Statistical Analysis Plan J1X-MC-GZHF (Final Version 3)

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

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STATISTICAL ANALYSIS PLAN

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

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2. ABBREVIATIONS

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

ADA	Anti-drug antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AUC	Area under the concentration versus time curve
AST	Aspartate aminotransferase
BW	Body weight
CI	Confidence interval
C_{max}	Maximum observed drug concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
ECG	Electrocardiogram
HR	Heart rate
ICH	International Conference on Harmonisation
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic
PG	Plasma glucose
PK	Pharmacokinetic
QD	Once daily
QTcF	QT interval corrected using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SNAC	Salcaprozate sodium
TBL	Total bilirubin
TE ADA	Treatment-emergent anti-drug antibody
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 September 2020), Protocol Amendment (a) (final version dated 05 March 2021) SAP Version 1 (final version dated 04 November 2020), and SAP Version 2 (final version dated 08 March 2021).

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 the study is to investigate the safety and tolerability of LY3493269 following 3 consecutive once daily (QD) oral doses in healthy participants.

The primary endpoint of the study is treatment-emergent adverse events (TEAEs).

4.2 Secondary Objective

The secondary objective of the study is to characterize the PK of LY3493269 following 3 consecutive QD oral doses in healthy participants.

The secondary endpoints of the study are:

- Area under the concentration versus time curve (AUC)

- 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 QD oral doses in healthy participants
  - Endpoint: Changes from baseline levels of fasting glucose, insulin, C-peptide, triglycerides, and body weight (BW)
- To assess PK of salcaprozate sodium (SNAC) following oral administration in healthy participants
  - Endpoint: AUC and C_{max}
- To explore the effect of LY3493269 on appetite and food intake following 3 consecutive QD oral doses in healthy participants
  - Endpoint: Change in visual analog scale (VAS) score for appetite assessment in a fasted state
- To characterize immunogenicity of LY3493269 following 3 QD oral doses in healthy participants
  - Endpoint: Incidence of treatment-emergent anti-drug antibody (TE ADA)
- To assess the product palatability of LY3493269 tablets.
  - Endpoint: Responses to tablet palatability questionnaire.

5. STUDY DESIGN

Study GZHF 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.

This study will evaluate the safety, tolerability, and PK of 3 consecutive QD oral doses of LY3493269. In addition, the PD effects of LY3493269 on fasting glucose, insulin, triglycerides, and appetite will be explored following the 3 consecutive oral QD doses of LY3493269.

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.

Study randomization shall occur after confirmation of eligibility.

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 600 mg SNAC)
- Cohort 2: 24 mg LY3493269 (with 600 mg SNAC)

- Cohort 3: 48 mg LY3493269 (with 600 mg SNAC)
- Cohort 4: 24 mg LY3493269 (with 300 mg SNAC)

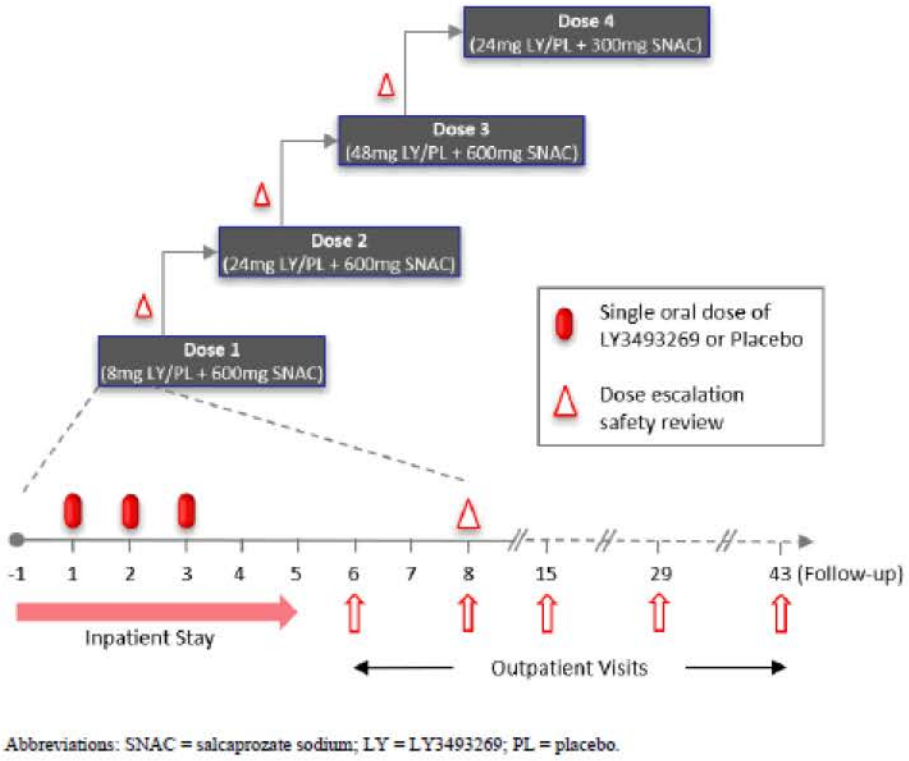
Cohorts 1 to 3 evaluate doses of LY3493269 from 8 to 48 mg, each dose in combination with 600 mg SNAC. Cohort 4 evaluates a 24-mg dose of LY3493269 with half the amount (300 mg) of SNAC.

The LY3493269 dose levels may be adjusted (for example, dose increments may be reduced, a dose level may be repeated, or a lower/intermediate dose may be administered) based on ongoing review of available safety, tolerability, PK, and PD data. Any proposal to adjust doses from those planned and stated in the protocol, together with supporting data, will be reviewed by an independent safety review panel.

Participants will undergo safety (including but not limited to adverse events [AEs], medical assessments, clinical laboratory tests, BW, vital signs, and electrocardiograms [ECGs]), PK, and PD assessments.

Safety data including, but not limited to AEs, clinical laboratory tests, vital signs, ECGs, BW, hypoglycemic events, and VAS assessments up to Day 8 from at least 8 participants who have received study intervention will be reviewed jointly by the principal investigator and sponsor before a joint decision is made to escalate to the next planned dose level.

A general schema for GZHF can be seen in **Figure 1**.



Abbreviations: SNAC = salcaprozate sodium; LY = LY3493269; PL = placebo.

Figure 1 - General schema for GZHF

6. TREATMENTS

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

Cohort	Study Treatment Name	Treatment order in TFL
All	Placebo QD	1
1	8 mg LY3493269 QD + 600 mg SNAC QD	2
2	24 mg LY3493269 QD + 600 mg SNAC QD	3
3	12 mg LY3493269 QD + 300 mg SNAC QD	4
4	4 mg LY3493269 QD + 300 mg SNAC 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 "Entered" population will consist of all participants who sign the informed consent form.

The "Enrolled" population will consist of all participants assigned to treatment, regardless of whether they take any doses of study treatment, or if they took the correct treatment. Participants will be analyzed according to the treatment group to which they were assigned.

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 data. Participants may be excluded from the PK summary statistics and statistical analysis if a participant has an AE of vomiting that occurs at or before 2 times median time of maximum observed drug concentration (t_{max}).

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

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when participants 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, 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 will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all participants up to the point of withdrawal, with any participants excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for participants 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 participants' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual participant's baseline value from the value at the timepoint. The individual participant'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 Participant Disposition

Participant disposition will be listed. The demographic variables age, sex, race, ethnicity, BW, height, HbA1c and body mass index will be summarized and listed.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

The PK parameter estimates will be performed by Lilly for LY3493269 and SNAC will be calculated using standard noncompartmental methods of analysis. The software and version used for the final analyses will be specified in the clinical study report.

The primary parameters for analysis will be C_{max}, AUC and t_{max}. The PK parameters for C_{max} and AUC(0-24) will be computed after the first, second, and third doses, with AUC(0-t_{last}) and AUC(0-∞) also calculated after the third dose. Other parameters, such as half-life, apparent clearance, and apparent volume of distribution, may be reported.

The PK data will be provided by Eli Lilly and Company for the analysis.

9.3.2 Pharmacokinetic Statistical Methodology

For all cohorts, log-transformed C_{max}, AUC(0-24), AUC(0-t_{last}) (Day 3 only), and AUC(0-∞) (Day 3 only) parameters of LY3493269 on Days 1 (first dose) and 3 (third dose) independently will be evaluated using a power model (where log-dose acts as an explanatory variable, and SNAC fitted as a dichotomous variable in which the variable equals 0 for those doses with 300 mg SNAC, and 1 for those with 600 mg SNAC) 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. The 90% CI will also be reported for the parameter of the SNAC variable. A subinterval within the highest and lowest doses may also be considered for assessment of dose proportionality using the same approach.

Example of the SAS code (for C_{max} and AUC[0-24]) for the analysis:

```
proc mixed data=xxx;
   class usubjid SNAC;
  model log_pk = log_dose SNAC / alpha=0.1 cl solution outpred=resids ddfm=kr;
  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 LY3493269 parameter t_{max} will be analyzed non-parametrically using the Kruskal-Wallis test to investigate its independence, and, hence, dose proportionality, with the respective p-value reported. For each dose, 90% CIs for the median will also be reported.

Example SAS code is as follows:

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

For Cohorts 1 and 2, and 3 and 4 independently, log-transformed dose normalized C_{max}, AUC(0-24), AUC(0-t_{last}) (Day 3 only), and AUC(0-∞) (Day 3 only) parameters of LY3493269 on Days 1 (first dose) and 3 (third dose) will be analyzed independently an analysis of variance model to assess dose proportionality. The model will include treatment as a fixed effect. The difference in least-square (LS) treatment means and respective LS means will be back transformed to produce the ratio of geometric means, and the 90% CIs of the LS means and difference between the means will be reported.

Example of the SAS code for the dose normalized analysis:

```
proc mixed data=xxx;
   class usubjid;
   model log_DNpk = treatment / alpha=0.1 cl solution outpred=resids ddfm=kr;
   ods output lsmeans=lsm diffs=estims;
run;
```

9.4 Pharmacodynamic Assessment

9.4.1 Pharmacodynamic Analysis

Pharmacodynamic data will be provided by Eli Lilly and Company for the analysis.

9.4.2 Pharmacodynamic Statistical Methodology

The PD parameters from the placebo-treated participants across all cohorts will be pooled for the final analysis.

All exploratory PD parameters, including the change from baseline parameters, will be summarized and listed by treatment group and visit. Individual observed and mean time profiles of the postdose PD parameters will be plotted by treatment groups.

The PD parameters that will be statistically analyzed, which have a baseline defined as Day 1 predose, are as follows:

- Fasting glucose
- Fasting insulin
- Fasting C-peptide
- Fasting triglycerides
- Body weight
- Appetite VAS

The PD parameters, as well as the change from baseline parameters, will be analyzed using a mixed effect model. In the model, treatment, visit, and treatment-by-visit interaction will be modelled as fixed effects; participants will be modelled as a random effect. Baseline will also be included as a covariate when the response involves change from baseline. An unstructured covariance structure will be used to model the covariance between a participant's multiple observations, with an alternative structure to be used if the model fails to converge, using a measure such as Akaike's information criterion to decide which structure will be used. If necessary, the response may be transformed before the analysis, with back-transforming to the original scale implemented for the results. For each PD parameter, the difference in LS treatment means, comparing LY3493269 (test) and placebo (reference), along with the 90% CI, will be reported.

Example of the SAS code to be used for the mixed effect model analysis:

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

9.5 Pharmacokinetic/Pharmacodynamic Analyses

PK/PD analyses or graphical explorations may be used to assess the relationship between LY3493269 doses and/or concentrations and

- Safety parameters, such as
  - QT interval corrected using Fridericia's formula (QTcF) interval
  - Blood pressure
  - Heart rate (HR)
  - PR interval,
- Tolerability parameters, such as
  - nausea

  - vomiting
  - diarrhea,
- PD parameters, such as
  - fasting glucose
  - fasting insulin
  - fasting C-peptide
  - fasting triglycerides
  - weight.

Endpoints may include but are not necessarily limited to those listed earlier.

The impact of anti-drug antibody (ADA) and its titers on LY3493269 clearance and drug effect, if applicable, may be evaluated.

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 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 participant has provided written informed consent and is ongoing at consent. A non-TEAE is defined as an AE which starts after informed consent but prior to dosing. A TEAE 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. TEAEs will be summarized by treatment, severity and relationship to the study drug. The frequency (the number of AEs, the number of participants experiencing an AE and the percentage of participants experiencing an AE) of TEAEs 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 (SAEs) will be listed.

Any AEs of special interest will be summarized and listed, these include cardiovascular events, gastrointestinal events (eg. , nausea, vomiting, diarrhea), hypersensitivity reactions, acute pancreatitis, and hypoglycemic events.

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. Glucose data will be listed and summarized by treatment together with changes from baseline, where baseline is defined as Day 1 predose.

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. Hypoglycemia is defined as follows:

- **Level 1 Hypoglycemia, Plasma glucose (PG) <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, PG <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.

- **Nocturnal Hypoglycemia:**

  Nocturnal hypoglycemia is a hypoglycemia event (including severe hypoglycemia) that occurs at night and presumably during sleep.

Investigator review of glucose results clinically indicative of hypoglycemia will be required.

To avoid duplicate reporting, all consecutive PG values <70 mg/dL (3.9 mmol/L) occurring within a 1-hour period may be considered to be a single hypoglycemic event

9.6.3 Concomitant medication

Concomitant medication will be coded using the World Health Organization (WHO) drug dictionary (Version WHODD MAR20B3). Concomitant medication will be listed.

9.6.4 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 the Day 1 predose assessment. Clinical chemistry, hematology and urinalysis data will be listed. Additionally, clinical

chemistry, hematology and urinalysis data outside the reference ranges will be listed and flagged on individual participant 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 Day 1 predose assessment. Figures of mean vital signs and mean changes from baseline profiles will be presented by treatment.

Values for individual participants will be listed.

Changes from baseline values will be analyzed using a repeated measurement mixed effect model. The model will include treatment, timepoint, and treatment-by-timepoint interaction as fixed effects; participant will be included as a random effect. Baseline will also be included as a covariate in the model. An unstructured covariance structure will be used to model the covariance between a participant's multiple observations, with an alternative structure to be used if the model fails to converge, using a measure such as Akaike's information criterion to decide which structure will be used. The difference in least-square treatment means, comparing LY3493269 (test) and placebo (reference), along with the 90% CI, will be reported. Example SAS code for the analysis:

```
proc mixed data=xxx;
   class time treat subject;
   model change = treat time treat*time base /residual ddfm=kr;
   repeated day / subject=subject type=un;
   lsmeans treat*day / cl pdiff alpha=0.1;
   ods output lsmeans=lsm diffs=estims;
run;
```

9.6.6 Electrocardiogram

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the PR, QT, QRS duration, RR and HR. In addition, 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 -0.5 h, -0.25, and predose assessments. Figures of mean ECG data and mean changes from baseline will be presented by treatment. The frequency of participants 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 participants 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 plasma LY3493269 concentration-ECG parameter analysis will be performed to assess the relationship between changes from baseline (mean of Day 1 -0.5 h, -0.25 h, and predose

triplicate assessments) in ECG parameters (QTc, PR interval, QRS duration, and HR) and plasma LY3493269 concentrations across all treatments. The change from baseline adjustment will be based on individual participant's Day 1 -0.5 h, -0.25 h, and predose values. 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 the lower limit of quantification/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:

$$\Delta ECG_{ijkl} = (\theta_0 + \eta_{0,i}) + \theta_1 TRT_j + (\theta_2 + \eta_{2,i}) C_{ijkl} + \theta_{3k} TIME_k + \theta_{4l} Day_l + \theta_5 TIME_k \times DAY_l + \theta_6 (ECG_{i,j,k=0,l=0} - \overline{ECG_{k=0,l=0}}) + \varepsilon_{ijkl}$$

where ΔECG_{ijkl} is the change from baseline in ECG parameter for participant i in treatment j at time k after dosing on day l. 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_{ijkl}, $\eta_{2,i}$ is the random effect associated with the slope θ_2, C_{ijkl} is the concentration for participant i in treatment j, time k, and day l, θ_{3k} is the fixed effect associated with time after dose k on the same day, θ_{4l} is the fixed effect associated to day l, θ_5 is the fixed effect associated with the interaction between time and day, θ_6 is the fixed effect associated with baseline $ECG_{i,j,k==0,l=0}$, $\overline{ECG_{k=0,l=0}}$ is the overall mean of $ECG_{i,j,k=0,l=0}$ (the mean of all the baseline ECG parameter values, at day 0, time 0), and ε_{ijkl} 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_{ijkl}, are Gaussian distributed with mean 0 and variance r.

If the model fails to converge, the interaction term will be omitted from the model, with day also omitted and time redefined to be time after the first dose if the model still fails to converge. The random effects may reduce to fixed effects and a different covariance structure may be used if there are further convergence issues.

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. The hysteresis loop plot between QTcF change from baseline concentration may be generated within 24 hours.

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=kr;
random intercept PKconc / type=un subject=subject;
estimate 'Placebo ' intercept 1 treat 1 0 PKconc 0/ CL alpha=0.1;
estimate 'XX mg LY3493269 ' intercept 1 treat 0 1 PKconc [cmax XXmg] / CL
alpha=0.1;
estimate 'XX mg LY3493269 - Placebo' treat -1 1 PKconc [cmax XXmg] / 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

Close hepatic monitoring

If a participant who had normal or near normal baseline alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBL) (i.e., <1.5× upper limit of normal [ULN]), experiences elevated ALT≥3× ULN, AST≥3× ULN, ALP≥2× ULN, or TBL≥2× ULN, laboratory tests should be repeated within 48 to 72 hours, including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyltransferase, and creatinine kinase to confirm the abnormality and to determine if it is increasing or decreasing.

In participants enrolled with elevated baseline ALT, AST, ALP or TBL (≥1.5× ULN), the thresholds for close monitoring are ALT≥2× baseline, AST≥2× baseline, ALP≥2× baseline, or TBL≥2× baseline.

At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses, (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor.

Comprehensive hepatic evaluation

If a study participant, who had baseline ALT, AST, ALP, TBL<1.5× ULN, experiences elevated ALT≥5× ULN, AST≥5× ULN, ALP ≥3× ULN, TBL ≥2× ULN, or elevated ALT, AST ≥3× ULN with hepatic signs/symptoms (severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia>5%), a comprehensive evaluation should be performed to search for possible causes of liver injury.

In participants who had elevated baseline ALT, AST, ALP, or TBL (≥1.5× ULN), the thresholds for performing this evaluation are ALT≥3× baseline, AST≥3× baseline, ALP≥2× baseline, TBL≥1.5× baseline, or ALT, AST ≥2× baseline with hepatic signs/symptoms.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time-international normalized ratio, viral hepatitis A, B, C, E, tests for autoimmune hepatitis, and an abdominal imaging study (for example, ultrasound or computed tomography scan).

Additional hepatic data collection in participants who have abnormal liver tests during the study

Additional hepatic safety data collection should be performed in participants who meet 1 or more of the following 5 conditions:

1. Elevation of serum ALT to ≥5× ULN on 2 or more consecutive blood tests (if baseline ALT<1.5x ULN)
   - In participants with baseline ALT≥1.5× ULN, the threshold is ALT≥3x baseline on 2 or more consecutive tests

2. Elevatation of TBL to ≥2× ULN (if baseline TBL <1.5× ULN)
   - In participants with baseline TBL ≥1.5× ULN, the threshold should be TBL ≥2x baseline

3. Elevation of serum ALP to ≥2× ULN on 2 or more consecutive blood tests (if baseline ALP <1.5× ULN)
   - In participants with baseline ALP≥1.5× ULN, the threshold is ALP ≥2× baseline on 2 or more consecutive blood tests

4. Hepatic event considered to be an SAE

5. Discontinuation of the investigational product due to a hepatic event

Where applicable, the following will be presented. The participants' 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 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 participant data listings.

9.6.8 Immunogenicity Assessments

The frequency and percentage of participants with pre-existing ADA and with TE ADA to LY3493269 will be tabulated and listed.

For participants 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 (1:10). For participants who are ADA positive at baseline, TE ADAs are defined as those with a 4-fold (2 dilution) increase in titer compared to baseline. The frequency and percentage of participants with cross-reactive and neutralizing antibodies, if measured, may also be tabulated for participants 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.

9.6.9 Appetite Analysis

To explore the effects of LY3493269 on meal intake and appetite sensation, participants will be asked to rate their appetite sensations using a 100-mm validated VAS for parameters of hunger, fullness, satiety, and prospective food consumption. Overall appetite will be derived using the four parameters. Overall appetite score is calculated as the average of the 4 individual scores:

$$Overall = (satiety + fullness + (100 - prospective\ food\ consumption) + (100 - hunger))/4$$

A higher overall appetite score indicates less appetite, and a lower score indicates more appetite.

The data will be listed and summarized, along with change from baseline (defined as Day 1 predose), by treatment and timepoint.

9.6.10 Hypersensitivity reactions

For all drug hypersensitivity reactions that occur, additional follow-up data will be collected to assess the participant's medical history, alternative causes, and symptoms.

These data will be listed.

9.6.11 Product Acceptability and Palatability Analyses

Responses from the product palatability questionnaires will be summarized categorically (frequency and percentage) and listed.

9.6.12 Body Weight

Body weight data, along with change from baseline, which is defined as Day 1 predose, will be summarized and listed. Figures of mean body weight data by treatment over time, as well as change from baseline, will be plotted.

9.6.13 Other assessments

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

10. INTERIM ANALYSES

Interim access to safety and tolerability (and any available PK or PD) data is scheduled to occur after every dosing session. The investigator will remain blinded, and the Lilly sponsor team will be unblinded during these reviews.

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 participants 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."

14. APPENDICES

Appendix 1: Document History

Status and Version	Date of Change	Summary/Reason for Changes
Final Version 1.0	NA	NA; the first version.
Final Version 2.0	08 Mar 2021	Included Day 1 in dose proportionality PK statistical analysis.
Final Version 3.0	24 SEP 2021	Removed SNAC statistical analysis, amended dose proportionality PK stats analysis to include all doses, and added independent dose normalized analysis.

NA = not applicable

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