Statistical Analysis Plan Version 5 -J2A-JE-GZGB

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

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STATISTICAL ANALYSIS PLAN

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

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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_{τ}	Area under the concentration versus time curve during the dosing interval
AUC(0-168)	Area under the concentration versus time curve from time zero to 168 h postdose
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 quantification
BW	Body weight
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
C_{max}	Maximum observed drug concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
ECG	Electrocardiogram
FG	Fasting glucose
GI	Gastrointestinal
HbA1c	Glycated hemoglobin
HDL	High-density lipoprotein
ICH	International Conference on Harmonisation
LDL	Low-density lipoprotein
LS	Least square
MAD	Multiple ascending dose

MedDRA	Medical Dictionary for Regulatory Activities
MMTT	Mixed meal tolerance test
PD	Pharmacodynamic
PK	Pharmacokinetic
QD	Once daily
QTcF	QT interval corrected using Fridericia's formula
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
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
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
VAS	Visual analog scale
VLDL	Very low-density lipoprotein
V_{ss}/F	Apparent volume of distribution at steady state after extra-vascular administration
V_z/F	Apparent volume of distribution during the terminal phase after extra-vascular administration
WC	Waist circumference
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 15 August 2021), and amendment (a) (final version dated 28 September 2021).

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

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

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

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

4. STUDY OBJECTIVES AND ENDPOINTS

4.1 Primary Objective and Endpoints

The primary objective of the study is:

> To investigate the safety and tolerability of LY3502970 following single and multiple oral once daily (QD) doses for 12 weeks in Japanese participants with type 2 diabetes mellitus (T2DM).

The primary endpoints of the study are:

> Treatment-emergent adverse events (TEAE)
>
> Serious adverse events (SAEs)

4.2 Secondary Objectives and Endpoints

The secondary objectives of the study are:

To characterize the PK profile of LY3502970 following single and multiple oral QD doses for 12 weeks in Japanese participants with T2DM.

To characterize the PD effects of LY3502970 following multiple oral QD doses for 12 weeks in Japanese participants with T2DM.

The secondary endpoints of the study are:

Maximum observed drug concentration (C_{max}) and area under the concentration versus time curve (AUC)

Changes from baseline in:

- Fasting glucose (FG)
- Glycated hemoglobin (HbA1c)
- Body weight (BW)

4.3 Exploratory Objective and Endpoints

The exploratory objective of the study is:

To characterize the PD effects of LY3502970 following multiple oral QD doses (parameters of glucose and lipid metabolism, endocrine pancreas function, insulin action, insulin secretion, energy balance) for 12 weeks in Japanese participants with T2DM

The exploratory endpoints of the study are:

Changes from baseline in PD biomarkers:

- Insulin
- C-peptide
- Glucagon

Changes from baseline in mixed meal tolerance test (MMTT) parameters:

- Glucose
- Insulin
- C-peptide

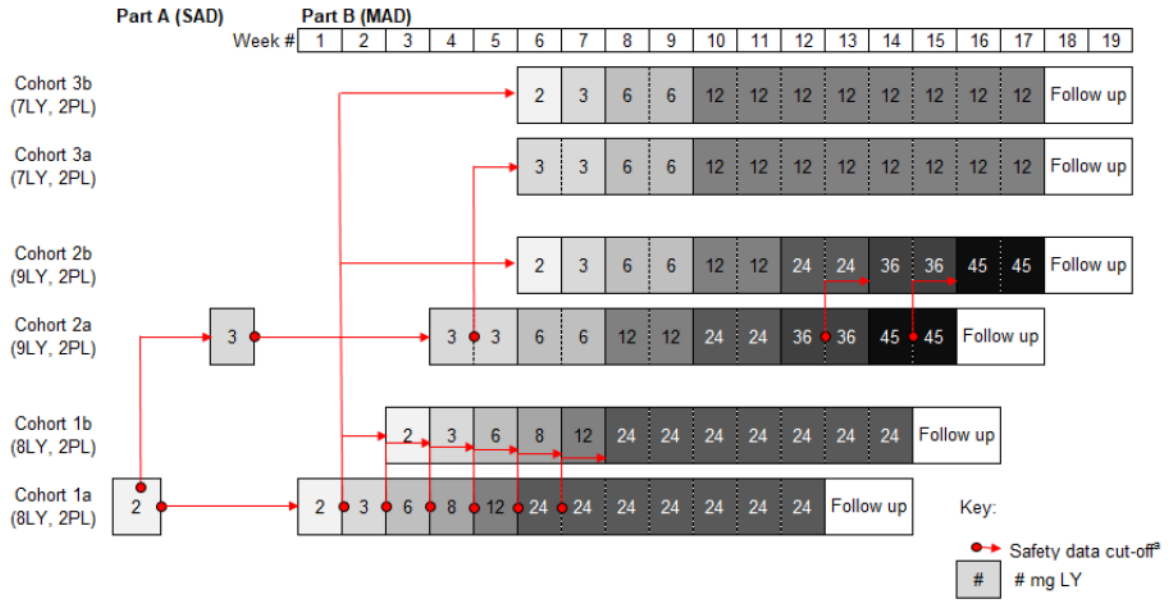
- Glucagon

- Changes from baseline in:
  - Daily glucose profile
  - Fasting lipids (triglycerides, total cholesterol, and low-density lipoprotein [LDL], high-density lipoprotein [HDL], and very low-density lipoprotein [VLDL] cholesterol)
  - Appetite visual analog scale (VAS)
  - Meal intake
  - Waist circumference (WC)

5. STUDY DESIGN

Study GZGB is a Phase 1, multicenter, participant- and investigator-blinded, parallel, placebo-controlled, randomized, single ascending dose (SAD) (Part A), and a 12-week multiple ascending dose (MAD) (Part B) study in Japanese participants with T2DM to investigate the safety, tolerability, PK, and PD of LY3502970 administered as a single oral dose or multiple [redacted], for 12 weeks. In Part A, SAD of LY3502970 will be administered in 2 subgroups (1a and 2a). After completing Part A, participants will subsequently be enrolled in Part B (12-week MAD). The safety data through Day 8 from each SAD cohort in Part A will be reviewed prior to initiation of the corresponding dose group in Part B.

A schema can be seen in Figure 1.



[redacted]

Figure 1. A study schema for GZGB

Participants will be screened within 28 days prior to enrollment, unless they require withdrawal from monotherapy of oral antidiabetic medication. Participants on monotherapy of oral antidiabetic medication, either metformin, dipeptidyl peptidase-4 inhibitor, or sodium-glucose co-transporter-2 inhibitor, will be required to withdraw from their treatment for at least 28 days washout prior to dosing study intervention. For these participants, the screening period may be increased by a maximum of 2 weeks, that is, participants may be screened within 42 days prior to enrollment.

Eligible participants who have satisfied the entry criteria and completed all screening assessments will return to the clinical research unit (CRU) on Day -1 for both Parts A and B for participation in the study. Participants may be admitted to the CRU on Day -2 at the discretion of the investigator.

Part A: Single-Ascending Dose

Participants randomized to Cohorts 1a and 2a will receive a single oral dose of LY3502970 or placebo on Day 1 after an overnight fast for at least 8 hours. Participants will remain resident in the CRU for PK sampling and safety monitoring until discharge on Day 5. Participants will then return to the CRU for 2 outpatient visits on Days 8 and 15 for additional safety assessments. Following completion of their participation in Part A, participants will be enrolled in Part B.

Safety assessments, including adverse events (AE), concomitant medications, medical assessments, clinical laboratory tests, vital signs, and electrocardiograms (ECG), and blood sampling for PK measurements, will be performed.

Part B: Multiple-Ascending Dose

Safety data through Day 8 from each SAD cohort in Part A will be reviewed prior to initiation of the corresponding dose group in Part B. For participants who participated in Part A, the lead-in period for Part B will occur between 1 to 2 weeks after completion (Day 15) of Part A.

The study intervention will be administered orally QD for up to 12 weeks in all cohorts (1a, 1b, 2a, 2b, 3a, and 3b). Participants in Cohort 1a will remain resident in the CRU for safety monitoring for the first 6 weeks of the treatment period and will be discharged on Day 38 following the completion of all scheduled assessments. Participants in all other cohorts will remain in the CRU 2 days after dosing (discharge following 48-hour assessments on Day 3) for safety monitoring. Participants will be admitted to the CRU for a maximum of 5 planned inpatient stays for PK, PD, and safety assessments. Participants will also return to the CRU for regular outpatient visits throughout the treatment and follow-up periods. Apart from the planned inpatient stays, participants may remain resident in the CRU for safety monitoring following each visit, at the investigator's discretion.

Safety assessments, including AEs, concomitant medications, medical assessments, clinical laboratory tests, vital signs, and ECGs, and blood sampling for PK and PD measurements will be performed. The timing of the sampling may be adjusted in view of emerging safety, tolerability, PK, and/or PD data during the study. These changes must be appropriately documented and communicated by the sponsor to the investigator.

Progression of Cohorts through Study GZGB

Up to 3 cohorts are planned; each cohort is split into 2 subgroups (that is, 'a' and 'b') for a staggered dosing approach. Each cohort will comprise participants randomized to receive either LY3502970 (denoted LY in the following list) or a corresponding placebo for 12 weeks as stated below:

Part A

- Cohort 1a; 8 LY:2 placebo; 2 mg
- Cohort 2a; 9 LY:2 placebo; 3 mg

Part B

- Cohorts 1a and 1b; 8 LY:2 placebo; 2 mg (1 week) → 3 mg (1 week) → 6 mg (1 week) → 8 mg (1 week) → 12 mg (1 week) → 24 mg (7 weeks)
- Cohort 2a; 9 LY:2 placebo; 3 mg (2 weeks) → 6 mg (2 weeks) → 12 mg (2 weeks) → 24 mg (2 weeks) → 36 mg (2 weeks) → 45 mg (2 weeks)

- Cohort 2b; 9 LY:2 placebo; 2 mg (1 week) → 3 mg (1 week) → 6 mg (2 weeks) → 12 mg (2 weeks) → 24 mg (2 weeks) → 36 mg (2 weeks) → 45 mg (2 weeks)

- Cohort 3a; 7 LY:2 placebo; 3 mg (2 weeks) → 6 mg (2 weeks) → 12 mg (8 weeks)

- Cohort 3b; 7 LY:2 placebo; 2 mg (1 week) → 3 mg (1 week) → 6 mg (2 weeks) → 12 mg (8 weeks)

Safety data review will be required for progression within cohorts, that is, from cohort 'a' to cohort 'b', for progression to the next cohort, and for dose-escalation decisions of 1 dose level to the next higher dose level. Participants in Cohorts 1a and 2a are expected to proceed from Part A to Part B; however, if a participant discontinues following Part A, they may be replaced for Part B.

The investigator and Lilly clinical pharmacologist will review all available safety data (AEs, vital signs, ECGs, concomitant medications, safety laboratory measurements, and medical assessments). Dosing following safety reviews will only occur after subsequent agreement between the investigator and the Lilly clinical pharmacologist.

If the investigator decides not to up-titrate the dose level as planned for individual participants for any reason(s), participants may be discontinued for doses ≤12 mg or may remain dosing at the current dose level through to the last planned dose on Day 84 for doses ≥24 mg.

6. TREATMENTS

Unless stated otherwise, the following is a list of the study treatment abbreviations that will be used in the TFLs.

Part	Cohort	Study Treatment Name	Treatment order in TFL
A	All in Part A	Placebo	1
	1a	2 mg LY3502970	2
	2a	3 mg LY3502970	3
B	All in Part B	Placebo QD	1
	3a and 3b	2(or 3)/3/6/12 mg LY3502970 QD	2
	1a and 1b	2/3/6/8/12/24 mg LY3502970 QD	3
	2a and 2b	2(or 3)/6/12/24/36/45 mg LY3502970 QD	4

In addition, the following is a list of the study treatment sequences that will be also used for the demographics, baseline characteristics, disposition, GI-AEs, vital signs and ECGs TFLs for Part B.

Part	Cohort	Study Treatment Name	Treatment order in TFL
B	All in Part B	Placebo QD	1
	3a	3/6/12 mg LY3502970 QD	2
	3b	2/3/6/12 mg LY3502970 QD	3
	3a and 3b	2(or 3)/3/6/12 mg LY3502970 QD	4
	1a and 1b	2/3/6/8/12/24 mg LY3502970 QD	5
	2a	3/6/12/24/36/45 mg LY3502970 QD	6
	2b	2/3/6/12/24/36/45 mg LY3502970 QD	7
	2a and 2b	2(or 3)/6/12/24/36/45 mg LY3502970 QD	8

The following is a list of the study treatments that will be used in the PK summaries TFLs.

Part	Day	Study Treatment Name	Treatment order in TFL
A	1	2 mg LY3502970	1
		3 mg LY3502970	2
B	1	2 mg LY3502970	1
		3 mg LY3502970	2
	28	6 mg LY3502970	1
		8 mg LY3502970	2
	84	12 mg LY3502970	1
		24 mg LY3502970	2
		45 mg LY3502970	3

7. SAMPLE SIZE JUSTIFICATION

Up to 65 participants may be enrolled to study intervention to ensure approximately 15 evaluable participants in each cohort (1, 2, and 3; Groups a and b combined) complete Part B of the study. Assuming that the dropout rate is higher at higher dose cohorts due to gastrointestinal (GI) tolerability, approximately 18, 20, and 22 participants will be randomized.

CCI [redacted]

Participants who are randomized but not administered treatment may be replaced to ensure that enough participants may complete the study. Participants in Cohorts 1a and 2a who discontinue prior to start of dosing in Part B may be replaced after consultation with the investigator and sponsor. This replacement participant may not repeat Part A and will go through the same treatment assignment from Part B as the discontinued participant. Participants who discontinue early during Part B will not be replaced.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Entered" population will consist of all participants who sign the informed consent form.

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

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

The "Pharmacokinetic" population will consist of all enrolled participants who received at least 1 dose of LY3502970 and have evaluable PK data. Participants may be excluded from the PK summary statistics and statistical analysis if a participant has an AE of vomiting that occurs at or before 2 times median time of maximum observed drug concentration (t_{max}).

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

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

9. STATISTICAL METHODOLOGY

9.1 General

Data listings will be provided for all data that is databased. Summary statistics and statistical analysis will only be presented for data where detailed in this SAP. For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation (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 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.

In part B, when summarizing by timepoint for safety and PD data, placebo data will only be summarized in which n>5 (i.e. timepoints that are collected in only one cohort for placebo are not summarized).

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

9.2 Demographics and Participant Disposition

Participant disposition will be summarized (for Part A and Part B seperately) and listed. The demographic variables age, sex, race, subrace, ethnicity, country of enrolment, site ID, BW, height, body mass index, duration of T2DM, use of oral antidiabetic medication (with subcategories of metformin, DPP4 inhibitor, and SGLT2 inhibitor if yes), Day 1 predose fasting plasma glucose, and Screening predose HbA1c (using %) will be summarized and listed. All other demographic variables will be listed only.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

All PK parameter estimates will be determined using non-compartmental procedures in validated software program (Phoenix WinNonlin Version 8.1 or later).

Part A (SAD)

Plasma concentrations of LY3502970 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-∞)	ng*h/mL	area under the concentration versus time curve from time zero to infinity
%AUC(t_{last}-∞)	%	percentage of AUC(0-∞) extrapolated
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
$t_{1/2}$	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
V_{ss}/F	L	apparent volume of distribution at steady state after extra-vascular administration

Part B (MAD)

Plasma concentrations of LY3502970 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(0-24)	ng*h/mL	area under the concentration versus time curve from time zero to 24h postdose
AUC	ng*h/mL	area under the concentration versus time curve during the dosing interval
AUC(0-∞)	ng*h/mL	area under the concentration versus time curve from time zero to infinity
%AUC(t_{last}-∞)	%	percentage of AUC(0-∞) extrapolated
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
$t_{1/2}$	h	half-life associated with the terminal rate constant (λz) in non-compartmental analysis (Day 84 only)
CL/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration (Days 28 and 84)
V_Z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration (Day 84 only)
Peak-to-trough ratio	N/A	C_{max} to 24 hour concentration sample (C_{24h}) following multiple dosing (Day 28 and Day 84 only)

For Part B, report AUC(0-∞) and %AUC(t_{last}-∞) parameters if extrapolation is less than 20%.

Additional PK parameters may be calculated, as appropriate.

Plasma PK analysis will, where possible, be carried out using actual postdose times recorded in the raw data.

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}.

The 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, 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 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 $t_{1/2}$ 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 last predicted observed 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 quantification (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 C_{min} for the dosing interval.

Individual Concentration vs. Time Profiles

Individual concentrations will be plotted utilizing actual sampling times.

The terminal point selections will be indicated on a semi-logarithmic plot.

Average Concentration vs. Time Profiles

The average concentration profiles will be graphed using scheduled (nominal) sampling times.

The average concentration profiles will be graphed using arithmetic average concentrations.

The pre-dose average concentration for single-dose data from non-endogenous compounds will be set to zero. Otherwise, only quantifiable concentrations will be used to calculate average concentrations.

Concentrations at a sampling time exceeding the sampling time window specified in the protocol, or ± 10%, will be excluded from the average concentration profiles.

Concentrations excluded from the mean calculation will be documented in the final study report.

A concentration average will be plotted for a given sampling time only if 2/3 of the individual data at the time point have quantifiable measurements that are within the sampling time window specified in the protocol or ± 10%. An average concentration estimated with less than 2/3 but more than 3 data points may be displayed on the mean concentration plot if determined to be appropriate and will be documented within the final study report.

Treatment of Outliers during Pharmacokinetic Analysis

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

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

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

For 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 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 CSR. Approval of the final CSR will connote approval of the exclusion

9.3.2 Pharmacokinetic Statistical Methodology

For Part B, on Day 84, log-transformed C_{max}, AUC(0-24), and AUC parameters of LY3502970 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.

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} will be analyzed on Day 84, 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;
```

9.4 Pharmacodynamic Assessment

9.4.1 Pharmacodynamic Analysis

All PD parameters will be summarized, as well as their change from baseline, with appropriate summary statistics by treatment group and day, including*:*

Fasting glucose (Day 1 predose)
HbA1c (Day 1 predose, Part B only)
Body weight (Day 1 predose, Part B only)
Biomarkers (Day 1 predose, Part B only)
- Insulin
- C-peptide
- Glucagon

MMTT parameters (Day -1, Part B only)
- Glucose
- Insulin
- C-peptide
- Glucagon
- AUCs of glucose, insulin and C-peptide
- Incremental AUCs of glucose, insulin and C-peptide
- HOMA2-IR
- HOMA2-B
- Matsuda index

- Insulinogenic index

Daily glucose profile (Day -1, Part B only)
Fasting lipids (Day 1 predose)

- Triglycerides
- Total cholesterol
- LDL cholesterol
- HDL cholesterol
- VLDL cholesterol

Meal intake (Day -1, Part B only)
Individual and overall appetite VAS (meal matched Day -1)
Waist circumference (Day 1 predose, Part B only)

The baseline timepoint is displayed in parenthesis for the PD parameters. The data will also be listed. Arithmetic mean plots over time by treatment for all parameters, as well as individual participant plots, will be produced.

The AUC for glucose, insulin, and C-peptide during an MMTT will be calculated using the trapezoidal rule, based on actual timings. Incremental AUC (subtracting baseline value during MMTT) will be calculated. A lookup table will be provided by Lilly to calculate the values of HOMA2-IR and HOMA2-B.

The following MMTT derived parameters will be derived by Labcorp:

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

For Part B only, all parameters in Section 9.4.1, a statistical analysis will be performed on the actual, and change from baseline values for the post-baseline timepoints, and the percentage change from baseline (for BW and WC only). The parameters may be transformed before the statistical analysis if deemed necessary. A mixed effects model will be used to evaluate treatment effects and treatment comparisons. The model will include treatment, timepoint and the

treatment-by-timepoint interaction as fixed effects, and participants will be included as a random effect. Baseline will also be included as a covariate. An unstructured covariance structure will be used to model the covariance between a participant's multiple observations, with an alternative structure to be used if the model fails to converge, using a measure such as Akaike's information criterion to decide which structure will be used. The difference in LS treatment means, comparing LY3502970 (test) and placebo (reference), along with the 90% CI, and respective LS means with 90% CIs will be reported.

Example of SAS code as follows:

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

9.5 Pharmacokinetic/Pharmacodynamic Assessment

9.5.1 Pharmacokinetic/Pharmacodynamic analyses

Pharmacokinetic/PD modeling may be evaluated to characterize the exposure-response relationships between LY3502970 concentrations and various PD endpoints, provided data are sufficient.

The relationship between LY3502970 doses and/or concentrations and efficacy (FG, HbA1c, weight) measures and tolerability (such as nausea, vomiting) may be assessed via PK/PD analyses or graphical explorations. Endpoints may include, but are not necessarily limited to, those listed earlier.

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 a condition that starts before the participant has provided written informed consent and is ongoing at consent. A non-TEAE is defined as an AE which starts after informed consent but prior to dosing. A TEAE is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose.

All AEs will be listed. Treatment-emergent AEs will be summarized by part, 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 part, treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 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. AEs by week of onset will be presented.

Discontinuations due to AEs will be listed.

Adverse events of special interest, which are cardiovascular events, GI events (nausea, vomiting, and diarrhea), and hypoglycemia, 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 part and 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 part and treatment. Hypoglycemia is defined as follows:

Level 1 hypoglycemia:

Glucose <70 mg/dL (3.9 mmol/L) and ≥54 mg/dL (3.0 mmol/L):

- Can alert a person to take action such as treatment with fast-acting carbohydrates. Providers should continue to counsel participants to treat hypoglycemia at this glucose alert value.

Level 2 hypoglycemia:

Glucose <54 mg/dL (3.0 mmol/L):

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

Level 3 hypoglycemia:
Severe hypoglycemia (in adults): A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. For example, participants had altered mental status, and could not assist in their own care, or were semiconscious or unconscious, or experienced coma with or without seizures, and the assistance of another person was needed to actively administer carbohydrate, glucagon, or other resuscitative actions. Glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of glucose concentration to normal is considered sufficient evidence that the event was induced by a low glucose concentration.

- The determination of a hypoglycemic event as an episode of severe hypoglycemia, as defined above, is made by the investigator based on the medical need of the participant to have required assistance and is not predicated on the report of a participant simply having received assistance.

- If a hypoglycemic event meets the criteria of severe hypoglycemia, the investigator must record the event as serious on the AE CRF and report it to Lilly as an SAE.

Other Hypoglycemia:

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

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

9.6.3 Concomitant medication

Concomitant medication will be coded using the World Health Organization (WHO) drug dictionary (Version September 2021). Concomitant medication will be listed.

9.6.4 Clinical laboratory parameters

All clinical chemistry, hematology, and amylase and lipase data, as well as the change from baseline, where baseline is defined as Day 1 predose, will be summarized by part, parameter and treatment sequence, and listed. Urinalysis data will be listed. Additionally, clinical chemistry, hematology, urinalysis, and amylase and lipase 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 part and treatment sequence 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 part and treatment. The figures will be produced on Day 1 (all parts), Day 28 (Part B only), and Day 84 (Part B only) separately.

Values for individual participants will be listed.

For the sitting vital signs, the change from baseline values will be statistically analyzed for each part independently using a repeated-measure mixed effects model to evaluate treatment effects and to report treatment comparisons for all timepoints. The model will include treatment, timepoint, and treatment-by-timepoint interaction as fixed effects, and participant modelled as a random effect. Baseline will also be included as a covariate. An unstructured covariance structure will be used to model the covariance between a participant's multiple observations, with an alternative structure to be used if the model fails to converge, using a measure such as Akaike's information criterion to decide which structure will be used. The LS treatment means, difference in LS treatment means, comparing LY3502970 (test) and placebo (reference), along with the 90% CI, will be reported.

Example of the SAS code for the analysis:

```
proc mixed data=xxx;
class treatment time subjid;
model CFB_VS = base treatment time time*treatment/residual ddfm=kr;
```

```
repeated time / subject=subjid type=un;
lsmeans time*treatment / cl pdiff alpha=0.1;
ods output lsmeans=lsm diffs=estims;
run;
```

9.6.6 Electrocardiogram

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the PR, QT, QRS duration 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 triplicate ECG data will be summarized by part and 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 part and 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 part and treatment.

Plasma PK Concentration versus Delta and Double Delta ECG Parameter Analysis (Part A and Part B combined)

A plasma LY3502970 concentration-ECG parameter analysis will be performed to assess the relationship between changes from baseline (mean of Day 1 predose triplicate assessment) in ECG parameters (QTcF, and HR) and plasma LY3502970 concentrations across all CCI treatments. The change from baseline adjustment will be based on individual participant's Day 1 predose value. Only matching PK and ECG parameter timepoints will be included in the analysis. Further details on how these will be calculated:

- Calculate the change from baseline at each postdose timepoint for each individual participant.
- Calculate the mean ECG parameter value across all participants at baseline.
- For each participant, subtract the mean baseline ECG parameter value from their own individual observed baseline ECG parameter value. This will be each participant's centered baseline ECG parameter value.
- Postdose BQL LY3502970 concentration data will be treated as missing (no imputation).

The relationship between LY3502970 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 LY3502970 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 linear mixed effects analysis model will be employed with change from baseline in ECG parameter as the dependent variable, LY3502970 concentration and baseline-centered ECG parameter value as continuous covariates, treatment (LY3502970 or placebo) and time as categorical factors, and a random intercept and slope of concentration per participant. Treatment will be fitted as a binary variable (Placebo=0 and LY3502970=1). The model will have the form[6]

$$\Delta ECG_{ijkl} = \left(\theta_0 + \eta_{0,i}\right) + \theta_1 TRT_j + \left(\theta_2 + \eta_{2,i}\right) C_{ijkl} + \theta_{3l} DAY_l + \theta_{4k} HOUR_k + \theta_5 (ECG_{ijk=0l=1} - \overline{ECG_{k=0l=1}}) + \varepsilon_{ijkl}$$

where ΔECG_{ijkl} is the change from baseline in ECG parameter for participant i on treatment j at hours postdose k on PK day l with k=1 l=1 being the first post-dose timepoint; θ_0 is the population mean intercept in the absence of treatment effect, $\eta_{0,i}$ is the random effect parameter associated with the intercept term θ_0, θ_1 is the fixed effect categorical parameter associated with treatment TRT_j (i.e. LY3502970), θ_2 is the population mean slope parameter of the assumed linear association between concentration and ΔECG_{ijk}, $\eta_{2,i}$ is the random effect parameter associated with the slope θ_2, C_{ijkl} is the concentration for participant i on treatment j at time postdose k on PK day l, θ_{3l} is the fixed effect parameter associated with PK day l, θ_{4k} is the fixed effect parameter associated with hours postdose k, θ_5 is the fixed effect parameter associated with the baseline-centered baseline ECG variable, $\overline{ECG_{k=0l=0}}$ is the overall mean of $ECG_{ijk=0l=1}$ (the mean of all the baseline ECG parameter values, at predose on Day 1), and ε_{ijkl} is the residual error. It will be assumed the random effects are multivariate Gaussian distributed with mean vector **0** and an unstructured covariance matrix G, whereas the residuals, ε_{ijkl}, are Gaussian distributed with mean 0 and variance r.

If the model fails to converge, in order of preference, different covariance structures may be explored, or the random effects may be removed. Model parameters are estimated using maximum likelihood, or restricted maximum likelihood approaches.

The estimated 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 dose and two-sided 90% CI at different dose levels will be calculated. The LS estimate of the treatment effect of LY3502970 and its 90% CI will also be reported. Hysteresis loop plots of delta ECG parameters versus LY3502970 plasma concentrations for the first 24 h, and scatter plots of paired ΔECG versus PK concentration with a linear regression line with a 90% CIwill also be provided. 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 day hour subjid;
model ΔECG = treat day hour centred_baseline_ECG PKconc / solution cl
alpha=0.1 ddfm=kr;
random intercept PKconc / type=un subject=subjid;
estimate 'Placebo' intercept 1 treat 1 0 PKconc 0/ CL alpha=0.1;
estimate 'YY mg LY3502970' intercept 1 treat 0 1 PKconc [geomean of cmax YYmg]
/ CL alpha=0.1;
estimate 'YY mg LY3502970 - Placebo' treat -1 1 PKconc [geomean of cmax 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 participant experiences elevated laboratory parameters, as detailed in Section 9.5.4 of the protocol, additional 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

To explore the effects of LY3502970 on food intake and appetite sensation, participants will be provided standardized mixed meals for morning, midday, and evening at 2, 6, and 10 hours after study intervention administration.

The meal and individual nutritional intake will be listed.

Overall appetite will be quantified using the 0- to 100-mm validated VAS for parameters of hunger, fullness, satiety, and prospective food consumption in the fasted state. Overall appetite will also be calculated, using the equation

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

A higher overall score indicates less appetite. The associated data, with baseline (defined as time matched Day -1), postdose values, and change from baseline will be summarized by part, treatment, and time point, and listed.

9.6.9 Body weight and waist circumference

Measurements of BW and WC will be measured twice at each scheduled timepoint, with the mean of the two measurements used as the observation at that timepoint. These data will be summarized by part, treatment sequence, and timepoint, and listed.

9.6.10 Other assessments

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

9.6.11 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

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.

6. Garnett, Christine & Bonate, Peter & Dang, Qianyu & Ferber, Georg & Huang, Dalong & Liu, Jiang & Mehrotra, Devan & Riley, Steve & Sager, Philip & Tornoe, Christoffer & Wang, Yaning. (2017). Scientific white paper on concentration-QTc modeling. Journal of Pharmacokinetics and Pharmacodynamics. 45. 1-15. 10.1007/s10928-017-9558-5.

13. DATA PRESENTATION

13.1 Derived Parameters

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

13.2 Missing Data

Missing data will not be displayed in listings.

13.3 Insufficient Data for Presentation

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

14. APPENDICES

Appendix 1: Document History

Status and Version	Date of Change	Summary/Reason for Changes
Final Version 1.0	NA	NA; the first version.
Final Version 2.0	21SEP2022	Removed some PK analyses
Final Version 3.0	18NOV2022	Amended treatment labels, added instructions for handling n<5 for placebo, added summary of disposition for Parts A and B separately
Final Version 4.0	16JAN2023	Amended treatment labels, amended ECGPK analysis to be only a combined analysis for Parts A and B, not two independent parts.
Final Version 5.0	30JAN2023	Added percentage change from baseline statistical analysis for body weight and waist circumference.

NA = not applicable

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Approved on 31 Jan 2023 GMT