J1D-MC-GZAA SAP v3

A Randomized, Placebo-Controlled, Subject- and Investigator-Blind, Single and Multiple Dose, Safety, Tolerability, and Pharmacokinetics Study of LY3463251 in Healthy and Overweight Healthy Subjects

NCT03764774

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STATISTICAL ANALYSIS PLAN

A Randomized, Placebo-Controlled, Subject- and Investigator-Blind, Single and Multiple Dose, Safety, Tolerability, and Pharmacokinetics Study of LY3463251 in Healthy and Overweight Healthy Subjects

Statistical Analysis Plan Status: Final Version 3
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Clinical Phase I

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1. TABLE OF CONTENTS

2. ABBREVIATIONS

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

ADA	Antidrug antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AUC	Area under the concentration versus time curve
AUC(0-∞)	Area under the concentration versus time curve from time 0 to infinity
AUC(0-τ)	Area under the concentration versus time curve during 1 dosing interval
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
%AUC(t_{last}-∞)	Percentage of AUC(0-∞) extrapolated
BQL	Below the quantifiable lower limit of the assay
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
C_{max}	Maximum observed drug concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Coefficient of variation
EC	Early Clinical
e.g.	For example (Latin: *exempli gratia*)
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
OGTT	Oral glucose tolerance test
PD	Pharmacodynamic
PK	Pharmacokinetic

R_A	Accumulation ratio based upon AUC(0-τ)
SAP	Statistical Analysis Plan
SD	Standard deviation
TBL	Total bilirubin
TEADA	Treatment-emergent antidrug antibodies
TEAE	Treatment-emergent adverse event
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
ULN	Upper limit of normal
Vss/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
VAS	Visual analog scale
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 25 September 2018), Protocol Amendment (a) (final version dated 11 October 2018), Protocol Amendment (b) (final version dated 02 December 2018), Protocol Amendment (c) (final version dated 06 September 2019), Protocol Amendment (d) (final version dated 02 February 2019), Protocol Amendment (e) (final version dated 09 October 2019), SAP Version 1 (dated 13 December 2018), and SAP Version 2 (dated 20 November 2019).

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 Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials[1] and the ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports[2].

4. STUDY OBJECTIVES

4.1 Primary Objective

- To determine the safety and tolerability of single doses of LY3463251 in healthy subjects and multiple doses of LY3463251 in overweight healthy subjects.

4.2 Secondary Objectives

- To determine the PK of LY3463251 following single doses in healthy subjects and multiple doses in overweight healthy subjects.

- To determine the PD effects of LY3463251 following multiple doses of LY3463251 in overweight healthy subjects.

4.3 Exploratory Objectives

- To determine the immunogenicity of LY3463251 following single and multiple doses.
- To evaluate the PD effect on the lipid profile of multiple doses of LY3463251 in overweight healthy subjects.

5. STUDY DESIGN

This is a single-site, randomized, placebo-controlled, dose-escalation study in healthy and overweight healthy subjects to evaluate the safety, tolerability, and PK of LY3463251 following single doses in healthy subjects and multiple doses in overweight healthy subjects. Additionally, the PD effects of multiple doses of LY3463251 on glycemic effects (including fasting plasma glucose, fasting serum insulin, and glucose and insulin during an oral glucose tolerance test [OGTT]), appetite, and body weight in overweight healthy subjects will be explored. The subjects and investigator will be blinded to the treatment assignment; the sponsor will not be blinded. The study will be conducted in 2 parts: Part A (single-ascending dose) and Part B (multiple-ascending dose).

Schematic representations of the study are presented in Figures 1 and 2.

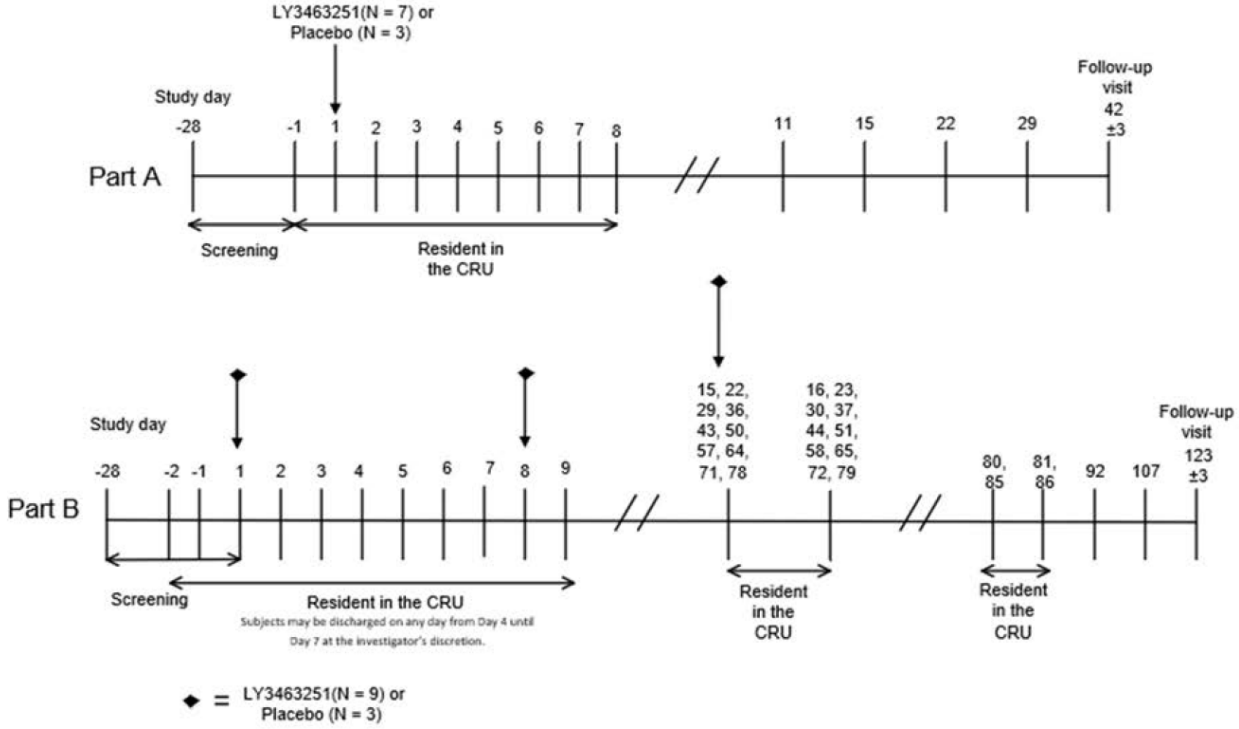

Figure 1 - Planned treatment periods

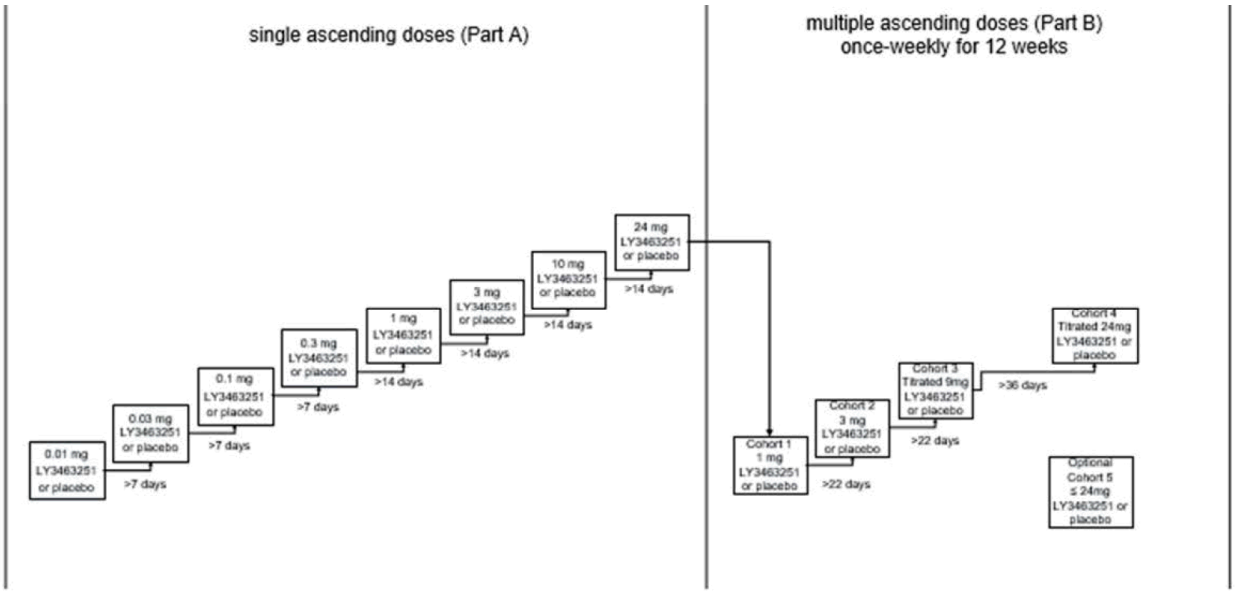

Figure 2 - Dose-escalation

6. TREATMENTS

Part A

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
0.01 mg LY3463251	2
0.03 mg LY3463251	3
0.1 mg LY3463251	4
0.3 mg LY3463251	5
1 mg LY3463251	6
3 mg LY3463251	7
10 mg LY3463251	8
24 mg LY3463251	9

The actual doses studied in the study may differ to the above doses.

Part B

Study Treatment Name	Treatment order in TFL
Placebo QW	1
1 mg LY3463251 QW	2
3 mg LY3463251 QW	3
3/6/9 mg LY3463251 QW	4
3/9/15/24 mg LY3463251 QW	5
X mg LY3463251 QW*	6

*Optional cohort

For titration cohorts, the full titrated dose schedule will be included in the treatment name.

7. SAMPLE SIZE JUSTIFICATION

It is planned to enroll 64 subjects into Part A and 60 subjects into Part B.

The sample size is customary for Phase 1 clinical studies evaluating safety and PK, and is not powered on the basis of statistical hypothesis testing.

Subjects who are randomized and who are discontinued from the study (providing that discontinuation did not result from a safety finding) may be replaced to ensure that enough subjects complete the study.

8. DEFINITION OF ANALYSIS POPULATIONS

The “Safety” population will consist of all enrolled subjects, whether or not they completed all protocol requirements.

The “Pharmacokinetic” population will consist of all subjects who received at least one dose of LY3463251 and have evaluable PK data.

The “Pharmacodynamic” population will consist of all subjects who received at least one dose of LY3463251 or placebo 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, 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 9.4 or greater.

9.2 Demographics and Subject Disposition

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

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

PK parameter estimates will be determined using non-compartmental procedures in validated software program (Phoenix WinNonlin Version 6.4 or later). The PK analysis will be performed by the Eli Lilly PK/PD group.

Plasma concentrations of LY3463251 will be used to determine the following PK parameters, when possible:

Part A

Parameter	Units	Definition
AUC(0-t_{last})	h*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
AUC(0-∞)	h*µg/mL	area under the concentration versus time curve from time zero to infinity
%AUC(t_{last}-∞)	%	percentage of AUC(0-∞) extrapolated
C_{max}	µg/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
$t_{½}$	h	half-life associated with the terminal rate constant (λz) 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

Part B

Parameter	Units	Definition
AUC(0-τ)	h*µg/mL	area under the concentration versus time curve during one dosing interval
C_{max}	µg/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
$t_{½}$	h	half-life associated with the terminal rate constant (λz) 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
R_A	N/A	accumulation ratio based upon AUC(0-τ) (Day 78 only)

Trough (predose) plasma concentrations of LY3463251 will be listed and summarized.

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.

Individual Concentration vs. Time Profiles

- Individual concentrations will be plotted utilizing actual sampling times from the trial.

- The terminal point selections will be indicated on a semi-logarithmic plot.

Average Concentration vs. Time Profiles

- The average concentration profiles will be plotted using scheduled (nominal) sampling times.
- The average concentration profiles will be plotted 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 obtained at a sampling time exceeding the specified time window in the protocol, or ± 10%, will be excluded.
- Concentrations excluded from the average 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.

9.3.2 Pharmacokinetic Statistical Methodology

All PK parameters will be summarized using descriptive statistics, and listed. Mean PK concentration-time profiles, as well as individual subject concentration-time profiles, will be presented graphically. All-subjects PK concentration- time plots will be presented graphically by treatment.

The degree of dose proportionality for LY3463251 will be assessed by fitting the power model to AUC(0-∞), AUC(0-τ) and C_{max} versus dose for each dose level of LY3463251. The estimated ratio of dose-normalized geometric means of PK parameters between the highest and lowest doses will be used to assess dose proportionality. In addition, the slope and its 90% confidence interval (CI) and the geometric least-square means for each dose level tested will be produced. The analysis will be performed separately for Parts A (AUC(0-∞) and C_{max}) and B (AUC(0-τ) and C_{max}). In the Part B, the analysis will be performed based on the last dose administration.

In the event that the power model is not a good representation of the data over the entire dose range tested, alternative models may be investigated. Log-transformed C_{max} and AUC least-squares means, and 90% CI estimates for each dose will be back-transformed to provide the geometric means and the corresponding 90% CIs.

Example SAS code for the analysis:

```
proc mixed data=pk1;
  model lvar=ldose / alpha=0.1 cl solution residual ddfm=kr;
  estimate 'xx mg' intercept 1 ldose a / cl; /*a=Log value of xx*/
  estimate 'yy mg' intercept 1 ldose b / cl; /*b=Log value of yy*/
  estimate 'zz mg' intercept 1 ldose c / cl; /*c=Log value of zz*/
  estimate 'zz mg - xx mg' ldose pp / alpha=0.1 cl; /*pp=Difference in log values of zz and xx*/
  ods output solutionf=est;
  ods output estimates=estims;
run;
```

9.4 Pharmacodynamic Assessment

9.4.1 Pharmacodynamic Analysis

The primary parameters will be:

- Fasting plasma glucose concentrations
- Fasting serum insulin concentrations
- C-peptide
- Fasting Lipoprotein, Cholesterol, and Triglycerides
- OGTT-derived-parameters
- Appetite
- Body weight

Fasting plasma glucose, serum insulin concentrations, lipoprotein, cholesterol, and triglycerides will be summarized and listed, alongside changes from baseline (predose on Day 1).

OGTT derived parameters will be estimated by the Lilly PK/PD group and will include:

- AUC(0-2 hours) for glucose and insulin
- Baseline corrected AUC(0-2 hours) for glucose and insulin
- HOMA-IR and HOMA-B based on fasting insulin and fasting glucose
- Insulinogenic index
- Insulin sensitivity (Matsuda Index)
- Predicted M-value for insulin sensitivity

Additional OGTT derived parameters may also be estimated (e.g. insulin secretion rate, OGIS etc.).

These parameters will be summarized and listed.

9.4.1.1 Pharmacodynamic Statistical Methodology

To investigate the effect of 12 weeks of dosing for the above PD parameters, the change from baseline parameters will be analyzed using a mixed effect with repeat measurements model with treatment, day, and treatment-by-day interaction as fixed effects, subjects as a random effect and baseline as a covariate. Least-squares means as well as 90% CIs for the difference will be

reported. An unstructured covariance structure will be used and a compound symmetric structure will be used if the model fails to converge.
Example SAS code:

```
proc mixed data=PD;
class subject day treatment;
model change = baseline treatment day treatment*day / ddfm=kr;
repeated day / subject=subject type=UN;
lsmeans treatment*day / pdiff=control cl alpha=0.1;
ods output lsmeans=lsm;
ods output diffs=diff;
run;
```

Comparisons between LY3463251 and placebo will be performed.

9.4.2 Appetite Analysis

The subjective rating of appetite sensations will be measured by a 100-mm visual analog scale (VAS) for parameters of hunger, fullness, satiety, and prospective food consumption. The VAS measurements will be performed 30 minutes prior to the start of the standardized breakfast and lunch, and at 30 minutes and 5 hours following the start of the standardized breakfast and lunch. The VAS measurements will be listed and summarized by treatment.

Baseline body weight will be computed as the average of the measurements taken on Days -1 and 1. Body weight data will be summarized by treatment and listed, alongside changes from baseline. Figures for body weight over time will also be presented by treatment.

9.4.3 Acetaminophen Analysis

Plasma concentrations of acetaminophen (Part B only) will be used to determine the following PK parameters in validated software program (Phoenix WinNonlin Version 8.1 or later). The analysis will be performed by the Eli Lilly PK/PD group.

Part B – Acetaminophen parameters

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

The parameters for acetaminophen will be calculated using the same methodology as PK parameters (Section 9.3)

9.4.4 Pharmacodynamic Statistical Methodology

The parameters C_{max}, AUC(0-∞) and AUC0-t_{last} of acetaminophen will be calculated and log-transformed to compare the gastric emptying effect of LY3463251 between days and between doses of LY3463251.

A mixed effect with repeat measurements model analysis with treatment, day, and treatment-by-day interaction as fixed effects and subject as a random effect will be used to perform the analysis. Least-squares means as well as 90% CIs for the difference will be reported. An unstructured covariance structure will be used and a compound symmetric structure will be used if the model fails to converge.
Example SAS code:

```
proc mixed data=PD;
class subject day treatment;
model parameter = treatment day treatment*day / ddfm=kr;
repeated day / subject=subject type=UN;
lsmeans treatment*day / pdiff=control cl alpha=0.1;
ods output lsmeans=lsm;
ods output diffs=diff;
run;
```

Comparisons between LY3463251 and placebo will be performed within a day. Between Day comparisons will also be performed within a treatment (i.e. Day 80 versus Day -2. Day 80 versus Day 3. Day 3 versus Day -2).

The parameter t_{max} of acetaminophen will be analyzed using a nonparametric method using the SAS procedure PROC UNIVARIATE. The treatment medians, median of difference and approximate 90% CI for the median of difference will be presented. The same comparisons as mentioned above will be performed.

PD parameters will be listed and summarized.

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 21.0 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 listed.

9.5.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version March 2018). Concomitant medication will be listed.

9.5.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by parameter and treatment, together with changes from baseline, where baseline is defined as Day 1 predose, 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.

9.5.4 Vital signs

Vital signs data will be summarized by treatment together with changes from baseline, where baseline is defined as the mean of the triplicate Day 1 predose assessment. Figures of mean vital signs and mean changes from baseline profiles will be presented by treatment.

Furthermore, values for individual subjects will be listed.

In addition, ambulatory blood pressure data will be listed and summarized by treatment. Baseline values will be defined as the mean value during the time-matched period on Day -1.

A mixed effect with repeat measurements model analysis with treatment, day, and treatment-by-day interaction as fixed effects, baseline as a covariate, and subject as a random effect will be used to analyze change from baseline vital signs data. Least-squares means as well as 90% CIs for the difference will be reported. An unstructured covariance structure will be used and a compound symmetric structure will be used if the model fails to converge.

Example SAS code:

```
proc mixed data=PD;
class subject day treatment;
model parameter = treatment day treatment*day / ddfm=kr;
repeated day / subject=subject type=UN;
lsmeans treatment*day / pdiff=control cl alpha=0.1;
ods output lsmeans=lsm;
ods output diffs=diff;
run;
```

Comparisons between LY3463251 and placebo will be performed

The relationship between the time-matched LY3463251 concentrations and changes from baseline in QTcF interval will be explored graphically using a scatter plot for Parts A and B separately. If this illustration suggests a relationship, a regression analysis using a linear

mixed-effects model will be performed. A plasma LY3463251concentration-QT analysis will be performed to assess the changes from baseline (Day 1 predose) in the QTcF interval relative to plasma LY3463251 concentrations across all active treatments. The change from baseline adjustment will be based on individual subject's Day 1 predose value, and an additional placebo adjustment will be based on the mean of time-matched placebo values. Further details on how these will be calculated:

- Calculate the change from baseline at each timepoint (delta QTcF) for each individual subject who received LY3463251concentrations.
- Calculate the mean change from baseline across all the placebo subjects at each timepoint.
- For each subject that received LY3463251concentrations at each corresponding timepoint subtract the mean placebo change from their own individual change from baseline.
- BLQ LY3463251concentrations data will be imputed to 50% of the LLOQ for the purposes of the analysis.

The analysis will be performed by plotting delta QTcF against LY3463251 concentrations, including all post dosing timepoints. A linear mixed-effects model will be performed on the delta QTcF values and will include LY3463251 concentration as a covariate. The estimated regression line and associated 90% CI will be fitted on the plot and the p-value for the slope reported. Estimated delta QTcF and 90% CI at the geometric mean C_{max} will also be presented.

If required, this analysis will also be repeated for other vital signs.

9.5.5 Hepatic Monitoring

If a subject experiences elevated alanine aminotransferase (ALT) ≥3× upper limit of normal (ULN), alkaline phosphatase (ALP) ≥2× ULN, or elevated total bilirubin (TBL) ≥2× ULN, liver 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 subjects' liver disease history and associated person liver disease history data will be listed. Any concomitant medication of acetaminophen/paracetamol will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography (MRE) scan, and a biopsy assessment 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 subject data listings.

9.5.6 Immunogenicity

The frequency and percentage of subjects with preexisting antidrug antibody (ADA) and with treatment-emergent ADAs (TEADA) to LY3463251 will be tabulated.

For subjects who are ADA negative at baseline, TEADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution of the assay (1:40). For subjects who are ADA positive at baseline, TEADAs are defined as those with a 4-fold (2 dilution) increase in titer compared to baseline. For subjects with TEADA, the distribution of maximum titers will be described. The frequency and percentage of subjects with neutralizing antibodies, if measured, may also be tabulated for subjects with TEADA.

The relationship between the presence of antibodies and the PK parameters and PD response including safety and efficacy to LY3463251 may be assessed.

All TEADAs will be listed.

9.5.7 Columbia-Suicide Severity Rating Scale

The Columbia Suicide Severity Rating Scale (C-SSRS) captures the occurrence, severity, and frequency of suicide-related thoughts and behaviours during the assessment period. The C-SSRS and Lilly Self-Harm Supplement Form data will be listed and summarized using standard descriptive statistics.

9.5.8 Injection-Site Reactions

Injection-site reaction data will be listed and summarized by treatment in frequency tables (if appropriate).

9.5.9 Other assessments

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

9.5.10 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 center of the table, such as, “No serious adverse events occurred for this study.”

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