Vital signs

Vital signs data will be summarized by treatment together with changes from baseline, where baseline is defined as 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)

The 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

Close hepatic monitoring

If a participant who had normal or near normal baseline alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBL) (i.e., <1.5× upper limit of normal [ULN]), experiences elevated ALT ≥3× ULN, AST ≥3× ULN, ALP ≥2× ULN, or TBL ≥2× ULN, laboratory tests should be repeated within 48 to 72 hours, including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyltransferase, and creatinine kinase to confirm the abnormality and to determine if it is increasing or decreasing.

In participants enrolled with elevated baseline ALT, AST, ALP or TBL (≥1.5× ULN), the thresholds for close monitoring are ALT ≥2× baseline, AST ≥2× baseline, ALP ≥2× baseline, or TBL ≥1.5× baseline.

At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses, (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor.

Comprehensive hepatic evaluation

If a study participant, who had baseline ALT, AST, ALP, TBL <1.5× ULN, experiences elevated ALT ≥5× ULN, AST ≥5× ULN, ALP ≥3× ULN, TBL ≥2× ULN, or elevated ALT, AST ≥3× ULN with hepatic signs/symptoms (severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia>5%), a comprehensive evaluation should be performed to search for possible causes of liver injury.

In participants who had elevated baseline ALT, AST, ALP, or TBL (≥1.5× ULN), the thresholds for performing this evaluation are ALT ≥3× baseline, AST ≥3× baseline, ALP ≥2× baseline, TBL ≥2× baseline, or ALT, AST ≥2× baseline with hepatic signs/symptoms.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time-international normalized ratio, viral hepatitis A, B, C, E, tests for autoimmune hepatitis, and an abdominal imaging study (for example, ultrasound or computed tomography scan).

Additional hepatic data collection in participants who have abnormal liver tests during the study

Additional hepatic safety data collection should be performed in participants who meet 1 or more of the following 5 conditions:

1. Elevation of serum ALT to ≥5× ULN on 2 or more consecutive blood tests (if baseline ALT <1.5× ULN)
   - In participants with baseline ALT ≥1.5× ULN, the threshold is ALT ≥3× baseline on 2 or more consecutive tests

2. Elevation of TBL to ≥2× ULN (if baseline TBL <1.5× ULN)
   - In participants with baseline TBL ≥1.5× ULN, the threshold should be TBL ≥2× baseline

3. Elevation of serum ALP to ≥2× ULN on 2 or more consecutive blood tests (if baseline ALP < 1.5× ULN)
   - In participants with baseline ALP ≥1.5× ULN, the threshold is ALP ≥2× baseline on 2 or more consecutive blood tests

4. Hepatic event considered to be an SAE

5. Discontinuation of the investigational product due to a hepatic event.

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

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

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

9.4.7 Immunogenicity Assessments

The frequency and percentage of participants with preexisting antidrug antibody (ADA) and with TE-ADA to lebrikizumab will be tabulated and listed.

For participants who are ADA negative at baseline, 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 neutralizing antibodies, if measured, may also be tabulated for participants with TE-ADA. TE-ADA titer characteristics will also be provided. The relationship between the presence of antibodies and the safety and PK parameters to lebrikizumab may be assessed.

9.4.8 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.

9.4.9 Injection-Site Reactions

Reported injection-site reactions will be characterized within the following categories:

- edema
- erythema
- induration
- pruritus
- pain

In addition, all positive responses of injection-site pain will require an additional assessment using a pain visual analog scale (VAS).

Injection-site reaction data will be listed and summarized by treatment in frequency tables. Pain VAS, if recorded, will be listed.

9.4.10 Other assessments

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

10. INTERIM ANALYSES

No interim statistical analyses are planned.

11. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

The statistical analyses of t_{max}, seen in Section 9.3.2, has been changed from a Wilcoxon signed-rank to a Wilcoxon rank-sum test as the study has a parallel design and no correlation is expected between the test and reference groups.

12. REFERENCES

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

13. DATA PRESENTATION

13.1 Derived Parameters

Individual derived parameters (e.g. PK parameters) and appropriate summary statistics will be reported to three significant figures. Observed concentration data, e.g. C_{max}, should be reported as received. Observed time data, e.g. t_{max}, should be reported as received. N and percentage values should be reported as whole numbers. Median values should be treated as an observed parameter and reported to the same number of decimal places as minimum and maximum values.

13.2 Missing Data

Missing data will not be displayed in listings.

13.3 Insufficient Data for Presentation

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

14. 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	02-MAR-2022	To document how to handle lab data which has been analyzed at multiple labs

NA = not applicable

Signature Page for VV-CLIN-018302 v1.0

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