Statistical Analysis Plan: I5Q-MC-CGAQ

Study Title: Pharmacokinetics and Pharmacodynamics of LY2951742 (galcanezumab) in Healthy Subjects Following Subcutaneous Administration of LY2951742 (galcanezumab) Solution in a Prefilled Syring or and Autoinjector

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STATISTICAL ANALYSIS PLAN

Pharmacokinetics and Pharmacodynamics of LY2951742 (galcanezumab) in Healthy Subjects Following Subcutaneous Administration of LY2951742 (galcanezumab) Solution in a Prefilled Syringe or an Autoinjector

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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
AI	autoinjector
ANOVA	analysis of variance
AUC	area under the concentration versus time curve
AUC(0-∞)	area under the concentration versus time curve from zero to infinity
%AUC(t_{last}-∞)	percent 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 quantifiable limit
C_{max}	maximum observed concentration
CI	confidence interval
CGRP	calcitonin gene-related peptide
CL/F	apparent total body clearance of drug calculated after extra-vascular administration
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
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic
PFS	prefilled syringe
PK	pharmacokinetic
SAP	Statistical Analysis Plan
SC	subcutaneous

SD	standard deviation
TFLs	Tables, Figures, and Listings
$t_{1/2}$	half-life
t_{max}	time of maximum observed concentration
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 31 May 2016).

This SAP describes the planned analysis of the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) 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 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 determine the relative bioavailability of 240 mg LY2951742 after subcutaneous (SC) administration of LY2951742 solution as a manual prefilled syringe (PFS) (reference) or autoinjector (AI) (test).

4.2 Secondary Objectives

- To assess plasma calcitonin gene-related peptide (CGRP) concentrations after SC administration of 240 mg LY2951742 solution as a PFS or AI.

- To assess the safety and tolerability of LY2951742 in healthy subjects after SC administration of 240 mg LY2951742 solution as a manual PFS or AI.

5. STUDY DESIGN

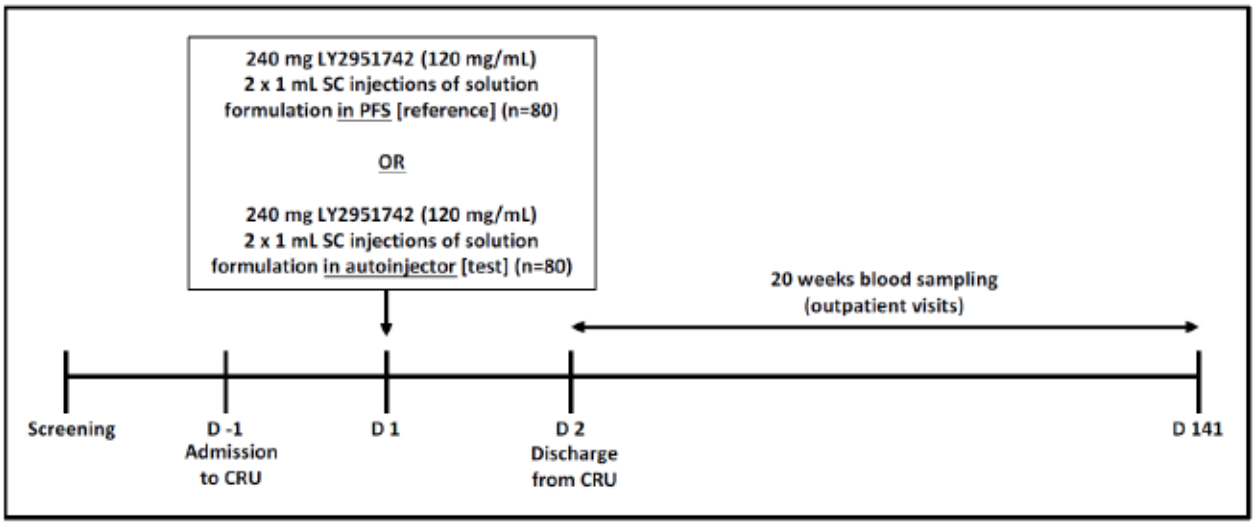
This will be a Phase 1, multi-center, open-label, 2-arm (PFS, AI), randomized, parallel group study where a single dose of 240 mg LY2951742 will be administered to healthy subjects.

Screening will occur up to 45 days prior to dosing with LY2951742.

Subjects will be admitted to the clinical research unit (CRU) on Day -1. Subjects will be randomized in a 1:1 ratio to 240 mg LY2951742 as a PFS (reference) or 240 mg LY2951742 as an AI (test). All doses will be administered in the morning of Day 1 as two 1-mL subcutaneous injections of 120 mg/mL solution of LY2951742. Subjects will be stratified to receive injections in the upper arm, abdomen, or thigh in each arm of the study, with similar numbers of subjects for each site of injection.

Subjects will remain resident at the CRU until the proce dures scheduled at 24 hours postdose have been completed on Day 2, or longer at the discretion of the investigator. All subsequent procedures will be performed on an outpatient basis over a period of approximately 20 weeks (5 half-lives of LY2951742) after study drug administration, including an end-of-study visit (Day 141).

Figure 1.



Abbreviations: CRU = clinical research unit; D = day; PFS = prefilled syringe; SC = subcutaneous

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
240 mg LY2951742 PFS	1
240 mg LY2951742 autoinjector	2

Abbreviations: PFS = prefilled syringe

7. SAMPLE SIZE JUSTIFICATION

Up to 160 subjects will be enrolled (80 in each arm). The number of subjects was determined on the basis of Study I5Q-MC-CGAO Part B interim data, a Phase 1 single-dose study evaluating 300 mg LY2951742 solution administered as a PFS. The percent coefficient of variation for LY2951742 maximum observed drug concentration (C_{max}) and area under the concentration versus time curve from zero to infinity ($AUC_{0-\infty}$) was approximately 35%. One-hundred sixty (160) subjects (80 per arm) will provide approximately 90% power to demonstrate that the 90% confidence interval (CI) of the ratio of geometric means between test and reference devices for the PK parameter falls within 0.8 to 1.25, assuming the true ratio is 0.95 and 12.5% of subjects will not contribute to the endpoint. Randomized and dosed subjects with insufficient collection of PK samples may be replaced at the discretion of the sponsor.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all subjects who received at least 1 dose of study drug, whether or not they completed all protocol requirements.

The "Pharmacokinetic" population will consist of all subjects who are compliant with dosing and have evaluable PK data.

The "Pharmacodynamic" population will consist of all subjects who are compliant with dosing and have evaluable PD 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: area under the concentration versus time curve [AUC] and C_{max}) the geometric mean and geometric 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.

Data analysis will be performed using SAS® Version 9.3 or greater.

9.2 Demographics and Subject Disposition

Subject disposition will be listed. The demographic variables age, sex, race, ethnicity, site ID, body weight, height, body mass index and smoking status will be summarized and listed. All other demographic variables will be listed.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

Noncompartmental methods applied with a validated software program Phoenix WinNonlin (Pharsight Corporation, Version 6.4 or higher) to the serum concentrations of galcanezumab will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-∞)	day × micrograms/mL	area under the concentration versus time curve of galcanezumab from zero to infinity
%AUC(t_{last}-∞)	Percent, %	Percent of AUC(0-∞) extrapolated of galcanezumab
AUC(0-t_{last})	day × micrograms/mL	area under the concentration versus time curve of galcanezumab from time zero to time t, where t is the last time point with a measurable concentration
C_{max}	micrograms/mL	maximum observed concentration of galcanezumab
t_{max}	day	time of maximum observed concentration of galcanezumab
$t_{1/2}$	day	half-life of galcanezumab
CL/F	L/h	apparent total body clearance of galcanezumab drug calculated after extra-vascular administration
V_z/F	L	apparent volume of distribution of galcanezumab during the terminal phase after extra-vascular administration

The PK parameters of galcanezumab will be listed for individual subjects, and summary statistics will be computed by treatment (PFS, AI) and injection site location (arm, abdomen, thigh, buttocks). 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 study report.

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.

9.3.1.1 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 three consecutive serum/plasma 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.

- Half-life ($t_{½}$) 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 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/plasma 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 <u>observed</u> C_{last} will be reported.

9.3.1.2 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/plasma 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.

9.3.1.3 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.

9.3.1.4 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 ± 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.

9.3.1.5 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 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 $n\geq6$, then an objective outlier test will be used to compare the atypical value to other values included in that calculation:
    a. Transform all values in the calculation to the logarithmic domain.
    b. Find the most extreme value from the arithmetic mean of the log transformed values and exclude that value from the dataset.
    c. Calculate the lower and upper bounds of the range defined by the arithmetic mean ±3*SD of the remaining log-transformed values.
    d. If the extreme value is within the range of arithmetic mean ±3*SD, then it is not an outlier and will be retained in the dataset.
    e. If the extreme value is outside the range of arithmetic mean ±3*SD, then it is an outlier and will be excluded from analysis.

If the remaining dataset contains another atypical datum suspected to be an outlier and $n \geq 6$ following the exclusion, then repeat step 2 above. This evaluation may be repeated as many times as necessary, excluding only one suspected outlier in each iteration, until all data remaining in the dataset fall within the range of arithmetic me an ±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 galcanezumab AUC(0-∞), AUC(0-t_{last}), and C_{max} will be log transformed and analyzed using an analysis of variance (ANOVA) model. The model will include fixed effects for injection device (PFS [reference] or AI [test]), investigative site, and injection site. The least squares means for the PFS and AI and the 90% CI for the difference in means will be estimated from the ANOVA model and back transformed from the log scale to provide estimates of the geometric means and 90% CIs for the ratio of the geometric means.

Example SAS code:

```
proc mixed data=pk;
    class device invsite injsite;
    model log_pk = device invsite injsite / cl residual;
    lsmeans device / alpha=0.1 cl pdiff;
    ods output lsmeans=lsmeans;
    ods output diffs=diffs;
run;
```

The t_{max} of galcanezumab between the PFS (reference) and AI (test) will be analyzed using a Wilcoxon rank-sum test. An estimate of the median difference and 90% CI will be calculated. Insert stats methodology here.

9.4 Pharmacodynamic Assessment

9.4.1 Pharmacodynamic Analysis

Noncompartmental methods applied with a validated software program Phoenix WinNonlin (Pharsight Corporation, Version 6.4 or higher) to the plasma concentrations of CGRP and will be used to determine the following PD parameters, when possible:

Parameter	Units	Definition
AUC(0-t_{last}), CGRP	day×ng/mL	area under the concentration versus time curve of CGRP from time zero to time t, where t is the last time point with a measurable concentration
$C_{max, CGRP}$	ng/mL	maximum observed concentration of CGRP
$t_{max, CGRP}$	day	time of maximum observed concentration of CGRP

The same general rules outlined in section 9.3.1.1 will be used for derivation of the PD parameters, where appropriate. The PD parameters will be listed for individual subjects, and summary statistics will be computed by treatment (PFS, AI) and injection site location (arm, abdomen, thigh, buttocks).

9.4.2 Pharmacodynamic Statistical Methodology

Log-transformed CGRP C_{max} and AUC(0-t_{last}) estimates will be evaluated by an ANOVA with fixed effects for injection device (PFS [reference] or AI [test]), investigative site, and injection site. The least squares means for PFS and AI and the 90% CI for the difference in means will be estimated from the ANOVA model and back transformed from the log scale to provide estimates of the geometric means and 90% CIs for the ratio of the geometric means. Similar SAS code to that for the PK analysis will be used.

The CGRP t_{max} between injection devices (PFS [reference] or AI [test]) will be analyzed using a Wilcoxon rank-sum test. An estimate of the median difference and 90% CI will be calculated.

9.5 Safety and Tolerability Assessments

9.5.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the adverse event (AE) will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as 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 19.1 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. Any serious AEs will be tabulated.

9.5.2 Injection Site Reactions

The number and percentage of subjects experiencing any ISR after dosing will be summarized. Furthermore, the number and percentage of subjects will be presented for each grade category for erythema, induration, pain, and pruritus. A table with number and percentage of subjects by maximum grade will also be presented. Moreover, descriptive statistics will be presented for parameters like erythema, induration etc. as these will also be recorded as the actual maximum linear diameter (to the nearest millimeter) as a continuous variable. These data will also be listed.

9.5.3 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version September 2015). Concomitant medication will be listed.

9.5.4 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.

9.5.5 Immunogenicity

Immunogenicity data will be listed and frequency tables will be presented.

9.5.6 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 will be presented by treatment. Furthermore, values for individual subjects will be listed.

9.5.7 Electrocardiogram (ECG)

ECGs will be performed for safety monitoring purposes only and will not be presented.

9.5.8 Other assessments

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

9.5.9 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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