Statistical Analysis Plan (v1.0): J4N-MC-YFAA

A Phase 1, Multicenter, Randomized, Placebo-Controlled, Double-Blind Trial of LY3885125 to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of a Single Ascending Dose in Participants With Dyslipidemia and Repeat-Doses in Participants With NAFLD.

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Statistical Analysis Plan

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SAP Author: PPD , MSc

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Not applicable.

SAP Amendments before database lock

Version	Issue Date	Section	Revision / Addition	Rationale
1.0	17-APR-2025	NA	Original document.	

REVIEW / APPROVAL SIGNATURES

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ApoB	apolipoprotein B
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
AUC	area under the concentration-time curve
CK-18	cytokeratin-18
Cmax	maximum observed concentration
CS	clinically significant
CSR	Clinical Study Report
DEC	Dose Escalation Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
ELF	enhanced liver fibrosis
FIB4	fibrosis-4
GGT	gamma-glutamyl transferase
HDL-C	high-density lipoprotein cholesterol
ISR	injection site reaction
LDL-C	low-density lipoprotein cholesterol
CCI	[redacted]
MedDRA	Medical Dictionary of Regulated Activities
CCI	[redacted]
MRI-PDFF	magnetic resonance imaging proton density fat fraction
NAFLD	non-alcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NCS	not clinically significant
CCI	[redacted]

Abbreviation	Definition
PCSK9	proprotein convertase substilisin/kexin type 9
PD	pharmacodynamics
PK	pharmacokinetics
CCI	[redacted]
PT	preferred term
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SE	standard error
SOC	system organ class
SRC	Safety Review Committee
TEAE	treatment-emergent adverse event
TFL	table, figure, listing
TG	triglyceride
Tmax	time of Cmax
VLDL-C	very low-density lipoprotein cholesterol

1 INTRODUCTION

This document details the planned statistical analyses for Eli Lilly and Company, protocol "J4N-MC-YFAA" study titled "A Phase 1, Multicenter, Randomized, Placebo-Controlled, Double-Blind Trial of LY3885125 to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of a Single-Ascending Dose in Participants with Dyslipidemia and Repeat-Doses in Participants with NAFLD".

The proposed analyses are based on the contents of the amended version of the protocol (dated 21-SEP-2023).

This study was planned as a Phase 1, multicenter, randomized, placebo-controlled, double-blind, 2-part study in participants with dyslipidemia, and participants with non-alcoholic fatty liver disease (NAFLD) and elevated alanine aminotransferase (ALT).

- **Part A (Cohorts 1 to 6):** placebo-controlled, Investigator- and participant-blind, single subcutaneous (SC) dose of LY3885125 in participants with dyslipidemia:
  - To evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of a single ascending dose (SAD) of LY3885125 in up to 5 cohorts (Cohorts 1 to 5).
  - Cohort 6 is optional and may consist of participants with dyslipidemia on a stable moderate or high intensity dose of statin; the decision to proceed with this cohort will be based on review of PK, PD, and safety data from previous cohorts.
  - Data from Part A will inform the Part B dose.
- **Part B:** placebo-controlled, Investigator- and participant-blind, repeat SC doses of LY3885125 in participants with NAFLD and elevated ALT:
  - To evaluate the safety, tolerability, PK, PD, and change of liver fat content from baseline to Weeks CCI by magnetic resonance imaging proton density fat fraction (MRI-PDFF) of a repeated dose of LY3885125 at DaysCCI .
  - The Part B dose will be based on data from Part A and will not exceed what has been studied in Part A. The protocol will be amended prior to initiation of Part B to define the dose and dosing frequency.

The study was to begin with Part A and proceed to Part B following reviews of safety, tolerability, and available PK and PD data. It was determined to discontinue the study after the completion of Cohort 5 in Part A.

Dose escalation decisions were made by the Dose Escalation Committee (DEC). Recommendations to temporarily suspend study drug intervention or terminate the study early were evaluated by a Safety Review Committee (SRC).

The identity of study intervention (LY3885125 or placebo) was blinded to participants, investigators, and site-facing sponsor personnel.

2 STUDY OBJECTIVES AND ENDPOINTS

Part A primary objective: To determine the safety and tolerability of LY3885125 after a single SC dose in participants with dyslipidemia.
Endpoint(s): • Adverse events (AEs). • Serious adverse events (SAEs).
Analysis set: Safety analysis set

Part A secondary objective: To assess the PK and PD of LY3885125 after a single SC dose.
Endpoint(s): • LY3885125 area under the concentration-time curve (AUC), maximum observed concentration (C_{max}), time of C_{max} (T_{max}). • Changes in proprotein convertase substilisin/kexin type 9 (PCSK9) and apolipoprotein B (ApoB) from baseline relative to placebo.
Analysis set: PK analysis set

Part A exploratory objective: To assess the effect of LY3885125 CCI [redacted] and immunogenicity.
Endpoint(s): • Changes in CCI [redacted] from baseline relative to placebo. • Changes in CCI [redacted] from baseline relative to placebo. • Prevalence of standard immunogenicity statuses.
Analysis set: PD analysis set

Part B objectives and endpoints are excluded from this SAP as the study will not proceed to Part B.

3 SAMPLE SIZE

Enrollment for Part A will enable completion of approximately CCI participants in 5 cohorts. Enrollment of CCI participants, randomized 10:9 to LY3885125:placebo, in the optional Cohort 6 was not performed. Likewise, enrolment of approximately CCI participants in a single cohort for Part B was not performed.

4 RANDOMIZATION

Part A consisted of 5 single-dose levels, Cohorts 1 to 5.

Part A Cohort	Number of Participants	Randomization (LY3885125:placebo)
1	[redacted]	6:2
2	[redacted]	6:2
3	[redacted]	9:2
4	[redacted]	9:2
5	[redacted]	9:2

Sentinel dosing was used in Part A to reduce the risk of exposing all participants in a cohort to study intervention and the potential for unexpected AEs occurring simultaneously. Two participants from each SAD cohort were included in the sentinel dosing regimen to allow for one participant treated with study intervention and one participant treated with placebo to be dosed prior to dosing the remaining participants in the cohort.

5 PLANNED ANALYSES

The Statistical Analysis Plan (SAP) and Table, Figure, Listing (TFL) Shells (and any amendments) must be approved prior to Part A database lock. If post database lock, additional statistical analyses or changes to the statistical analysis are required, then those will be documented in a Post Database Lock Statistical Analysis Plan Addendum.

5.1 Analysis Sets

5.1.1 Screened Set

All participants that signed informed consent.

The screened set is used for participant disposition.

5.1.2 Full Analysis Set

All randomized participants.

The full analysis set is used to analyze disposition and baseline characteristics.

5.1.3 Safety Analysis Set

All participants who are exposed to study intervention.

The safety analysis set is used to analyze the endpoints and assessments related to safety.

5.1.4 Pharmacodynamics (PD) Analysis Set

All participants in the safety analysis set who have at least one PD assessment.

The PD analysis set is used to analyze PD endpoints.

5.1.5 Pharmacokinetics (PK) Analysis Set

All participants who have received at least one dose of LY3885125 and have sufficient concentration-time data to estimate PK parameters.

The PK analysis set is used for the PK analyses.

5.1.6 Immunogenicity Analysis Set

All participants who are exposed to study intervention and who had at least one valid (non-missing and interpretable) baseline or post-baseline immunogenicity assessment.

The Immunogenicity analysis set is used for the Immunogenicity analyses.

5.2 Derived Data

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be re-calculated.

5.2.1 Race

Where more than one race category has been selected for a participant, the participant will be reported in the category labelled "Multiple Race" in the summary tables. The listings will reflect the original selected categories.

5.2.2 Baseline

In Part A, baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the participant receives the first dose of study drug.

5.2.3 Early Terminations Assessments

Early termination assessments will be excluded from tabulations and will be listed only.

5.2.4 Duration / Study Day / Time

Study day will be calculated as the number of days from first dose of study drug.

- For events on or after the first dose, then
  - study day = date of event – date of first dose of study drug + 1
- For events before the first dose, then
  - study day = date of event – date of first dose of study drug

5.2.5 Conventions for Missing and Partial Dates

It is not expected that there will be any missing dates for events occurring during study conduct. Historical dates such as dates of medical history or prior medications may be missing or partial. Dates (historical or during study conduct) will only be imputed if a full date is needed for a calculation or to support a definition.

All dates presented in the individual participant listings will be as recorded on the Electronic Case Report Form (eCRF).

5.2.5.1 Missing Adverse Events Dates

In the rare case that an AE start date or time is missing and it is unclear whether the AE is treatment emergent or not then a conservative approach will be taken, and it will be assumed that the AE is treatment emergent and occurred after first dosing. If an adverse event stop date is missing it will be assumed that the AE is ongoing.

5.2.6 Inexact Values

In the case where a variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes.

See section 5.9.2 for methods for handling inexact values specifically for PK concentration data.

5.2.7 Electrocardiogram (ECG) Data

For ECG data recorded on continuous scales, if replicate (i.e., triplicate) values are recorded at a time point, the mean or the replicates rounded to the integer will be used for summarization. For overall interpretation if more than one value is recorded, the most severe (worst case) of the respective readings will be taken.

5.2.8 Unscheduled Visits

Only scheduled post-baseline laboratory and vital signs values will be tabulated unless otherwise stated. Post-baseline repeat / unscheduled assessments will be included in all listings in the relevant appendices to the CSR.

5.2.9 Pharmacokinetic Parameters

5.2.9.1 Plasma PK Parameters

The following PK parameters in plasma will be calculated for LY3885125 for single dose cohorts (Part A):

Parameter	Definition
C_{max}	Maximum observed concentration
T_{max}	Time of the maximum concentration
AUC_{0-24}	Area under the concentration-time curve from time-zero 24 h postdose; calculated using the linear trapezoidal rule
AUC_{last}	Area under the concentration-time curve from time-zero to the time of the last quantifiable concentration; calculated using the linear trapezoidal rule
AUC_{inf}	Area under the concentration-time curve from time-zero extrapolated to infinity; calculated as: $AUC_{inf} = AUC_{last} + C_{last}/\lambda_z$ Note: Additional criteria for reporting AUC_{inf} are summarized below

Parameter	Definition
AUC_{Extrap} (%)	Percentage of AUC_{inf} based on extrapolation; calculated as: $AUC_{Extrap} = 100 \times [1-(AUC_{last}/AUC_{inf})]$
λ_z (Lambda-z, k_{el})	Apparent elimination rate constant; calculated as the slope of the linear regression through the terminal log-linear segment of the concentration-time curve Note: Additional criteria for reporting λ_z are summarized below
$t_{1/2}$	Observed terminal elimination half-life; calculated as: $t_{1/2} = \ln(2)/\lambda_z$
CL/F	Apparent total body clearance after SC administration, calculated as: CL/F = Dose/AUC_{inf}, where F is the bioavailability
V_z/F	Apparent volume of distribution after SC administration, calculated as: $V_z/F = Dose/(AUC_{inf} \times \lambda_z)$, where F is the bioavailability
C_{last}	Last observed quantifiable concentration
T_{last}	Time of the last observed quantifiable concentration

Lambda-z (λ_z) and AUC_{inf} Reporting Criteria

The following criteria will be used to report λ_z:

- At least three quantifiable concentrations will be used in the regression
- C_{max} or data prior to C_{max} will not be included in the regression.
- The adjusted regression coefficient (R^2 adj) should be ≥ 0.80.

If these acceptance criteria are not met, λ_z reported for individual subjects will be retained in PK parameter tables for informational purposes; λ_z will be excluded from summary statistics. Parameters calculated using λ_z ($t_{1/2}$, CL/F, V_z/F) will be reported as ND (not determinable). Lambda-z (λ_z) and descriptive parameters (λ_z time range, Adj R^2, etc.) will be presented in a separate listing.

If lambda-z acceptance criteria are met and AUC_{inf} is estimable, the following criteria are used to report AUC_{inf}:

• The percentage of AUC_{inf} based on extrapolation should be <20.0%.

If the percentage of AUC_{inf} based on extrapolation is 30.0% or greater, AUC_{inf} and AUC_{Extrap} will be retained in a PK parameter table for informational purposes; these parameters will be excluded from summary statistics, subsequent PK calculations (e.g., CL/F and V_z/F), and statistical analysis (e.g., ANOVA).

5.2.9.2 Urine PK Parameters

The following PK parameters in urine will be calculated for LY3885125 after single doses (Part A):

Parameter	Definition
Ae	Amount of drug excreted in urine for each collection interval, calculated as: Ae = concentration x volume
Total Ae	Total amount of drug excreted over the entire 24-hour sampling interval
Fe (%)	Percentage of dose excreted in urine for each collection interval, calculated as: Fe (%) = Ae/Dose x 100
Total Fe (%)	Total percentage of dose excreted in urine over the entire 24-hour sampling interval, calculated as: Total Fe (%) = Total Ae/Dose x 100
CL_r	Renal clearance, calculated as: CL_r = Total Ae/AUC_{0-24}

5.2.10 Classification of ADA

Subjects are classified according to the following table for ADA[1].

ADA category	Criteria
Subjects with baseline immunogenicity data	Subjects with a valid ADA assessment at baseline
Subjects with post-baseline immunogenicity data	Subjects with any valid ADA assessment post-baseline

ADA category	Criteria
Subjects with baseline and post-baseline immunogenicity data	Subjects with both a valid ADA assessment at baseline and any valid ADA assessment post-baseline
Subjects with baseline or post-baseline immunogenicity data	Subjects with any valid ADA assessment at baseline or post-baseline
ADA+ prevalence at baseline	Subjects with a positive ADA assessment at baseline
ADA+ prevalence at post-baseline	Subjects with any positive ADA assessment post-baseline
ADA+ prevalence at both baseline and post-baseline	Subjects with both a positive ADA assessment at baseline and any positive ADA assessment post-baseline
ADA Positive at baseline or post-baseline	Subjects with any positive ADA assessment at baseline or post-baseline
Treatment-Emergent ADA+	Treatment-boosted ADA+; or treatment-induced ADA+
Treatment-boosted ADA+	Subjects who were ADA positive at both baseline and post-baseline, but had an increase in ADA titer from baseline to post-baseline
Treatment-induced ADA+	Subjects who were ADA negative or missing at baseline and became ADA positive post-baseline

ADA prevalence is defined as the proportion of subjects in category “ADA Positive”.

ADA incidence is defined as the proportion of subjects in category “Treatment-Emergent ADA+”.

5.3 Conventions

All data listings, summaries, figures, and statistical analyses will be generated using SAS version 9.4 or higher[2].

Part A summaries will be presented by treatment group. Treatment group labels for Part A TFLs will be displayed as follows, with the addition of “Part A Overall (N=XX)”, when appropriate:

LY3885125 CCI (N=XX)	LY3885125 CCI (N=XX)	LY3885125 CCI (N=XX)	LY3885125 CCI (N=XX)	LY3885125 CCI (N=XX)	Pooled LY3885125 (N=XX)	Pooled Placebo (N=XX)

Part A listings will be sorted in the following order: treatment group, participant, parameter, and visit unless otherwise stated. All data will be listed, participants who were not randomized will be displayed after the randomized treatment groups/ arms.

Continuous variables will be summarized by the number of non-missing observations, mean, median, standard deviation, and minimum and maximum.

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of participants in the column header unless otherwise specified in the footnote. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

Means, medians and percentiles will be displayed to one more decimal place than the data**,** dispersion statistics (e.g., standard deviation) will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data. Percentages will be displayed with one decimal place.

PK data listings, summaries, figures, and statistical analyses will be generated using Phoenix™ WinNonlin® (Version 8.3.4.295 or higher)[3] or SAS (Version 9.4 or higher)[2]. PK concentration data will be summarized by treatment/dose level at each nominal sample time. PK parameter data will be summarized by treatment/dose level.

Plasma PK concentration-time data and PK parameters will be summarized by the number of non-missing observations (n), mean, standard deviation (SD), median, minimum (min), maximum (max), coefficient of variation (CV%), geometric mean (geo. mean), and geometric mean CV%.

Urine PK concentrations, Ae, and Fe% will be summarized by n, mean, SD, median, min, max, and CV% for each collection interval. Urine PK parameters (Total Ae, Total Fe%), CLr) will be summarized by n, mean, SD, median, min, max, CV%, geo. mean, and geo. CV%.

Individual subject plasma PK data (concentration-time data and PK parameters) will be reported to 3 significant figures. For summary statistics, n will be reported as a whole number; mean, standard deviation, median, minimum, maximum, CV%, geometric mean, and geometric mean CV% will be reported to 3 significant figures. For the dose proportionality assessment, slope will be presented to 4 decimal places and associated 90% confidence intervals will be reported to 2 decimal places.

5.4 Participant Disposition

Participant disposition will be summarized as follows:

- The number of participants who failed screening and the reasons for failure will be tabulated, by study part, for all participants.
- The number of participants, who entered the study, were randomized, and who are in each analysis set will be summarized by treatment group and overall for Part A, for the screened set.
- The number of early withdrawals and the reasons for withdrawals will be tabulated by treatment group and overall for Part A, for the full analysis set.

5.5 Protocol Deviations

Major protocol deviations will be summarized by code. A listing of protocol deviations will be provided within Appendix 16.2 of the clinical study report (CSR).

5.6 Baseline Comparability

The comparability of treatment groups with respect to participant demographics and baseline characteristics will be assessed in a descriptive manner. No formal statistical testing will be performed.

Standard continuous or categorical variable summaries will be presented by treatment group for the following variables based on the Safety Analysis Set.

- Demographic data
- Disease history
- Medical history

5.7 Medical History

Separate tabulations of previous and ongoing conditions at screening will be presented by treatment group and overall for the safety analysis set. Conditions will be presented by Medical Dictionary of Regulated Activities (MedDRA) primary system organ class (SOC) and preferred term (PT).

5.8 Prior and Concomitant Medications

Separate tabulations will be produced for prior and concomitant medications presented by treatment group and overall for the Safety Analysis Set. Prior medications are defined as all medications starting and stopping before the date of first dose of study drug. Concomitant medications are defined as medications taken on or after the date of first dose of study drug.

Concomitant medications will be summarized using Anatomic Therapeutic Chemical (ATC) Level 2.

5.9 Pharmacokinetic Analyses

5.9.1 Concentration-Time Data

LY3885125 plasma concentration-time data will be tabulated by nominal time and treatment/dose level for single dose cohorts and by nominal time, study day, and treatment/dose level multiple dose cohorts using descriptive statistics. For presentation of the individual data and summary statistics, concentrations below the limit of quantitation (BLQ) will be set to zero. Nominal and relative time will be presented in hours.

LY3885125 plasma samples will be collected at:

Part A (Single Dose Cohorts):

Day 1: CCI [redacted] hours postdose. Plasma samples may be collected during the monitoring extension at CCI [redacted] hours postdose.

Mean plasma concentration-time data will be presented graphically on linear and semi-logarithmic scales using nominal times. Individual subject concentration-time data will be presented graphically on linear and semi-logarithmic scales using actual times. For individual subject concentration-time data, spaghetti plots (all subjects in one plot per treatment and study day) and all treatments in one plot for each subject will be created. The following concentration-time profiles will be created:

Part A (Single Dose Cohorts):

- Mean concentration-time profile comparing treatments/dose levels
- All subject concentration-time profiles for each treatment/dose level

Urine will be collected and tabulated by collection interval for Part A (single dose cohorts) during the following intervals: CCI [redacted] hours post-dose for each period.

The PK Analysis Set will be used in the tabulation of concentration-time data and in the creation of concentration-time profiles. The Safety Analysis Set will be used for the concentration-time listings.

5.9.2 PK Methodology

Concentration-time data for LY3885125 in plasma and urine will be analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 8.3.4.295 or higher, Certara,

L.P.)[3] in conjunction with Certara Integral™ (Version 24.4.2 or higher, Certara, USA, Inc.)[4]. The PK Analysis Set will be used in the PK analysis.

During the PK analysis, plasma and urine concentrations below the limit of quantification (BLQ) up to the time of the first quantifiable concentration will be treated as zero. Embedded (plasma values between 2 quantifiable concentrations) and terminal plasma BLQ concentrations will be treated as "missing". Calculation of the PK characteristics in plasma will be based on actual elapsed times [h] relative to dosing, urine PK analysis will be based on collection interval.

At least 3 consecutive quantifiable concentrations are required to estimate AUC_{last}. If a PK profile has at least 1 quantifiable concentration, then C_{max}, and T_{max} will be reported; other parameters will be reported as missing (ND).

5.9.3 Statistical Analysis

5.9.3.1 Dose Proportionality

The PK parameters for LY3885125 C_{max}, AUC_{0-24}, AUC_{last}, and AUC_{inf} after single doses (Part A) will be compared across doses to assess dose proportionality (i.e., proportionality of a change in systemic exposure with a change in dose). Statistical analyses will be done using a power model with mixed effects (Smith, 2000)[5] of the following general form:

$$\ln(PK) = \ln(\beta_0) + \beta_1 \cdot \ln(Dose) + \varepsilon,$$

Where

PK is the PK parameter tested (e.g. C_{max} or AUC)

$\ln(\beta_0)$ is the y-intercept,

β_1 is the slope (a value of $\beta_1 \approx 1$ indicates linearity), and

ε is an error term

The estimate of slope, β_1 will be reported along with the corresponding 2-sided 90% CIs. If the 90% CI of β_1 includes 1 and the estimate of β_1 is relatively close to 1, PK data may appear to be dose proportional. Dose proportionality plots will be created as well.

5.10 Pharmacodynamic Analyses

5.10.1 PCSK9 and Apo Panel

Descriptive statistics of the observed values and change from baseline (continuous data) will be presented by treatment group and visit for PCSK9 and ApoB.

CCI [redacted]

[redacted]

5.11 Safety Analyses

The safety analyses will be presented by the treatment received for the safety analysis set.

5.11.1 Adverse Events

Treatment emergent adverse events (TEAE) are reported according to protocol as any AE that has an onset on or after the dose of study drug or any pre-existing condition that has worsened on or after the first dose of study drug. The following TEAE flag will be applied to distinguish AEs from TEAEs:

- Any AE that has a start date and time on or after the first dose of study drug

A treatment-related AE is defined as an AE with a causality of "Possibly Related", "Probably Related", or "Related" to LY3885125. If an AE has missing relationship it is assumed to be related to the study drug for analysis purposes.

Maximum severity (Severe) will be assumed for an AE with missing severity.

Events that occur after the last follow-up visit or early termination visit will only be included in any TFLs if they are "Possibly Related", "Probably Related", or "Related" to LY3885125.

The following tables will be presented for AEs incidence and/or number of events will be reported as appropriate, by treatment group and overall:

- Overall summary of TEAEs
- TEAEs by system organ class and preferred term
- Treatment related TEAE by system organ class and preferred term
- Serious TEAE by system organ class and preferred term
- TEAE by system organ class, preferred term and maximum severity
- TEAE by system organ class, preferred term and relationship
- TEAEs leading to early withdrawal by system organ class and preferred term
- Listing of Serious TEAEs (presented in the Table section of the appendices).
- Listing of Deaths (presented in the Table section of the appendices).

Adverse event incidence is counted only once per system organ class and once per preferred term. The number and percent of participants experiencing events are reported. Outputs reported at maximum severity show the highest severity reported by a patient per system organ class and preferred term.

All AEs will be listed.

5.11.2 Injection Site Reactions (ISR)

ISR data will be listed only.

5.11.3 Hypersensitivity Laboratory Measurements

Hypersensitivity labs header data will be listed only. Analysis of the lab results themselves will not be completed as part of this analysis plan and will be outlined in a separate document.

5.11.4 Laboratory Data

Descriptive statistics of the observed values and change from baseline (continuous data) will be presented by treatment group and visit for each hematology, urinalysis and serum chemistry parameter. Each measurement (continuous data) will be classed as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables in relation to the normal range from baseline to each follow-up visit will be presented.

A listing of any abnormal laboratory measurements recorded throughout the study will be presented.

Laboratory data will be presented in SI units.

5.11.5 Vital Signs

Descriptive statistics for observed values and changes from baseline in the following vital signs will be presented by treatment group and visit:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Respiration rate (breath / min)
- Body temperature (degrees Celsius)
- Body weight (kg)

5.11.6 Electrocardiogram Data

Descriptive statistics for observed values and changes from baseline in the following ECG variables will be tabulated at each follow-up:

- Heart rate (bpm)
- PR interval (ms)
- QRS complex (ms)
- QT interval (ms)
- QTc interval (ms)
- QTcF interval (ms) [Fridericia's formula]
- QTcB interval (ms) [Bazett's formula]
- RR interval (ms)

Number and percentage of subjects that meet each of the following categories will be presented:

- Largest postdose assessment of QTcF > 450
- Largest postdose assessment of QTcF > 480
- Largest postdose assessment of QTcF > 500
- Largest QTcF change from baseline > 30
- Largest QTcF change from baseline >60

Shift tables in relation to the overall interpretation (Normal; Abnormal Not Clinically Significant [NCS], and Abnormal Clinically Significant [CS]) from baseline to each follow-up visit will be presented.

The relationship between plasma PK concentrations of LY3885125 and ΔQTcF will be quantified using a linear mixed-effects modelling approach[6]. The model will have ΔQTcF as the dependent variable, plasma PK concentrations of LY3885125 as the explanatory variate (0 for placebo), baseline QTcF as an additional covariate, study treatment (active = 1 or placebo = 0) and time (i.e., post-dose time point: categorical) as fixed effects, and random effects on intercept and slope per participant. In all calculations, concentrations in participants who received placebo will be set to zero. LY3885125 plasma PK concentrations below the quantifiable limit at pre-dose will be set to zero and after dosing will be set to 1/2 the lower limit of quantitation in the concentration-QTc analysis.

An unstructured covariance matrix will be specified for the random effects. If convergence cannot be achieved even after appropriate rescaling of the concentrations, the random effect on the slope and intercept will be dropped, in this order, until convergence is achieved. The degrees of freedom (df) estimates will be determined by the Kenward-Roger method. From the model, the slope (i.e., the regression parameter for the concentration) and the treatment effect-specific intercept (defined as the difference between active and placebo) will be estimated together with the 2-sided 90% CI. The estimates for the time effects will be reported with standard error (SE).

The following SAS codes can be used to conduct the LME model in the example:

```
proc mixed data=PKQTc method=reml;
  class USUBJID AVISTPT;
  model ΔQTcF=PTRTAN CONC1 AVISTPT CBASE / solution cl noint alpha=0.1
        alphap=0.1 covb ddfm=kr;
  random int CONC1 / type=un subject=USUBJID s;
run;
```

Throughout the LME modelling, for any timepoints where triplicate values are collected for QTcF, then the arithmetic average of the triplicates should be analysed.

A scatter plot of QTcF data vs LY3885125 plasma PK concentration will also be presented for all timepoints where an ECG and PK sample were drawn within the same 10 minute window, with unique formatting for each treatment group.

All ECG data, including details of any abnormalities, will be listed.

5.11.7 Physical Examination

Physical examination data will maintained at the SDTM level, but will not be presented in any tables or listings. Details of any consequential findings will be visible in medical history or AE outputs.

5.12 Immunogenicity Analysis

The n count and % for each immunogenicity parameter will be summarized for all subjects in the Immunogenicity Analysis Set by treatment group.

6 INTERIM ANALYSIS

There are no planned interim analyses for this study.

7 DATA SAFETY MONITORING BOARD ANALYSIS

No data safety monitoring board (DSMB) analyses are planned.

8 CHANGES TO PLANNED PROTOCOL ANALYSIS

There are no changes to the planned protocol analysis.

9 REFERENCES

1. Shankar G, The APS Journal, 16(4): 658-673, 2014
2. SAS Institute Inc., Cary, NC, 27513, USA
3. Phoenix™ WinNonlin® (Version 8.3.4.295 or higher, Certara, L.P.)
4. Certara Integral™ (Version 24.4.2 or higher, Certara, USA, Inc.)
5. Smith et. al. (2000) Confidence Interval Criteria for Assessment of Dose Proportionality, Pharmaceutical Research Vol. 17, No. 10, 2000
6. Daoqing Li (2024) Implementation on concentration-QTc modelling, PharmaSUG China 2024 – Paper SA-10047

10 LIST OF TABLES, FIGURES AND LISTINGS

The following table includes details of the tables, figures and listings to be included within each section of the eCTD. The eCTD section is shown in bold. The following validation methods maybe used:

- Independent programming of numbers and manual review of format (IP)
- Independent programming by statistician of numbers and manual review of format (Stat IP)
- Manual review (MR)
- Code review (CR)

Section Number	Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.1.1	**Participant Disposition**			
	14.1.1.1	Participant Disposition, Part A – Screened Set	IP	-
	14.1.1.2	Screening Failures – All Participants	IP	-
14.1.2	**Protocol Deviations**			
	14.1.2.1	Protocol Deviations, Part A – Safety Analysis Set	IP	-
14.1.3	**Demography, Baseline Characteristics, Treatment Compliance, and Analysis Sets**			
	14.1.3.1	Analysis Sets, Part A – Screened Set	IP	-
	14.1.3.2	Demographics, Part A – Full Analysis Set	IP	-
	14.1.3.3.1	Previous Medical History by System Organ Class and Preferred Term, Part A – Full Analysis Set	IP	-
	14.1.3.3.2	Ongoing Medical History by System Organ Class and Preferred Term, Part A – Full Analysis Set	IP	14.1.3.3.1
14.3	**Safety Data**			
14.3.1	**Adverse Events**			
	14.3.1.1	Overall Summary of Treatment Emergent Adverse Events, Part A – Full Analysis Set	IP	-
	14.3.1.2	Treatment Emergent Adverse Events by System Organ Class and Preferred Term, Part A – Safety Analysis Set	IP	-
	14.3.1.3	Treatment-Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term, Part A – Safety Analysis Set	IP	14.3.1.2

Section Number	Table Number	Table Title	Validation Method	Shell Number (if repeat)
	14.3.1.4	Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term, Part A – Safety Analysis Set	IP	14.3.1.2
	14.3.1.5	Treatment Emergent Adverse Events Leading to Early Termination by System Organ Class and Preferred Term, Part A – Safety Analysis Set	IP	14.3.1.2
	13.3.1.6	Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity, Part A – Safety Analysis Set	IP	-
	14.3.1.7	Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Strongest Relationship, Part A – Safety Analysis Set	IP	-
14.3.2	**Other Adverse Events**			
	14.3.2.1	Listing of Deaths – Full Analysis Set	IP	(Listing) 16.2.7.1
	14.3.2.2	Listing of Serious Adverse Events – Full Analysis Set	IP	-
	14.3.2.3	Listing of Abnormal Laboratory Values – Safety Analysis Set	IP	-
14.3.4	**Other**			
	14.3.4.1	Vital Signs, Descriptive Statistics for Observed Values and Change from Baseline, Part A – Safety Analysis Set	IP	-
	14.3.4.3.1	Hematology Data, Descriptive Statistics for Observed Values and Change from Baseline, Part A – Safety Analysis Set	IP	-
	14.3.4.3.2	Hematology Data, Normal Range Shifts, Part A – Safety Analysis Set	IP	-
	14.3.4.4.1	Serum Chemistry Data, Descriptive Statistics for Observed Values and Change from Baseline, Part A – Safety Analysis Set	IP	14.3.4.3.1
	14.3.4.4.2	Serum Chemistry Data, Normal Range Shifts, Part A – Safety Analysis Set	IP	14.3.4.3.2
	14.3.4.5.1	Urinalysis Data, Descriptive Statistics for Observed Values and Change from Baseline, Part A – Safety Analysis Set	IP	-

Section Number	Table Number	Table Title	Validation Method	Shell Number (if repeat)
	14.3.4.5.2	Urinalysis Data, Normal Range Shifts, Part A – Safety Analysis Set	IP	-
	14.3.4.6.1	Safety ECG Data, Descriptive Statistics for Observed Values and Change from Baseline, Part A – Safety Analysis Set	IP	-
	14.3.4.6.2	Safety ECG Data, Descriptive Statistics for QTcF Thresholds, Part A – Safety Analysis Set	IP	-
	14.3.4.6.3	Safety ECG Data, Overall Interpretation Shift from Baseline to Worst Post Baseline, Part A – Safety Analysis Set	IP	-
	14.3.4.7.1	Prior Medications by ATC Level 3 and Preferred Name, Part A – Full Analysis Set	IP	-
	14.3.4.7.2	Concomitant Medications by ATC Level 3 and Preferred Name, Part A – Full Analysis Set	IP	14.3.4.7.1
	14.3.4.8.1	PCSK9 Data, Descriptive Statistics for Observed Values and Change from Baseline, Part A – PD Analysis Set	IP	-
	14.3.4.8.2	Apo Panel Data, Descriptive Statistics for Observed Values and Change from Baseline, Part A – PD Analysis Set	IP	14.3.4.8.1
	14.3.4.8.3	CCI [redacted]	IP	14.3.4.8.1
	14.3.4.9	Linear Mixed-Effects Model for Plasma PK Concentrations of LY3885125 and ΔQTcF, Part A – PK Analysis Set	Stat IP	-
	14.3.4.10	Summary of Immunogenicity Parameters by Treatment Group – Immunogenicity Analysis Set	IP	-
14.4.1	**PK Analysis**			
	14.4.1	Descriptive Statistics for Concentration-Time Data of LY3885125 in Plasma after Single Ascending Subcutaneous Doses of LY3885125 – PK Analysis Set	IP	-

Section Number	Table Number	Table Title	Validation Method	Shell Number (if repeat)
	14.4.2	LY3885125 Plasma Pharmacokinetic Parameters after Single Ascending Subcutaneous Doses of LY3885125 – PK Analysis Set	IP	-
	14.4.3	Amount of LY3885125 Excreted in Urine per Collection Interval – PK Analysis Set	IP	-
	14.4.4	Percentage of LY3885125 Dose Excreted in Urine per Collection Interval – PK Analysis Set	IP	-
	14.4.5	LY3885125 Urine Pharmacokinetic Parameters after Single Ascending Subcutaneous Doses of LY3885125 – PK Analysis Set	IP	-
	14.4.6	Dose-Proportionality Assessment of LY3885125 in Plasma after Single Ascending Subcutaneous Doses of LY3885125 – PK Analysis Set	MR	-

Section Number	Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
14.3.7	**Other Safety**			
	14.3.7.1	Scatter Plot of PK Concentration vs. QTcF – PK Analysis Set	IP	-
14.4	**PK Analysis**			
	14.4.1	Mean Plasma Concentration-Time Profiles of LY3885125 after Single Ascending Subcutaneous Doses of LY3885125 on Linear and Semi-logarithmic Scales – PK Analysis Set	MR	-
	14.4.2	All Subject Plasma Concentration-Time Profiles of LY3885125 after Single Ascending Subcutaneous Doses of LY3885125 on Linear and Semi-logarithmic Scales – PK Analysis Set	MR	-
	14.4.3	Plasma Concentration-Time Profiles for LY3885125 with Linear Regression for Estimating the Terminal Elimination Rate – PK Analysis Set	MR	-
	14.4.4	Assessment of LY3885125 C_{max} vs. Dose – PK Analysis Set	MR	-
	14.4.5	Assessment of LY3885125 AUC_{last} vs. Dose – PK Analysis Set	MR	14.4.4
	14.4.6	Assessment of LY3885125 AUC_{inf} vs. Dose – PK Analysis Set	MR	14.4.4

Section Number	Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2.1	**Participant Disposition**			
	16.2.1.1	Participant Disposition – Screened Set	IP	-
	16.2.1.2	Screen Failures		
16.2.2	**Protocol Deviations**			
	16.2.2.1	Protocol Deviations – Safety Analysis Set	IP	-
16.2.3	**Demography, Baseline Characteristics, Treatment Compliance, and Analysis Sets**			
	16.2.3.1	Analysis Sets – Screened Set	IP	-
	16.2.4.1	Demographics – Full Analysis Set	IP	-
	16.2.4.2	Previous Medical History – Full Analysis Set	IP	-
	16.2.4.3	Ongoing Medical History – Full Analysis Set	IP	-
	16.2.4.4	Prior Medications – Full Analysis Set	IP	-
	16.2.4.5	Concomitant Medications – Full Analysis Set	IP	-
	16.2.5.1	Dosing Information – Safety Analysis Set	IP	-
16.2.6	**PK**			
	16.2.6.1	Plasma LY3885125 Concentration Listing by Subject – Safety Analysis Set	MR	-
	16.2.6.2	Urine LY3885125 Concentration, Volume, Ae, and Fe% Listing by Subject and Collection Interval – Safety Analysis Set	MR	-
	16.2.6.3	Terminal Elimination Rate for LY3885125 for Individual Subjects – PK Analysis Set	MR	-
	16.2.6.4	Plasma PK Output Text – PK Analysis Set	MR	-
	16.2.6.5	Urine PK Output Text – PK Analysis Set	MR	-
	16.2.6.6	SAS Output Text for Dose Proportionality Assessment – PK Analysis Set	MR	-
16.2.7	**Safety – Adverse Events**			
	16.2.7.1	Adverse Events – Safety Analysis Set	IP	-

Section Number	Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
	16.2.7.2	Injection Site Reactions – Safety analysis Set	IP	-
	16.2.7.3	Hypersensitivity Laboratory Measurements – Safety Analysis Set	IP	-
16.2.8	**Safety – Labs**			
	16.2.8.1	Hematology – Safety Analysis Set	IP	-
	16.2.8.2	Serum Chemistry – Safety Analysis Set	IP	16.2.8.1
	16.2.8.3	Urinalysis – Safety Analysis Set	IP	-
16.2.8	**Safety – Other**			
	16.2.8.6	Vital Signs Data – Safety Analysis Set	IP	-
	16.2.8.7	ECG Data – Safety Analysis Set	IP	-
	16.2.8.9	Height and Weight Data – Safety Analysis Set	IP	-
	16.2.8.10	Pharmacodynamic Data – PD Analysis Set	IP	-
	16.2.8.11	Immunogenicity Data – Immunogenicity Analysis Set	IP	-

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