Statistical Analysis Plan J1X-MC-GZHA (v2)

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

NCT04178733

Approval Date: 28-Jan-2020

STATISTICAL ANALYSIS PLAN

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Statistical Analysis Plan Status: Final Version 2
Statistical Analysis Plan Date: 22-January-2020

Study Drug: LY3493269

Sponsor Reference: J1X-MC-GZHA
Covance CRU Study: 1001215-8415534

Clinical Phase I

Approval Date: 28-Jan-2020 GMT

1. TABLE OF CONTENTS

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
AUC	Area under the concentration versus time curve
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(0-∞)	Area under the concentration versus time curve from time zero to infinity
AUC(0-168 h)	Area under the concentration versus time curve from time zero to 168 hours postdose
%AUC(t_{last}-∞)	Percentage of AUC(0-∞) extrapolated
BQL	Below the lower limit of quantitation
CI	Confidence interval
CL	Total body clearance of drug calculated after intravenous administration
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
CV	Coefficient of variation
ECG	Electrocardiogram
ICH	International Conference on Harmonisation
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects repeated measures
OGTT	Oral glucose tolerance test
PD	Pharmacodynamic
PG	Plasma Glucose
PK	Pharmacokinetic
QTcF	The QT interval corrected using Fridericia's formula

R_A	Accumulation ratio (AUC(0-∞))/AUC(0-168 h))
SAD	Single ascending dose
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
$t_{½}$	half-life associated with the terminal rate constant (λz) in non-compartmental analysis
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
ULN	Upper limit of normal
VAS	Visual analog scale
V_z	Volume of distribution during the terminal phase after intravenous administration
V_z/F	Apparent volume of distribution during the terminal phase after extra-vascular administration
V_{ss}	Volume of distribution at steady state after intravenous administration
V_{ss}/F	Apparent volume of distribution at steady state after extra-vascular administration
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 10 October 2019) and SAP version 1 (dated 02 December 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, PK and PD 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

Primary

- To evaluate the safety and tolerability of LY3493269 following single subcutaneous (SC) and intravenous (IV) doses in healthy participants.

Secondary

- To characterize the PK of LY3493269 following single SC and IV doses in healthy participants.

Exploratory

- To investigate the PD effects of LY3493269 following single SC doses in healthy participants.
- To explore immunogenicity of LY3493269 following single doses in healthy participants.
- To explore the effect of LY3493269 on appetite and food intake following single SC doses in healthy participants.

5. STUDY DESIGN

Study GZHA is a Phase 1, single-site, randomized, placebo controlled, single-ascending dose (SAD) study in healthy participants, to evaluate the safety, tolerability, and PK of LY3493269 administered as single SC doses and as a single IV dose. The PD effects of SC doses of LY3493269 on glycemic effects (including fasting glucose, insulin, and glucose and insulin during an oral glucose tolerance test [OGTT]) and appetite will be explored. For the SC cohorts, the investigator and participants will be blinded. The IV Cohort is open label with no placebo.

The planned LY3493269 SC doses for this study range from 0.15 mg to 7.5 mg. These 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 SC or IV 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, body weight, vital signs and ECGs]), PK and PD assessments.

Subcutaneous Administration Cohorts 1 through 6

This study includes up to 6 planned SC cohorts:

- SC Cohort 1: 0.15 mg (6 LY3493269: 2 Placebo)
- SC Cohort 2: 0.5 mg (6 LY3493269: 2 Placebo)
- SC Cohort 3: 1.5 mg (6 LY3493269: 2 Placebo)
- SC Cohort 4: 3.0 mg (6 LY3493269: 2 Placebo)
- SC Cohort 5: 5.0 mg (6 LY3493269: 2 Placebo)
- SC Cohort 6: 7.5 mg (6 LY3493269: 2 Placebo)

Cohorts 2 to 6 will be initiated only if the investigator and Eli Lilly and Company clinical pharmacologist deem the safety results in the preceding cohort to be acceptable through Day 8 from at least 6 participants dosed. In addition, all planned participants in the current cohort should have been dosed prior to escalation to the next cohort.

Intravenous Administration Cohort

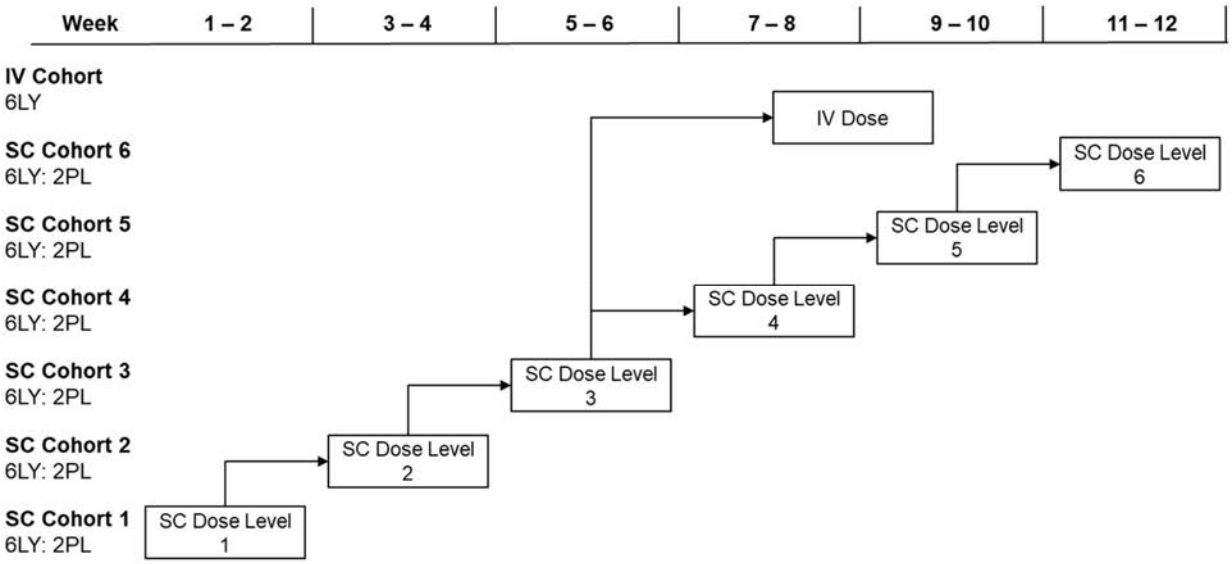
This study includes a single IV cohort (IV Cohort), where up to 6 healthy participants should complete dosing at the same level to provide sufficient PK sampling. The IV Cohort will be initiated based on review of safety and tolerability data from SC Cohort 3 and available 7-day PK data and/or PD data from at least 2 preceding SC cohorts.

All participants will receive LY3493269 only (that is no placebo group), as a single IV bolus dose. The planned dose is 0.5 mg. This dose is expected to be safe while providing plasma concentrations that can be adequately measured over the sampling time period enabling adequate characterization of the PK profile. The IV dose may be increased to a maximum of 1.5 mg or

decreased to a minimum of 0.25 mg depending on emerging data. It is intended that the IV dose will be administered sequentially, with 1 participant having completed the dosing and observed for at least 20 minutes before the next participant is dosed.

In the IV Cohort, 2 participants will initially receive the planned 0.5 mg dose. An additional 4 participants will receive investigational product following joint investigator and sponsor review of safety and tolerability data through at least 4 days postdose (including Day 5 safety labs and assessments) from the 2 initial participants.

Figure GZHA.1 illustrates the study design.



Abbreviations: IV = intravenous; LY = LY3493269; PL = Placebo; SC = subcutaneous.

6. TREATMENTS

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

Study Treatment Name	Treatment order in TFL
Placebo SC	1
0.15 mg LY3493269 SC	2
0.5 mg LY3493269 SC	3
0.5 mg LY3493269 IV	4
1.5 mg LY3493269 SC	5
3.0 mg LY3493269 SC	6
5.0 mg LY3493269 SC	7

7.5 mg LY3493269 SC	8

7. SAMPLE SIZE JUSTIFICATION

Up to 70 participants may be enrolled so that approximately 54 participants complete the study.

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

Participants who are randomized but not administered treatment prior to discontinuation may be replaced to ensure that approximately 8 participants complete each SC Cohort, and 6 to complete the IV cohort.

Participants who discontinue early mat 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 subjects who received at least one dose of study drug or placebo.

The "Pharmacokinetic" population will consist of all subjects who received at least one dose of study drug and have evaluable PK data.

The "Pharmacodynamic" population will consist of all subjects who received at least one dose of study drug 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 (e.g. the PK parameters: area under the concentration versus time curve [AUCs] and maximum observed drug concentration [C_{max}]) the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all subjects up to the point of withdrawal, with any subjects excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for subjects included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Mean change from baseline is the mean of all individual subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The individual subject's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

Data analysis will be performed using SAS® Version 9.4 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 using non-compartmental procedures in validated software program (Phoenix WinNonlin Version 8.1 or later).

Plasma concentrations of LY3493269 will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-t_{last})	h*ng/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(0-168 h)	h*ng/mL	area under the concentration versus time curve from time zero to 168 hours postdose
AUC(0-∞)	h*ng/mL	area under the concentration versus time curve from time zero to infinity
%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
$t_{½}$	h	half-life associated with the terminal rate constant (λz) in non-compartmental analysis
CL	L/h	total body clearance of drug calculated after intravenous administration
CL/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration
R_A	N/A	Accumulation ratio (AUC(0-∞))/AUC(0-168 h))
V_z	L	volume of distribution during the terminal phase after intravenous administration
V_Z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration
V_{ss}	L	volume of distribution at steady state after intravenous administration
V_{ss}/F	L	apparent volume of distribution at steady state after extra-vascular administration

Additional PK parameters may be calculated, as appropriate.

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.

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.

General PK Parameter Rules

- Actual sampling times will be used in the final analyses of individual PK parameters, except for non-bolus pre-dose sampling times which will be set to zero.

- C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than one time point, t_{max} will be assigned to the first occurrence of C_{max}.

- AUC parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive concentrations above the LLOQ, with at least one of these concentrations following C_{max}.

- AUC(0-∞) values where the percentage of the total area extrapolated is more than 20% will be flagged. Any AUC(0-∞) value excluded from summary statistics will be noted in the footnote of the summary table.

- Half-life ($t_{½}$) will be calculated, when appropriate, based on the apparent terminal log-linear portion of the concentration-time curve. The start of the terminal elimination phase for each subject will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in plasma concentrations. Half-life will only be calculated when a reliable estimate for this parameter can be obtained comprising of at least 3 data points. If $t_{½}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{½}$ value excluded from summary statistics will be documented in the footnote of the summary table.

- A uniform weighting scheme will be used in the regression analysis of the terminal log-linear portion of the concentration-time curve.

- The parameters based on predicted last observed drug concentration will be reported.

Individual PK Parameter Rules

- Only quantifiable concentrations will be used to calculate PK parameters with the exception of special handling of certain concentrations reported below the lower limit of quantitation (BQL). Plasma concentrations reported as BQL will be set to a value of zero when all of the following conditions are met:

    - The compound is non-endogenous.

    - The samples are from the initial dose period for a subject or from a subsequent dose period following a suitable wash-out period.

    - The time points occur before the first quantifiable concentration.

- All other BQL concentrations that do not meet the above criteria will be set to missing.

- Also, where two or more consecutive concentrations are BQL towards the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

- For multiple-dosing data, when pre-dose concentrations are missing, the value to be substituted will be the minimum observed drug concentration for the dosing interval.

Individual Concentration vs. Time Profiles

- Individual concentrations will be plotted utilizing actual sampling times.
- The terminal point selections will be indicated on a semi-logarithmic plot.

Average Concentration vs. Time Profiles

- The average concentration profiles will be graphed using scheduled (nominal) sampling times.
- The average concentration profiles will be graphed using arithmetic average concentrations.
- The pre-dose average concentration for single-dose data from non-endogenous compounds will be set to zero. Otherwise, only quantifiable concentrations will be used to calculate average concentrations.
- Concentrations at a sampling time exceeding the sampling time window specified in the protocol, or ± 10%, will be excluded from the average concentration profiles.
- Concentrations excluded from the mean calculation will be documented in the final study report.
- A concentration average will be plotted for a given sampling time only if 2/3 of the individual data at the time point have quantifiable measurements that are 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.

Treatment of Outliers during Pharmacokinetic Analysis

Application of this procedure to all PK analyses is not a requirement. Rather, this procedure provides justification for exclusion of data when scientifically appropriate. This procedure describes the methodology for identifying an individual value as an outlier for potential exclusion, but does not require that the value be excluded from analysis. The following methodology will not be used to exclude complete profiles from analysis.

Data within an Individual Profile
A value within an individual profile may be excluded from analysis if any of the following criteria are met:

- For PK profiles during single dosing of non-endogenous compounds, the concentration in a pre-dose sample is quantifiable.

- For any questionable datum that does not satisfy the above criteria, the profile will be evaluated and results reported with and without the suspected datum.

Data between Individual Profiles

1. If n<6, then the dataset is too small to conduct a reliable range test. Data will be analyzed with and without the atypical value, and both sets of results will be reported.

2. If n≥6, then an objective outlier test will be used to compare the atypical value to other values included in that calculation:

    a. Transform all values in the calculation to the logarithmic domain.

    b. Find the most extreme value from the arithmetic mean of the log transformed values and exclude that value from the dataset.

    c. Calculate the lower and upper bounds of the range defined by the arithmetic mean ±3*SD of the remaining log-transformed values.

    d. If the extreme value is within the range of arithmetic mean ±3*SD, then it is not an outlier and will be retained in the dataset.

    e. If the extreme value is outside the range of arithmetic mean ±3*SD, then it is an outlier and will be excluded from analysis.

If the remaining dataset contains another atypical datum suspected to be an outlier and n ≥ 6 following the exclusion, then repeat step 2 above. This evaluation may be repeated as many times as necessary, excluding only one suspected outlier in each iteration, until all data remaining in the dataset fall within the range of arithmetic mean ±3*SD of the log-transformed values.

Reporting of Excluded Values
Individual values excluded as outliers will be documented in the final report. Approval of the final report will connote approval of the exclusion.

9.3.2 Pharmacokinetic Statistical Methodology

PK dose proportionality will be assessed. Log-transformed C_{max}, AUC(0-t_{last}) and AUC(0-∞) of LY3493269 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.

A statistical analysis using the Kruskal-Wallis test[3] will be conducted to investigate the dose proportionality (independence) of t_{max}. The p-value will be calculated for the overall dose comparison.

All PK parameters will be summarized using descriptive statistics. Geometric means of the IV dose group and corresponding SC dose group will be used to discuss absolute bioavailability.

Examples of the SAS code that will be used are as follows:

```
proc mixed data=xxx;
model log_pk = log_dose / 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;
```

Kruskal-Wallis Test

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

9.4 Pharmacodynamic Assessment

9.4.1 Pharmacodynamic Analysis

The oral glucose tolerance test (OGTT) will be used to derive the following PD endpoints/biomarkers by Covance:

- Fasting (Pre-OGTT) glucose, insulin, C peptide and glucagon. Baseline for these parameters will be the Day -1 Pre-OGTT concentration.
- Concentrations of glucose, insulin, C peptide and glucagon during the OGTT. Baseline for these parameters will be the time-matched Day -1 Pre-OGTT concentration.
- AUC(0-2h) for glucose, insulin, C peptide and glucagon during the OGTT, derived using the trapezoidal rule. Baseline for these parameters will be the Day -1 AUC.

In addition, the following OGTT derived parameters will also be derived:

- HOMA-IR and HOMA-B based on fasting insulin and fasting glucose[4,5]

$$HOMA - IR = (FPI \times FPG)/22.5$$

$$HOMA - B = (20\ x\ FPI)/(FPG - 3.5)$$

where FPI = fasting plasma insulin in μU/mL, FPG = fasting plasma glucose in mmol/L

Or alternatively,

$$HOMA - IR = (FPI \times FPG)/405$$

$$HOMA - B = (360\ x\ FPI)/(FPG - 63)$$

where FPI = fasting plasma insulin in μU/mL, FPG = fasting plasma glucose in mg/dL

- Insulinogenic index[4,5]

$$IGI = \frac{\Delta Insulin_{0-30min}}{\Delta Glucose_{0-30min}}$$

where glucose is in mg/dL and insulin is in μU/mL

- Insulin sensitivity (Matsuda Index)[6]

$$\text{ISI} = \frac{10000}{\sqrt{G0 * I0 * \frac{Glucose\ AUC(0-2h)}{2h} * \frac{Insulin\ AUC(0-2h)}{2h}}}$$

where glucose is in mg/dL and insulin is in μU/mL

- OGIS[7]

$$OGIS = \frac{1}{2} \times (B + sqrt(B^2 + 4 \times p5 \times p6 \times (G90 - Gcl) \times Cl_{OGTT}))$$

$$\text{where, } B = (p5 \times (G90 - Gcl) + 1) \times Cl_{OGTT}$$

$$Cl_{OGTT} = p4 \times \frac{\frac{p1 \times D_0 - V \times \frac{G120 - G90}{T}}{G90} + \frac{p3}{G0}}{I90 - I0 + p2}$$

$$p1 = 6.50,\ p2 = 1951,\ p3 = 4514,\ p4 = 792,\ p5 = 11.8 \times 10^{-3},\ p6 = 173$$

D_0, glucose dose of OGTT normalized for body surface area (mmol/m^2)

V = 10^4 (glucose distribution volume, ml/m^2)

T = 30 (time interval between G120 and G90, min)

Gcl = 5 (typical clamp glucose concentration, mmol/L)

OGIS (ml/min.m^2)

BMI (kg/m^2)

Fasting glucose (mmol/L)

Fasting insulin (pmol/L)

2h Glucose (mmol/L)

- Predicted clamp-derived insulin sensitivity (M value)[8]

$$log_e PREDIM = A + B \times log_e(OGIS) + C \times log_e(BMI) + D \times log_e(2hGlucose) + E \times log_e(FastingInsulin)$$

$$PREDIM = e^{log_e(PREDIM)}$$

$$where\ A = 2.8846219, B = 0.5208520, C = -0.8223363, D = -0.4191242, E = -0.2427896\ and\ OGIS = OGTT\ derived\ Oral\ glucose\ insulin\ sensititivity\ index$$

CCI

[redacted]

Individual observed (spaghetti plots) and mean time profile of the postdose PD parameters, including baseline corrected parameters, will be plotted by treatment group.

Absolute values as well as change from baseline fasting glucose, insulin and C-peptide will be analyzed statistically. Parameters will be untransformed before statistical analyses. The parameters will be analyzed using mixed-effects repeated measures (MMRM) models to evaluate treatment effects as well as treatment comparisons. The model will include treatment, timepoint, and treatment-by-timepoint interaction as fixed effects, and subject as a random effect. Baseline values will be included as a covariate for the change from baseline analysis. An unstructured covariance structure will be used and a compound symmetry structure may be used if this fails to converge. Least-squares means as well as 90% CIs for the difference of LY3493269 compared with placebo will be reported.

Example of SAS code (for the change from baseline analysis) as follows.

```
proc mixed data=xxx;
class treatment timepoint subject;
model change = baseline treatment timepoint treatment*timepoint
/residual ddfm=kr;
repeated timepoint / subject=subject type=UN;
lsmeans treatment*timepoint / cl pdiff alpha=0.1;
ods output lsmeans=lsm diffs=estims;
run;
```

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 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 22.0 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.

Discontinuations due to AEs will be listed.

9.5.2 Glucose Monitoring and Hypoglycemia

During the study, blood glucose concentrations will be monitored for safety assessments. Glucose data will be listed, and if sufficient data is collected, 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:

Documented Glucose Alert Level (Level 1), Plasma Glucose (PG) ≤70 mg/dL (3.9 mmol/L):

– Symptomatic hypoglycemia: an event during which typical symptoms of hypoglycemia are accompanied by PG ≤70 mg/dL (3.9 mmol/L)

– Asymptomatic hypoglycemia: an event not accompanied by typical symptoms of hypoglycemia but with PG ≤70 mg/dL (3.9 mmol/L)

– Unspecified hypoglycemia: an event during which PG ≤70 mg/dL (3.9 mmol/L) but no information relative to symptoms of hypoglycaemia

Documented Clinically Significant Hypoglycemia (Level 2) PG <54 mg/dL (3.0 mmol/L):

– Symptomatic hypoglycemia: an event during which typical symptoms of hypoglycemia are accompanied by PG <54 mg/dL (3.0 mmol/L)

– Asymptomatic hypoglycemia: an event not accompanied by typical symptoms of hypoglycemia but with PG <54 mg/dL (3.0 mmol/L)

– Unspecified hypoglycemia: an event during which PG ≤<4 mg/dL (3.0 mmol/L) but no information relative to symptoms of hypoglycemia was recorded.

Severe hypoglycemia (Level 3): an event requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. During these episodes, the subject has an altered mental status and cannot assist in their care, is semiconscious or unconscious, or experienced coma with or without seizures and may require parenteral therapy. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of blood glucose concentration to normal is considered sufficient evidence that the event was induced by a low PG concentration (≤70 mg/dL [3.9 mmol/L]).

Other Hypoglycemia:

Nocturnal hypoglycemia: any hypoglycemic event (documented symptomatic, asymptomatic, probable symptomatic, or severe hypoglycemia) that occurs between bedtime and waking

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

9.5.3 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version March 2019). Concomitant medication will be listed.

9.5.4 Clinical laboratory parameters

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

9.5.5 Vital signs

Vital signs data will be summarized by treatment group 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 subjects will be listed.

For change from baseline values, a mixed-model repeated-measure model with treatment, time (of measurement), and treatment-by-time interaction as fixed effects, subject as a random effect, and baseline as covariate will be used to determine the effects of LY3493269. Least-squares means as well as 90% CIs for the difference of LY3493269 compared with placebo will be

reported. An unstructured covariance structure will be used and a compound symmetry structure may be used if this fails to converge.

Example of SAS code (for the change from baseline analysis) as follows.

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proc mixed data=xxx;
class treatment timepoint subject;
model change = baseline treatment timepoint treatment*timepoint
/residual ddfm=kr;
repeated timepoint / subject=subject type=UN;
lsmeans treatment*timepoint / cl pdiff alpha=0.1;
ods output lsmeans=lsm diffs=estims;
run;
```

The relationship between the time-matched LY3493269 concentrations and changes from baseline and mean time-matched placebo for all vital signs parameters will be explored graphically using a scatter plot. A regression analysis using a linear mixed-effects model will be performed. A plasma LY3493269 concentration- vital signs data analysis will be performed to assess the changes from baseline (Day 1 predose) and mean time-matched placebo for each vital sign relative to plasma LY3493269 concentrations across all active treatments. The change from baseline adjustment will be based on each individual subject's Day 1 predose value, and an additional placebo adjustment will be based on mean time-matched placebo values. The analysis will be performed by plotting double delta vital signs measurement against LY3493269 concentrations, including all post dosing timepoints. A linear mixed-effects model will be performed on the double delta vital signs values and will include LY3493269 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 vital signs result and 90% CI at the geometric mean C_{max} will also be presented.

Example of SAS code as follows:

```
proc mixed data=xxx;
  class subject;
  model DDchg = concentration / solution cl alpha=0.1 ddfm=kr;
  random subject;
  ods output estimates=est;
  ods output solutionf=sol;
run;
```

9.5.6 Electrocardiogram (ECG)

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the PR, QT, RR, QRS duration 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 mean of triplicate data will be used for reporting. The ECG data will be summarized by treatment group together with changes from baseline, where baseline is defined as the mean of the triplicate Day 1 predose assessments (-30, -15 and 0 minute). 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 QTcF postdose values, according to the following categories: >450 ms, >480 ms and >500 ms, will be summarized by treatment.

The relationship between the time-matched LY3493269 concentrations and changes from baseline and mean time-matched placebo on QTcF will be explored graphically using a scatter plot. A regression analysis using a linear mixed-effects model will be performed. A plasma LY3493269 concentration-QTcF analysis will be performed to assess the changes from baseline (Day 1 predose) and mean time-matched placebo in the QTcF interval relative to plasma LY3493269 concentrations across all active treatments. The change from baseline adjustment will be based on each individual subject's Day 1 predose value, and an additional placebo adjustment will be based on mean time-matched placebo values. The analysis will be performed by plotting double delta QTcF against LY3493269 concentrations, including all post dosing timepoints. A linear mixed-effects model will be performed on the double delta QTcF values and will include LY3493269 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. The analysis will also be produced for heart rate and PR.

Example of SAS code as follows:

```
proc mixed data=xxx;
  class subject;
  model DDchg = concentration / solution cl alpha=0.1 ddfm=kr;
  random subject;
  ods output estimates=est;
  ods output solutionf=sol;
run;
```

9.5.7 Immunogenicity Assessments

The frequency and percentage of subjects with pre-existing antidrug antibody (ADA) and with treatment-emergent ADAs (TE ADA) to LY3493269 may be tabulated and listed if available.

For subjects who are ADA negative at baseline, TE ADAs are defined as those with a signal increase, greater than assay variability, compared to baseline. The frequency of cross-reactive binding to native GIP, GLP-1 or neutralizing antibodies may also be tabulated in TE ADA+ participants, when available.

9.5.8 Injection-Site Reactions

Injection-site assessments for local tolerability will be conducted, when reported as

- an AE from a subject, or

- a clinical observation from an investigator.

Reported injection-site reactions will be characterized within the following categories:

- edema
- erythema
- induration
- pruritus
- pain

In case of an AE of injection-site reaction, pain data will be listed.

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

9.5.9 Appetite Analysis

To explore the effects of LY3493269 on meal intake and appetite sensation, subjects will be asked to rate their appetite sensations using a 100-mm visual analog scale (VAS) for parameters of hunger, fullness, satiety, and prospective food consumption prior to dosing on Day 1, and in the fasted state while inpatient as well as on scheduled outpatient visits.

The VAS is presented as a 10-cm (100-mm) line, anchored by verbal descriptors, usually "extremely" and "not at all". Subjects are required to rate their subjective sensations on four 100 mm scales combined with questions similar to the following:

1. "How hungry do you feel?"

2. "How satisfied do you feel?"

3. "How full do you feel?"

4. "How much do you think you could eat?"

A staff member will use a caliper to measure the distance from 0 to the mark that the subject placed on the VAS and record the measurement in the source document. Overall appetite score is calculated as the average of the 4 individual scores: [satiety + fullness + (100-prospective food consumption) + (100-hunger)] / 4.

The individual VAS measurements and overall appetite score will be listed and summarized by treatment and timepoint, alongside change from baseline (Day 1 predose).

The individual parameters, and overall score, will be analyzed using an MMRM model to evaluate treatment effects as well as treatment comparisons. The model will include treatment, timepoint, and treatment-by-timepoint interaction as fixed effects, and subject as a random effect. An unstructured covariance structure will be used and a compound symmetry structure may be used if this fails to converge. Least-squares means as well as 90% CIs for the difference of LY3493269 compared with placebo will be reported. The distribution of the data will be tested prior to analyses and should the distribution indicate a parametric analysis not to be

appropriate, a non-parametric analysis will be used instead. Change from baseline (Day 1 predose) will also be analysed, with a covariate for baseline added to the model.

9.5.10 Body Weight

Body weight data will be listed and summarized by treatment group, alongside changes from baseline (Day 1 predose).

Change from baseline body weight will be analyzed using an MMRM model to evaluate treatment effects as well as treatment comparisons. The model will include treatment, timepoint, and treatment-by-timepoint interaction as fixed effects, and subject as a random effect. Baseline values will be included as a covariate for the change from baseline analysis. An unstructured covariance structure will be used and a compound symmetry structure may be used if this fails to converge. Least-squares means as well as 90% CIs for the difference of LY3493269 compared with placebo will be reported.

9.5.11 Hypersensitivity reactions

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

These data will be listed.

9.5.12 Hepatic Monitoring

If a subject experiences elevated alanine aminotransferase ≥3× upper limit of normal (ULN), alkaline phosphatase ≥2× ULN, or elevated total bilirubin ≥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 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 subject data listings.

9.5.13 Pancreatic Safety

Serum amylase and lipase measurements will be collected as part of the clinical laboratory testing at time points specified in the protocol Additional measurements may be performed at the investigator's discretion.

Further diagnostic assessments will be recommended whenever lipase and/or amylase are confirmed to be ≥3× ULN at any visit post-treatment sequence allocation even if the participant is asymptomatic. If pancreatitis is suspected, the case will be further defined during an adjudication process.

These data will be listed.

9.5.14 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. This schedule may be modified as applicable, based on emerging safety and/or tolerability data. The purpose of these reviews is to guide dose selection for the next dosing cohort. Prior to confirming the dose and initiating the IV Cohort, preliminary PK data from at least 2 preceding SC cohort must be reviewed.

The investigator and the Lilly sponsor team will jointly make the determination regarding dose escalation based upon their review of the safety and tolerability data, and PK or PD results if available. In addition, these data may be used to guide dose selection and inform the need to adjust timing of procedures/sampling schedules for the current or future studies.

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.

3. Lehmann EL. Nonparametrics: Statistical Methods Based on Ranks. San Francisco, CA: Holden-Day; 1975.

4. Seltzer et al, 1967: Seltzer et al, Insulin Secretion in Response to Glycemic Stimulus: Relation of Delayed Initial Release to Carbohydrate Intolerance in Mild Diabetes Mellitus. The Journal of Clinical Investigation. 1967; 46(3):323-335.

5. Utzschneider et al, 2009: Utzschneider et al. Oral disposition index predicts the development of future diabetes above and beyond fasting and 2-h glucose levels. Diabetes Care. 2009 Feb; 32(2):335-41.

6. Matsuda et al 1999, based on 2h OGTT: Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care. 1999; 22(9):1462-1470.

7. Tura et al. Prediction of clamp-derived insulin sensitivity from the oral glucose insulin sensitivity index. Diabetologia. 2018 May; 61(5):1135-1141

8. Tura et al 2018, based on 2h OGTT: Prediction of clamp-derived insulin sensitivity from the oral glucose insulin sensitivity index. Diabetologia. 2018 May; 61(5):1135-1141.

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 = 423890fd-cd31-4770-9311-686210af71e0

Approver: PPD

Approval Date & Time: 28-Jan-2020 15:12:31 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 28-Jan-2020 15:18:02 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 28-Jan-2020 15:27:31 GMT

Signature meaning: Approved