Statisical Analysis Plan J2T-MC-KGBV (1.0)

A Phase 1, Participant- and Investigator-blinded, Randomized, Single-dose Study to Investigate the Safety and Pharmacokinetics of Lebrikizumab in Healthy Chinese Participants

NCT06243198

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Statistical Analysis Plan

A Phase 1, Participant- and Investigator-blinded, Randomized, Single-dose Study to Investigate the Safety and Pharmacokinetics of Lebrikizumab in Healthy Chinese Participants

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LIST OF ABBREVIATIONS

Abbreviations pertain to the SAP only (not the TFLs).

%AUC(t_{last}-∞)	percentage of AUC(0-∞) that is due to extrapolation from the last measurable concentration to infinity
ADA	anti-drug antibodies
ADaM	Analysis Data Model
AE	adverse event
AESI	adverse event of special interest
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
BLQ	below the limit of quantification
CDISC	Clinical Data Interchange Standards Consortium
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
CMQ	Customized MedDRA Query
CRU	clinical research unit
CSR	clinical study report
DMP	data management plan
ECG	electrocardiogram
eCRF	electronic case report form
HLT	high level term
ICH	International Council for/Conference on Harmonisation
ISR	injection site reaction
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MSSO	Maintenance and Support Services Organization
PK	pharmacokinetic(s)
PT	preferred term
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 anti-drug antibodies
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
t_{max}	time of maximum observed drug concentration
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
WHODrug	World Health Organization Drug Dictionary

1. INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Initial Version dated 01 September 2023).

This SAP describes the planned analysis of the PK, safety, and tolerability data from this study. A detailed description of the planned TFLs to be presented in the CSR is provided in the accompanying TFL shells document.

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 about this study (eg, objectives, study design) is given to help the reader's interpretation.

This SAP must be finalized prior to first participant visit. Additionally, the SAP and TFL shells should be finalized prior to any programming activities commencing.

This SAP supersedes any 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 accordingly in the CSR. Any substantial deviations from this SAP will be agreed with Eli Lilly and Company and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the ICH E3 guideline *Structure and Content of Clinical Study Reports*, ICH E8 guideline *General Considerations for Clinical Trials*, ICH E9 guideline *Statistical Principles for Clinical Trial*.[1,2,3]

The document history is presented in Appendix 1.

2. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To describe the safety of single SC doses of 250 mg and 500 mg lebrikizumab in healthy Chinese participants	Incidence of TEAEs and SAEs
Secondary	
To evaluate the PK of single SC doses of 250 mg and 500 mg lebrikizumab in healthy Chinese participants	C_{max}, AUC(0-∞), and AUC(0-t_{last}) of lebrikizumab

Exploratory	
To assess the immunogenicity of single SC doses of 250 mg and 500 mg lebrikizumab in healthy Chinese participants	Incidence of TE ADA

Abbreviations: AUC(0-t_{last}) = area under the concentration versus time curve from time zero to t, where t is the last time point with a measurable concentration; AUC(0-∞) = area under the concentration versus time curve from time zero to infinity; C_{max} = maximum observed drug concentration; PK = pharmacokinetic; SAE = serious adverse event; SC = subcutaneous; TE ADA = treatment-emergent anti-drug antibody; TEAE = treatment-emergent adverse event

3. STUDY DESIGN

This is a Phase 1, participant- and investigator-blinded, randomized, placebo-controlled, single-dose study to investigate the safety, tolerability, and PK of lebrikizumab in healthy Chinese participants.

Approximately 24 healthy Chinese participants who have satisfied the entry criteria and completed all screening assessments will be enrolled to ensure at least 20 evaluable participants complete the study. Due to effect of body weight on PK, enrolment of participants with similar body weights between the cohorts is preferred. Participants will be assigned sequentially into 1 of 2 cohorts, each with 12 participants. Within each cohort, participants will be randomized in a blinded manner to lebrikizumab or placebo. The planned doses are as follows:

- Cohort 1: single 250 mg dose of lebrikizumab or placebo via SC injection (n=12; 10 lebrikizumab, 2 placebo)
- Cohort 2: single 500 mg dose of lebrikizumab or placebo via SC injection (n=12; 10 lebrikizumab, 2 placebo)

The duration of the study is approximately 21 weeks, and will consist of 3 periods:

- Screening period: Day -28 to Day -2
- Inpatient period: Day -1 to Day 8
    - single SC dose on Day 1
- Follow-up period: discharge until Day 120 ± 3 days.

Screening period

All participants will be screened within 28 days prior to enrollment.

Inpatient period

Eligible participants will be admitted to the CRU on Day -1. On Day 1, participants will be randomized, and will receive either lebrikizumab or placebo via SC injection.

Participants may be allowed to leave the CRU after completing assessments on Day 8, or later at the investigator's discretion.

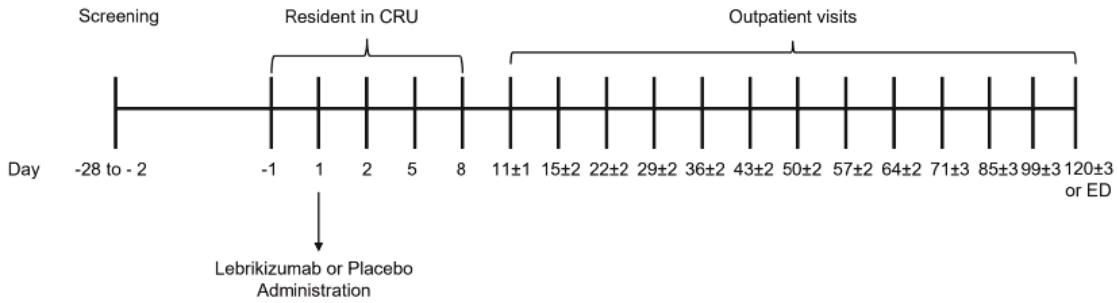
Follow-up period

Participants will return for PK and immunogenicity sampling and safety assessments at predefined times up to approximately 120 days postdose.

Safety and tolerability will be assessed through safety laboratory assessments, 12-lead ECGs, vital sign measurements, recording of AEs, and physical examinations.

A schematic of the study design is presented in Figure 1.

Figure 1: Study Design



Abbreviations: CRU = clinical research unit; ED = early discontinuation.

4. BLINDING

This is a randomized participant- and investigator-blind study. All measures possible must be taken to maintain the blind; access to the blinding information will be restricted to authorized personnel as described in the protocol. Staff who prepare the study intervention will not be blinded to treatment allocation.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted for medical management of the event. In such cases, the unblinding is to be conducted according to the protocol.

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

5. SAMPLE SIZE JUSTIFICATION

Approximately 24 participants will be enrolled in 2 dosing cohorts for at least 20 evaluable participants to complete the study. The sample sizes described are customary for Phase 1

studies evaluating safety and PK parameters and are not powered on the basis of statistical hypothesis testing. Each cohort will comprise approximately 12 participants with a randomization ratio of 5:1 between lebrikizumab and placebo. Participants who discontinue the study before completing may be replaced at the discretion of the sponsor and investigator. The replacement participant can complete the entire study period.

6. STUDY TREATMENTS

The study treatment names, and ordering to be used in the TFLs are presented in Table 1.

Table 1: Presentation of Study Treatments in TFLs

Study Treatment	Order in TFLs
Placebo SC	1
250 mg lebrikizumab SC	2
500 mg lebrikizumab SC	3

Abbreviations: SC = subcutaneous

All TFLs will be based on actual treatments.

7. DEFINITIONS OF POPULATIONS

Any protocol deviations will be considered prior to database lock for their importance and taken into consideration when assigning participants to populations.

7.1. Enrolled Population

The “Enrolled” population will consist of all participants assigned to study intervention, regardless of whether they take any doses, or whether they took the correct treatment. Participants will be analyzed according to the treatment group to which they were assigned.

7.2. Safety Population

The “Safety” population will consist of all enrolled participants randomly assigned to study intervention and who received a dose of study treatment (lebrikizumab or placebo). Participants will be analyzed according to the intervention they actually received.

7.3. Pharmacokinetic Population

The “Pharmacokinetic” population will consist of all enrolled participants who received a full dose of lebrikizumab and have evaluable PK data. Participants will be analyzed according to the intervention they actually received.

8. STATISTICAL METHODOLOGY

8.1. General

Listings will be provided for all data captured in the database. Listings will include all participants assigned to the Enrolled population and include data up to the point of study completion or discontinuation. Participants are generally considered to have completed the study if they complete the scheduled follow-up visit (rather than early discontinuation visit). Any participant who discontinues the study will be identified accordingly in the listings. Summaries will include the participants assigned to the relevant population based on data type.

Data analysis will be performed using CCI .

ADaM datasets will be prepared using CCI .

Where reference is made to 'valid' data, this refers to non-missing data which meet the predetermined criteria (eg, are not flagged for exclusion).

Where reference is made to 'all calculations', this includes, but is not limited to, summary statistics, baseline derivation, and changes from baseline.

All figures will be produced on linear-linear or discrete-linear scales, as applicable, unless specifically stated otherwise.

8.1.1. Calculation of the Summary Statistics

For continuous data the following rules will be applied:

- Missing values will not be imputed, unless specifically stated otherwise.
- Unrounded data will be used in the calculation of summary statistics.
- If the number of participants with valid observations (n) <3, summary statistics will not be calculated, with the exception of n, minimum, and maximum.
- In general, as early discontinuation data are not associated with any scheduled time point, they will be excluded from all calculations of summary statistics. Exceptions may be made where justified.

For categorical data the following rules will be applied:

- For ordered categorical data (eg, AE severity), all categories between the possible minimum and maximum categories will be included, even if n = 0 for a given category.
- For non-ordered categorical data (eg, race), only those categories for which there is at least 1 participant represented will be included; unless specifically stated otherwise.
- Missing values will not be imputed, unless specifically stated otherwise. A 'missing' category will be included for any parameter for which information is missing. This will ensure that the population size totals are consistent across different parameters.

8.1.2. Unscheduled Readings

Any value recorded in addition to the original value will be defined as an unscheduled value. As unscheduled values are not associated with any scheduled time point, they will be excluded from all calculations.

8.1.3. Definitions of Baseline and Change from Baseline

The baseline will be defined as the last scheduled value recorded prior to dosing. If the date/time of the value is incomplete or missing, it will be excluded from the baseline calculation, unless the incomplete date/time indicates the value was recorded prior to dosing.

Individual changes from baseline will be calculated by subtracting the individual participant's baseline value from the value at the postdose time point.

The summary statistics for change from baseline will be derived from individual participant' values (eg, mean change from baseline will be the mean of the individual changes from baseline for all participants, rather than difference between the mean value at the postdose time point and mean value at baseline).

See Section 8.1.2 for more detail on handling unscheduled readings in the calculations.

8.2. Participant Disposition and Population Assignment

Participant disposition and population assignment will be listed.

A summary table by treatment will be provided, based on the safety population.

8.3. Screening Demographics and Baseline Characteristics

The screening demographics and baseline characteristics including age, sex, race, ethnicity, height, body weight, and body mass index will be listed.

A summary table by treatment will be provided, based on the safety population.

8.4. Prior and Concomitant Medication

Prior medication will be defined as medication that ends prior to dosing. Concomitant medication will be defined as medication that starts during or after dosing or starts but does not end prior to dosing.

Prior and concomitant medications will be coded using the WHO Drug Dictionary (version number is documented in the DMP). Prior and concomitant medications will be listed.

8.5. Pharmacokinetic Assessments

8.5.1. Pharmacokinetic Analysis

Noncompartmental methods applied with CCI to the serum concentrations of lebrikizumab will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-t_{last})	ng.h/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-∞)	ng.h/mL	area under the concentration versus time curve from time zero to infinity
%AUC(t_{last}-∞)	%	percentage of AUC that is due to extrapolation from the last measurable concentration to infinity
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
$t_{1/2}$	h	half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
CL/F	L/h	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 CSR.

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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. 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 3 consecutive serum concentrations above the LLOQ, with at least 1 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 footnotes of the listing.
- $t_{½}$ will be calculated, when appropriate, based on the apparent terminal log-linear portion of the concentration-time curve. The start of the terminal elimination phase for each participant will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in serum concentrations. $t_{½}$ 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 footnotes of the listing.
- A uniform weighting scheme will be used in the regression analysis of the terminal log-linear portion of the concentration-time curve.
- The parameters based on predicted 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 limit of quantification (BLQ). Serum concentrations reported as BLQ 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 BLQ concentration occurs before the first quantifiable concentration.

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

- Also, where 2 or more consecutive concentrations are BLQ 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 mean 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 two-thirds 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 two-thirds 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 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.

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 PK profiles during multiple dosing, the concentration of the pre-dose sample exceeds all measured concentrations for that individual in the subsequent post-dose samples.
- For 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 there are fewer than 6 data points, 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 there are 6 or more data points, 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 there are still 6 or more data points following the exclusion, then repeat Step 2 above. This evaluation may be repeated as many times as necessary, excluding only 1 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.

8.5.2. Presentation of Pharmacokinetic Data

All PK parameters will be listed.

Arithmetic mean (+ SD) figures, overlaying individual figures, and individual figures by treatment and time postdose will be provided for serum PK concentrations. All figures will be produced on both linear-linear and linear-logarithmic scales. If required, this figure will be repeated using a subset of timepoints, which will be produced on the linear-linear scale only. The +SD bars will only be displayed on the linear-linear scale.

Summary tables by treatment will be provided for all PK parameters.

Exploratory graphical analyses relating lebrikizumab serum exposure and immunogenicity may be conducted.

8.5.3. Pharmacokinetic Statistical Methodology

No inferential statistical analyses are planned.

8.6. Safety and Tolerability Assessments

8.6.1. Adverse Events

All AEs will be coded using MedDRA (version number is documented in the DMP).

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 TEAE will be defined as an AE that starts during or after dosing, or starts prior to dosing and increases in severity after dosing.

A treatment-related TEAE will be defined as a TEAE that is related to the study treatment, as determined by the investigator.

All AEs will be listed. In addition to the data recorded in the database, the listings will include derived onset time and duration. Onset time will be calculated from the time of dosing for TEAEs only.

The frequency of participants with TEAEs and the number of TEAEs will be summarized for the following categories:

- TEAEs (overall, serious, leading to discontinuation, and leading to death) by treatment
- TEAEs by severity and treatment
- Treatment-related TEAEs (overall, serious, leading to discontinuation, and leading to death) by treatment
- Treatment-related TEAEs by severity and treatment

The frequency of participants will be summarized separately for TEAEs and treatment-related TEAEs by the following:

- System organ class, preferred term, and treatment
- Preferred term and treatment

AEs of special interest will be listed separately and are the following for this study:

- conjunctivitis
- keratitis
- ISRs, and
- hypersensitivity reactions.

Conjunctivitis

Conjunctivitis events are AESI and will be identified using Customized MedDRA Query (CMQ) PTs (Table 1) nested within the following categories: Conjunctivitis and Keratitis.

The number and percentage of participants with at least 1 TEAE of conjunctivitis or keratitis will be summarized by treatment using MedDRA PT nested within categories (conjunctivitis and keratitis).

Table 2 - Search Criteria for Conjunctivitis and Keratitis

Conjunctivitis	Search Criteria Based on Selected PTs		
Narrow Conjunctivitis CMQ	Conjunctivitis	Conjunctivitis bacterial	Conjunctivitis viral
	Conjunctivitis allergic	Atopic keratoconjunctivitis	

Keratitis	
High Level Term	Corneal infections, oedemas and inflammations
Preferred Term	Keratitis
	Atopic keratoconjunctivitis
	Allergic keratitis
	Ulcerative keratitis
	Vernal keratoconjunctivitis

Injection-site Reactions

For ISRs, events will be mapped to the MedDRA HLT of injection-site reactions, excluding PTs related to joint (the excluded PTs were determined by the most current MedDRA version):

- Injection site joint discomfort
- Injection site joint effusion
- Injection site joint erythema
- Injection site joint infection
- Injection site joint inflammation
- Injection site joint movement impairment
- Injection site joint pain
- Injection site joint swelling
- Injection site joint warmth

Hypersensitivity Reactions

The current standard MedDRA SMQs, published by MSSO, will be used to search for ISR events. The TEAEs are characterized as follows:

- Anaphylactic reaction SMQ (20000021; narrow, algorithm per SMQ guide, and broad)
- Hypersensitivity SMQ (20000214; narrow and broad), and
- Angioedema SMQ (20000024; narrow and broad).

Additional information on the AESIs described above may be found in the compound-level safety standards documentation.

For the AE data the following rules will apply:

- For the derivation of treatment-emergent status (applicable to all AEs): If the start date/time of an AE is incomplete or missing, an AE will be assumed to be a TEAE, unless the incomplete start date/time or the end date/time indicates an AE started before dosing.

- For the derivation of treatment-related status (applicable to TEAEs only): If the study treatment relationship for a TEAE is missing, a TEAE will be assumed to be a treatment-related TEAE.

- For the derivation of onset time (applicable to TEAEs only): If the start date/time of a TEAE is missing, onset time will not be calculated. If the start date/time of a TEAE is incomplete, where possible, the minimum possible onset time will be calculated and presented in '≥DD:HH:MM' format (eg, if the date/time of dosing is 01MAY2019/08:00 and recorded start date/time of a TEAE is 03MAY2019, then the minimum possible onset time will be calculated by assuming a TEAE started at the first hour and minute of 03MAY2019 [03MAY2019/00:00], thus will be presented as onset time ≥01:16:00 in the listing). If the start date of a TEAE is the same as the date of dosing but the start time of a TEAE is missing, an onset time will be presented as '≥00:00:01'. Any clock changes will be accounted for in the derivation.

- For the derivation of duration (applicable to all AEs): If the end date/time of an AE is missing, duration will not be calculated. If the start or end date/time of an AE is incomplete, where possible, the maximum possible duration will be calculated and presented in '≤DD:HH:MM' format (eg, if the start of an AE date/time is 01MAY2019/08:00 and its recorded end date/time is 03MAY2019, then the maximum possible duration will be calculated by assuming an AE ended at the last hour and minute of 03MAY2019 [03MAY2019/23:59], thus will be presented as duration ≤02:15:59 in the listing). Any clock changes will be accounted for in the derivation.

- For the calculation of TEAE summary statistics: If the severity of a TEAE is missing, that TEAE will be counted under the 'missing' category.

- For the calculation of TEAE summary statistics: Where changes in severity are recorded in the eCRF, each separate severity of the AE will be reported in the listings, only the most severe will be used in the summary tables.

8.6.2. Clinical Laboratory Parameters

All clinical laboratory parameters, and their changes from baseline, will be listed, as applicable; any value outside the clinical reference range will be flagged. Separate listings

will be provided for any parameter for which there is any individual participant value outside the respective clinical reference range.

Summary tables by treatment and time point will be provided for clinical chemistry and hematology parameters, and their changes from baseline.

Values recorded as <x, ≤x, >x, or ≥x will be displayed in the listings as recorded. For the calculation of summary statistics, <x and ≤x values will be set to 0.5 × x, whereas >x and ≥x values will be set to 1.1 × x.

8.6.3. Vital Signs Parameters

All vital signs parameters, and their changes from baseline, will be listed.

Summary tables by treatment and time point will be provided for all vital signs parameters, and their changes from baseline. Figures of mean vital signs and mean changes from baseline will be presented over time by treatment.

8.6.4. 12-lead Electrocardiogram Parameters

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.

8.6.5. Injection-Site Reactions and Visual Analog Scale Pain Scores

ISR data (erythema, induration, categorical pain, pruritus, and edema) will be listed and, if there are sufficient data, summarized by treatment in frequency tables.

In addition, if injection-site pain is reported, the intensity of pain will be quantified using the 100-mm validated pain VAS. All data will be listed.

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).

8.6.6. Injection-Site Reactions

ISR data (erythema, induration, categorical pain, pruritus, and edema) will be listed and, if there are sufficient data, summarized by treatment in frequency tables.

8.6.7. Hepatic Monitoring

If a participant experiences elevated 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.

8.6.8. 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.

8.6.9. Immunogenicity Assessments

Immunogenicity data will be listed and frequency tables will be presented if analyzed. The frequency and percentage of participants with pre-existing ADA and with TE ADA will be presented. TE ADA are those that are boosted or induced by exposure to study drug, with a 4-fold increase in titer compared to baseline if ADA were detected at baseline or a titer 2-fold greater than or equal to the minimum required dilution of 1:10 (i.e. ≥1:20) if no ADA were detected at baseline. The distribution of maximum titers will also be tabulated in TE ADA positive participants by treatment.

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

8.6.10. Other Assessments

All other safety and tolerability assessments not detailed in the above sections will be listed only.

9. INTERIM ANALYSES

No interim analyses are planned for this study.

10. SIGNIFICANT CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSES

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

11. REFERENCES

1. ICH. ICH Harmonised Tripartite Guideline: Structure and content of clinical study reports (E3). 30 November 1995.

2. ICH. ICH Harmonised Tripartite Guideline: General considerations for clinical trials (E8). 17 July 1997.

3. ICH. ICH Harmonised Tripartite Guideline: Statistical principles for clinical trials (E9). 5 February 1998.

12. APPENDICES

Appendix 1: Document History

Status and Version	Date of Change	Summary/Reason for Changes
Final Version 1.0	NA	NA; the first version.

NA = not applicable

Signature Page for VV-CLIN-147161 v1.0

Approval	PPD 21-Mar-2024 18:01:16 GMT+0000

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