Statistical Analysis Plan J1X-MC-GZHC

Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Multiple-Ascending Subcutaneous Doses of LY3493269 in Patients with Type 2 Diabetes Mellitus

NCT04515576

Approval Date: 03-Aug-2020

STATISTICAL ANALYSIS PLAN

Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Multiple-Ascending Subcutaneous Doses of LY3493269 in Patients with Type 2 Diabetes Mellitus

Statistical Analysis Plan Status: Final
Statistical Analysis Plan Date: 02-June-2020

Study Drug: LY3493269

Sponsor Reference: J1X-MC-GZHC
Covance CRU Study: 1000071-8441078

Clinical Phase I

Approval Date: 03-Aug-2020 GMT

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2. ABBREVIATIONS

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

%AUC(t_{last}-∞)	Percentage of AUC(0-∞) extrapolated
AE	Adverse event
ADA	Antidrug antibody
AUC	Area under the concentration versus time curve
AUCτ	Area under the concentration versus time curve during the dosing interval
AUC(0-∞)	Area under the concentration versus time curve from time zero to infinity
AUC(0-24)	Area under the concentration versus time curve from time zero to 24 h postdose
$AUC_{0\text{-}120min}$	Area under the concentration versus time curve from time zero to 120 minutes
AUC(0-168)	Area under the concentration versus time curve from time zero to 168 h postdose
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
BMI	Body mass index
BQL	Below the quantifiable lower limit of the assay
CI	Confidence interval
C_{last}	Last quantifiable drug concentration
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
C_{max}	Maximum observed drug concentration
$C_{predose}$	Predose observed drug concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
ECG	Electrocardiogram
FG	Fasting glucose

ΔG30	30-minute glucose in OGTT-baseline (0 minute) fasting glucose in OGTT
HbA1c	Glycated hemoglobin
HDL	High-density lipoprotein
HOMA2-B	Homeostatic model assessment for beta-cell function
HOMA2-IR	Homeostatic model assessment for insulin resistance
ΔI30	30-minute insulin in OGTT-baseline (0 minute) fasting insulin in OGTT
ICH	International Conference on Harmonisation
LDL	Low-density lipoprotein
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
OGIS	Oral glucose insulin sensitivity
OGTT	Oral glucose tolerance test
QW	Once-weekly
PD	Pharmacodynamic
PG	Plasma glucose
PK	Pharmacokinetic
R_A(AUC)	Accumulation ratio based upon AUCτ
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
T2DM	Type 2 diabetes mellitus
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

VLDL	Very low-density lipoprotein
V_z/F	Apparent volume of distribution during the terminal phase 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 27 May 2020) and protocol amendment (a) (final version dated 11 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, PK and PD analyses of data. In general, the analyses are based on information from the protocol, unless they have been modified in 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 4 once-weekly subcutaneous (SC) doses.

The primary endpoints of the study are:

- Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs).

4.2 Secondary Objectives

The secondary objectives of the study are:

- To characterize the PK of LY3493269 following 4 once-weekly SC doses.

- To evaluate the change in fasting glucose (FG) following 4 once-weekly SC doses of LY3493269 and dulaglutide.

The secondary endpoints of the study are:

- Maximum observed drug concentration (C_{max}) and area under the concentration versus time curve (AUC).
- Change from baseline in FG.

4.3 Exploratory Objectives

The exploratory objectives of the study are:

- To explore PD effects of LY3493269 and dulaglutide following 4 once-weekly SC doses.
- To characterize the immunogenicity of LY3493269 following 4 once-weekly SC doses.

The exploratory PD endpoints of the study are:

- Change from baseline in mean daily plasma glucose (PG) (6-point PG profile).
- Change from baseline in glycated hemoglobin (HbA1c).
- Change from premeal fasting during oral glucose tolerance test (OGTT) for:
  - PG concentrations
  - insulin concentrations
  - C-peptide concentrations
  - glucagon concentrations.
- Change from baseline in indices of beta-cell function in:
  - homeostatic model assessment for beta-cell function (HOMA2-B)
  - disposition index from OGTT
  - 30 minute insulin in OGTT-baseline (0 minute) fasting insulin in OGTT (ΔI30)/30 minute glucose in OGTT-baseline (0 minute) FG in OGTT (ΔG30) from OGTT
  - Insulin AUC from 0 to 120 minutes ($AUC_{0\text{-}120min}$) from OGTT.
- Change from baseline in:
  - Fasting insulin indices:
    - homeostatic model assessment for insulin resistance (HOMA2-IR)
    - fasting insulin.
  - postprandial insulin sensitivity indices
    - Matsuda
    - Oral glucose insulin sensitivity (OGIS)
    - Stumvoll.
- Change from baseline in fasting lipid parameters:
  - triglycerides
  - total cholesterol, and
  - low-density lipoprotein (LDL)-, high-density lipoprotein (HDL)-, and very low-density lipoprotein (VLDL)-cholesterol.
- Change from baseline in body weight.
- Change from baseline in waist circumference.

- Change from baseline in gastric emptying.
- Change in appetite visual analog scale at fasting.

The exploratory endpoint for immunogenicity is:

- Incidence of treatment-emergent antidrug antibody (ADA).

5. STUDY DESIGN

Study GZHC is a Phase 1, randomized, investigator- and patient-blind, placebo-controlled, comparator-controlled, 4-week multiple-dose escalation study in patients with type 2 diabetes mellitus (T2DM).

Trulicity (dulaglutide) will be used as a positive control for PD of glucagon-like-peptide 1 pharmacology.

A general schema for GZHC can be seen in Figure 1.

Up to 4 cohorts are planned to receive a weekly dose of study intervention for 4 weeks. Patients found to be eligible according to the study entry criteria will be randomly assigned to receive LY3493269, placebo, or dulaglutide. Patients not randomly assigned to LY3493269 will receive a CCI once-weekly (QW) for 4 weeks. Depending on their cohort, patients randomly assigned to LY3493269 will receive CCI QW for 4 weeks. Cohorts 1 and 2 will receive 4 fixed doses. Cohorts 3 and 4 will receive the weekly doses in stepwise increments, as guided by emerging tolerability, PK, and/or PD data in the preceding dose cohorts.

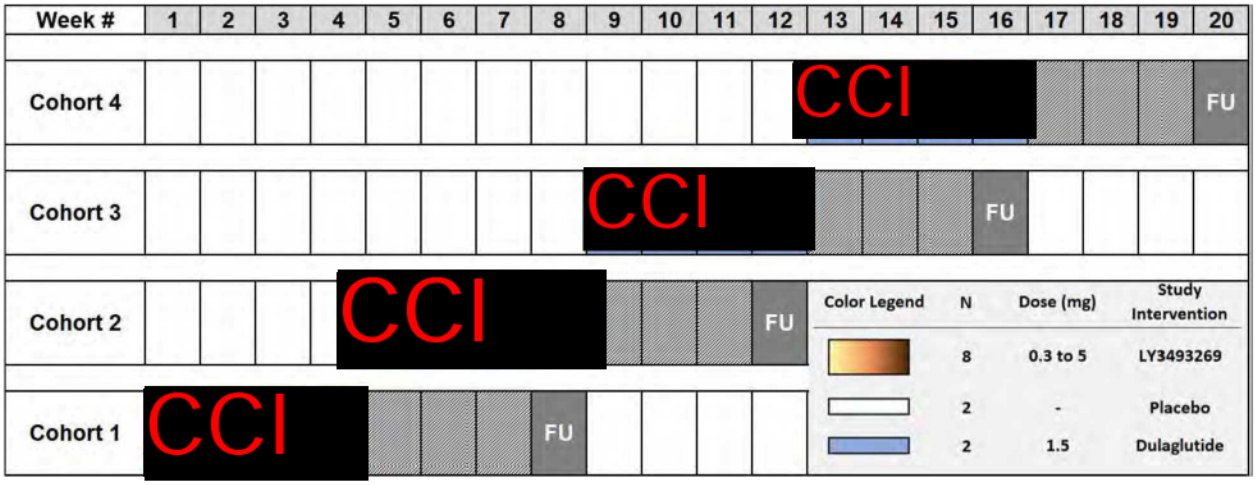

Figure 1 - General schema for GZHC

7. SAMPLE SIZE JUSTIFICATION

Approximately 64 patients may be randomly assigned to study intervention such that approximately 12 evaluable patients from each of the 4 cohorts complete the study. In each cohort, patients will be randomly assigned to

- 8 LY3493269
- 2 dulaglutide, and
- 2 placebo.

If patients are discontinued during the study, additional patients may be enrolled as replacements for these patients. The sample size is considered sufficient for evaluating the primary objective of this study.

8. DEFINITION OF ANALYSIS POPULATIONS

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

The "Pharmacokinetic" population will consist of all patients who received at least 1 dose of LY3493269 and have evaluable PK sample.

The "Pharmacodynamic" population will consist of all patients who received at least 1 dose of study intervention and have evaluable PD sample.

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: 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 patients up to the point of withdrawal, with any patients excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for patients 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 patients' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual patient's baseline value from the value at the timepoint. The individual patient'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 Patient Disposition

Patient disposition will be listed. The demographic variables age, sex, race, ethnicity, body weight, height and body mass index will be summarized and listed. In addition, screening HbA1c, fasting serum triglyceride, and fasting PG will be summarized and listed.

All other demographic variables will be listed only.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

Noncompartmental methods applied with a validated software program (Phoenix WinNonlin Version 8.1 or later) to the plasma concentrations of LY3493269 will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-t_{last})	ng.h/mL	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
AUC(0-168)	ng.h/mL	area under the concentration versus time curve from time zero to 168h postdose
AUCτ	ng.h/mL	area under the concentration versus time curve during the dosing interval
C_{max}	ng/mL	maximum observed drug concentration
$C_{predose}$	ng/mL	predose observed drug concentration
t_{max}	h	time of maximum observed drug concentration
$t_{1/2}$	h	half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis at Week 4 only
CL/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration at Week 4 only (for Cohorts 1 and 2)
V_Z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration at Week 4 only (for Cohorts 1 and 2)
Peak-to-Trough	NA	peak to trough ratio (for Cohorts 1 and 2)
R_A(AUC)	NA	accumulation ratio based upon AUCτ (Cohorts 1 and 2 only) $$\text{RA(AUC)} = \frac{AUC(Week\ 4)}{AUC(Week\ 1)}$$

Additional PK parameters may be calculated, as appropriate.

The software and version used for the final analyses will be specified in the CSR. Any exceptions or special handling of data will be clearly documented within the final study report.

Formatting of tables, figures and abbreviations will follow the Eli Lilly Global PK/PD/TS Tool: NON-COMPARTMENTAL PHARMACOKINETIC STYLE GUIDE. The version of the tool effective at the time of PK analysis will be followed.

General PK Parameter Rules

- Actual sampling times will be used in the final analyses of individual PK parameters, except for pre-dose sampling times which will be set to zero. For multiple dose profiles, the pre-dose time will be set to zero unless a time deviation falls outside of the protocol blood collection time window which is considered to impact PK parameter derivation.

- C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than one timepoint, 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 plasma concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}.

- Half-life ($t_{1/2}$) 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 patient 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 $t_{1/2}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{1/2}$ 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 drug concentration (C_{last}) 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 patient 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.

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.

<u>Data Within an Individual Profile</u>
A value within an individual profile may be excluded from analysis and will be decided at time of review if any of the following criteria are met:

- For PK profiles during multiple dosing, the concentration of the pre-dose sample exceeds all measured concentrations for that individual in the subsequent post-dose samples.
- 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

Log-transformed C_{max} and AUC(0- τ) parameters of LY3493269 after the first dose 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. Between patient estimates will also be provided.

Example of the SAS code for the analysis:

```
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;
```

The 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;
```
Insert stats methodology here.

9.4 Pharmacodynamic Assessment

9.4.1 Pharmacodynamic Analysis

Plasma concentrations of acetaminophen will be used to determine the following parameters using non-compartmental procedures in validated software program (Phoenix WinNonlin Version 8.1 or later).

Parameter	Units	Definition
AUC(0-∞)	ng.h/mL	area under the concentration versus time curve from time zero to infinity
AUC(0-24)	ng.h/mL	area under the concentration versus time curve from time zero to 24h postdose
%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
$t_{1/2}$	h	half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
CL/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration
V_Z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration

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

All PD parameters will be summarized and tabulated by treatment group and day. Appropriate summary statistics, as well as changes from baseline, will be provided for all of the parameters including (where the baseline is defined in the brackets next to the parameter):

- Mean daily PG from 6-point glucose profile (Day -2)
- HbA1c (Day 1 predose)
- PG concentrations following the OGTT (Day -1)

- Insulin concentrations during the OGTT (Day -1 pre-OGTT)
- C-peptide concentrations during the OGTT (Day -1 pre-OGTT)
- Glucagon concentrations during the OGTT (Day -1 pre-OGTT)
- HOMA2-B (Day -1)
- Disposition index from OGTT (Day -1)
- ΔI30/ΔG30 from OGTT (Day -1)
- Insulin $AUC_{0\text{-}120min}$ from OGTT (Day -1)
- HOMA2-IR (Day -1)
- Fasting insulin (Day -1)
- Matsuda (Day -1)
- OGIS (Day -1)
- Stumvoll (Day -1)
- Triglycerides (Day 1 predose)
- Total cholesterol (Day 1 predose)
- LDL-, HDL-, and VLDL-cholesterol (Day 1 predose)
- Gastric emptying (Day -1)
- Appetite visual analog scale at fasting (Day 1 predose)
- FG (Day 1 predose)
- Fasting C-peptide

Individual observed and mean time profiles of the postdose PD parameters will be plotted by treatment groups.

Additionally, the endpoints body weight and waist circumference, as well as change from baseline, defined as Day -2, will be summarized and tabulated by treatment group and day.

The 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 FG[3,4]

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

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

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[3,4]

$$IGI = \frac{\Delta I30}{\Delta G30},$$

where $\Delta I30$ is the change in insulin from time zero to 30 minutes, $\Delta G30$ is the change in glucose from time zero to 30 minutes, glucose is in mg/dL and insulin is in µU/mL.

- Insulin sensitivity (Matsuda Index)[5]

$$\text{ISI} = \frac{10000}{\sqrt{G0 \times I0 \times \frac{AUC_G(0-2h)}{2h} \times \frac{AUC_I(0-2h)}{2h}}},$$

where glucose is in mg/dL and insulin is in µU/mL, AUC_G is the AUC of glucose, AUC_I is the AUC of insulin, G0 is the glucose observation at time zero, I0 is the insulin observation at time zero.

- OGIS[6]

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

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

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

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

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),

Fasting glucose (mmol/L),

Fasting insulin (pmol/L),

- Predicted clamp-derived insulin sensitivity (M value)[7]

$$log_e PREDIM = A + B \times log_e(OGIS) + C \times log_e(BMI) + D \times log_e(G120) + E \times log_e(IF),$$

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

where $A = 2.8846219, B = 0.5208520, C = -0.8223363, D = -0.4191242,$

$E = -0.2427896, IF = Fasting\ insulin$, BMI = Body mass index,

$and\ OGIS = OGTT\ derived\ Oral\ glucose\ insulin\ sensititivity\ index.$

- Stumvoll index[8]

$$\text{SI} = 0.222 - 0.00333 \times BMI - 7.79 \times 10^{-5} \times I120 - 0.000422 \times age,$$

where insulin is in pmol/L.

Exploratory mechanistic biomarkers include:

- Fasting lipid panel (triglycerides, total cholesterol, LDL-, HDL- and VLDL-cholesterol). Baseline for these parameters will be Day 1 predose.

9.4.2 Pharmacodynamic Statistical Methodology

The PD parameters from the placebo-treated patients across all cohorts will be pooled for the final analysis. Dulaglutide-treated patients will also be similarly pooled.

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, as well as the change from baseline parameters, will be analyzed using a repeated measure mixed effect model. In the model, treatment, visit, and treatment-by-visit interaction will be modelled as fixed effects; patients 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 patient's multiple observations, with an alternative structure such as compound symmetry to be used if the model fails to converge. If necessary, the response may be transformed before the analysis. For each PD parameter, the difference in least-square treatment means, comparing both LY3493269 (test) and dulaglutide (reference), LY3493269 (test) and placebo (reference), and dulaglutide (test) and placebo (reference), along with the 90% CI and p-value, will be reported. For the change of baseline responses that have only one timepoint, an analysis of covariance model will be fitted instead.

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

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

The primary acetaminophen PK parameters, C_{max}, AUC(0-∞), and AUC(0-24) will be analyzed to assess the gastric-emptying effect of LY3493269 using a repeated measure mixed effect model. The response will be the log of the baseline adjusted PK parameter, where the baseline adjustment is the ratio of the value to Day -1 value. The model will include treatment, day, and treatment-by-day interaction as fixed effects; patient will be used as a random effect. Baseline (which is defined as the Day -1 value) will also be included as covariate for the analysis. An unstructured covariance structure will be used, with an alternative structure such as compound symmetry used if the model fails to converge. The difference in least-square treatment means, comparing LY3493269 (test) to dulaglutide (reference), LY3493269 (test) to placebo (reference), and dulaglutide (test) to placebo (reference), along with the 90% CI, and their respective least-squares means will be back-transformed to produce the ratio of geometric means and the CIs; the p-value will also be reported.

Example of SAS code for the analysis:

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

The parameter t_{max} of acetaminophen will be analyzed non-parametrically with medians, the median of the differences comparing LY3493269 (test) and dulaglutide (reference), LY3493269 (test) to placebo (reference), and dulaglutide (test) to placebo (reference), and corresponding 90% CI presented alongside the p-value from the Wilcoxon signed-rank test.

Example SAS code to be used for the Wilcoxon signed-rank test:

```
proc univariate data = xxx cipctldf(alpha = 0.1);
 var ref test dif;
 ods output quantiles = quant;
 ods output testsforlocation = out;
run;
```

9.5 Pharmacokinetic/Pharmacodynamic Analysis

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

- Safety parameters, such as
  - QTcF interval
  - blood pressure
  - HR
  - PR interval
- Tolerability parameters, such as
  - nausea
  - vomiting
  - diarrhea
- PD parameters, such as
  - FG
  - HbA1c
  - VAS score
  - weight.

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

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 patient 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 patients experiencing an AE and the percentage of patients 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 events, injection-site reactions, hypersensitivity reactions, acute pancreatitis, and hypoglycemic events. AEs by day of onset will be presented.

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:

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

  – **Documented Symptomatic hypoglycemia:** any time a patient feels that he or she is experiencing symptoms and/or signs associated with hypoglycemia and has a PG level of ≤70 mg/dL (3.9 mmol/L).

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

  – Documented Unspecified hypoglycemia: any event with no information about symptoms of hypoglycaemia available, but with a measured PG of ≤70 mg/dL (3.9 mmol/L).

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

  – Documented Symptomatic hypoglycemia: any time a patient feels that he or she is experiencing symptoms and/or signs associated with hypoglycemia are has a PG level of <54 mg/dL (3.0 mmol/L)

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

  – Documented Unspecified hypoglycemia: any event with no information about symptoms of hypoglycaemia available, but with a measured PG <54 mg/dL (3.0 mmol/L).

- **Severe hypoglycemia (Level 3):**

  – Severe hypoglycemia: an episode with severe cognitive impairment requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Blood glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of BG to normal is considered sufficient evidence that the event was induced by a low BG concentration.

- **Other Hypoglycemia:**

  Nocturnal hypoglycemia: any hypoglycemic event that occurs between bedtime and waking.

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

9.6.3 Concomitant medication

Concomitant medication will be coded using the 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 patient 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 patients will be listed.

Changes from baseline values will be analyzed using a repeated measurement mixed effect model. The model will include treatment, visit, and treatment-by-visit interaction as fixed effects; patients 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, with an alternative structure such as compound symmetry used if the model fails to converge. The difference in least-square treatment means, comparing both LY3493269 (test) and dulaglutide (reference), and LY3493269 (test) and placebo (reference), along with the 90% CI, will be reported.

Example SAS code for the analysis:

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

9.6.6 Electrocardiogram (ECG)

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the PR, QT, 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 ECG data will be summarized by treatment together with changes from baseline, where baseline is defined as the mean of the triplicate Day 1 -0.5h, Day 1 -0.25h, and Day 1 predose assessments. Figures of mean ECG data and mean changes from baseline will be presented by treatment. The frequency of patients 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 patients 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 predose triplicate assessments) in ECG parameters (QTc, PR interval, 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 patient's Day 1 predose value. Further details on how these will be calculated:

- Calculate the baseline ECG value for each patient, which is the mean of ECG parameter values of each individual patient over 3 predose time points at day 1.
- Calculate the change from baseline at each timepoint for each individual patient.
- Calculate the mean ECG parameter value across all patients at baseline.
- For each patient subtract the mean ECG parameter value from their own individual observed ECG parameter value. This will be each patient's centered ECG parameter value.
- BQL LY3493269 concentration data will be imputed to $LLOQ/\sqrt{2}$ for the purposes of the analysis.

The relationship between LY3493269 concentrations and ECG parameters will be explored graphically by plotting delta ECG, which is defined as the change from baseline of the ECG parameter values against LY3493269 concentrations, including all post dosing timepoints. Double delta ECG, which is defined as the placebo-corrected change from baseline of the ECG will also be plotted.

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 patient. Treatment will be fitted as a binary variable (Placebo, or LY3493269). The model will have the form

$$\Delta ECG_{ijk} = (\theta_0 + \eta_{0,i}) + \theta_1 TRT_j + (\theta_2 + \eta_{2,i}) C_{ijk} + \theta_{3k} TIME_k + \theta_5 (ECG_{i,j=0} - \overline{ECG_0}) + \varepsilon_{ijk},$$

where ΔECG_{ijk} is the change from baseline in ECG parameter for patient 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 patient i in treatment j and time k, θ_{3k} is the fixed effect associated with time k, θ_5 is the fixed effect associated with baseline $ECG_{i,j=0}$, $\overline{ECG_0}$ is the overall mean of $ECG_{i,j,k=0}$ (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 patient day;
model ΔECG = treat time day baseline_ECG PKconc / solution cl alpha=0.1
ddfm=kr;
random intercept PKconc / type=un subject=patient;
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 patient 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 patients' 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 patient data listings.

9.6.8 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.

9.6.9 Appetite analysis

To explore the effects of LY3493269 on meal intake and appetite sensation, patients will be asked to rate their appetite sensations using a 100-mm validated visual analog scale (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: (satiety + fullness + (100-prospective food consumption) + (100-hunger) / 4). The higher overall appetite score indicates less appetite, and the 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.

Absolute values and change from baseline observations for each of the individual scores and overall appetite will be analysed using a repeated measure mixed-model. The model will include treatment, visit, and treatment-by-visit interaction as fixed effects; patients will be included as a random effect. Baseline will also be included as a covariate in the model for the change from baseline analysis. An unstructured covariance structure will be used, with an alternative structure such as compound symmetry used if the model fails to converge. The difference in least-square treatment means, comparing both LY3493269 (test) and dulaglutide (reference), and LY3493269 (test) and placebo (reference), along with the 90% CI, will be reported.

Example SAS code for the analysis (for change from baseline data):

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

9.6.10 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.

9.6.11 Injection-site reactions

Injection-site reaction data, including erythema, induration, pain, pruritus and edema will be listed and summarized by treatment and timepoint in frequency tables.

9.6.12 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.

3. 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.

4. 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.

5. 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.

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

7. 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.

8. Lewandowski KC et al. Limitations of insulin resistance assessment in polycystic ovary syndrome. *Endocr Connect*. 2018;7(3):403-412.

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 patients 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 = 2df59ed1-e743-4ed0-8c81-d88570a6a15c

Approver: CCI

Approval Date & Time: 29-Jul-2020 13:55:57 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 29-Jul-2020 14:16:57 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 30-Jul-2020 04:51:19 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 03-Aug-2020 14:57:45 GMT

Signature meaning: Approved