Statistical Analysis Plan J2A-MC-GZPC ver1

A Phase 1, Parallel, Single-Dose, Open-Label, Single-Period Study of LY3502970 in Participants with Normal Renal Function and Participants with Renal Impairment.

NCT05936138

Approval Date: 12 July 2023

Statistical Analysis Plan

Sponsor:	Eli Lilly and Company
Protocol Number:	J2A-MC-GZPC
Protocol Title:	A Phase 1, Parallel, Single-Dose, Open-Label, Single-Period Study of LY3502970 in Participants with Normal Renal Function and Participants with Renal Impairment
ICON Project Identifier:	ELLBEQ69-0D1OUY (0219/2434)
SAP Version Date:	12-Jul-2023

1.0 Approvals

The undersigned have approved this Statistical Analysis Plan for use in this study.

Name of Biostatistician / Title:	PPD / Senior Biostatistician, ICON
Signature of Biostatistician / Date:	PPD
Name of Sponsor Representative / Title:	PPD / Advisor – Statistics, Eli Lilly and Company
Signature of Sponsor Representative / Date:	
Name of Sponsor Representative / Title:	PPD / Director – PK/PD, Eli Lilly and company
Signature of Sponsor Representative / Date:	

2.0 Table of Contents

3.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical methods that will be used during the analysis and reporting of data collected under Eli Lilly and Company Protocol J2A-MC-GZPC.

This SAP should be read in conjunction with the study protocol and electronic case report form (eCRF). This version of the plan has been developed using the protocol dated 10-May-2023 (including all amendments up to this protocol date) and the eCRF version 1.0 dated 31-May-2023.

An approved and signed SAP is a requirement for database lock.

This SAP only covers the results that will be processed by the ICON Early Clinical and Bioanalytical (IEB) Biostatistics Department.

ICON IEB will perform the pharmacokinetic (PK), safety and tolerability evaluation.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified in this SAP. Any post-hoc or unplanned analyses, or significant changes from the planned analysis in this SAP performed to provide results for inclusion in the clinical study report (CSR) but not included in this SAP, will be clearly identified in the CSR. Changes to planned analyses do not require an updated SAP but should be included in the CSR if significant.

4.0 Changes to Analysis

4.1 Changes from Protocol

There are no changes from the protocol.

4.2 Changes from Previous Version of Approved SAP

This is the first version of the SAP.

5.0 Study Objectives

5.1 Primary

To evaluate the PK of a single oral dose of LY3502970 in participants with severe renal impairment and participants with end-stage renal disease compared to control participants with normal renal function.

5.1.1 Primary Endpoint

LY3502970 AUC(0-inf), AUC(0-tlast), and Cmax

5.2 Secondary

To evaluate the safety and tolerability of a single oral dose of LY3502970 in participants with severe renal impairment and participants with end-stage renal disease compared to control participants with normal renal function.

5.2.1 Secondary Endpoint

Number and incidence of serious adverse events (SAEs) and treatment-emergent adverse events (TEAEs).

5.3 Exploratory

- To evaluate plasma concentrations of endogenous organic anion–transporting polypeptide (OATP1B) biomarker coproporphyrin 1 in participants with severe renal impairment and participants with end-stage renal disease.

- To evaluate the effect of renal impairment on plasma protein binding of LY3502970 and coproporphyrin 1.

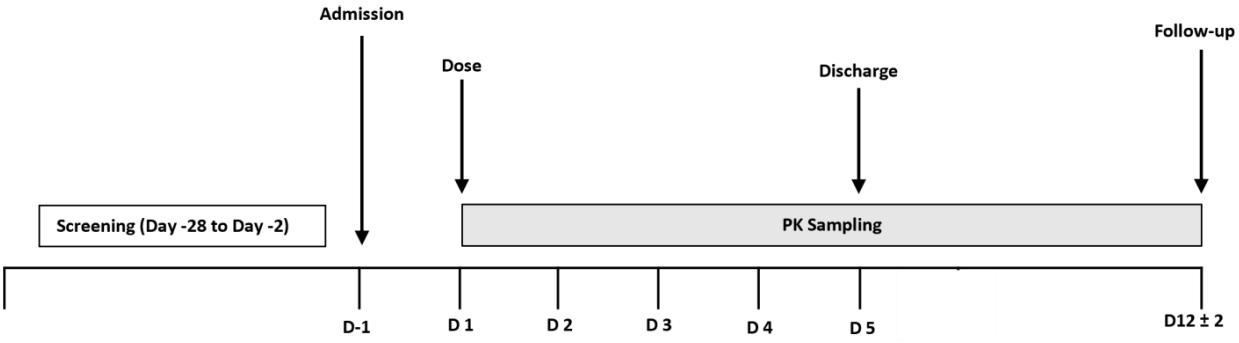
5.3.1 Exploratory Endpoint

- Plasma concentrations of coproporphyrin 1.
- Unbound LY3502970 PK including fraction unbound (Fu), unbound AUC, and unbound Cmax.
- Unbound coproporphyrin 1 including Fu, unbound AUC and Cmax.

6.0 Study Design

This study will be a multi-site, parallel, single-dose, open-label, single-period study of LY3502970 in participants with severe renal impairment and participants with end-stage renal disease compared to control participants with normal renal function.

The schema below illustrates the study design. PK blood sampling and safety assessments, including vital sign measurement, physical examination, clinical laboratory tests, safety electrocardiograms (ECGs), and adverse event (AE) recording, will be performed according to the schedule of activities (SoA) in Appendix 3.



Abbreviations: D = day; PK = pharmacokinetic

Note: For participants in Group 3 that require hemodialysis, administration of LY3502970 should occur 24 ± 2 hours after a hemodialysis session and should occur during the longest window between two hemodialysis sessions. Subsequent hemodialysis sessions should be scheduled as clinically appropriate.

Assignment to Renal Groups

Participants will be enrolled within the groups shown:

Group	Classification	Specifications	Approximate Number of Participants to be Enrolled	Number of Participants to Complete
1	Normal renal function	eGFR: greater than or equal to 90 mL/min and without T2DM	26	8
2	Severe renal impairment	eGFR: 15-29 mL/min and not requiring hemodialysis		6
3	End-stage renal disease	eGFR: less than 15 mL/min or requiring hemodialysis		6

Abbreviations: eGFR = estimated glomerular filtration rate; T2DM = type 2 diabetes mellitus.

Participants with T2DM will be permitted to enroll in Groups 2 and 3 only.

Participants will be assigned to Groups 1, 2 and 3 based on screening and baseline eGFR values determined by the chronic kidney disease epidemiology collaboration (CKD-EPI) equation using serum creatinine and converted to absolute eGFR values by factoring in individual body surface area (BSA), see protocol Appendix 7. If the eGFR value differs for a participant between screening and baseline such that the participant would be classified into different renal groups, then the value produced from the central laboratory baseline sample will be the definitive value used to assign that participant to a renal group.

Participant Matching

Participants with normal renal function enrolled in Group 1 will be matched by age ±15 years, sex, and body weight ±10 kg, as far as is practically possible, to participants in Group 2 and 3.

Matching participants with normal renal function will be enrolled on up to a 1-to-1 basis; however, they may be matched to 2 participants with renal impairment, as long as the 2 are in different renal impairment groups. Participants who do not complete all the study procedures may be replaced in order to target the planned number of completers listed.

Study Visits

Screening

Participants will undergo screening procedures up to 28 days prior to enrollment.

Treatment and Assessment Period

Participants will be admitted to the clinical research unit (CRU) on Day -1.

Participants will be administered a single dose of LY3502970 on Day 1 and will remain in the CRU until after assessments are completed on Day 5. Participants may stay longer in the CRU at the investigator's discretion. For participants in Group 3 that require hemodialysis, administration of LY3502970 should occur 24 ± 2 hours after the end of a hemodialysis session and should occur during the longest window between 2 hemodialysis sessions.

Clinical laboratory tests, physical examination, vital signs, 12-lead ECGs, and AEs will be monitored to assess safety and tolerability.

Blood samples for PK analysis will be collected postdose through the final follow-up visit.

Follow-up

Participants will return for a follow-up on Day 12 ± 2 days.

6.1 Sample Size Considerations

The primary objective of this study is to estimate the PK parameters of LY3502970 after a single [redacted] mg dose in participants with severe renal impairment and participants with end-stage renal disease compared to control participants with normal renal function. There are no formal statistical hypotheses planned to be tested in this study.

Approximately 26 participants will be enrolled so that at least 20 complete the study. At least 8 participants to complete for the control group. At least 6 participants to complete for each of the severe renal impairment and end-stage renal impairment groups.

The sample size is not selected to satisfy a prior statistical requirement to make PK comparison between each tested renal impairment group and the healthy control group. Rather, the sample size is chosen to fulfil the regulatory requirement to provide adequate precision of the PK parameters of interest (AUC and Cmax) for each tested group using regression model with absolute eGFR as a regressor (Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing, FDA draft guidance 2020). The aforementioned sample size will provide at least 80% probability that the 90% CI of PK parameters AUC and Cmax is within 60% and 140% of the geometric mean estimate of the PK parameters in each renal function group. The coefficient of variation used for sample size calculation are 36.5% and 39.5% for AUC and Cmax, respectively.

Participants who do not complete all the study procedures may be replaced in order to target the planned number of completers listed.

6.2 Randomization and Blinding

This is an open-label study; no randomization or blinding will be conducted.

7.0 Overview of Planned TFL Deliveries

7.1 Pre-lock TFL

There will be 1 run of TFL produced after database freeze and prior to lock. This draft of the safety tables, figures and listings (TFLs) will be provided prior to database lock to assist in review of the database. As a result of draft TFLs review comments, revisions will be included in the post-lock TFL delivery.

Comments affecting the database will be provided to Data Management for resolution prior to Lock.

7.2 Final Analysis

The updated safety TFLs and draft PK/biomarker TFLs will be provided after database lock. After Sponsor comments have been incorporated, the TFLs will be finalized and provided to Medical Writing for incorporation in the first draft CSR.

8.0 Definitions and General Analysis Methods

8.1 General Data Handling

8.1.1 Rounding

8.1.1.1 Listings

In listings, collected data (from CRF or external source) will be presented with the same precision as the original data as entered or received. Derived data will be rounded for presentation purposes.

8.1.1.2 Summary Tables

8.1.1.2.1 General Tables

The following will be rounded regardless of data type

Percentages (including %CV)	P-Value	Geometric Mean Ratios and associated CIs
1 decimal place	4 decimal places (<0.0001 if result is 0.0000 after rounding)	3 decimal places

8.1.1.2.2 General Data

The following summary statistics will be rounded relative to the number of decimal places collected.

Statistic	Mean/Median	Standard Deviation	Minimum/ Maximum
# of decimal places in addition to that collected in data	+1 decimal place	+2 decimal place	+0 decimal places

The above rule can be applied directly to collected data. For derived data rounding will occur prior to summarization (in the derived dataset as determined by the statistician) so a specific number of decimal places will have to be assumed to apply the above rounding rules for summary statistics. For data with inconsistent number of decimals in raw data the most frequently occurring numbers of decimals will be used unless that number is large and causes difficulties in presentation in which case it will be trimmed to a presentable number (2-3 decimals).

8.1.1.2.3 Pharmacokinetic/Biomarker Tables

Pharmacokinetic/biomarker concentration data is generally recorded to 3 significant digits. Based on this convention, the following parameters will have summary statistics be presented to the following number of significant digits. If recorded to a different precision, Cmax will have the same precision as the bioanalytical data.

Parameter	AUC, Cmax, CL/F, Vz/F, Vss/F, t½
Statistic	**Arithmetic Mean, Median, Arithmetic Standard Deviation, Geometric Mean, Geometric %CV, Minimum, Maximum**
Precision	3 significant digits (1 decimal place for Geometric %CV)

Pharmacokinetic time data is recorded on the CRF and pharmacokinetic time parameters will be rounded based on collection.

Parameter	Tmax, tlast	
Statistic	**Median**	**Minimum/ Maximum**
# of decimal places	3 decimal places	2 decimal places

8.1.2 Imputation

Unless otherwise noted, data will not be imputed.

8.1.3 Daylight Savings Time Adjustments

In the event that clinic dates fall across Daylight Savings Time, all clinic procedures for the remainder of the treatment period will be adjusted accordingly to account for the corrected actual time-lapse between procedures. All duration calculations for times post-daylight savings time that will be relative to a time prior to daylight savings will be programmatically adjusted for the hour that was gained or lost on the morning of the time change.

8.1.4 General Descriptive Statistics

Continuous variables will be summarized with the following descriptive statistics and nomenclature: n = number of participants, mean = arithmetic mean, SD = arithmetic standard deviation, Min = minimum value, median = median value, and Max = maximum value.

Categorical variables will be summarized and presented with the following nomenclature: n = frequency and % = percentage. Percentages by categories will be based on the number of participants exposed within a renal group. The categories will be presented in the tables exactly as they appear in the CRF / Database. Categories of NOT REPORTED, MISSING, and/or UNKNOWN may be excluded from summaries if null (0).

Specific data types may include additional descriptive statistics or exclude some noted above. For any deviations from the general set of descriptive statistics they will be noted in the sections related to the analysis of that data.

Data summarized in tables will have an associated listing. Data listed but not summarized will be noted in specific data type sections.

8.1.5 Pooling

No data pooling across groups.

8.1.6 Unscheduled Measurements

Unscheduled and early termination measurements will be included in the listings. With the exception of unscheduled measurements used for baseline, unscheduled and early termination measurements will be excluded from the descriptive statistics and statistical analysis.

8.2 Common Variable Definitions

8.2.1 Baseline Definition

Unless otherwise stated, baseline is defined as the last observation recorded up to the study drug administration. The last observation can be an unscheduled / repeated measurement.

8.2.2 Participant Grouping

Label	Grouping
Study Drug	LY3502970 [redacted] mg capsule

Label	Grouping
Renal Function Group	Group 1: Normal renal function Group 2: Severe renal impairment Group 3: End-stage renal disease

8.2.3 ADaM Datasets and Metadata

The analysis datasets will be generated in accordance with Clinical Data Interchange Standard Consortium (CDISC) Analysis Data Model (ADaM) Version 2.1.

ADaM compliant datasets will be delivered to the sponsor. A define.xml file version 2 with the corresponding metadata and Analysis Data Reviewer's Guide (ADRG) will be included. Analysis results (analysis displays or program details) metadata (ARM) are excluded from the define.xml.

8.3 Software

The statistical analysis and reporting will be done using SAS® for Windows™ Version 9.4 or higher (SAS Institute, Inc.).

PK parameter calculations will primarily be done using Phoenix® WinNonlin® (WNL) version 8 or higher (Certara, L.P.). Additional PK computations may be performed in SAS®.

8.4 Statistical Methods

8.4.1 Statistical Outlier Determination

No statistical outlier analysis is planned. Anomalous values will be assessed on a case-by-case basis and documented in the CSR.

8.4.2 Hypothesis Testing

There are no formal statistical hypotheses planned to be tested in this study.

8.5 TFL Layout

The layout of TFLs will be according to the ICON IEB standards.

Table, Figure and listing shells are provided with and approved as part of this SAP. Small changes to shell layout due to the nature of the data may be required after lock at the discretion of the ICON Biostatistician. Other changes to the shells may be out of scope. The TFLs will be provided as a single document in Adobe PDF format (in Letter (for US submission), A4 (for submission outside of US)), and as individual files for each table, figure and listing in Rich Text Format (.rtf).

9.0 Analysis Sets

The following participant level Analysis Sets (populations) will be used for summaries in the study.

9.1 Entered Set

All participants who sign the informed consent form (ICF).

9.2 Enrolled Set

All participants who are assigned to LY3502970, regardless of whether they take any doses.

9.3 Safety Set

The Safety Set will consist of all participants who receive 1 dose of LY3502970, whether or not they completed all protocol requirements. This set will be used for the safety data summaries, and baseline characteristic summaries. This set will be analyzed as treated.

9.4 Pharmacokinetic Set

The PK Set will consist of all participants who receive 1 dose of LY3502970 and have evaluable PK data. This set will be used for the PK concentration/parameter summaries and primary analysis. This set will be analyzed as treated.

9.5 Coproporphyrin 1 Biomarker Set

The Biomarker Set will consist of all participants who receive 1 dose of LY3502970 and have evaluable coproporphyrin 1 data. This set will be analyzed as treated.

10.0 Demographic Data

10.1 Participant Disposition

The number and percentage of participants of each analysis set will be presented. The number and percentage of participants who completed and who withdrew from the study prematurely and a breakdown of the corresponding reasons for withdrawal will also be presented.

All disposition data will be listed.

10.2 Protocol Deviations

Protocol deviations will be collected and reported per ICON's Protocol Deviation Management Standard Operating Procedure (SOP) and relevant Work Instruction (WI). Participant-level deviations will be extracted and pulled into the study tabulation model (SDTM) dataset from ICON's Clinical Trial Management. Deviations that have been reported and coded as "Important" will be listed by participant.

10.3 Demographics

Participant demographics at screening will be summarized by renal function group. The summary will include the participants' site ID, country, age (years), sex, race, ethnicity, weight (kg), height (cm), and body mass index (BMI) (kg/m^2). The summary will also include eGFR calculated using the CKD-EPI Equation and absolute eGFR.

Absolute eGFR will be calculated as:

Absolute eGFR (mL/min) = eGFR (mL/min/1.73m2) x BSA (m2)/1.73.

Where body surface area (BSA) is calculated as:

BSA (m2)= sqrt(height (cm) x body weight (kg)/3600)

Demographics will be summarized for the Safety set. All demographic data, as collected during the screening visit, will be listed by participant.

10.4 Medical History

Medical history, categorized by preferred term according to MedDRA, will be listed by participant.

10.5 Participant Characteristics

Substance use will be listed by participant.

The genotyping information will be listed only if the genotyping is available.

10.6 Concomitant Medications

Concomitant medications collected on the eCRF as defined by the protocol will be categorized by medication group and subgroup according to WHO Drug Dictionary. All concomitant medications will be listed by participant. Medications with an end date prior to the first dose of study drug will be considered prior medications and will be noted in the listing. If the end date (e.g. partial or missing date) does not confirm that the medication was stopped prior to first dose the medication will not be flagged as prior.

10.7 Treatment Compliance and Exposure

The number and percentage of participants receiving each dose of study drug will be summarized by renal function group.

Exposure data will be listed by participant.

11.0 Pharmacokinetic Data

11.1 Pharmacokinetic Variables

Concentrations of LY3502970 will be collected in plasma.

PK parameters of LY3502970 will be calculated for plasma. A full list and definitions of parameters can be found in Appendix 2.

Protein binding (fraction bound) of LY3502970 will be provided in plasma by the Bioanalytical lab at each time point, and the arithmetic mean of all reported values for a participant will be calculated. Individual and mean values for fraction bound will be listed by participant. Mean values will be used to derive the fraction of free LY3502970 in plasma. The fraction of free drug (commonly called fraction of unbound drug; Fu) is defined as the ratio of the free drug and total drug (i.e., Fu=Drug Unbound / Drug Total).

11.2 Plasma Pharmacokinetic Summaries

11.2.1 Plasma Concentrations

The pre-dose concentration for single-dose data from non-endogenous compounds will be set to zero in individual and mean concentration-time plots. Otherwise, only quantifiable concentrations will be used to calculate descriptive statistics. BQL values that occur after the first quantifiable point will be considered missing. Descriptive statistics (number of participants, arithmetic mean, arithmetic SD, geometric mean, geometric coefficient of variation [%CV], median, min, and max) will be used to summarize the plasma concentrations by renal function group at each scheduled timepoint. Concentrations at a sampling time exceeding the sampling time in the protocol ± 10% will be excluded from the concentration descriptive statistics. A concentration will be included in the mean concentration-time plots 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 in the protocol ± 10%. A concentration estimated with less than 2/3 but more than 3 data points may be included in the mean concentration-time plots if determined to be appropriate and will be documented within the final study report. Concentrations excluded from the mean calculation or mean concentration-time plots will be documented in the final study report.

Linear (+/-SD) and semi-logarithmic plots of the arithmetic mean plasma concentration by scheduled sampling time will be provided by renal function group. These plots will show time in hours. The plots will present all calculated means and will include a reference line for the lower limit of quantification (LLOQ).

Linear and semi-logarithmic plots of the individual plasma concentration by actual sampling time will be provided by participant (one participant per page). These plots will show time in hours. Individual plots will use the BQL handling procedure described below for “Plasma Pharmacokinetic Parameters”. The plot on the semi-logarithmic scale will indicate all data points from the start time to end time used in the regression for the determination of the terminal phase rate constant.

11.2.2 Plasma Pharmacokinetic Parameters

11.2.2.1 Calculation and Summary of PK Parameters

Plasma PK parameters for LY3502970 will be estimated using non-compartmental methods with WinNonlin®. The PK parameters will be estimated from the concentration-time profiles, and AUCs will be calculated using linear up / log down method. The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive plasma concentrations above the LLOQ, with at least 1 of these concentrations following Cmax. AUC(0-inf) values where the percentage of the total area extrapolated is more than 20% will be flagged and excluded from summary statistics. In estimating the PK parameters, BQL values at the beginning of the profile will be set to zero. BQL values that occur after the first quantifiable point will be considered missing. Predose concentrations for LY3502970 will be imputed as 0 for parameter generation. If an entire concentration-time profile is BQL then the profile will be excluded from PK analysis. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If the actual time is missing, the scheduled time will be substituted and flagged.

Cmax and Tmax will be reported from observed values. If Cmax occurs at more than one time point, Tmax will be assigned to the first occurrence of Cmax. tlast will also be reported from observed values.

Half-life (t½) will be calculated, when appropriate, based on the apparent terminal log-linear portion of the concentration-time curve. The start of the terminal elimination phase for each participant will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in plasma concentrations. Half-life will only be calculated when a reliable estimate for this parameter can be obtained comprising of at least 3 data points.

When applicable, parameters based on the last predicted concentration (Clast) will be reported (e.g., AUC%Extrap, AUC(0-inf), Vz/F, Vss/F and CL/F).

Plasma PK parameters (AUC(0-inf), AUC(0-tlast), and Cmax) will be calculated for unbound LY3502970.

Derivation Description	Derivation Method
Free LY3502970 PK parameters	Total LY3502970 PK parameter * (1-plasma protein binding) Note: the arithmetic mean of all plasma protein binding values reported for a participant will be used in the calculation as a fraction (converted if presented as a percentage, %/100)

Descriptive statistics (number of participants, arithmetic mean, arithmetic SD, geometric mean, geometric %CV, median, min, and max) will be used to summarize the calculated PK parameters by renal function group. For Tmax and tlast, only median, min and max will be presented.

The following flags will be used to exclude parameters that meet the predefined criteria for summary and analysis.

Criteria Name	Exclusion Criteria	Parameters to be Evaluated using the Exclusion Criteria
Extrapolation	AUC%Extrap > 20%	AUC(0-inf), t½, CL/F, Vz/F, Vss/F
Regression	Adj Rsq < 0.8	AUC(0-inf), t½, CL/F, Vz/F, Vss/F
Span	Span < 2	t½ (Flag in listing only; do not exclude from descriptive statistics)

Note: Flags will be applied to parameters prior to derivation of additional parameters in SAS and will be used to exclude derived parameters as well.

All parameters will be listed by participant, parameters that meet the exclusion criteria will be accompanied by an indication of criteria met. Exclusion criteria will be documented in the footnote of the summary table and all flags and exclusions will be summarized in the CSR.

Participants may be excluded from the PK summary statistics and statistical analysis if a participant has an AE of vomiting that occurs at or before 2 times median time of maximum observed drug concentration (Tmax).

Diagnostic parameters are listed but not summarized.

11.2.2.2 Statistical Analysis of PK parameters

Linear regression analyses will be used to model the relationship between log-transformed PK parameters for total and unbound LY3502970 derived from participants with normal renal function and those with severe renal impairment or end-stage renal disease (namely AUC(0-inf), AUC(0-tlast) and Cmax) and baseline absolute eGFR, potentially accounting for baseline body weight. The regression model will have log-transformed PK parameters as response variable, and include independent variable absolute eGFR. The covariate of baseline body weight may be included in the model if there is no collinearity exist between baseline absolute eGFR and body weight, and if baseline body weight is a significant covariate. Other baseline covariates may be included in the model too.

From this linear regression model, the geometric mean of each PK parameter and corresponding 90% confidence interval (CI) for each renal function group will be estimated using the geometric mean of absolute eGFR for each renal function group along with the geometric mean ratio (GMR) of each PK parameter and corresponding 90% CI between each renal impairment group and normal renal function group using the geometric mean difference in absolute eGFR between each renal impairment group and normal renal function group. If the linear regression doesn't hold between 2 groups, a linear regression allowing different slopes or intercepts may be fit to further explore the relationship.

Scatter plots of log-transformed total and unbound AUC(0-inf), AUC(0-tlast), and Cmax versus baseline absolute eGFR with a linear regression line and 90% CI will be created for visual examination of the relationship.

Similar analyses and plots will be generated using BSA-adjusted eGFR as the independent variable. BSA-adjusted eGFR (in mL/min/1.73m2) can be derived by the formula given in section 10.3.

Values of Tmax (without log-transformation) of LY3502970 will be compared between each impaired renal function group versus control group using the Wilcoxon Rank Sum test, and each median difference and associated 90% CI will be estimated using the method of Hodges-Lehmann. A significant difference is defined as $p < 0.1$.

12.0 Coproporphyrin 1 Biomarker Data

Plasma concentrations of coproporphyrin 1 BQL will be set to ½ LLOQ in the computation of descriptive statistics. Descriptive statistics (number of participants, arithmetic mean, arithmetic SD, geometric mean, geometric %CV, median, min, and max) will be used to summarize the plasma concentrations of coproporphyrin 1 by renal function group at each scheduled timepoint. The concentration data will also be listed.

A linear (+/-SD) plot of the arithmetic mean plasma concentration of coproporphyrin 1 by scheduled sampling time will be provided by renal function group. This plot will show time in hours. The plot will present all calculated means and will include a reference line for the lower limit of quantification (LLOQ).

A linear plot of the individual plasma concentration of coproporphyrin 1 by actual sampling time will be provided by participant (one participant per page). This plot will show time in hours. Individual plots will use the BQL handling procedure described below.

Parameter estimates AUC(0-tlast) and Cmax for Coproporphyrin 1 will be calculated by standard noncompartmental methods of analysis. The AUCs will be calculated using linear trapezoidal linear interpolation method. In estimating the parameters, BQL values will be set to ½ LLOQ. If an entire concentration-time profile is BQL then the profile will be excluded from analysis. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If the actual time is missing, the scheduled time will be substituted and flagged.

Plasma parameters (AUC(0-tlast) and Cmax) will be calculated for unbound coproporphyrin 1. Protein binding (fraction bound) of coproporphyrin 1 will be provided in plasma by the bioanalytical lab at each time point, and the arithmetic mean of all reported values for a participant will be calculated. Individual and mean values for fraction bound will be listed by participant. Mean values will be used to derive the fraction of free coproporphyrin 1 in plasma (Fu).

Derivation Description	Derivation Method
Free coproporphyrin 1 parameters	Total coproporphyrin 1 parameter * (1-plasma protein binding) Note: the arithmetic mean of all plasma protein binding values reported for a participant will be used in the calculation as a fraction (converted if presented as a percentage, %/100)

Descriptive statistics (number of participants, arithmetic mean, arithmetic SD, geometric mean, geometric %CV, median, min, and max) will be used to summarize the calculated parameters by renal function group. All parameters will also be listed by participant.

13.0 Safety Data

13.1 Adverse Events

AE summaries will include all AEs that started or worsened (indicated by a new entry on the (e)CRF).

Treatment emergence will be evaluated for all AEs. Treatment-emergent adverse events (TEAE) are those that occur or worsen after the first dose of study drug.

The following missing data will be imputed as defined (for calculations/summary tables only and will not be presented in listings):

Missing Data Point	Imputation Purpose	Derivation Description
Start Time	Calculation of Onset/Duration	Start Time=00:01
End time	Calculation of Onset/Duration	End Time=23:59
Severity	Summary Display	Severity=Severe
Relationship	Summary Display	Relationship =Related
Start Time on dosing day	TEAE determination	TEAE=Y
Start Date	TEAE determination	TEAE=Y

A summary of number and percentage of participants reporting TEAEs, TEAEs by severity and relationship, SAEs, and participants who discontinued study drug due to an AE will be provided.

A summary of the number and percentage of participants reporting each TEAE and number of TEAEs, categorized by system organ class and preferred term coded according to the MedDRA, will be presented by renal function group and overall. For counting by participant, participants will only be counted once within each body system or preferred term.

A summary of the number and percentage of participants reporting each TEAE will be presented by relationship to study drug (as recorded on the eCRF). Participants with multiple events within a system organ class or preferred term will be counted under the category of their most drug-related event within that system organ class and/or preferred term.

A summary of the number and percentage of participants reporting each TEAE will be presented by severity (as recorded on eCRF). Participants with multiple events within a system organ class or preferred term will be counted under the category of their most severe event within that system organ class or preferred term.

A summary of the number and percentage of participants reporting each adverse event of special interest (AESI) (please refer to Protocol Section 8.3.3) will be presented.

All AEs (including non-treatment-emergent events) recorded on the eCRF will be listed by participant.

A separate listing of AEs leading to study drug discontinuation will be provided.

13.2 Deaths and Serious Adverse Events

A listing of deaths and other SAEs will be provided by participant.

13.3 Laboratory Data

Clinical laboratory data will be presented as received from Laboratory (no conversion factors applied) using CDISC Synonyms.

Descriptive statistics summarizing continuous laboratory results of clinical chemistry, and hematology by renal function group and scheduled time will be provided.

Urinalysis data will be listed.

All laboratory data will be listed by participant, including laboratory tests not listed in the protocol. A separate listing of out-of-range values will also be provided. Normal ranges will be used directly from the clinical laboratory (source data) and will be included in the listings for reference.

13.4 Vital Signs

Descriptive statistics summarizing vital signs and changes from baseline by renal function group and scheduled time will be provided.

All vital signs will be listed by participant.

13.5 Electrocardiograms

Descriptive statistics summarizing ECG parameters by renal function group and scheduled time will be provided.

All ECG parameters and the corresponding abnormalities will be listed by participant.

13.6 Other Observations Related to Safety

The hepatic event data will be listed by participant.

The hypoglycemic event data will be listed by participant.

Physical Exams will be performed but collected as a procedure and thus data is not included. Any clinically significant findings in a physical examination should be reported as AEs.

14.0 References

SAS Institute, Inc., SAS® Version 9.4 software, Cary, NC.

Clinical Study Protocol. A Phase 1, Parallel, Single-Dose, Open-Label, Single-Period Study of LY3502970 in Participants with Normal Renal Function and Participants with Renal Impairment. Final, 10 May 2023.

Appendix 1: List of End of Text Outputs

Output	Title	Analysis Set
Section 14.1 – Disposition and Demographic Data		
Table 14.1.1	Summary of Participant Disposition	Entered
Table 14.1.2	Summary of Demographics	Safety
Table 14.1.3	Summary of Study Drug Administration	Safety
Section 14.2 – Pharmacokinetic and Biomarker Data		
Table 14.2.1	Summary of LY3502970 Plasma Concentrations	PK
Table 14.2.2	Summary of LY3502970 Plasma Pharmacokinetic Parameters	PK
Table 14.2.3.1	Statistical Analysis (Linear Regression) of Primary PK Parameters and Absolute eGFR	PK
Table 14.2.3.2	Statistical Analysis (Linear Regression) of Primary PK Parameters and BSA-Adjusted eGFR	PK
Table 14.2.3.3	Statistical Analysis of Tmax	PK
Figure 14.2.4.1	Plot of Mean (± SD) LY3502970 Plasma Concentrations Versus Time on a Linear Scale	PK
Figure 14.2.4.2	Plot of Mean LY3502970 Plasma Concentrations Versus Time on a Semi-Log Scale	PK
Figure 14.2.5.1	Plot of Individual LY3502970 Plasma Concentrations Versus Time on a Linear Scale	PK
Figure 14.2.5.2	Plot of Individual LY3502970 Plasma Concentrations Versus Time on a Semi-Log Scale	PK
Figure 14.2.6.1	Scatter Plot of Individual Plasma Pharmacokinetic Parameters versus Absolute eGFR	PK
Figure 14.2.6.2	Scatter Plot of Individual Plasma Pharmacokinetic Parameters versus BSA-Adjusted eGFR	PK
Table 14.2.7.1	Summary of Coproporphyrin 1 Plasma Concentrations	Biomarker
Table 14.2.7.2	Summary of Coproporphyrin 1 Parameters	Biomarker
Figure 14.2.8.1	Plot of Mean (± SD) Coproporphyrin 1 Plasma Concentrations Versus Time on a Linear Scale	Biomarker
Figure 14.2.8.2	Plot of Individual Coproporphyrin 1 Plasma Concentrations Versus Time on a Linear Scale	Biomarker
Section 14.3 – Safety Data		
Table 14.3.1.1	Summary of Adverse Events	Safety
Table 14.3.1.2	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety
Table 14.3.1.3	Summary of Treatment Emergent Adverse Events by Relationship to Study Drug	Safety
Table 14.3.1.4	Summary of Treatment Emergent Adverse Events by Severity	Safety
Table 14.3.1.5	Summary of Adverse Events of Special Interest by System Organ Class and Preferred Term	Safety

Table 14.3.2	Listing of Deaths and Other Serious Adverse Events	All Participants
Table 14.3.4	Listing of Abnormal Laboratory Values	All Participants
Table 14.3.5	Summary of Laboratory Results	Safety
Table 14.3.6	Summary of Vital Signs	Safety
Table 14.3.7	Summary of 12-Lead Electrocardiogram Results	Safety

Output	Title
Section 16.2.1 – Disposition	
Listing 16.2.1	Participant Disposition
Section 16.2.2 – Protocol Deviations	
Listing 16.2.2	Important Protocol Deviations
Section 16.2.3 – Excluded Participants	
Listing 16.2.3	Analysis Sets
Section 16.2.4 – Demographics and Baseline Characteristics	
Listing 16.2.4.1	Participant Demographics
Listing 16.2.4.2	Medical History
Listing 16.2.4.3	Prior and Concomitant Medications
Listing 16.2.4.4.1	Substance Use - Alcohol
Listing 16.2.4.4.2	Substance Use - Caffeine
Listing 16.2.4.4.3	Substance Use - Tobacco
Listing 16.2.4.4.4	Substance Use - Nicotine Replacement Therapy
Listing 16.2.4.4.5	Substance Use - Recreational Drug Use
Listing 16.2.4.5	Genetics Samples Collection
Section 16.2.5 – Compliance	
Listing 16.2.5	Study Drug Administration
Section 16.2.6 – Pharmacokinetic and Biomarker Data	
Listing 16.2.6.1	LY3502970 Plasma Concentrations
Listing 16.2.6.2	LY3502970 Plasma Pharmacokinetic Parameters
Listing 16.2.6.3	LY3502970 Plasma Pharmacokinetic Diagnostic Parameters
Listing 16.2.6.4	Coproporphyrin 1 Plasma Concentrations
Listing 16.2.6.5	Coproporphyrin 1 Parameters
Section 16.2.7 – Adverse Events Data	
Listing 16.2.7.1	Adverse Events
Listing 16.2.7.2	Adverse Events Leading to Study Drug Discontinuation
Section 16.2.8 – Laboratory Data	
Listing 16.2.8.1	Clinical Laboratory Results – Chemistry
Listing 16.2.8.2	Clinical Laboratory Results – Hematology

Listing 16.2.8.3	Clinical Laboratory Results – Urinalysis
Listing 16.2.8.4	Clinical Laboratory Results – Additional Assessments
Listing 16.2.8.5	Clinical Laboratory Results – Hepatic Event
Section 16.2.9 Other Safety Data	
Listing 16.2.9	Vital Signs
Listing 16.2.10	12-Lead Electrocardiogram Results
Listing 16.2.11.1	Hepatic Event - Prespecified Medical History
Listing 16.2.11.2	Hepatic Event - Liver Related Signs and Symptoms
Listing 16.2.11.3	Hepatic Event - Associated Person Medical History - Liver Disease
Listing 16.2.11.4	Hepatic Event - Prespecified Concomitant Therapy
Listing 16.2.11.5	Hepatic Event - Substance Use - Alcohol Change
Listing 16.2.11.6	Hepatic Event - Substance Use - Recreational Drug Use Change
Listing 16.2.11.7	Hepatic Event - Hepatic Monitoring Procedures
Listing 16.2.11.8	Hepatic Event - Biopsy Assessment - Liver
Listing 16.2.11.9	Hepatic Event - Hepatic Risk Factor Assessment
Listing 16.2.12	Hypoglycemic Events

Other Appendix Outputs:	
Output	**Title**
Appendix 16.1.9.2.1	Statistical Appendices 1: SAS Outputs for Statistical Analysis (Linear Regression) of Primary PK Parameters and Absolute eGFR
Appendix 16.1.9.2.2	Statistical Appendices 2: SAS Outputs for Statistical Analysis (Linear Regression) of Primary PK Parameters and BSA-Adjusted eGFR
Appendix 16.1.9.2.3	Statistical Appendices 3: SAS Outputs for Statistical Analysis of Tmax

Shells will be provided in a separate document to support the approved SAP.

Appendix 2: Parameter Definitions

Plasma Parameter	Description	Analyte	Programming Notes
Cmax, Cmax_Fu	Maximum observed concentration.	LY3502970 Coproporphyrin 1	Cmax from WNL for unbound analytes: Cmax*fu (calculated in SAS)
AUC(0-tlast), AUC(0-tlast)_Fu	Area under the concentration-time curve time 0 to time of last quantifiable concentration.	LY3502970 Coproporphyrin 1	AUClast from WNL for unbound analytes: AUClast*fu (calculated in SAS)
AUC(0-inf), AUC(0-inf)_Fu	Area under the concentration-time curve from time 0 extrapolated to infinity.	LY3502970	AUCINF_pred from WNL for unbound analytes: AUCINF_pred *fu (calculated in SAS) To be excluded from analysis/summaries if the following exclusion criteria are met: • Extrapolation, • Regression
Fu	Fraction of drug unbound in plasma	LY3502970 Coproporphyrin 1	determined by ex vivo protein binding assay 1 – mean plasma protein binding (calculated in SAS)
Tmax	Time to maximum observed concentration.	LY3502970	Tmax from WNL
tlast	Time of the last time point with an observed measurable concentration	LY3502970	tlast from WNL
t½	Terminal elimination phase half-life based on the apparent terminal log-linear portion of the concentration-time curve. A uniform weighting scheme will be used in the regression analysis of the terminal log-linear portion of the concentration-time curve.	LY3502970	HL_Lambda_z from WNL To be excluded from analysis/summaries if any of the following exclusion criteria are met: • Extrapolation • Regression • Span (flag only; do not exclude from summaries)
CL/F	Apparent clearance after extra-vascular dose.	LY3502970	CL_F_pred from WNL To be excluded from analysis/summaries if any of the the following exclusion criteria are met: • Extrapolation, • Regression

Vz/F	Apparent volume of distribution after extra-vascular dose.	LY3502970	Vz_F_pred from WNL To be excluded from analysis/summaries if any of the following exclusion criteria are met: • Extrapolation, • Regression
Vss/F	apparent volume of distribution at steady state after extra-vascular dose	LY3502970	Calculated in SAS as Cl_F_pred*MRTINF_pred To be excluded from analysis/summaries if any of the following exclusion criteria are met: • Extrapolation, • Regression

The following diagnostic parameters will be listed for LY3502970:

Diagnostic Parameter	Description	SAS Programming Notes
AUC%Extrap	Percentage of AUC(0-inf) due to extrapolation from the last quantifiable concentration predicted to infinity.	AUC_%Extrap_pred from WNL
Adj Rsq	Goodness of fit statistic for the log-linear terminal elimination phase	Rsq_adjusted from WNL
Lz	Terminal phase rate constant Note: In Phoenix, use Best Fit method used to determine regression.	Lambda_z from WNL
Lz_Start	Start time used in the regression for the determination of Lz.	Lambda_z_lower from WNL
Lz_End	End time used in the regression for the determination of Lz.	Lambda_z_upper from WNL
Lz_N	Number of points used in the regression for the determination of Lz.	No_points_lambda_z from WNL
Span	Number of half-lives used in the regression for the determination of Lz.	Span from WNL

Appendix 3: Protocol Schedule of Assessments

Procedure	Screening	Baseline	Treatment Period					Follow -up/ED	Comments
Days	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**12(± 2)**	
Informed consent	X								
Admission to CRU		X							
Discharge from CRU							X		Stay may be extended at investigator discretion.
Non-residential Visit	X							X	
Medical Assessment	X								Includes medical history and complete physical examination at screening, and symptom-directed examination at other times.
HbA1c	X								
FSH	X								If needed to confirm postmenopausal status. See Protocol Appendix 2 in Section 10.2 for details.
Serum Pregnancy	X								Female participants only. See Protocol Appendix 2 in Section 10.2 for details.
Urine Pregnancy		X							Female participants only. See Protocol Appendix 2 in Section 10.2 for details. A serum pregnancy test may be used, if urine testing is not possible.
Urine drug screen	X	X							Salivary drug screen may be performed if a urine sample can't be obtained. See Protocol Appendix 2 in Section 10.2 for details.
Ethanol testing	X	X							See Protocol Appendix 2 in Section 10.2 for details.

Procedure	Screening	Baseline	Treatment Period					Follow -up/ED	Comments
Days	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**12(± 2)**	
Serology	X								See Protocol Appendix 2 in Section 10.2 for details.
Genetics sample		X							
Height	X								
eGFR	X	X							Local and central laboratory used for each testing occasion. See Protocol Section 9.2.2.
Cystatin C		P							
LY3502970 Administration			X						See footnote for schema in Protocol Section 1.2
Weight	X	X	P					X	
Vital signs	X	X	P	X	X	X	X	X	
Hematology, Clinical Chemistry, Urinalysis	X		P, 8*			X		X	Local Laboratory. See Protocol Appendix 2 in Section 10.2 for details. *Clinical chemistry only at 8 hours postdose.
Single 12-lead ECG	X		P					X	ECGs must be recorded before blood collection.
Plasma LY3502970 PK samples			0.5, 1, 2, 4, 6, 8, 12, 16	24, 36	48	72	96	X	Times are relative to dosing time. The exact date and time of sample collection must be recorded.
Plasma coproporphyrin 1			P, 4, 12	24					
LY3502970 protein binding			4, 8, 12						
Coproporphyrin 1 protein binding			P, 4, 12	24					
AEs/Concomitant Medications	X	X	X	X	X	X	X	X	

Abbreviations: AE = adverse event; BSA = body surface area; CKD = chronic kidney disease; CKD-EPI = chronic kidney disease epidemiology collaboration; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating

hormone; HbA1c = glycated hemoglobin; P = predose; PK = pharmacokinetics.
Note: If multiple procedures take place at the same time point, the following order of the procedure should be used: ECG, vital signs, and venipuncture. PK sampling times are given as targets to be achieved within reasonable limits.

15.0 Document History

Version Date	Modified/Reviewed By	Brief Summary of Changes
12-Jul-2023	PPD	Created from template EDSREP 009 T 01 G.

Signature Page for VV-CLIN-122828 v1.0

Approval	PPD Statistician 12-Jul-2023 17:11:09 GMT+0000

Approval	PPD PKPDPMx 12-Jul-2023 17:13:20 GMT+0000

Signature Page for VV-CLIN-122828 v1.0