Statistical Analysis Plan J2A-GH-GZGX(v3.0)

A Multiple Dose Titration Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3502970 in Chinese Participants who have Obesity or are Overweight with Weight-related Comorbidities

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STATISTICAL ANALYSIS PLAN

A Multiple Dose Titration Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3502970 in Chinese Participants who have Obesity or are Overweight with Weight-related Comorbidities

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Clinical Phase I

1. TABLE OF CONTENTS

2. ABBREVIATIONS

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

%AUC(t_{last}-inf)	Percentage of AUC(0-∞) extrapolated
AE	Adverse event
AQL	Above the quantifiable limit
AUC	Area under the concentration versus time curve
AUC(0-24)	Area under the concentration versus time curve from time zero to 24 hours
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
BMI	Body mass index
BQL	Below the quantifiable lower limit of the assay
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
C_{last}	Last quantifiable drug concentration
C_{max}	Maximum observed drug concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
C-SSRS	Columbia Suicide-Severity Rating Scale
CV	Coefficient of variation
DAUC(0-24)	AUC(0-24) normalized by dose administered
DAUC(0-t_{last})	AUC(0-t_{last}) normalized by dose administered
DC_{max}	C_{max} normalized by dose administered
DMP	Data Management Plan
ECG	Electrocardiogram
GZGX	J2A-GH-GZGX
HbA1c	Glycated hemaglobin

ICH	International Conference on Harmonisation
IWRS	Interactive web-response system
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
PHQ-9	Patient health questionnaire-9
PK	Pharmacokinetic
QD	Once daily
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SS	Steady state
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, and Listings
t_{last}	Last time point where the concentration is above the limit of quantitation
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 amendment (b) (final version dated 15 March 2024).

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. This SAP must be finalized prior to first participant visit. 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

Objectives	Endpoints
Primary	
To investigate the safety and tolerability of LY3502970 following multiple oral once daily (QD) doses in Chinese participants with obesity or who are overweight with weight-related comorbidities	Number and incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
Secondary	
To characterize the PK profile of LY3502970 following multiple oral QD doses in Chinese participants with obesity or who are overweight with weight-related comorbidities. To characterize the PD effects of LY3502970 following multiple oral QD doses in Chinese participants with obesity or who are overweight with weight-related comorbidities.	Maximum observed drug concentration (C_{max}) and area under the concentration versus time curve from time 0 to 24 hours (AUC[0-24]) Changes from baseline in: o Body weight o Body mass index o Waist circumference Changes from baseline in: o Fasting plasma glucose o Fasting insulin o Glycated hemoglobin (HbA1c) o Lipid profiles

5. STUDY DESIGN

Study J2A-GH-GZGX (GZGX) is a Phase 1, investigator- and participant-blind, 2-cohort, randomized, placebo-controlled, 16-week (Cohort 1) and 24-week (Cohort 2) multiple dose titration study in Chinese participants with obesity or who are overweight with weight-related comorbidities.

The schema for GZGX can be seen in Figure 1.

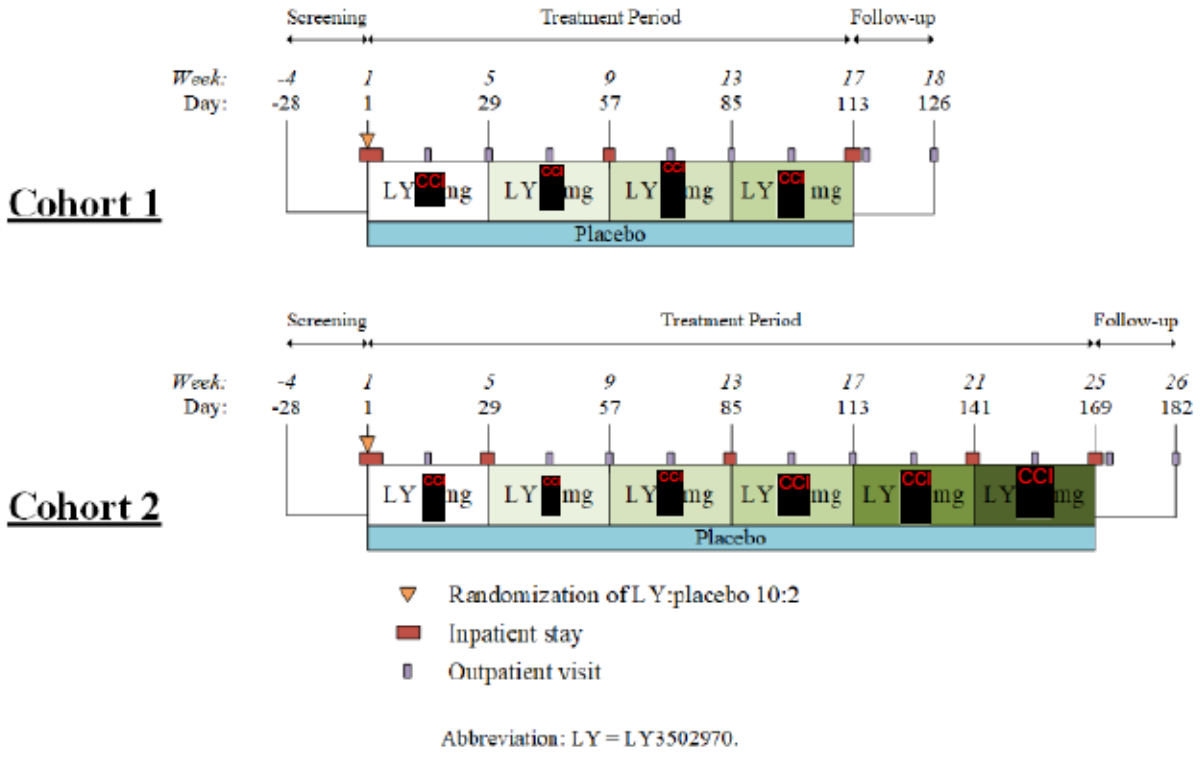

Figure 1: Study schema for GZGX

Screening

All participants will be screened within 28 days prior to Day 1.

Treatment and Assessment Period

Participants may be admitted to the clinical research unit (CRU) in advance if judged to be required by the investigator. It is intended that eligible participants will attend an inpatient visit at the CRU on Days -1, 56, and 112 for Cohort 1 and on Days -1, 28, 84, 140, and 168 for Cohort 2.

On Day 1, participants will be randomized 10:2 to either LY3502970 or placebo, and 1:1 to Cohort 1 or 2, with a computer-generated allocation code using an interactive web-response system (IWRS).

Overall, approximately 24 Chinese participants may be enrolled. Approximately 12 participants in each cohort will be randomized (10 participants to LY3502970 and 2 participants to placebo) to ensure approximately 8 participants receiving LY3502970 in each cohort complete the study.

From Day 1 to Day 112 of Cohort 1, participants will receive an oral QD dose of LY3502970 at 4 dose levels, or placebo. From Day 1 to Day 168 of Cohort 2, participants will receive an oral QD dose at 6 dose levels of LY3502970, or placebo.

Prior to discharge from the CRU (Day 3), participants will be instructed on the symptoms and treatment of hypoglycemia. Participants may be allowed to leave the CRU after completing assessments on Days 3, 57, and 114 for Cohort 1 and on Days 3, 29, 85, 141, and 170 for Cohort 2, or later at the investigator's discretion. Participants will return for outpatient visits for PK sampling and PD and safety assessments at predefined times. Participants may be required to remain at the CRU longer than the planned days at the investigator's discretion.

Progression of Cohorts through Study GZGX

Two cohorts are planned. Participants will be randomized to 1 of 2 cohorts comprising approximately 12 participants each. Participants will be randomized to receive stepwise dose titration of either LY3502970 or corresponding placebo for 16 weeks in Cohort 1 and 24 weeks in Cohort 2. Participants will receive a stepwise dose titration of LY3502970 or placebo, with each dose level administered for 4 weeks as shown:

- Cohort 1
    - LY3502970 Level 1; [redacted] mg for 4 weeks,
    - LY3502970 Level 2; [redacted] mg for 4 weeks,
    - LY3502970 Level 3; [redacted] mg for 4 weeks,
    - LY3502970 Level 4; [redacted] mg for 4 weeks.
- Cohort 2
    - LY3502970 Level 1; [redacted] mg for 4 weeks,
    - LY3502970 Level 2; [redacted] mg for 4 weeks,
    - LY3502970 Level 3; [redacted] mg for 4 weeks,
    - LY3502970 Level 4; [redacted] mg for 4 weeks,
    - LY3502970 Level 5; [redacted] mg for 4 weeks,
    - LY3502970 Level 6; [redacted] mg for 4 weeks

In Cohort 2, the duration of titration steps may be amended, and additional step-through doses may be added based on data obtained from Cohort 1. In addition, the dosage and dose titration scheme for either cohort may be further modified based on emerging safety and tolerability data. Any changes to the planned dose will be reviewed and approved by the sponsor and the investigator.

Safety data review will be planned for progression between stepwise dose titration within cohorts. The investigator and Lilly clinical physician or clinical research physician may review all available safety data including adverse events (AEs), vital signs, electrocardiograms (ECGs), safety laboratory measurements, and physical assessments. Any available PK or PD data may

also be considered for dose titrations. Individual patient data will not be made available to the investigator to avoid unblinding.

If the investigator decides not to up-titrate the dose level as planned for individual participants for any reason, participants should be discontinued for doses equal to or less than CCI mg. Participants may remain at the current dose level for doses greater than CCI mg through to the last planned dose on Day 112 for Cohort 1 or on Day 168 for Cohort 2.

Follow-up Period

Following the final assessments between Days 113 and 116 for Cohort 1 and Days 169 to 172 for Cohort 2, a follow-up visit approximately 2 weeks after the last dose of study intervention will be performed.

6. BLINDING

This is a randomized participant- and investigator-blind study. All measures possible must be taken to maintain the blind; access to the blinding information will be restricted to authorized personnel as described in the protocol.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted for medical management of the event. In such cases, the unblinding is to be conducted according to the protocol.

The Fortrea biometrics and Eli Lilly study teams will be unblinded throughout the study.

7. TREATMENTS

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

Study Treatment Name	Treatment order in TFL
Placebo QD	1
CCI mg LY3502970 QD	2
CCI mg LY3502970 QD	3

The following is a list of the study treatment abbreviations that will be used in the PK parameter TFLs and PK concentration figures by profile day:

Cohort	Profile day	Study Treatment Name	Treatment order in TFL
1 and 2	1	CCI mg LY3502970	1
2	28	mg LY3502970 SS	2
1	56	mg LY3502970 SS	3
2	84	mg LY3502970 SS	4

1	112	CCI mg LY3502970 SS	5
2	140	mg LY3502970 SS	6
2	168	mg LY3502970 SS	7

Abbreviations: SS = steady state

8. SAMPLE SIZE JUSTIFICATION

No formal statistical hypothesis testing will be performed.

The sample size is customary for Phase 1 studies evaluating safety and PK parameters. Approximately 24 Chinese participants who have obesity or are overweight with weight-related comorbidities may be enrolled so that 20 participants complete the study. The use of a 10:2 LY3502970:placebo ratio is intended to ensure that approximately 8 participants complete all planned LY3502970 doses in each cohort.

Participants who are randomized but discontinue before completing the study may be replaced to ensure that enough participants may complete the study.

9. DEFINITION OF ANALYSIS POPULATIONS

The "Enrolled" population will consist of all participants randomly assigned to study intervention or placebo.

The "Safety analysis set" population will consist of all participants who are exposed to at least 1 dose of study intervention or placebo. Participants will be analyzed according to the intervention they actually received.

The "Pharmacokinetic analysis set" population will consist of all enrolled participants who receive at least 1 dose of study intervention 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 analysis set" population will consist of all enrolled participants who receive at least 1 dose of study intervention or placebo 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.

10. STATISTICAL METHODOLOGY

10.1 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 number of observations; for log-normal data (e.g. the PK parameters: area under the concentration versus time curves [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.

For change from baseline summary statistics, each individual change from baseline will be calculated by subtracting the individual participant's baseline value from the value at that time point. The individual participants' change from baseline values will be used to calculate the summary statistics (arithmetic mean, arithmetic SD, median, minimum, maximum and number of observations) using a SAS procedure such as Proc Univariate.

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

10.2 Demographics and Participant Disposition

Participant disposition will be listed. The demographic variables age, sex, country of enrolment, site ID, body weight, waist circumference, height and body mass index (BMI) will be summarized and listed. All other demographic variables, including race and ethnicity, will be listed only.

10.3 Pharmacokinetic Assessment

10.3.1 Pharmacokinetic Analysis

Noncompartmental methods applied with a validated software program (WinNonlin Phoenix v8.3.5 or later) to the plasma concentrations of LY3502970 will be used to determine the following PK parameters, when possible.

PK Parameters

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 (Days 112 and 168 only)
AUC(0-24)	ng.h/mL	area under the concentration-time curve during one dosing interval
AUC(0-∞)	ng.h/mL	area under the concentration versus time curve from zero to infinity (Days 112 and 168 only)
%AUC(t_{last}-inf)	%	fraction of AUC(0-∞) extrapolated (Days 112 and 168 only)
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
t_{last}	h	last time point where the concentration is above the limit of quantitation (Days 112 and 168 only)
$t_{1/2}$	h	half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis (Days 112 and 168 only)
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
DAUC(0-t_{last})	ng.h/mL/mg	AUC(0-t_{last}) normalized by dose administered
DAUC(0-24)	ng.h/mL/mg	AUC(0-24) normalized by dose administered
DC_{max}	ng/mL/mg	C_{max} normalized by dose administered

Additional PK parameters may be calculated and additional analysis may be performed, 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 CSR.

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

General PK Parameter Rules

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

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

AUC parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least 1 of these concentrations following C_{max}. AUC(0-∞) values where the percentage of the total area extrapolated is more than 20% will be flagged. Any AUC(0-∞) value excluded from summary statistics will be noted in the footnote of the summary table.

Half-life (t½) 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 t½ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any t½ value excluded from summary statistics will be documented in the footnote of the summary table.

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

The parameters based on predicted last quantifiable drug concentration (C_{last}) will be reported.

Individual PK Parameter Rules

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

- The compound is non-endogenous.
- The samples are from the initial dose period for a 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.

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 CSR.

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 CSR.

Treatment of Outliers in Pharmacokinetic Analysis

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

<u>Data within an Individual Profile</u>

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

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

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

Data between Individual Profiles

1. If n<6, then the dataset is too small to conduct a reliable range test. Data will be analysed 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 1 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.

10.3.2 Pharmacokinetic Statistical Methodology

All PK parameters will be summarized by treatment and listed. Arithmetic mean plasma LY3502970 concentration plots and individual participant plots will be produced.

Log-transformed C_{max} and AUC(0-24) parameters of LY3502970 at steady state 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). Results of the dose proportionality analysis will be presented. 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.

Example of the SAS code for the power model analysis:

```
proc mixed data=xxx;
class usubjid;
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*/
random usubjid;
ods output solutionf=est;
ods output estimates=estims;
run;
```

10.4 Pharmacodynamic Assessment

10.4.1 Pharmacodynamic Analysis

The following PD measures are collected in this study:

Body weight
BMI
Waist circumference
Fasting plasma glucose
Fasting insulin
HbA1c
Lipid profiles

All PD parameters, as well as their change from baseline, where baseline is defined as the last non-missing value prior to the first dose, will be summarized by treatment and time point, and listed.

Figures of mean values, as well as mean change from baseline, will be plotted by treatment over all time points. Individual participant (spaghetti) plots by treatment arm will also be provided.

10.4.2 Pharmacodynamic Statistical Methodology

The PD parameters body weight, BMI, waist circumference, and fasting plasma glucose, as well as their change from baseline (last non-missing value prior to the first dose), will be analyzed using a mixed model repeated measures[3] to evaluate treatment effects and to report treatment comparisons for all time points after Day 1 predose. Parameters may be log-transformed prior to analysis if required. The model will include treatment, time point, and treatment-by-time point interaction as fixed effects, and participant as a random effect. Baseline will also be included as a covariate for all models. An unstructured covariance structure will be used to model the covariance between a participant's multiple observations. An alternative structure will be used if the model fails to converge, using a measure, such as Akaike's information criterion, to decide which structure will be used. The difference in least squares treatment means, comparing LY3502970 and placebo along with the 90% CI, will be reported, as well as each treatments least squares mean and 90% CI.

Example of the SAS code for the analysis:

```
proc mixed data=xxx;
class treatment time subjid;
model aval = base treatment time time*treatment/residual ddfm=kr2;
repeated time / subject=subjid type=un;
lsmeans treatment*time / cl pdiff alpha=0.1;
ods output lsmeans=lsm diffs=estims;
run;
```

10.5 Safety and Tolerability Assessments

10.5.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the AE will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as a condition 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 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 treatment arm, 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 is documented in the Data Management Plan [DMP]) 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 SAEs will be listed. Adverse events by day of onset will be presented. Adverse events of special interest will be listed separately and are as follows:

pancreatic events,
cardiovascular events
hepatic events
nausea, vomiting, and diarrhea
hypoglycemia
Constipation.

Discontinuations due to AEs will be listed.

10.5.2 Glucose Monitoring and Hypoglycemia

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, if there is a suitable number of occurrences of hypoglycaemic events, summarized by treatment arm. Hypoglycemia is defined as follows:

Level 1 hypoglycemia:

Glucose less than 70 mg/dL (3.9 mmol/L) and equal to or greater than 54 mg/dL (3.0 mmol/L): Level 1 hypoglycemia can alert a person to take action such as treatment with fast-acting carbohydrates. Providers should continue to counsel participants to treat hypoglycemia at this glucose alert value.

- **Documented symptomatic hypoglycemia** is defined as any time a participant feels that he or she is experiencing symptoms and/or signs associated with hypoglycemia.
- **Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia.
- **Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available.

Level 2 hypoglycemia:

Glucose less than 54 mg/dL (3.0 mmol/L): Level 2 hypoglycemia is also referred to as documented or blood glucose confirmed hypoglycemia with glucose less than 54 mg/dL (3.0 mmol/L). This glucose threshold is clinically relevant regardless of the presence or absence of symptoms of hypoglycemia.

- **Documented symptomatic hypoglycemia** is defined as any time a participant feels that he or she is experiencing symptoms and/or signs associated with hypoglycemia.
- **Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia.
- **Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available.

Level 3 hypoglycemia:

Severe hypoglycemia: 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, were semiconscious, 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.

Other hypoglycemia category:

Nocturnal hypoglycemia is defined as any hypoglycemic event (including severe hypoglycemia) that occurs between bedtime and waking.

Relative hypoglycemia is defined as an event during which the participant reports symptoms of hypoglycemia, but with a measured blood glucose

concentration >63 mg/dL (3.5 mmol/L), equivalent to plasma glucose 70 mg/dL (3.9 mmol/L).
Probably symptomatic hypoglycemia is an event during which the symptoms of hypoglycemia are not accompanied by a plasma glucose.

10.5.3 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (version is documented in the DMP). Concomitant medication will be listed.

10.5.4 Clinical laboratory parameters

All clinical chemistry and hematology data, as well as the change from baseline, where baseline is defined as Day 1 predose, will be summarized by treatment arm and time point, 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.

Values recorded as <x, ≤x (that is, BQL), >x, or ≥x (that is, above the quantifiable limit [AQL]) will be displayed in the listings as recorded. For the calculation of summary statistics, BQL values will be set to 0.5 × x, whereas AQL values will be set to 1.1 × x.

10.5.5 Vital signs

Vital signs data will be summarized by treatment arm and time point together with changes from baseline, where baseline is defined as the last non-missing value prior to the first dose. Figures of mean vital signs and mean changes from baseline will be presented over time by treatment arm.

Values for individual participants will be listed.

10.5.6 Electrocardiogram

ECGs will be performed for safety monitoring purposes only and will not be presented. Any clinically significant findings from ECGs will be reported as an AE.

10.5.7 Hepatic Monitoring

If a participant experiences elevated laboratory parameters, as detailed in Section 8.2.7.2. 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. Use of acetaminophen during the study, which has potential for hepatotoxicity, will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography (MRE) 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, if deemed appropriate, 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.

10.5.8 Suicidal Ideation and Behavior Risk Monitoring Data

Suicide-related thoughts and behaviors occurring during treatment will be summarized by treatment and listed based on responses to the Columbia Suicide-Severity Rating Scale (C-SSRS) questionnaire. Data collected from the patient health questionnaire-9 (PHQ-9) will also be listed separately.

10.5.9 Pancreatic Monitoring

The frequency of pancreatic amylase or fasting lipase values ≥3× upper limit of normal (ULN) will be summarized by treatment arm and listed.

10.5.10 Other assessments

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

11. INTERIM ANALYSES

No interim statistical analyses are planned.

12. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

13. 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. Brown H, Prescott R. Applied Mixed Models in Medicine. Chichester: John Wiley & Sons, 1999.

14. DATA PRESENTATION

14.1 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. Number of observations 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.

14.2 Missing Data

Missing data will not be displayed in listings.

14.3 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.”

15. 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	12DEC2023	Added additional hypoglycemia categories
Final Version 3.0	17JUN2024	Number of participants to be enrolled changed from ‘up to 24’ to ‘approximately 24’ in study design and sample size section as per protocol amendment (b)

NA = not applicable

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Approval	PPD Statistician 17-Jun-2024 11:49:07 GMT+0000

Approval	PPD PKPDPMx 17-Jun-2024 15:04:08 GMT+0000

Approval	PPD Statistician 18-Jun-2024 02:08:23 GMT+0000

Approval	PPD PKPDPMx 18-Jun-2024 12:41:21 GMT+0000

Signature Page for VV-CLIN-138483 v2.0

Approved on 18 Jun 2024 GMT