Statistical Analysis Plan: J1X-MC-GZHI (Final Version 2.0)

An Open-Label, Multiple-Dose Study to Investigate the Pharmacokinetics of LY3493269 Oral Formulations Administered in a Fed or Fasted State in Healthy Participants

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STATISTICAL ANALYSIS PLAN

An Open-Label, Multiple-Dose Study to Investigate the Pharmacokinetics of LY3493269 Oral Formulations Administered in a Fed or Fasted State in Healthy Participants

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Clinical Phase I

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2. ABBREVIATIONS

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

%AUC(t_{last}-∞)	Percentage of AUC(0-∞) extrapolated
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AUC	Area under the concentration versus time curve
AUC(0-∞)	area under the concentration versus time curve from time zero to infinity
AUC(0-t_{last})	Area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
AUC_{τ}	Area under the concentration versus time curve during one dosing interval
BQL	Below the quantifiable lower limit of the assay
C10	Sodium caprate
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
C_{min}	Minimum observed drug concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
DMP	Data Management Plan
EC	Early Clinical
ECG	Electrocardiogram
F_{Abs}	Absolute bioavailability of each oral treatment compared to an intravenous formulation

F_{Rel}	Relative bioavailability of the test formulation compared to reference formulation
ICH	International Conference on Harmonisation
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
PK	Pharmacokinetic
R_A	Accumulation ratio
SAP	Statistical Analysis Plan
SD	Standard deviation
SNAC	Salcaprozate sodium
SOP	Standard Operating Procedure
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
TBL	Total bilirubin
TEADAs	Treatment-emergent anti-drug antibody
TEAEs	Treatment-emergent adverse event
TFLs	Tables, Figures, and Listings
t_{last}	Time of the last quantifiable concentration
t_{max}	Time of maximum observed drug concentration
ULN	Upper limit of normal
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
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 18 September 2022).

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 (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 evaluate and compare the PK of up to 3 test capsule formulations with a reference tablet formulation of LY3493269 following 3 consecutive once-daily oral doses in healthy participants	• Area under the concentration versus time curve (AUC) and maximum observed drug concentration (C_{max})
Secondary	
• To evaluate the PK of up to 2 LY3493269 formulations when administered in a fed condition following 3 consecutive once-daily oral doses in healthy participants	• AUC and C_{max}

• To assess the safety and tolerability of up to 3 test capsule formulations of LY3493269 with that of a reference tablet formulation following 3 once-daily oral doses in healthy participants	• Treatment-emergent adverse events (TEAEs)
Exploratory	
• To assess PK of salcaprozate sodium (SNAC) and sodium caprate (C10) following oral administration in healthy participants	• AUC and C_{max}

5. STUDY DESIGN

This is a 2-part, open-label study with a parallel design to be conducted in healthy participants.

The purpose of this study is to evaluate and compare the PK of up to 3 test capsule formulations with a reference tablet formulation of LY3493269 following 3 consecutive once-daily oral doses in healthy participants.

Study details include:

- The study duration will be up to 71 days.
- The treatment duration involves consecutive once-daily dosing up to 3 days.
- The visit frequency will be one inpatient stay (Day -1 through Day 5) and 5 outpatient visits.

In Parts A and B, eligible participants will receive 3 once-daily doses of study intervention.

The maximum total duration of study participation for each participant may be up to 71 days, across the following study intervals:

- Screening, approximately 28 days
- Study period, approximately 15 days, and
- Follow up, approximately 28 days after the last dose of study intervention.

The study shall target 10 participants completing each treatment – that is, these participants must complete Day 8 PK assessments after receiving all 3 consecutive daily doses of the study treatment.

Part A

Part A of the study is an initial characterization of 2 test capsule formulations, compared with a reference tablet formulation. Participants will be randomly assigned to receive 1 of the 3 possible treatments as follows:

- Treatment A1: Test capsule formulation 1
- Treatment A2: Test capsule formulation 2
- Treatment A3: Reference tablet formulation

Test formulations 1 and 2 and the reference formulation will be administered in the fasted state.

Part B

Part B of the study will investigate the test capsule formulations 1, 2, or 3 or the reference tablet formulation.

An initial review of safety and PK data from Part A will be conducted to determine the test or reference formulation(s) to be evaluated in Part B. Participants will be assigned to 1 of the 2 possible treatments as follows:

- Treatment B1: Test formulations 1, 2, or 3 (referred to as "X" from this point forward)
- Treatment B2: Test formulations 1, 2, or 3 or reference formulation (referred to as "Y" from this point forward).

The 3 test formulations will be administered in either the fasted or fed state depending on the review of safety and PK data from Part A. If the reference formulation is selected as Treatment B2, it will be administered in the fasted state.

Depending on the review results, the selected formulation(s) will be administered in either the fed or fasted state.

Treatments B1 and B2 may be initiated concurrently if the formulations "X" and "Y" and administration conditions are determined for both treatment groups after the first review. Otherwise, a second review of available PK data from Treatment B1 may be conducted prior to the initiation of Treatment B2.

Changes from the Planned Study Design

At the time of writing this SAP amendment, the Sponsor has decided not to proceed with Part B of the study. All further references to Part B are no longer applicable.

6. BLINDING

This is a randomized, open-label study.

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 labels that will be used in the TFLs. Where the abbreviation is used, the TFLs will include a footnote.

Part	Study Treatment Name	Abbreviation	Treatment order in TFLs
A	Test capsule 1: 4 mg LY3493269 + 280 mg C10 (fasted)	A1	1
	Test capsule 2: 4 mg LY3493269 + 280 mg C10 (fasted)	A2{Insert brief description of indication}	2
	Reference tablet: 4 mg LY3493269 + 300 mg SNAC (fasted)	A3	3
B	Test capsule X: 4 mg LY3493269 + 280 mg C10 (TBC)	B1	4
	TBC Y: 4 mg LY3493269 + TBC (TBC)	B2	5

Abbreviations: C10 = sodium caprate; SNAC = salcaprozate sodium; TBC = to be confirmed.

"X" can be test formulations 1, 2 or 3; "Y" can be test formulations 1, 2, 3 or reference formulation; The 3 test formulations will be administered in either the fasted or fed state depending on the review of safety and PK data from Part A. If the reference formulation is selected as Treatment B2, it will be administered in the fasted state. All TFLs will be based on actual treatments.

8. SAMPLE SIZE JUSTIFICATION

Up to approximately 70 participants may be randomly assigned to study intervention to ensure approximately 10 evaluable participants from each of the 5 planned treatment groups complete the study. CCI [redacted]

Participants who are randomly assigned but not administered treatment prior to discontinuation may be replaced to ensure that the target number of participants complete the study.

Participants who discontinue early may be replaced after consultation with the investigator and sponsor. The replacement participant will be assigned to the same treatment as the discontinued participant.

9. DEFINITION OF ANALYSIS POPULATIONS

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

The "Randomized/Enrolled" population will consist of all participants assigned to treatment, regardless of whether they take any doses of study treatment, or whether 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 enrolled participants who received at least one dose of LY3493269. Participants will be analyzed according to the intervention they actually received.

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

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: 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 summarized and 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 (Phoenix WinNonlin v8.3.5) to the plasma concentrations of LY3493269, SNAC, and C10 will be used to determine the following PK parameters in Parts A and B, when possible:

Profile Day 1

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_{τ}	ng.h/mL	area under the concentration versus time curve during one dosing interval
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
t_{last}	h	time of the last quantifiable concentration

Profile Day 2

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
$AUC_{\tau,day\ 2}$	ng.h/mL	area under the concentration versus time curve during one dosing interval at day 2
$C_{max,day\ 2}$	ng/mL	maximum observed drug concentration
$t_{max,day\ 2}$	h	time of maximum observed drug concentration
t_{last}	h	time of the last quantifiable concentration

Profile Day 3

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
$AUC_{\tau,day\ 3}$	ng.h/mL	area under the concentration versus time curve during one dosing interval at day 3
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
$C_{max,day\ 3}$	ng/mL	maximum observed drug concentration
$t_{max,day\ 3}$	h	time of maximum observed drug concentration
t_{last}	h	time of the last quantifiable concentration
$t_{½}$	h	half-life associated with the terminal rate constant (λz) 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
R_A	none	accumulation ratio (based on AUC_τ on Profile Days 1 and 3)
F_{Rel}	%	relative bioavailability of the test formulation compared to reference formulation (based on AUC[0-∞])
F_{Abs}	%	absolute bioavailability of each oral treatment compared to an intravenous formulation (based on dose-normalized [DN] AUC[0-∞]): $F_{Abs} = \frac{\text{Oral DN}^a\ AUC(0-\infty)}{\text{IV}^b\ \text{DN}\ AUC(0-\infty)} \times 100$ [a] derived by dividing by the total oral dose administered (12) [b] obtained from study J1X-MC-GZHA, using the geometric mean AUC(0-∞) of [redacted] LY3493269 IV

Additional PK parameters may be calculated, as appropriate. The software and version used for the final analyses will be specified in the clinical study report. 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}, $C_{max,day\ 2}$, $C_{max,day\ 3}$, t_{max}, $t_{max,day\ 2}$, $t_{max,day\ 3}$, and t_{last} will be reported from observed values. On a given profile day, 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}. AUC(0-∞) values where the percentage of the total area extrapolated is more than 20% will be flagged. Any AUC(0-∞) value excluded from summary statistics will be noted in the footnote of the summary table.
- Half-life ($t_{½}$) will be calculated, when appropriate, based on the apparent terminal log-linear portion of the concentration-time curve. The start of the terminal elimination phase for each participant will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in plasma concentrations. Half-life will only be calculated when a reliable estimate for this parameter can be obtained comprising of at least 3 data points. If $t_{½}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{½}$ value excluded from summary statistics will be documented in the footnote of the summary table.
- A uniform weighting scheme will be used in the regression analysis of the terminal log-linear portion of the concentration-time curve.
- The parameters based on observed 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.
- For multiple-dosing data, when pre-dose concentrations are missing, the value to be substituted will be minimum observed drug concentration (C_{min}) for the dosing interval.
- For C10 and SNAC:
    - Predose concentrations that are BLQ will be set to half the LLOQ.
    - If quantifiable predose concentrations are observed for any of the PK profile days, the postdose concentrations of the impacted PK profile day(s) will be baseline-adjusted prior to calculation of PK parameters. Baseline-adjustment will be performed by subtracting the PK profile day's quantifiable predose concentration from each postdose concentration belonging to that same PK profile day.

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.
- Observed (unadjusted) concentrations will be plotted for C10 and SNAC.

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.

- Observed (unadjusted) concentrations will be plotted for C10 and SNAC.

Treatment of Outliers during Pharmacokinetic Analysis

Application of this procedure to all pharmacokinetic 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 pharmacokinetic 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 pharmacokinetic 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 $n\geq6$, then an objective outlier test will be used to compare the atypical value to other values included in that calculation:
    a. Transform all values in the calculation to the logarithmic domain.
    b. Find the most extreme value from the arithmetic mean of the log transformed values and exclude that value from the dataset.
    c. Calculate the lower and upper bounds of the range defined by the arithmetic mean ±3*SD of the remaining log-transformed values.
    d. If the extreme value is within the range of arithmetic mean ±3*SD, then it is not an outlier and will be retained in the dataset.
    e. If the extreme value is outside the range of arithmetic mean ±3*SD, then it is an outlier and will be excluded from analysis.

If the remaining dataset contains another atypical datum suspected to be an outlier and $n\geq6$ following the exclusion, then repeat step 2 above. This evaluation may be repeated as many times as necessary, excluding only one suspected outlier in each iteration, until all data remaining in the dataset fall within the range of arithmetic mean ±3*SD of the log-transformed values.

Reporting of Excluded Values

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

10.3.2 Pharmacokinetic Statistical Methodology

The PK parameters of LY3493269 will be evaluated to estimate the relative bioavailability. Log-transformed AUC_{τ}, $AUC(0\text{-}t_{last})$, $AUC(0\text{-}\infty)$ (profile day 3 only) and C_{max} of LY3493269 will be evaluated in a mixed model for repeated measures with fixed effects for treatment, profile day and the treatment-by-day interaction, and a random effect for participant. 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. The geometric least squares means, ratio of geometric least squares means and corresponding 90% CI will be reported.

One model including all treatments (A1, A2, A3, B1 and B2) will be used to present the following comparisons for each profile day:

- Test capsule X versus Reference tablet, where X=1, 2 or 3.
- Fed versus fasted, for matching formulation.
- 240 mL versus 120 mL water administration, for matching formulation and dietary status.

Example SAS code:

```
proc mixed data=xxx;
  by param;
  class treat day subjid;
  model lpk = treat day treat*day / residual ddfm=kr2;
  repeated day / subject=subjid type=un;
  lsmeans treat*day / cl pdiff alpha=0.1;
  ods output lsmeans=lsm diffs=dif;
run;
```

The parameter t_{max} of LY3493269 will be analyzed non-parametrically. Estimates of the median difference, approximate 90% CI and p-value from the Wilcoxon rank sum test will be calculated.

All PK parameters will be summarized using descriptive statistics.

Additional analysis may be conducted if deemed necessary.

10.4 Safety and Tolerability Assessments

10.4.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the adverse event (AE) will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as 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 the first dose.

A treatment-emergent AE is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose.

All AEs will be listed. 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 serious AEs will be listed. AEs by day of onset will be presented.

Discontinuations due to AEs will be listed.

Adverse events of special interest (AESI) are nausea, vomiting, diarrhea, skin burning sensations and related AEs. AESIs will be listed.

10.4.2 Skin Burning Sensations and Related AEs

Healthy participants in this short-exposure study may experience AEs of skin burning sensation and related AEs. If this AE does occur, dedicated CRF will be used by site personnel to collect detailed information about the event on initial presentation of this AE, and on subsequent visits until the AE resolves.

The data will be summarized by treatment and listed.

10.4.3 Glucose Monitoring and Hypoglycemia

During the study, plasma glucose concentrations will be monitored for safety assessments. Glucose data will be listed and summarized by treatment together with changes from baseline, where baseline is defined as Day 1 pre-breakfast.

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 <70 mg/dL (3.9 mmol/L) and ≥ 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 <54 mg/dL (3.0 mmol/L): This is 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 of 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.

- **Other hypoglycemia categories:**

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

10.4.4 Concomitant medication

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

10.4.5 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by treatment and time point together with change from baseline, where baseline is defined as Day 1 predose, 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 $1.1 \times x$.

10.4.6 Vital signs

Vital signs data will be summarized by treatment and time point together with changes from baseline, where baseline is defined as the Day 1 predose assessment. Figures of mean vital signs and mean changes from baseline profiles will be presented by treatment.

Values for individual participants will be listed.

Change from baseline in supine blood pressure and pulse rate will be analyzed using a mixed model for repeated measures. The model will include baseline (Day 1 predose) as a covariate, treatment, timepoint and the treatment-by-timepoint interaction as fixed effects, and participant as a random effect. 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. Follow-up data will not be included in the model.

One model including all treatments (A1, A2, A3, B1 and B2) will be used to present comparisons of each test formulation versus the reference formation at each post-dose timepoint. The difference in least squares means, along with the 90% confidence interval, will be reported.

Example SAS code:

```
proc mixed data=xxx;
  by param;
  class treat time subjid;
  model chg = base treat time treat*time / residual ddfm=kr2;
  repeated time / subject=subjid type=un;
  lsmeans treat*time / cl pdiff alpha=0.1;
  ods output lsmeans=lsm diffs=dif;
run;
```

10.4.7 Electrocardiogram (ECG)

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.

10.4.8 Hepatic Monitoring

If a participant experiences elevated laboratory parameters, as detailed in Section 8.2.5.1 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 there are sufficient data available, 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.

10.4.9 Immunogenicity Assessments

Immunogenicity data may be listed and frequency tables may be presented if analysed. The frequency and percentage of participants with pre-existing antidrug antibody (ADA) and with treatment-emergent ADAs (TE ADAs) may be presented. TE ADAs are those that are boosted or induced by exposure to study drug, with a 4-fold increase in titer compared to baseline if ADAs were detected at baseline or a titer 2-fold greater than the minimum required dilution (1:10) if no ADAs were detected at baseline, where baseline is defined as Day 1 predose.

Venus blood samples will be stored for future analysis to determine antibody production against LY3493269. Any analysis, whether performed at a later date or during this study, will be performed by Eli Lilly. If applicable, the frequency and percentage of participants with cross-reactive binding to native GIP, GLP-1 or neutralizing antibodies, if measured, may also be tabulated for participants with TE ADA.

The relationship between the presence of antibodies and PK parameters of LY3493269 may be assessed if deemed appropriate.

10.4.10 Hypersensitivity reactions

For all drug hypersensitivity reactions that occur, additional follow-up data will be collected to assess the participant's medical history, alternative causes, and symptoms.

These data will be listed.

10.4.11 Elevated Lipase or Amylase

If a patient experiences elevated serum amylase or lipase values ≥3× 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.

11. INTERIM ANALYSES

No formal interim statistical analyses are planned.

Data Review during the Study

The following reviews will be the responsibility of Eli Lilly.

Part A

A review of available safety and PK data will be conducted to determine the test formulation(s) to be evaluated in Part B.

This review will include data from at least 8 participants who have completed 3 consecutive doses of the study intervention in each of the 3 planned treatment groups, and who have completed protocol assessments up to Day 8.

Part B

Emerging PK data from Part A will determine the formulations to be tested as Treatments B1 and B2, as well as the conditions (fed or fasted) under which the test or reference formulations are administered. If deemed appropriate, an interim review of PK data from Treatment B1 may be conducted prior to the initiation of Treatment B2. This review will include data from at least 8 participants who have completed 3 consecutive doses of the study intervention, and who have completed protocol assessments up to Day 8.

12. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

Part B of this study has been cancelled.

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	30JUN2023	Added additional PK parameter, F_{Abs}, following request from Sponsor. AUC(0-∞) on profile day 3 added to statistical analysis following request from Sponsor. Part B of the study has been cancelled – text added to Sections 5 and 12 to clarify. "Labcorp Drug Development" amended to "Fortrea" throughout.

NA = not applicable

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Approval	PPD PKPDPMx 04-Jul-2023 13:18:29 GMT+0000
Approval	PPD Statistician 04-Jul-2023 13:26:07 GMT+0000
Approval	PPD PKPDPMx 05-Jul-2023 06:48:24 GMT+0000
Approval	PPD Statistician 05-Jul-2023 17:10:22 GMT+0000

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Approved on 05 Jul 2023 GMT