Statistical Analysis Plan J2A-MC-GZGN 2.0

A Multiple Dose Study to Assess the Pharmacokinetics, Safety, and Tolerability of Tablet and Capsule Formulations of LY3502970 in Healthy Overweight and Obese Participants

NCT05841238

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STATISTICAL ANALYSIS PLAN

A Multiple Dose Study to Assess the Pharmacokinetics, Safety, and Tolerability of Tablet and Capsule Formulations of LY3502970 in Healthy Overweight and Obese Participants

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Investigational Medicinal Product: LY3502970

Protocol Reference: J2A-MC-GZGN
CCI Drug Development Study: 8508685

Clinical Phase I

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1. TABLE OF CONTENTS

2. ABBREVIATIONS

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

AE	Adverse event
AESI	Adverse events of special interest
AUC	Area under the concentration versus time curve
$AUC_{(0-24)}$	Area under the concentration versus time curve from time zero to 24 hours postdose
BQL	Below the quantifiable lower limit of the assay
C-SSRS	Columbia-Suicide Severity Rating Scale
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
CV	Coefficient of variation
DF	Dual-fill
DMP	Data Management Plan
EC	Early Clinical
ECG	Electrocardiogram
EPB	Extemporaneously prepared blended
ICH	International Conference on Harmonisation
LLOQ	Lower limit of quantification
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
PK	Pharmacokinetic
QD	Once daily

SAP	Statistical Analysis Plan
SD	Standard deviation
SOP	Standard Operating Procedure
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
V_z/F	Apparent volume of distribution during the terminal phase after extra-vascular administration
ULN	Upper limit of normal
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 06 February 2023), Protocol Amendment (b) (final version dated 17 May 2023), and Protocol Addendum (1) (final version dated 30 June 2023).

This SAP describes the planned analysis of the safety, tolerability and pharmacokinetic (PK) 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 (eg, objectives, study design) is given to help the reader's interpretation. Version 1 of this SAP was 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 characterize and compare the PK of multiple doses of LY3502970 in different formulations in healthy overweight and obese participants	Area under the concentration versus time curve from time 0 to 24 hours postdose ($AUC_{[0-24]}$), maximum observed drug concentration (C_{max}), and time of maximum observed drug concentration (t_{max}).

Objectives	Endpoints
Secondary	
To assess the effect of a high-fat meal on the PK of LY3502970 tablets and capsules in healthy overweight and obese participants	$AUC_{(0-24)}$, C_{max}, and t_{max}
To assess the PK of high doses of LY3502970 in healthy overweight and obese participants	$AUC_{(0-24)}$, C_{max}, and t_{max}
To describe the safety and tolerability of different formulations of LY3502970 in healthy overweight and obese participants	Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
To characterize and compare the PK of LY3502970 from the different capsule formulations in healthy overweight and obese participants.	$AUC_{(0-24)}$, C_{max}, and t_{max}

5. STUDY DESIGN

Study GZGN is a Phase 1, 2-part, multiple-dose titration study in healthy overweight and obese participants.

Figure 1 shows the study schema for Fortrea CRU Inc, Madison and Daytona. Details for the differentiation of Part B for Fortrea CRU Inc, Dallas, may be found in this section.

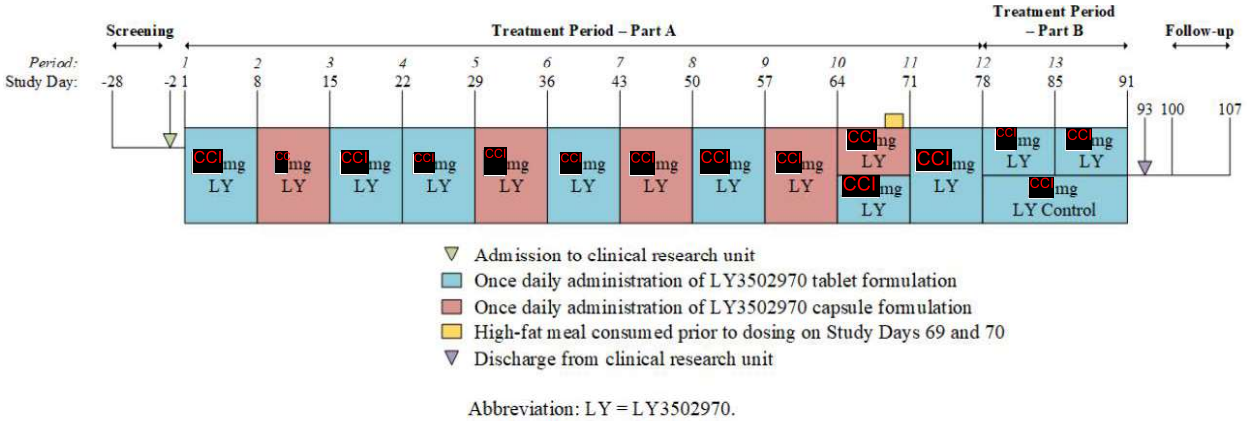

Figure 1 - J2A-MC-GZGN Study Schema

Screening

All participants will be screened between 28 to 3 days prior to Day 1.

Treatment and Assessment Period

Eligible participants will be admitted to the Clinical Research Unit (CRU) on Day -2.

Participants will be enrolled in Parts A and B. Approximately 50 participants will be enrolled to ensure 32 completers of Parts A and B.

Part A (Periods 1 to 11)

Throughout Periods 1 to 11, participants will receive a once daily (QD) oral dose of LY3502970 in the tablet or capsule formulation, depending on the period of the study. In Period 10, participants will be randomized 1:1 to receive CCI mg LY3502970 capsule or CCI mg LY3502970 tablet. Participants will be in a fasted state in all periods, except for Period 10. On Days 1 to 5 of Period 10, that is, Study Days 64 to 68, participants will consume a standard meal prior to dosing. On Days 6 and 7 of Period 10, that is, Study Days 69 and 70, participants will consume a high-fat meal prior to dosing. Following Period 11, all participants will continue to Part B of the study.

Progression of Doses through Part A of Study GZGN

During the treatment period of Part A, doses will be escalated in a stepwise manner for all participants on a weekly basis for 11 weeks, with the following dose levels and formulations administered QD for 7 days as shown:

- Period 1: CCI mg LY3502970 tablet
- Period 2: CCI mg LY3502970 capsule
- Period 3: CCI mg LY3502970 tablet
- Period 4: CCI mg LY3502970 tablet
- Period 5: CCI mg LY3502970 capsule
- Period 6: CCI mg LY3502970 tablet
- Period 7: CCI mg LY3502970 capsule
- Period 8: CCI mg LY3502970 tablet
- Period 9: CCI mg LY3502970 capsule
- Period 10: CCI mg LY3502970 capsule or CCI mg LY3502970 tablet, in fed state, and
- Period 11: CCI mg LY3502970 tablet.

Part B (Periods 12 and 13)

Fortrea CRU Inc, Madison and Daytona:

Throughout Periods 12 and 13, participants will receive a QD oral dose of LY3502970 in the tablet formulation. Participants will be randomized 3:1 to receive either LY3502970 dose titration tablets or CCI mg LY3502970 tablets based on a computer-generated allocation code.

Fortrea CRU Inc, Dallas:

Participants will receive a CCI-mg dual-fill (DF) capsule for 7 days in Period 12 and then an extemporaneously prepared CCI-mg blended capsule of LY3502970 for 7 days in Period 13. A comparative analysis of PK data from Periods 12 and 13 will be performed.

Participants may be allowed to leave the CRU after completing the safety assessments on Period 13, Day 9, or later at the investigator's discretion.

Progression of Doses through Part B of Study GZGN

Fortrea CRU Inc, Madison and Daytona:

During the treatment period of Part B, participants randomized to receive dose titration LY3502970 tablets will receive a stepwise dose titration of LY3502970 on Day 1 of Periods 12 and 13, with each of the following dose levels and formulations administered QD for 7 days as shown:

- Period 12: CCI mg LY3502970 in tablet formulation, and
- Period 13: CCI mg LY3502970 in tablet formulation.

Participants randomized to the control group will receive CCI mg LY3502970 in tablet formulation QD for 7 days in both Periods 12 and 13.

Fortrea CRU Inc, Dallas:

Period 12

In Period 12, instead of being randomized to receive CCI-mg LY3502970 dose titration tablets or CCI-mg LY3502970 tablets, all participants will receive a single CCI-mg DF LY3502970 capsule QD for 7 days.

Period 13

In Period 13, instead of being randomized to receive CCI-mg LY3502970 dose titration tablets or CCI-mg LY3502970 tablets, all participants will receive a single CCI-mg extemporaneously prepared blended (EPB) LY3502970 capsule QD for 7 days.

Follow-up Period

A follow-up visit will be performed approximately 7 to 14 days after discharge from the CRU.

6. BLINDING

Part A is a randomized, open-label study.

Part B is a randomized participant- and investigator-blind study for all study sites, except Fortrea CRU Inc, Dallas, for which this is an open-label non-randomized 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. Staff who prepare the study intervention will not be blinded to treatment allocation.

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.

Part	Treatment Label	Order in TFLs
A	CCI mg LY3502970 tablet (fasted)	1
	CCI mg LY3502970 capsule (fasted)	2
	CCI mg LY3502970 tablet (fasted)	3
	CCI mg LY3502970 tablet (fasted)	4
	CCI mg LY3502970 capsule (fasted)	5
	CCI mg LY3502970 tablet (fasted)	6
	CCI mg LY3502970 capsule (fasted)	7
	CCI mg LY3502970 tablet (fasted)	8
	CCI mg LY3502970 capsule (fasted)	9
	CCI mg LY3502970 capsule (fed)	10
	CCI mg LY3502970 tablet (fed)	11
	CCI mg LY3502970 tablet (fasted)	12
B	CCI mg LY3502970 tablet (fasted) (Period 12)	13
	CCI mg LY3502970 tablet (fasted) (Period 13)	14
	CCI mg LY3502970 DF capsule (fasted)	15
	CCI mg LY3502970 EPB capsule (fasted)	16
	CCI mg LY3502970 tablet (fasted)	17
	CCI mg LY3502970 tablet (fasted)	18

8. SAMPLE SIZE JUSTIFICATION

CCI [redacted]

[redacted]

CCI

[redacted]

[redacted]

[redacted]

9. DEFINITION OF ANALYSIS POPULATIONS

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

The "Safety analysis set" population will consist of all participants who are exposed to at least 1 dose of LY3502970. Participants will be analyzed according to the intervention they actually received.

The "PK analysis set" will consist of all enrolled participants who receive 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 adverse event (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 (eg the PK parameters: area under the concentration time curve [AUC] 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, race, ethnicity, country of enrolment, site ID, body weight, height and body mass index will be summarized and listed.

All other demographic variables will be listed only.

10.3 Pharmacokinetic Assessment

10.3.1 Pharmacokinetic Analysis

Noncompartmental methods applied with a validated software program (WinNonlin Phoenix Version 8.3.5 or later) to the 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 from time zero to 24 hours postdose
C_{max}	ng/mL	Maximum observed drug concentration
t_{max}	h	Time of maximum observed drug concentration
CL/F	L/h	Apparent total body clearance of drug calculated after extra-vascular administration

Additional PK parameters may be calculated or 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.

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

In addition, the relationship between the LY3502970 capsule and tablet formulations regarding C_{max} and AUC parameters will be explored using all data across Periods 1 to 11.

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

General PK Parameter Rules

- Actual sampling times will be used in the final analyses of individual PK parameters, except for non-bolus pre-dose sampling times which will be set to zero.
- C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than one time point, t_{max} will be assigned to the first occurrence of C_{max}.
- AUC parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}.
- 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 observed 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 during PK Analysis

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

Data within an Individual Profile

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

- For PK profiles during single dosing of non-endogenous compounds, the concentration in a pre-dose sample is quantifiable.
- For any questionable datum that does not satisfy the above criteria, the profile will be evaluated and results reported with and without the suspected datum.

Data between Individual Profiles

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

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

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

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

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

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

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

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

Reporting of Excluded Values

Individual values excluded as outliers will be documented in the final CSR. Approval of the final CSR will connote approval of the exclusion.

10.3.2 Pharmacokinetic Statistical Methodology

All PK parameters will be listed and summarized by treatment using descriptive statistics.

Primary Statistical Analysis

CCI

[redacted]

Secondary Analysis

CCI

[redacted]

CCI [redacted]

CCI [redacted]

10.4 Safety and Tolerability Assessments

10.4.1 Adverse events

Where changes in severity are recorded in the 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. TEAEs 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 TEAEs 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. AEs by day of onset will be presented.

Discontinuations due to AEs will be listed.

A listing of adverse events of special interest (AESIs) will be presented. AESIs include:

- Nausea
- Vomiting
- Diarrhea events
- Pancreatic events (See Section 8.2.7.1 of Protocol for more details)
- Cardiovascular events
- Hepatic events
- Hypoglycemia.

10.4.2 Glucose Monitoring and Hypoglycemia

During the study, plasma glucose concentrations will be monitored for safety assessments. For Part A, glucose data will be listed and summarized by time point.

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:

- **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.

- **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.

- **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.

- **Nocturnal hypoglycemia** is a hypoglycaemia event (including severe hypoglycaemia) that occurs at night and presumably during sleep.

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

10.4.3 Concomitant medication

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

10.4.4 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by 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 $<x$, $\leq x$, $>x$, or $\geq x$ will be displayed in the listings as recorded. For the calculation of summary statistics, $<x$ and $\leq x$ values will be set to $0.5 \times x$, whereas $>x$ and $\geq x$ values will be set to $1.1 \times x$.

10.4.5 Vital signs

Vital signs data will be summarized by time point together with changes from baseline, where baseline is defined as the Day -2 assessment. Mean vital signs and mean changes from baseline will be plotted over time.

Values for individual participants will be listed.

10.4.6 Body Weight

Body weight will be summarized by time point together with changes from baseline, where baseline is defined at screening. Mean body weight and mean changes from baseline will be plotted over time.

Values for individual participants will be listed.

10.4.7 Fasting Plasma Glucose

Fasting plasma glucose will be summarized by time point together with changes from baseline, where baseline is defined at screening. Mean fasting plasma glucose observed and change from baseline values will be plotted over time.

Values for individual participants will be listed.

10.4.8 Electrocardiogram (ECG)

Single ECGs in Part A 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.

10.4.9 Columbia-Suicide Severity Rating Scale (C-SSRS)

Data from the C-SSRS evaluation will be listed.

10.4.10 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.

10.4.11 Elevated Lipase or Amylase

If a participant experiences elevated serum amylase or lipase values ≥3× upper limit of normal (ULN), additional monitoring and tests may be performed to confirm the abnormality.

The frequency of serum amylase or lipase values ≥3× ULN will be summarized by treatment and listed.

10.4.12 Other assessments

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

10.4.13 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

11. INTERIM ANALYSES

No interim statistical analyses are planned. If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the protocol and SAP must be amended.

12. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

CCI [redacted]

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.

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	11AUG2023	Incorporate changes introduced by Protocol Addendum (1), both Protocol Amendments (a and b), as well as make minor editorial / formatting changes. Sample size text updated following updated calculations by Sponsor.

NA = not applicable

Signature Page for VV-CLIN-124125 v1.0

Approval	PPD Statistician 11-Aug-2023 12:03:56 GMT+0000

Approval	PPD PKPDPMx 11-Aug-2023 13:14:34 GMT+0000

Approval	PPD Statistician 11-Aug-2023 13:50:29 GMT+0000

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