J2A-MC-GZGC Statistical Analysis Plan

A Multiple-Dose Study in Participants with Type 2 Diabetes Mellitus to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3502970

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STATISTICAL ANALYSIS PLAN

A Multiple-Dose Study in Participants with Type 2 Diabetes Mellitus to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3502970

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Clinical Phase I

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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
AUC	Area under the concentration versus time curve
AUC(0-∞)	Area under the concentration versus time curve from time zero to infinity
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
BQL	Below the lower limit of quantitation
C_{max}	Maximum observed drug concentration
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
ECG	Electrocardiogram
HbA1c	Glycated hemoglobin
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
MMTT	Mixed meal tolerance test
PD	Pharmacodynamic
PG	Plasma glucose
PK	Pharmacokinetic
QTcF	QT interval corrected using Fridericia's formula
R_A	Accumulation ratio based upon AUC(0-24)
SAP	Statistical Analysis Plan
SD	Standard deviation
TFLs	Tables, Figures, and Listings
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-

	compartmental analysis
T2DM	Type 2 diabetes mellitus
t_{max}	Time of maximum observed drug concentration
ULN	Upper limit of normal
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 12 May 2020).

This SAP describes the planned analysis of the safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical and PK analyses of data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Eli Lilly and Company. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon with Eli Lilly and Company and identified in the CSR. Any minor deviations from the TFLs may not be documented in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials[1] and the ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports[2].

4. STUDY OBJECTIVES

4.1 Primary Objective

To investigate the safety and tolerability of multiple oral doses of LY3502970 in participants with type 2 diabetes mellitus (T2DM).

4.2 Secondary Objectives

- To characterize the PK of LY3502970 after multiple oral doses in participants with T2DM.
- To investigate the effects of LY3502970 on fasting plasma glucose (PG) and fasting insulin following multiple oral doses administered to participants with T2DM.

4.3 Exploratory Objectives

- To investigate the PD effects of LY3502970 following multiple oral doses administered to participants with T2DM.

- To evaluate the efficacy of multiple oral doses of LY3502970 in participants with T2DM.

5. STUDY DESIGN

Study GZGC is a multicenter, randomized, participant- and investigator-blinded, placebo-controlled, multiple-dose, Phase 1 study with 3 study periods. The study is designed to investigate the safety, tolerability, PK, PD, and efficacy of LY3502970 in participants with T2DM for 12 weeks. Up to 5 cohorts, Cohorts A through E, are planned. Each cohort comprises approximately 12 participants with T2DM with approximately 9 receiving LY3502970. For all cohorts, LY3502970 administration by oral dosing will begin on Day 1 and continue through Day 84.

The study will consist of 3 intervals:

- screening and baseline, approximately 4 weeks
- treatment period, 12 weeks
- follow-up, 1 to 2 weeks

A study schema for GZGC can be seen in Figure 1.

Based on the safety, tolerability and PD response of participants after 4 weeks of dosing in Cohort A, the doses and titration steps will be decided for Cohorts B, C, D, and E. The intention will be to evaluate a range of final doses (after 4 to 8 weeks of within cohort dose escalation) that travers the potential estimated efficacious dose range.

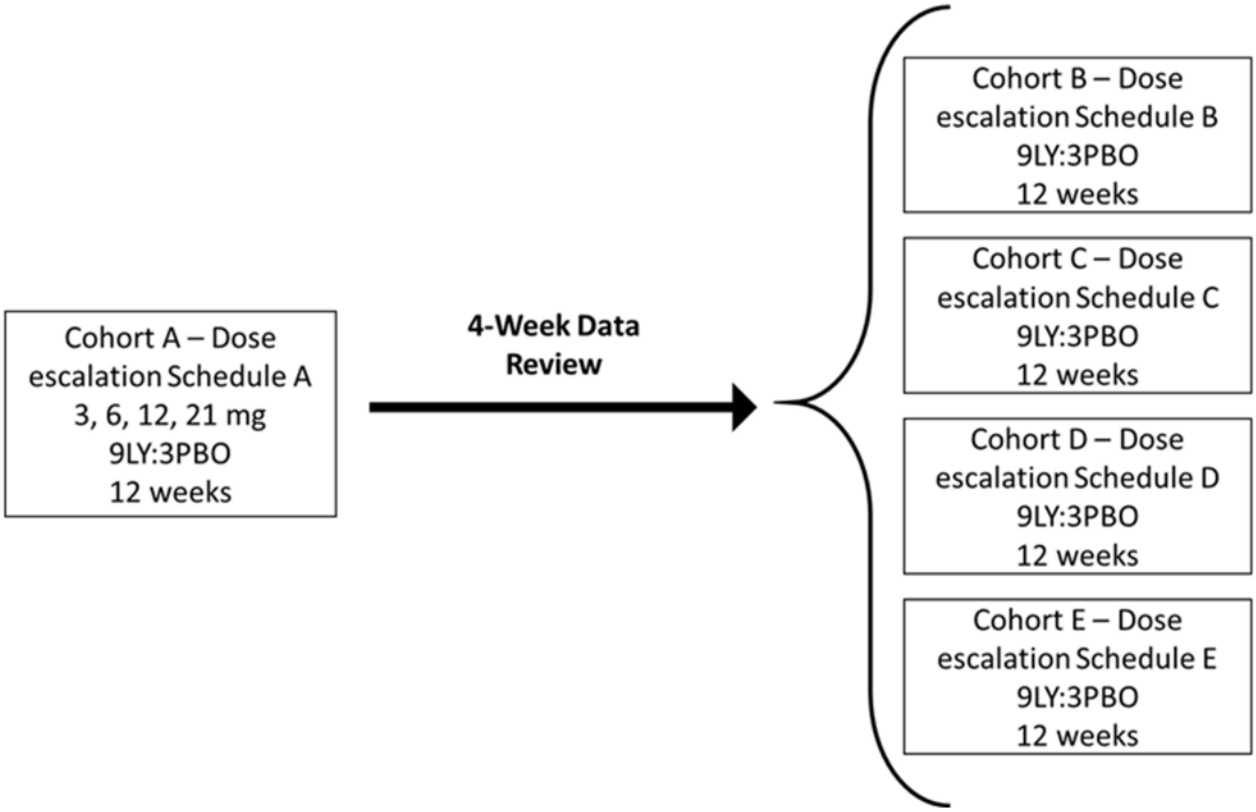

Figure 1 - General Schema for GZGC

6. TREATMENTS

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

Cohort	Study Treatment Name	Treatment order in TFL
All	Placebo QD	1
A	Up titration to 21 mg LY3502970 QD	2
B	Up titration to AA mg LY3502970 QD	3
C	Up titration to BB mg LY3502970 QD	4
D	Up titration to CC mg LY3502970 QD	5
E	Up titration to DD mg LY3502970 QD	6

7. SAMPLE SIZE JUSTIFICATION

The sample size is customary for Phase 1 studies evaluating safety, PK, and/or PD parameters, and is considered sufficient to evaluate the primary objective of this study.

A maximum of 72 participants will be randomly assigned to study intervention such that approximately 60 evaluable participants complete the study.

Participants who are randomized but not administered treatment may be replaced to ensure that enough participants may complete the study.

8. DEFINITION OF ANALYSIS POPULATIONS

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

The "Pharmacokinetic" population will consist of all randomized participants who received at least one dose of LY3502970 and have at least one evaluable PK sample. Participants may be excluded from the PK summary statistics and statistical analysis if a participant has an adverse event (AE) of vomiting that occurs at or before 2 times median time of maximum observed drug concentration (t_{max}).

The "Pharmacodynamic" population will consist of all randomized participants who received at least one dose of LY3502970 or placebo and have at least one evaluable PD sample. Participants may be excluded from the PD summary statistics and statistical analysis if a participant has an AE of vomiting that occurs at or before 2 times median t_{max}.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when participants are assigned to analysis populations.

9. STATISTICAL METHODOLOGY

9.1 General

Data listings will be provided for all data that is databased. Summary statistics and statistical analysis will only be presented for data where detailed in this SAP. For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation (SD), median, minimum, maximum and N; for log-normal data (e.g. the PK parameters: area under the concentration vs time curve [AUC] 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 participants up to the point of withdrawal, with any participants excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for participants included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

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

Data analysis will be performed using SAS® Version 9.4 or greater.

9.2 Demographics and Participant Disposition

Participant disposition will be listed. The demographic variables age, sex, race, ethnicity, country of enrolment, site ID, body weight, height, and body mass index will be summarized and listed. In addition, baseline glycated hemoglobin (HbA1c)), Metformin use, Duration of diabetes, and fasting blood glucose 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 LY3502970 will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-24)	ng*h/mL	area under the concentration versus time curve during one dosing interval of 24 hours
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_{ss}/F	L/h	total body clearance of drug calculated after extra-vascular administration
V_z/F	L	volume of distribution during the terminal phase after extra-vascular administration
R_A	N/A	accumulation ratio based upon AUC(0-24)
Peak-to-trough ratio	N/A	Cmax to 24 hour concentration sample (C_{24h}) following multiple dosing (Day 28 and Day 84 only)

Trough (predose) plasma concentrations of LY3502970 will be listed and summarized.

Additional PK parameters may be calculated, as appropriate. The software and version used for the final analyses will be specified in the CSR. Any exceptions or special handling of data will be clearly documented within the final study report.

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

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. For non-bolus, 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 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 lower limit of quantification, with at least one of these concentrations following C_{max}.

- AUC from time zero to infinity [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 participant 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 the predicted last quantifiable 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 participant 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.
- During the terminal elimination phase, the concentration is quantifiable and follows 2 consecutive concentrations that are below the quantitation limit (BQL).
- 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.
- For pharmacokinetic profiles during multiple dosing, the concentration of the predose sample exceeds all measured concentrations for that individual in the subsequent post-dose samples.

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 $n\geq6$, 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 $n \geq 6$ 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(0-24) parameters of LY3502970 will be evaluated at the maintenance dose for the primary endpoint (Day 84) 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.

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;
```

The parameter t_{max} at the maintenance dose for the primary endpoint (Day 84) 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 treatment, 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

The pharmacokinetics of acetaminophen will be used as "pharmacodynamics" measure of the effect of LY3502970 on gastric emptying. Plasma concentrations of acetaminophen will be used to determine the following parameters in validated software program (Phoenix WinNonlin Version 8.1 or later).

Acetaminophen parameters

Parameter	Units	Definition
AUC(0-∞)	ng.h/mL	area under the concentration versus time curve from zero to infinity
AUC(0-t_{last})	ng.h/mL	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
%AUC(t_{last}-∞)	%	percentage of AUC(0-∞) extrapolated
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
t½	h	half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis

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

All PD parameters will be summarized with appropriate summary statistics by treatment group and day, including:

- Fasting PG and fasting insulin (including change from baseline and baseline adjusted value)
- AUC for glucose and insulin during a mixed meal tolerance test (MMTT) (including the baseline adjusted value, where the Day -1 AUC is the baseline AUC)
- C-peptide, glucose, and insulin concentrations during the MMTT (including change from baseline)
- Lipid profile (including change form baseline)
- Visual analog scale for appetite (including change from baseline)
- Gastric emptying using acetaminophen (including baseline-corrected values [see Section 9.4.2])
- Insulin sensitivity, using HOMA2-IR and Matsuda index
- Beta-cell function, using the insulinogenic index and HOMA2-B
- HbA1c (including absolute change from baseline)
- Body weight (Including change from baseline)

The AUC for glucose and insulin during an MMTT will be calculated using the trapezoidal rule, based on actual timings, on Days -1, 28 (Cohort A), 42 (Cohort B-E), 56 and 84. In addition to the AUC, an incremental AUC (subtracting baseline value during MMTT) will be calculated. The AUC and incremental AUC on Day -1 will be used as baseline for statistical analysis of change from baseline and placebo. Baseline corrected AUC will also be calculated, where the Day -1 AUC is the baseline AUC. A lookup table will be provided by Lilly to calculate the values of HOMA2-IR and HOMA2-B.

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

- Insulinogenic index[3,4]

$IGI = \frac{\Delta Insulin_{0-30min}}{\Delta Glucose_{0-30min}}$, where glucose is in mg/dL and insulin is in µU/mL.

- Insulin sensitivity (Matsuda Index)[5]

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

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.

9.4.2 Pharmacodynamic Statistical Methodology

The PD parameters of interest, and changes from baseline in each parameter will be analyzed using a linear mixed effect model. The PD parameters may be transformed before statistical analysis, if deemed necessary. The model will include treatment, time, and the treatment by time interaction as fixed effects, with baseline also included as a fixed effect for the change from baseline analysis; participants will be included as a random effect. 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 (LY3502970 – Placebo), along with the 90% CIs, will be reported.

Example of SAS code as follows:

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

To evaluate the gastric emptying effect of LY3502970, C_{max} and AUC of acetaminophen will be summarized by day, and a linear repeated-measure mixed-effect model will be fit to the logged baseline-corrected parameters C_{max} and AUC of acetaminophen on Days 1 and 84. The baseline-

adjusted observation will be the ratio of the observation to the Day -1 value (which we define as baseline). The model will include the log of the baseline, treatment, day, and treatment-by-day interaction as fixed effects; participants will be included as a random effect. 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 (LY3502970–Placebo) along with the 90% CIs will be back-transformed to produce the ratio of geometric means and the CIs comparing LY3502970 to Placebo.

Example of SAS code to be used for the model:

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

The parameter t_{max} of acetaminophen will be summarized by day. The statistical analyses will be conducted separately for Day 1 and Day 84, non-parametrically with medians, the median of the differences and corresponding 90% CI presented alongside the p-value from the Wilcoxon rank-sum test.

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

```
proc npar1way data=aaa wilcoxon(alpha=0.1);
class dose ;
var tmax;
run;
```

All PD parameters, including the baseline-corrected parameters, will be summarized and tabulated by treatment group and day. Summary statistics will be provided.

The individual observed and mean time profile of postdose PD parameters will be plotted by treatment group.

9.5 Pharmacokinetic/Pharmacodynamic Analyses

Exploratory PK/PD modeling may be used to characterize exposure-response relationships between LY3502970 concentrations and various PD endpoints (i.e., HbA1c, glucose, body weight, and gastric emptying), provided data are sufficient.

9.6 Safety and Tolerability Assessments

9.6.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the AE will be reported in the listings, only the most severe will be used in the summary

tables. A pre-existing condition is defined as an AE that starts before the participant has provided written informed consent and is ongoing at consent. A non-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 participants experiencing an AE and the percentage of participants 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. Any AEs of special interest will be listed, these include cardiovascular events, pancreatic events, nausea, vomiting and diarrhea. 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):**

  – **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)**

  – 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 noinformation 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.

Investigator review of glucose results clinically indicative of hypoglycemia will be required. To avoid duplicate reporting, all consecutive PG values ≤70mg/dL (3.9 mmol/L) occurring within a 1-hour period may be considered to be a single hypoglycemic event.

9.6.3 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version September 2019 B3). 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, 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 participant data listings.

9.6.5 Vital signs

Vital signs data will be summarized by treatment together with changes from baseline, where baseline is defined as the Day 1 predose assessment. Figures of mean vital signs and mean changes from baseline profiles will be presented by treatment. For changes from baseline values, a linear mixed effect repeated measure model will be fitted. The model will include treatment, time, and treatment-by-time interaction as fixed effects; baseline as a covariate and participants will be used as a random effect with an unstructured covariance structure. If convergence cannot be achieved with this covariance structure, an alternative structure, such as a compound

symmetry covariance, will be used. The difference in least-square treatment means (LY3502970 – Placebo) along with the 90% CIs will be reported.

Example SAS code for the analysis:

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

Values for individual participants will be listed.

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 predose assessment. Figures of mean ECG data and mean changes from baseline will be presented by treatment. The frequency of participants with a maximum increase from baseline in QTcF interval will be summarized for each treatment according to the following categories: >30 ms and >60 ms. In addition, the frequency of participants with QTcF postdose values, according to the following categories: >450 ms, >480 ms and >500 ms, will be summarized by treatment.

Plasma PK Concentration versus delta and double delta ECG parameter analysis

A plasma LY3502970 concentration-ECG parameter analysis will be performed to assess the relationship between changes from baseline (mean of Day 1 predose triplicate assessments) in ECG parameters (QTc, PR, and RR intervals, QRS duration, and heart rate) and plasma LY3502970 concentrations across all treatments. The change from baseline adjustment will be based on individual participant's Day 1 predose value. Further details on how these will be calculated:

- Calculate the baseline ECG value for each participant, which is the mean of ECG parameter values of each individual participant over 3 predose time points at day 1.
- Calculate the change from baseline at each timepoint for each individual participant.
- Calculate the mean ECG parameter value across all participants at baseline.

- For each participant subtract the mean ECG parameter value from their own individual observed ECG parameter value. This will be each participant's centered ECG parameter value.
- BLQ LY3502970 concentration data will be imputed to 50% of the LLOQ for the purposes of the analysis.

The relationship between LY3502970 concentrations and ECG parameters will be explored graphically by plotting delta ECG parameter values against LY3502970 concentrations, including all post dosing timepoints.

A mixed effects analysis model will be employed with change from baseline in ECG parameter as the dependent variable, LY3502970 concentration and centered ECG parameter value as continuous covariates, treatment and time as categorical factors, and a random intercept and slope per participant. Treatment will be fitted as a binary variable (Placebo, or LY3502970). The model will have the form

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

where ΔECG_{ijk} is the change from baseline in ECG parameter for participant i in treatment j at time k, θ_0 is the population mean intercept in the absence of treatment effect, $\eta_{0,i}$ is the random effect associated with the intercept term θ_0, θ_1 is the fixed effect categorical variable associated with treatment TRT_j , θ_2 is the population mean slope of the assumed linear association between concentration and ΔECG_{ijk}, $\eta_{2,i}$ is the random effect associated with the slope θ_2, C_{ijk} is the concentration for participant i in treatment j and time k, θ_{3k} is the fixed effect associated with time k, θ_4 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 subject;
model ΔECG = treat time baseline_ECG PKconc / solution cl alpha=0.1 ddfm=kr;
random intercept PKconc / type=un subject=subject;
estimate 'XX mg LY3502970' intercept 1 treat 0 1 PKconc [cmax XXmg] / CL
alpha=0.1;
estimate 'YY mg LY3502970' intercept 1 treat 0 1 PKconc [cmax YYmg] / CL
alpha=0.1;
ods output covparms=covp(where=(covparm="Residual"));
```

```
ods output solutionF=sol;
ods output estimates=estim;
run;
```

Similar code will be used for the analysis of ΔΔECG.

9.6.7 Hepatic Monitoring

If a participant 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 participants' liver disease history and associated person liver disease history data will be listed. Any concomitant medications that have potential for hepatotoxicity, including acetaminophen will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography scan, and biopsy assessments will be listed, if performed.

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

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

9.6.8 Appetite analysis

Overall appetite will be quantified using the 0- to 100-mm validated visual analog scale. The associated data will be listed, with baseline (defined as Day 1 predose), postdose values, and change from baseline summarized by treatment and time point.

9.6.9 Other assessments

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

10. INTERIM ANALYSES

No interim statistical analyses are planned.

11. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

12. REFERENCES

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

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.

13. DATA PRESENTATION

13.1 Derived Parameters

Individual derived parameters (e.g. PK parameters) and appropriate summary statistics will be reported to three significant figures. Observed concentration data, e.g. C_{max}, should be reported as received. Observed time data, e.g. t_{max}, should be reported as received. N and percentage values should be reported as whole numbers. Median values should be treated as an observed parameter and reported to the same number of decimal places as minimum and maximum values.

13.2 Missing Data

Missing data will not be displayed in listings.

13.3 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of participants or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No serious adverse events occurred for this study.”

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