Statistical Analysis Plan J2A-MC-GZPB (2.0)

A Phase 1, Multicenter, Parallel, Single-Dose, Open-Label, Single-Period Study of LY3502970 in Participants with Normal Hepatic Function and Participants with Mild, Moderate, or Severe Hepatic Impairment

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STATISTICAL ANALYSIS PLAN

A Phase 1, Multicenter, Parallel, Single-Dose, Open-Label, Single-Period Study of LY3502970 in Participants with Normal Hepatic Function and Participants with Mild, Moderate, or Severe Hepatic Impairment

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Investigational Medicinal Product: LY3502970

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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]).

AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate 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-∞),u	Unbound AUC(0-∞), calculated as AUC(0-∞)*F_u
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(0-t_{last}),u	Unbound AUC(0-t_{last}), calculated as AUC(0-tlast)*F_u
BG	Blood glucose
BQL	Below the lower limit of quantitation
C_{last}	Last quantifiable drug concentration
C_{max}	Maximum observed drug concentration
$C_{max,}$u	Unbound C_{max}, calculated as C_{max}*F_u
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
CL/F,u	Unbound CL/F, calculated as dose/AUC(-∞),u
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
DMP	Data Management Plan
ECG	Electrocardiogram
F_u	Mean unbound fraction
GLSM	Geometric least squares mean

HbA1c	Hemoglobin A1c
ICF	Informed consent form
ICH	International Conference on Harmonisation
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
OATP1B	organic anion–transporting polypeptide 1B
PG	Plasma glucose
PK	Pharmacokinetic
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System organ class
T2DM	Type 2 diabetes mellitus
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, and Listings
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
t_{max}	Time of maximum observed drug concentration
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 27 March 2023) and Protocol Amendment (d) (final version dated 28 March 2024).

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

Objective	Endpoints
Primary	
To evaluate the PK of a single oral dose of LY3502970 in participants with mild, moderate, or severe hepatic impairment compared to control participants with normal hepatic function	LY3502970 area under the concentration time curve from time zero to infinity (AUC[0-∞]), area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration (AUC[0-tlast]), and maximum observed drug concentration (C_{max})

Objective	Endpoints
Secondary	
To evaluate the safety and tolerability of a single oral dose of LY3502970 in participants with mild, moderate, or severe hepatic impairment compared to control participants with normal hepatic function	Number and incidence of serious adverse events (SAEs) and treatment-emergent adverse events (TEAEs)
Exploratory	
To evaluate plasma concentrations of endogenous organic anion–transporting polypeptide 1B (OATP1B) biomarker coproporphyrin 1 in participants with mild, moderate, or severe hepatic impairment compared to control participants with normal hepatic function	Plasma concentrations of coproporphyrin 1
To evaluate the effect of hepatic impairment on plasma protein binding of LY3502970 and coproporphyrin 1	• Unbound LY3502970 PK including fraction unbound (F_u), unbound AUC, and unbound C_{max} • Unbound coproporphyrin 1 concentration and F_u

5. STUDY DESIGN

Study J2A-MC-GZPB (GZPB) will be a multicenter, parallel, single-dose, open-label, single-period study of LY3502970 in participants with normal hepatic function and participants with mild, moderate, or severe hepatic impairment.

The schema in Figure 1 illustrates the study design.

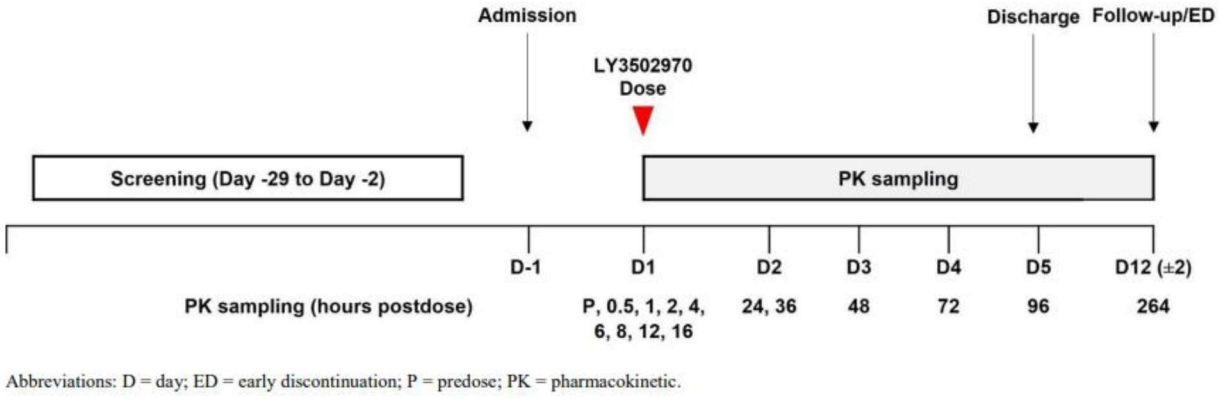

Figure 1 - GZPB Study design

Treatment groups

Participants will be enrolled within the groups shown in Table 1.

Table 1 - Hepatic impairment classified using the Child-Pugh classification

Group	Classification		Approximate Number to be Enrolled	Number to Complete
1	Control	Normal hepatic function	9 to 15	At least 9
2	Child-Pugh A	Mild hepatic impairment	At least 6	At least 6
3	Child-Pugh B	Moderate hepatic impairment	At least 6	At least 6
Participants from Group 4 will only be enrolled following review of safety, tolerability, and PK data up to at least 12 days postdose from at least 2 participants each from Groups 1 to 3.				
4	Child-Pugh C	Severe hepatic impairment	Up to 6	2 to 6*

* Efforts will be made to achieve 6 completers with severe hepatic impairment in Group 4; however, acknowledging the difficulties in recruiting this participant population, 2 participants will be considered acceptable.

Hepatic impairment will be classified using the Child-Pugh classification. For participants with hepatic impairment, Child-Pugh classification parameters will be calculated at screening and check-in on Day -1. Participants will be assigned to groups according to the Child-Pugh classification parameters collected at check-in on Day -1.

Participants with normal hepatic function enrolled in Group 1 will be matched by sex, age ± 10 years, and weight ±10 kg to participants in Group 2, 3, and 4, as far as is practically feasible.

Participants in Group 1 will not be matched to more than 1 hepatically-impaired participant in any given impairment group; however, they may be matched to more than 1 participant from Groups 2, 3, and 4. For example, 1 participant in Group 1 may be matched to a participant in Group 2, as well as a participant in Group 3. However, a participant in Group 1 could not be matched to 2 participants in Group 2.

Following dosing of at least 2 participants each in Groups 1, 2, and 3, an interim access to data is planned. Screening of participants in Group 4 will only take place after satisfactory review of the safety, tolerability, and PK data up to at least 12 days postdose. Safety data will be reviewed by the Lilly study team on a regular basis while participants are enrolled in the study.

Study visits

Treatment and assessment period

Participants will be admitted to the Clinical Research Unit (CRU) on Day -1 and will receive a CCI dose of LY3502970 on Day 1 following an overnight fast. Participants will remain in the CRU for PK, safety, and tolerability assessments until discharge on Day 5.

Follow-up

Participants will return for a follow-up visit on Day 12. The total duration of participation from screening through follow-up is expected to be approximately 6 weeks.

6. BLINDING

This is a non-randomized, open-label study.

7. TREATMENT

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

Study Treatment Name	Classification	Order in TFL
CCI LY3502970	Normal hepatic function	1
	Mild hepatic impairment	2
	Moderate hepatic impairment	3
	Severe hepatic impairment	4

8. SAMPLE SIZE JUSTIFICATION

Approximately 33 participants will be enrolled in the trial, with up to 15 controls, at least 6 participants with mild and 6 participants with moderate hepatic impairment and up to 6 participants with severe hepatic impairment.

This sample size is based on the FDA guidance (FDA 2003) and was not selected to satisfy an a priori statistical requirement.

The trial will be open label and participants will be allocated a group based on their Child-Pugh classification.

9. DEFINITION OF ANALYSIS POPULATIONS

The “Entered” population will consist of all participants who signed the informed consent form (ICF).

The "Enrolled" population will consist of all participants assigned to study intervention, regardless of whether they take any doses.

The "Safety" population will consist of all enrolled participants who received at least 1 dose of study intervention (LY3502970).

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

The "Coproporphyrin 1 Biomarker" population will consist of all participants who received at least 1 dose of study intervention (LY3502970) and have evaluable coproporphyrin 1 data.

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: 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, race, ethnicity, country of enrolment, site ID, body weight, height, body mass index, Child-Pugh classification, and

screening hemoglobin A1c (HbA1c) will be summarized and listed. For patients with type 2 diabetes mellitus (T2DM) only, duration of T2DM will also be presented. 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 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-t_{last})	ng.h/mL	Area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
AUC(0-∞)	ng.h/mL	Area under the concentration versus time curve from time zero to infinity
C_{max}	ng/mL	Maximum observed drug concentration
t_{max}	h	Time of maximum observed drug concentration
$t_{1/2}$	h	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
CL/F	L/h	Apparent total body clearance of drug calculated after extra-vascular administration
V_Z/F	L	Apparent volume of distribution during the terminal phase after extra-vascular administration
V_{SS}/F	L	Apparent volume of distribution at steady state after extra-vascular administration

To evaluate the effect of hepatic impairment on plasma protein binding of LY3502970, following unbound LY3502970 PK parameters will be calculated using the mean F_u for each participant if deemed appropriate:

Parameter	Unit	Definition
F_u		Mean unbound fraction
AUC(0-t_{last}),u	ng.h/mL	Unbound AUC(0-t_{last}), calculated as AUC(0-t_{last})*F_u
AUC(0-∞),u	ng.h/mL	Unbound AUC(0-∞), calculated as AUC(0-∞)*F_u
C_{max},u	ng/mL	Unbound C_{max}, calculated as C_{max}*F_u

The mean F_u for each participant will be calculated from the protein binding sampling time points at 4, 8, and 12 hours postdose.

Pharmacokinetics of Coproporphyrin 1 for Pharmacodynamic Evaluation

The following PK parameters will be calculated for coproporphyrin 1.

Parameter	Units*	Definition
AUC(0-t_{last})	pg.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
C_{max}	pg/mL	Maximum observed plasma concentration
t_{max}	h	Time of maximum observed plasma concentration

* The units of AUC(0-t_{last}) and C_{max} will be consistent with the units recorded in the data transfer.

To evaluate the effect of hepatic impairment on plasma protein binding of coproporphyrin 1, following unbound coproporphyrin 1 PK parameters will be calculated using the mean F_u for each participant if deemed appropriate:

Parameter	Unit	Definition
F_u		Mean unbound fraction
AUC(0-t_{last}),u	ng.h/mL	Unbound AUC(0-t_{last}), calculated as AUC(0-t_{last})*F_u
C_{max},u	ng/mL	Unbound C_{max}, calculated as C_{max}*F_u

The mean F_u for each participant will be calculated from the protein binding sampling time points at predose, 8, and 24 hours postdose.

Descriptive statistics will be used to summarize the plasma concentrations of endogenous OATP1B biomarker coproporphyrin 1 in hepatic impairment participants.

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.

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 1 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 ($t_{1/2}$) will be calculated, when appropriate, based on the apparent terminal log-linear portion of the concentration-time curve. The start of the terminal elimination phase for each participant will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in plasma concentrations. Half-life will only be calculated when a reliable estimate for this parameter can be obtained comprising of at least 3 data points. If $t_{½}$ 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 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 2 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 ± X%. 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 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 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 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 report. Approval of the final report will connote approval of the exclusion.

10.3.2 Pharmacokinetic Statistical Methodology

LY3502970

PK parameters will be evaluated to estimate the PK of LY3502970 in control participants with normal hepatic function and participants with hepatic impairment. The PK parameters will be plotted by hepatic impairment group and the overall Child-Pugh score. Arithmetic mean (+/-SD) and individual participant profile plots of plasma LY3502970 concentrations will be provided by hepatic impairment group.

Log-transformed C_{max}, AUC(0-∞), and AUC(0-tlast) will be analyzed using analysis of covariance (ANCOVA), with hepatic group as fixed effect and body weight as a covariate, to

assess the difference between hepatic impairment participants based on Child-Pugh classification (test) and healthy participants with normal hepatic function (reference).

The geometric least squares means (GLSMs) for each hepatic group, GLSM ratios between each hepatic impairment level versus the reference group, and the corresponding 90% confidence intervals (CIs) will be estimated from this model will be presented.

The same analysis will also be applied on the unbound PK parameters.

Example SAS code:

```
proc mixed data = <data in>;
   by parcat1 pkday paramcd;
   class hep_grp;
   model log_pk = weight hep_grp / cl residual ddfm = kr2;
   lsmeans hep_grp / cl pdiff = control('normal') alpha = 0.1;
   ods output lsmeans = <data out>;
   ods output diffs = <data out>;
   ods output covparms = <data out>;
run;
```

The t_{max} will be analyzed using a Wilcoxon rank sum test. Estimates of the median difference based on the observed medians, approximate 90% CIs, and corresponding p-values will be reported.

Example SAS code:

```
proc npar1way data = <data in> hl(refclass = 1) alpha = 0.1;
   by parcat1 pkday paramcd;
   class hep_grp;
   var aval;
   exact wilcoxon;
   ods output hodgeslehmann = <data out>;
   ods output wilcoxontest = <data out>;
run;
```

Biomarker (coproporphyrin 1) and plasma protein binding

Plasma concentrations of endogenous OATP1B biomarker coproporphyrin 1 and plasma protein binding data will be summarized by hepatic impairment group, and listed.

10.4 Pharmacokinetic / Safety Analyses

Scatter plots of PK parameters (AUC[0-t_{last}], AUC[0-∞], and C_{max}) versus hepatic function measures such as total bilirubin (TBL) concentration, albumin concentration, prothrombin

time/international normalized ratio, alanine aminotransferase (ALT) concentration, and aspartate aminotransferase (AST) concentration will be produced.

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-TEAE is defined as an AE which starts after informed consent but prior to dosing. A TEAE is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose.

All AEs will be listed. TEAEs will be summarized by hepatic impairment group, 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 hepatic impairment group, Medical Dictionary for Regulatory Activities (MedDRA) (version is documented in the Data Management Plan [DMP]) system organ class (SOC) and preferred term (PT). 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. Investigational Product-related SAEs will be listed.

Discontinuations due to AEs will be listed.

Adverse events of special interest and other safety topics as specified in the protocol section 8.3.3 will be listed.

10.5.2 Concomitant medication

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

10.5.3 Clinical laboratory parameters

Clinical chemistry, hematology, and coagulation data will be summarized by hepatic impairment group. All clinical chemistry, hematology, urinalysis, and coagulation data will be listed. Additionally, clinical chemistry, hematology, urinalysis, and coagulation 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, values recorded as $<x$, $\leq x$, $>x$, or $\geq x$ will be excluded.

10.5.4 Vital signs

Supine vital signs data will be summarized by hepatic impairment group and time point together with changes from baseline, where baseline is defined as the Day 1 predose assessment. Figures of mean supine vital signs and mean changes from baseline will be presented over time by hepatic impairment group.

Values for individual participants will be listed.

10.5.5 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.

Glucose Monitoring and Hypoglycemia

During the study, only for participants with T2DM blood glucose (BG) concentrations will be monitored for safety assessments.

Episodes of hyperglycemia (fasting plasma/serum glucose >270 mg/dL [15 mmol/L]) will be reported and listed under AESI's listing.

Hypoglycemic events will be appropriately recorded in the CRF. In the case of a hypoglycemic event, the actual BG 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 for participants with T2DM only.

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): Level 2 hypoglycemia 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 or absence of symptoms of hypoglycemia.

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, 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 Eli Lilly as an SAE**.**

Nocturnal hypoglycemia:

Nocturnal hypoglycemia is a hypoglycemic event, including severe hypoglycemia, that occurs at night and presumably during sleep.

Hepatic Monitoring:

If a participant experiences elevated laboratory parameters, as detailed in Section 8.2.7 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 hepatic impairment group, 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.

10.5.6 Other assessments

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

10.5.7 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

11. INTERIM ANALYSES

Following dosing of at least 2 participants each in Groups 1, 2, and 3, an interim access to preliminary data is planned. Screening of participants in Group 4 will only take place after a review of the safety, tolerability, and PK data from these participants up to at least 12 days postdose. Exposure, safety, and tolerability from Groups 2 and 3 will be reviewed to determine whether Group 4 dosing will occur. Safety data will be reviewed by the Lilly study team on a regular basis while participants are enrolled in the study.

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. [FDA] United States Food and Drug Administration. Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling. May 2003. Accessed March 10, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetics-patients-impaired-hepatic-function-study-design-data-analysis-and-impact-dosing-and.

14. DATA PRESENTATION

14.1 Derived Parameters

Individual derived parameters (e.g. PK parameters) and appropriate summary statistics will be reported to 3 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	12Jun2024	Updated to remove references to Labcorp Drug Development on Page 1 and the page header; also to formally accept the changes made as per the latest protocol amendment (d).

NA = not applicable

Signature Page for VV-CLIN-156854 v1.0

Approval	PPD Statistician 12-Jun-2024 13:38:19 GMT+0000

Approval	PPD Statistician 12-Jun-2024 14:32:11 GMT+0000

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