Statistical Analysis Plan: J1X-MC-GZHB (V2)

A Multiple-Ascending Dose Study to Investigate the Safety, Tolerability, and Pharmacokinetics of LY3493269 in Healthy Participants

NCT04498390

Approval Date: 15-Feb-2021

STATISTICAL ANALYSIS PLAN

A Multiple-Ascending Dose Study to Investigate the Safety, Tolerability, and Pharmacokinetics of LY3493269 in Healthy Participants

Statistical Analysis Plan Status: Final Version 2.0
Statistical Analysis Plan Date: 11-February-2021

Study Drug: LY3493269

Sponsor Reference: J1X-MC-GZHB
Covance CRU Study: 1001215-8439717

Clinical Phase I

Approval Date: 15-Feb-2021 GMT

1. TABLE OF CONTENTS

2. ABBREVIATIONS

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

AE	Adverse event
ADA	Anti-drug antibody
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AUC	Area under the concentration versus time curve
BQL	Below the quantifiable lower limit of the assay
C10	Permeation enhancer sodium caprate
CI	Confidence interval
C_{max}	Maximum observed drug concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
EC	Early Clinical
ECG	Electrocardiogram
ICH	International Conference on Harmonisation
LLOQ	Lower limit of quantification
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
PD	Pharmacodynamic
PG	Plasma Glucose
PK	Pharmacokinetic
QD	Once daily
SAP	Statistical Analysis Plan
SD	Standard deviation
SOP	Standard Operating Procedure
TBL	Total bilirubin
TE	Treatment emergent

TE ADA	Treatment-emergent anti-drug antibodies
TEAE	Treatment emergent adverse event
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
ULN	Upper limit of normal
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 11 June 2020 and final amendment a dated 22 July 2020).

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 with Eli Lilly and Company. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. 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 with Eli Lilly and Company 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

The primary objective of this study is:

- To investigate the safety and tolerability of LY3493269 following 3 consecutive once-daily oral doses in healthy participants.

The primary endpoint for this study is:

- Treatment emergent adverse events (TEAEs).

4.2 Secondary Objective

The secondary objective of this study is:

- To characterize the PK of LY3493269 following 3 consecutive once-daily oral doses in healthy participants.

The secondary endpoints of this study are:

- Area under the concentration versus time curve (AUC) and maximum observed drug concentration (C_{max}).

4.3 Exploratory Objectives

The exploratory objectives of the study are:

- To investigate the PD effects of LY3493269 following 3 consecutive once-daily oral doses in healthy participants.
- To assess PK of permeation enhancer sodium caprate (C10) following oral administration in healthy participants.
- To explore the effect of LY3493269 on appetite and food intake following 3 consecutive once-daily oral doses in healthy participants.
- To characterize immunogenicity of LY3493269 following 3 once-daily oral doses in healthy participants.

The exploratory endpoints of the study are:

- Changes from baseline levels of fasting glucose, insulin, C-peptide, triglycerides, and body weight.
- AUC and C_{max}.
- Change in visual analogue scale (VAS) score for appetite assessment in a fasted state.
- Incidence of treatment-emergent antidrug antibody (ADA).

5. STUDY DESIGN

Study GZHB is a Phase 1, single-center, randomized, placebo-controlled, multiple dose, dose-escalation study in 4 planned cohorts of up to 14 healthy participants randomly assigned in each cohort.

In each cohort, up to 14 participants may be randomly assigned to achieve 10 completers with 8 participants receiving LY3493269 and 2 participants assigned to receive placebo. Participants who are randomly assigned but not administered treatment prior to discontinuation may be replaced to ensure that the target number of participants complete the study.

This is an investigator- and participant-blind study; the sponsor is not blinded.

A general schema for the study can be seen in Figure 1.

The planned LY3493269 oral doses for this study range from 8 to 48 mg, administered in the 4 planned “dose cohorts”:

- Cohort 1: 8 mg LY3493269 (with 500 mg C10)
- Cohort 2: 24 mg LY3493269 (with 500 mg C10)
- Cohort 3: 48 mg LY3493269 (with 500 mg C10)
- Cohort 4: 24 mg LY3493269 (with 250 mg C10)

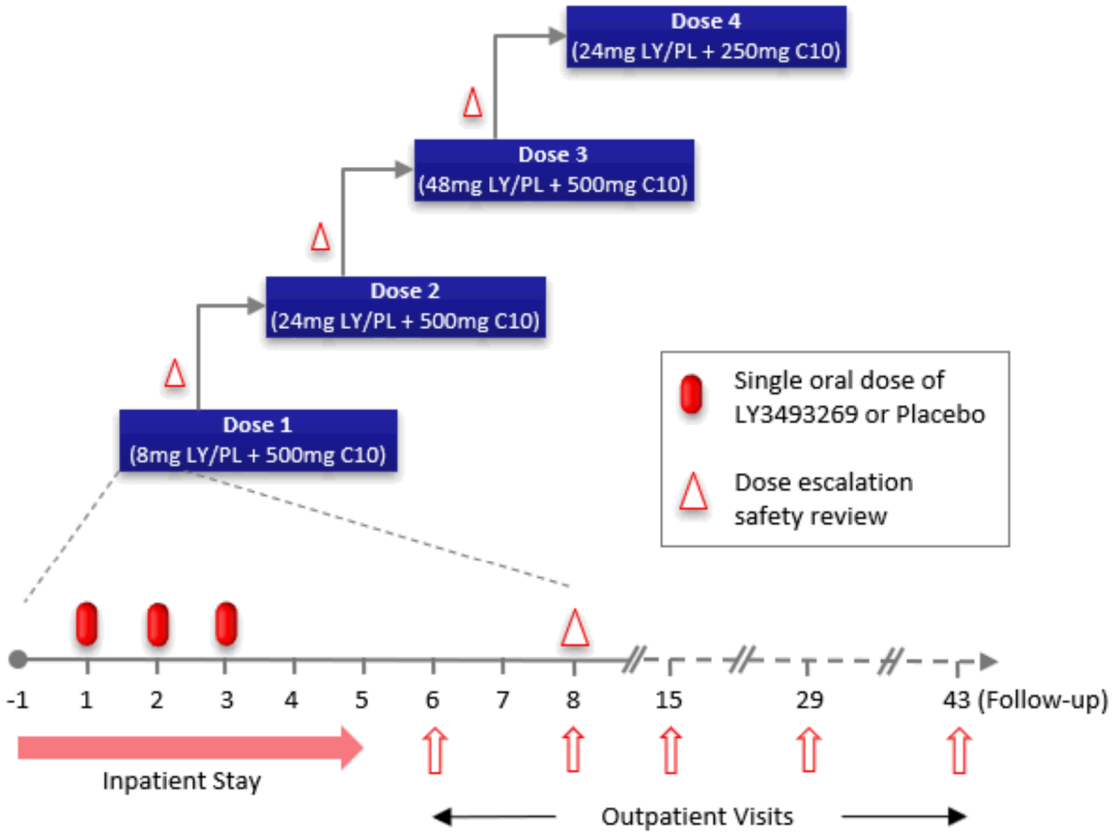

Figure 1 - A general schema of GZHB

6. TREATMENTS

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

Cohort	Study Treatment Name	Study Treatment Abbreviation	Treatment order in TFL
All	Placebo	Placebo	1
1	8 mg LY3493269 with 500 mg C10 QD	8 mg LY + 500 mg C10 QD	2
2	24 mg LY3493269 with 500 mg C10 QD	24 mg LY + 500 mg C10 QD	3
3	48 mg LY3493269 with 500 mg C10 QD	48 mg LY + 500 mg C10 QD	4
4	24 mg LY3493269 with 250 mg C10 QD	24 mg LY + 250 mg C10 QD	5

7. SAMPLE SIZE JUSTIFICATION

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

Up to approximately 56 participants may be randomly assigned to study intervention to ensure approximately 10 evaluable participants (8 receiving LY3493269 and 2 receiving placebo) from each of the 4 cohorts complete the study. Participants who are randomized but not administered treatment prior to discontinuation may be replaced to ensure that the target number of participants complete the study.

Participants who discontinue early may be replaced after consultation with the investigator and sponsor. The replacement participant will be assigned to the same treatment as the discontinued participant.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.

The "Pharmacokinetic" population will consist of all participants who received at least 1 full dose of LY3493269 and have evaluable PK sample. Subjects may be excluded from the PK summary statistics and statistical analysis if a subject has an adverse event of vomiting that occurs at or before 2 times median t_{max}.

The "Pharmacodynamic" population will consist of all participants who received at least 1 dose of LY3493269 and have evaluable PD data Subjects may be excluded from the PD summary statistics and statistical analysis if a subject has an adverse event of vomiting that occurs at or before 2 times median t_{max}.

All protocol deviations that occur during the study including those related to COVID-19, 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: AUCs 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.

All protocol deviations and data issues (eg, missing data or data outside of the protocol windows) that occur during the study, including those related to COVID-19, will be considered prior to database lock for their severity/impact on how the data will be displayed and analyzed statistically.

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, 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 by Lilly using non-compartmental procedures in validated software program (Phoenix WinNonlin Version 8.1 or later) using standard noncompartmental methods of analysis. The software and version used for the final analyses will be specified in the clinical study report.

Any exceptions or special handling of data will be clearly documented within the final study report.

Concentrations of LY3493269 and C10 will be used to determine the following PK parameters, when possible: C_{max}, AUC, and t_{max}. Pharmacokinetic parameters for C_{max} and AUC from time zero to 24 hour, AUC(0-24) will be computed after the first, second, and third doses, AUC(0-inf) will be calculated after the third dose. AUC(0-tlast) will also be calculated. Other parameters, such as half-life, apparent clearance, and apparent volume of distribution may be reported. If deemed necessary, additional model-based analysis may be performed for LY3493269 or data may be combined with Study GZHA for further analysis.

Individual concentration versus time profiles will be plotted utilizing actual sampling times. The terminal point selections will be indicated on a semi-logarithmic plot. Average concentration versus time profiles will be plotted using nominal sampling times and will use arithmetic mean concentrations

9.3.2 Pharmacokinetic statistical methodology

All PK parameters will be summarized using descriptive statistics. Mean PK concentration-time profiles will be presented graphically, these outputs will be the responsibility of Lilly. The inferential PK statistical analyses detailed below will be the responsibility of Covance.

Dose proportionality assessment

PK dose proportionality will be assessed for LY3493269 on Day 1 and Day 3 separately. Log-transformed C_{max}, AUC(0-24), AUC(0-infinity) and AUC(0-tlast) of LY3493269 from Cohorts 1 to 3 will be evaluated using a power model (where log-dose acts as an explanatory variable) to estimate ratios of dose-normalized geometric means and corresponding 90% confidence intervals (CIs). The estimated ratio of dose-normalized geometric means of PK parameters between the highest and lowest doses will be used to assess dose proportionality. A subinterval within the highest and lowest doses may also be considered for assessment of dose proportionality using the same approach.

Example SAS code is as follows:

```
proc mixed data=xxx;
model log_pk = log_dose / alpha=0.1 cl solution outpred=resids ddfm=kr2;
estimate 'xx mg' intercept 1 log_dose yy / alpha=0.1 cl; /*Log value of xx*/
estimate 'zz mg - xx mg' log_dose pp / alpha=0.1 cl; /*Difference in log
values of zz and xx*/
ods output solutionf=est;
ods output estimates=estims;
run;
```

The parameter t_{max} of LY3493269 from Cohorts 1 to 3 will be analyzed non parametrically using the Kruskal-Wallis test to investigate its independence, with the respective p-value reported.

Example SAS code is as follows:

```
proc npar1way data=xxx
  class dose;
  var pk;
  ods output KruskalWallisTest =krusk;
run;
```

C10 dose comparison

Log-transformed Day 1 and Day 3 C_{max}, AUC(0-24), AUC(0-infinity) and AUC(0-tlast) of LY3493269 from Cohorts 2 and 4 will be analyzed separately to compare the PK parameters following differing doses of C10. Each parameter will be analyzed using a linear model with treatment as a fixed effect. The lsmeans along with the difference between Cohort 2 (500mg C10) and Cohort 4 (250mg C10) will be estimated from the model along with the associated 90% CI. These will be back transformed to obtain the geometric lsmeans, the ratio of Cohort 2 (500mg C10) versus Cohort 4 (250mg C10) and the associated 90% CI.

Example SAS code is as follows:

```
proc mixed data=xxx;
model log_pk = treatment /residual ddfm=kr2;
lsmeans treatment / pdiff alpha=0.1 cl;
ods output diffs=diffs;
ods output lsmeans=lsmeans;
run;
```

The Day 1 and Day 3 parameter t_{max} of LY3493269 from Cohorts 2 and 4 will be analyzed non parametrically separately for each day. Estimates of the median difference between Cohort 2 (500mg C10) versus Cohort 4 (250mg C10), 90% CIs, and p-values from the Wilcoxon rank sum test will be calculated.

9.4 Pharmacodynamic Assessment

9.4.1 Pharmacodynamic analysis

All PD parameters, including the baseline-corrected parameters, will be summarized and tabulated by treatment and visit. This includes absolute and change from baseline values, where baseline is defined as Day 1 predose, in:

- Fasting glucose.
- Fasting insulin.
- Fasting C-peptide.
- Fasting triglycerides.
- Body weight.
- Appetite visual analog scale (VAS) for parameters of hunger, fullness, satiety, and prospective food consumption. Overall appetite score is calculated as the average of the 4 individual scores: satiety + fullness + (100-prospective food consumption) + (100-hunger) / 4). The higher overall appetite score indicates less appetite, and the lower score indicates more appetite.

9.4.2 Pharmacodynamic statistical methodology

To determine the effect of LY3493269 on the PD endpoints (raw values, as well as change from baseline), each parameter will be analyzed using repeated measure mixed effect models. The model will include treatment, visit, and treatment-by-visit as fixed effects and subject as a random effect. Baseline values, as well as other influencing variables, may be used as covariates. An unstructured covariance structure will be used to model the correlation between a participant's multiple observations; an alternative appropriate structure will instead be used if the model fails to converge. For each PD endpoint, the difference in least-square treatment means, comparing each LY3493269 treated group and the pooled placebo group, along with the 90% CI will be reported. A comparison will also be reported for 24 mg LY3493269 + 500 mg C10 versus 24 mg LY3493269 + 250 mg C10.

Pharmacodynamic parameters may be transformed before statistical analyses if deemed necessary. Back-transforming to the original scale will be implemented if transformations of the parameters are done.

Example SAS code is as follows:

```
proc mixed data=xxx;
class subject treatment visit;
model PD = treatment visit treatment*visit /residual ddfm=kr2;
repeated visit/ subject=subject type=un;
lsmeans treatment*visit / cl pdiff alpha=0.1;
ods output lsmeans=lsm diffs=estims;
run;
```

Summary statistics will be provided for all the PD parameters stated in Section 9.4.1. The individual observed and mean time profile of the postdose PD parameters will be plotted by treatment for raw values and changes from baseline.

9.5 Pharmacokinetic/Pharmacodynamic Analysis

Pharmacokinetic/PD analyses or graphical explorations may be used to assess the relationship between LY3493269 doses and/or concentrations. These will only be performed if there is a clear trend for dose-related effect that informs dose-selection for future protocols.

9.6 Safety and Tolerability Assessments

9.6.1 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 23.0 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 by the investigator. Any serious AEs will be listed. Any AEs of special interest will be listed, these include cardiovascular events, gastrointestinal (GI) events (nausea, vomiting and diarrhea), hypersensitivity reactions and hypoglycemic events.

Barcharts of the frequency of gastrointestinal events of nausea, vomiting and diarrhea, by severity will be presented for each day by treatment.

Discontinuations due to AEs will be listed.

9.6.2 Glucose Monitoring and Hypoglycemia

During the study, blood glucose concentrations will be monitored for safety assessments.

Hypoglycemic events will be appropriately recorded in the CRF. In the case of a hypoglycemic event, the actual blood glucose value, if measured, will be recorded in the CRF, together with any treatments administered. Each category of hypoglycemic events (defined below) will be listed and summarized by treatment.

Participants will be trained by site personnel about signs and symptoms of hypoglycemia and how to treat hypoglycemia.

The investigator should use the following classification of hypoglycemia:

Level 1 hypoglycemia:

Glucose <70 mg/dL (3.9 mmol/L) and ≥54 mg/dL (3.0 mmol/L): Level 1 hypoglycemia can alert a person to take action such as treatment with fast-acting carbohydrates. Providers should continue to counsel participants to treat hypoglycemia at this glucose alert value.

Level 2 hypoglycemia:

Glucose <54 mg/dL (3.0 mmol/L): This is also referred to as documented or blood glucose confirmed hypoglycemia with glucose <54 mg/dL (3.0 mmol/L). This glucose threshold is clinically relevant regardless of the presence of absence of symptoms of hypoglycemia.

Level 3 hypoglycemia:

Severe hypoglycemia (in adults): A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. For example, participants had altered mental status, and could not assist in their own care, or were semiconscious or unconscious, or experienced coma with or without seizures, and the assistance of another person was needed to actively administer carbohydrate, glucagon, or other resuscitative actions. Glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of glucose concentration to normal is considered sufficient evidence that the event was induced by a low glucose concentration.

- The determination of a hypoglycemic event as an episode of severe hypoglycemia, as defined above, is made by the investigator based on the medical need of the participant to have required assistance and is not predicated on the report of a participant simply having received assistance.
- If a hypoglycemic event meets the criteria of severe hypoglycemia, the investigator must record the event as serious on the AE eCRF and report it to Lilly as an SAE.

9.6.3 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version WHODD MAR20B3/C3). Concomitant medication will be listed.

9.6.4 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized, along with change from baseline, where baseline is defined as Day 1 predose, 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 and flagged on individual subject data listings.

9.6.5 Vital signs

Vital signs data will be summarized by treatment together with changes from baseline, where baseline is defined as the mean of the Day 1 predose assessments (-30, -15 and 0 minutes). Figures of mean vital signs and mean changes from baseline profiles will be presented by treatment.

Values for individual subjects will be listed.

For the change from baseline values, a repeated measure mixed effect model will be used to determine the effects of LY3493269. The model will include treatment, timepoint, and treatment-by-timepoint interaction as fixed effects and subject as a random effect. Baseline will also be included as a covariate. An unstructured covariance structure will be used to model the correlation between a participant's multiple observations; an alternative appropriate structure will instead be used if the model fails to converge. Least-square treatment means, the difference in least-square treatment means, comparing each LY3493269 treated group and the placebo group, along with the 90% CI will be reported.

9.6.6 Electrocardiogram (ECG)

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the PR interval, QT, QRS duration, RR and heart rate. In addition, QT interval corrected using Fridericia's formula (QTcF) will be calculated as follows:

$$QTcF = \frac{QT}{\sqrt[3]{\left(60/HR\right)}}$$

The ECG data will be summarized by treatment together with changes from baseline, where baseline is defined as the mean of the triplicate Day 1 predose assessments (-30, -15 and 0 minutes). Figures of mean ECG data and mean changes from baseline will be presented by treatment. The frequency of subjects with a maximum increase from baseline in QTcF interval will be summarized for each treatment according to the following categories: >30 ms and >60 ms. In addition, the frequency of subjects with QTcF postdose values, according to the following categories: >450 ms, >480 ms and >500 ms, will be summarized by treatment.

Plasma PK Concentration versus delta and double delta ECG parameter analysis

A time-matched plasma LY3493269 concentration-ECG parameter analysis will be performed to assess the relationship between changes from baseline (mean of Day 1 predose triplicate assessments) in ECG parameters (QTc, PR, and RR intervals, QRS duration, and heart rate) and plasma LY3493269 concentrations across all treatments. The change from baseline adjustment will be based on individual participant's Day 1 predose value. Further details on how these will be calculated:

- Calculate the baseline ECG value for each participant, which is the mean of ECG parameter values of each individual participant over 3 predose time points at day 1.
- Calculate the change from baseline at each timepoint for each individual participant.
- Calculate the mean ECG parameter value across all participants at baseline.
- For each participant subtract the mean ECG parameter value from their own individual observed ECG parameter value. This will be each participant's centered ECG parameter value.
- BLQ LY3493269 concentration data will be imputed to LLOQ/square root(2) for the purposes of the analysis.

The relationship between LY3493269 concentrations and ECG parameters will be explored graphically by plotting delta ECG parameter values against LY3493269 concentrations, including all post dosing timepoints.

A mixed effects analysis model will be employed with change from baseline in ECG parameter as the dependent variable, LY3493269 concentration and centered ECG parameter value as continuous covariates, treatment and time as categorical factors, and a random intercept and slope per participant. Treatment will be fitted as a binary variable (Placebo, or LY3493269). The model will have the form

$$\Delta ECG_{ijk} = (\theta_0 + \eta_{0,i}) + \theta_1 TRT_j + (\theta_2 + \eta_{2,i}) C_{ijk} + \theta_{3,k} TIME_k + \theta_4 (ECG_{i,j=0} - \overline{ECG_0}) + \varepsilon_{ijk},$$

where ΔECG_{ijk} is the change from baseline in ECG parameter for participant i in treatment j at time k, θ_0 is the population mean intercept in the absence of treatment effect, $\eta_{0,i}$ is the random effect associated with the intercept term θ_0, θ_1 is the fixed effect categorical variable associated with treatment TRT_j , θ_2 is the population mean slope of the assumed linear association between concentration and ΔECG_{ijk}, $\eta_{2,i}$ is the random effect associated with the slope θ_2, C_{ijk} is the concentration for participant i in treatment j and time k, θ_3 is the fixed effect associated with time, θ_4 is the fixed effect associated with baseline $ECG_{i,j=0}$, $\overline{ECG_0}$ is the overall mean of $ECG_{i,j0}$ (the mean of all the baseline ECG parameter values, at time 0), and ε_{ijk} is the residual error. It will be assumed the random effects are multivariate Gaussian distributed with mean vector 0 and an unstructured covariance matrix G, whereas the residuals, ε_{ijk}, are Gaussian distributed with mean 0 and variance r.

The predicted mean change from baseline and placebo-corrected change from baseline in ECG parameter (ΔECG and ΔΔECG respectively) at the observed geometric mean C_{max} of each

treatment (slope estimate * C_{max} + treatment effect) and two-sided 90% CI at different dose levels will be calculated. Residual plots will be produced to assess the adequacy of the model.

Example of SAS code as follows:

```
proc mixed data=xxx;
by param;
class treat time subject;
model ΔECG = treat time baseline_ECG PKconc / solution cl alpha=0.1 ddfm=kr2;
random intercept PKconc / type=un subject=subject;
estimate 'Placebo ' intercept 1 treat 1 0 PKconc 0/ CL alpha=0.1;
estimate 'YY mg LY3493269 ' intercept 1 treat 0 1 PKconc [cmax YYmg] / CL
alpha=0.1;
estimate 'YY mg LY3493269 - Placebo' treat -1 1 PKconc [cmax YYmg] / CL
alpha=0.1;
ods output covparms=covp(where=(covparm="Residual"));
ods output solutionF=sol;
ods output estimates=estim;
run;
```

9.6.7 Hepatic Monitoring

If a subject experiences 1 or more of the elevations in the table below then the liver tests will be performed to confirm the abnormality.

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN
ALP <1.5x ULN	ALP ≥2x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥2x baseline (except for patients with Gilbert's syndrome)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin level; ULN = upper limit of normal.

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 medications that have potential for hepatotoxicity, including acetaminophen will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography (MRE) scan, and biopsy assessments will be listed, if performed.

Hepatic risk factor assessment data will be listed. Liver related signs and symptoms data will be summarized by treatment and listed. Alcohol and recreational drug use data will also be listed.

All hepatic chemistry, hematology, coagulation, and serology data will be listed. Values outside the reference ranges will be flagged on the individual subject data listings.

9.6.8 Hypersensitivity reactions

Hypersensitivity reactions will be listed.

9.6.9 Immunogenicity assessments

The frequency and percentage of patients with pre-existing ADA and with treatment-emergent ADAs (TE ADA) to LY3493269 will be tabulated and listed when data becomes available.

For patients who are ADA negative at baseline, TE ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution of the assay. For patients who are ADA positive at baseline, where baseline is defined as Day 1 predose, TE ADAs are defined as those with a 4-fold (2 dilution) increase in titer compared to baseline. The frequency and percentage of patients with cross-reactive and neutralizing antibodies, if measured, may also be tabulated for patients with TE ADA.

The relationship between the presence of antibodies and PK exposures and PD response including safety and efficacy to LY3493269 may be assessed.

9.6.10 Other assessments

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

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.”

Leo Document ID = 86d4ae5c-ce09-4a7c-986b-938357831980

Approver: PPD

Approval Date & Time: 11-Feb-2021 14:24:23 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 12-Feb-2021 05:58:01 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 15-Feb-2021 02:56:06 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 15-Feb-2021 12:44:07 GMT

Signature meaning: Approved