Statistical Analysis Plan I5Q-MC-CGAY

A Randomized, Placebo-Controlled, Single-Dose Study to Assess the Pharmacokinetics, Safety, and Tolerability of Galcanezumab in Healthy Chinese Subjects

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STATISTICAL ANALYSIS PLAN

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2. ABBREVIATIONS

Abbreviations pertain to the Statistical Analysis Plan (SAP) only (not the tables, figures and listings [TFLs]).

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(t_{last}-∞)	Percentage of AUC(0-∞) extrapolated
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
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
CRF	Case Report Form
CSR	Clinical Study Report
CRU	Clinical Research Unit
CV	Coefficient of variation
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
ICH	International Council on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic
PK	Pharmacokinetic
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
TFLs	Tables, Figures, and Listings
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis

t_{max}	Time of maximum observed drug concentration
V_z/F	Apparent volume of distribution during the terminal phase after extra-vascular adminstration
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final draft created in May 2018). The final draft SAP, used for submission, was created on 14th May 2018.

This SAP describes the planned analysis of the safety, tolerability and pharmacokinetic (PK) 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 analyses of PK and safety/tolerability data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement between Eli Lilly and Company and Covance Early Clinical (EC) Biometrics. 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 signed off prior to first subject administration 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 between Eli Lilly and Company and Covance EC Biometrics 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 Council 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

- To investigate the PK of galcanezumab following a single subcutaneous (SC) administration of galcanezumab to healthy Chinese subjects.

4.2 Secondary Objective

- To investigate the safety and tolerability of a single SC administration of galcanezumab to healthy Chinese subjects.

4.3 Exploratory Objective

- To evaluate galcanezumab with respect to immunogenicity in healthy Chinese subjects.

5. STUDY DESIGN

This is a Phase 1, single-center, randomized, subject- and investigator-blind, placebo-controlled, parallel-group, single-dose study in healthy Chinese subjects. Subjects will be assigned to 1 of 2 cohorts and randomized to receive galcanezumab or placebo (4:1 ratio), as described in Section 7.2 of the protocol. Subjects will receive the following treatments:

- Cohort A: a single dose of 120 mg galcanezumab or placebo
- Cohort B: a single dose of 240 mg galcanezumab or placebo

Dosing of cohorts may be conducted in parallel or sequentially at the discretion of the Investigator.

Subjects will be admitted to the clinical research unit (CRU) on Day -1 and will be discharged after all assessments have been completed on Day 3. A single SC dose of galcanezumab or placebo will be administered according to randomization on the morning of Day 1. Subjects will return for outpatient visits for up to 5 months after dosing for safety, tolerability, immunogenicity, and PK assessments.

Safety and tolerability will be assessed throughout the study by means of vital sign measurements, clinical laboratory tests, electrocardiogram (ECG), physical examinations and adverse event (AE) recording.

6. TREATMENTS

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

Study Treatment Name	**Treatment order in TFL**
Placebo	1
120 mg galcanezumab	2
240 mg galcanezumab	3

7. SAMPLE SIZE JUSTIFICATION

Approximately 30 subjects may be enrolled in this study to adjust for any discontinuations and try to ensure that approximately 20 subjects complete the study (10 per cohort; 8 galcanezumab and 2 placebo). The sample size is customary for Phase 1 studies evaluating safety and PK, and is not powered on the basis of statistical hypothesis testing. Subjects who receive treatment may not be replaced.

8. DEFINITION OF ANALYSIS POPULATIONS

Safety analyses will be conducted for all enrolled subjects, whether or not they completed all protocol requirements.

Pharmacokinetic and immunogenicity analyses will be conducted on the full analysis set. This set includes all data from all randomized subjects receiving at least 1 dose of the investigational product according to the treatment the subjects actually received.

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 collected and added to the database. 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 number of subjects (N); for log-normal data (e.g. the PK parameters: area under the concentration versus time curve [AUC] and maximum observed drug concentration [C_{max}]) the geometric mean and geometric percent coefficient of variation (CV%) will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all 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. For vital signs and immunogenicity, baseline is defined as Day 1 predose.

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, tobacco/nicotine habits, body weight, height and body mass index will be summarized and listed.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Parameter Estimation

Pharmacokinetic parameters for galcanezumab will be calculated using noncompartmental methods in the validated software program, Phoenix WinNonlin (Certara, Version 6.4 or later).

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

Parameter	Units	Definition
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
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
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 (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

The software and version used for the final analysis will be specified in the clinical study report. Any exceptions or special handling of data will be clearly documented within the final study report.

Pharmacokinetic analysis will, where possible, be conducted using actual PK sampling postdose times recorded in the raw data. If actual times are missing, nominal times may be used with sponsor approval.

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 PK 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 serum concentrations above the lower limit of quantification (LLOQ), 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. If AUC(0-∞) cannot be determined for all subjects an alternative AUC measure, such as AUC to a fixed time point, may be used in the assessment exposure between dose groups.

- 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 $t_{1/2}$ 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 the last predicted 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 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.

Data between Individual Profiles

1. If n<6, then the dataset is too small to conduct a reliable range test. Data will be analyzed with and without the atypical value, and both sets of results will be reported.

2. If n≥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

The PK parameter estimates for galcanezumab will be listed and summarized using appropriate descriptive statistics and figures. In addition, summary and individual figures of serum concentrations of galcanezumab will be produced.

9.4 Safety and Tolerability Assessments

9.4.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), 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 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. Treatment-emergent AEs will be summarized by treatment, 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 treatment-emergent AEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 (or later) 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. Any serious AEs will be tabulated.

9.4.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version September 2017). Concomitant medication will be listed.

9.4.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by parameter and treatment, and listed. Urinalysis data will be listed. Additionally clinical chemistry, hematology and urinalysis data outside the reference ranges will be listed.

Values for any clinical chemistry, hematology and urinalysis values outside the reference ranges will be flagged on the individual subject data listings.

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. Figures of mean vital signs and mean changes from baseline profiles by treatment will be presented by treatment.

Furthermore, values for individual subjects will be listed.

9.4.5 Electrocardiogram (ECG)

If available, the ECG data will be listed for individual subjects.

9.4.6 Injection Site Assessments

As applicable, details regarding Injection Site Reactions (ISR) will be summarized by treatment, in frequency tables, and listed for individual subjects.

9.4.7 Immunogenicity

The frequency and percentage of subjects with pre-existing anti-drug antibodies (ADA) and with treatment-emergent ADA to galcanezumab will be summarized and listed for individual subjects. Treatment-emergent ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA). For the treatment-emergent ADA+ patients the distribution of maximum titers will be described. The frequency of neutralizing antibodies will also be tabulated in treatment-emergent ADA+ patients.

The relationship of ADA to PK parameters and safety endpoints may be assessed.

9.4.8 Other assessments

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

9.4.9 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

No interim statistical analyses are planned.

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.

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 subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the centre of the table, such as, “No serious adverse events occurred for this study.”

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