GZGA Statistical Analysis Plan Final Version 3

A Single- and Multiple-Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3502970 in Healthy Subjects.

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STATISTICAL ANALYSIS PLAN

A Single- and Multiple-Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3502970 in Healthy Subjects

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2. ABBREVIATIONS

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

A_e(t1-t2)	amount excreted in urine, by interval and cumulative
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AUC	Area under the concentration versus time curve
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-∞)	area under the concentration versus time curve from time zero to infinity
AUC(0-24)	area under the concentration versus time curve from time zero to 24h postdose
AUCτ	area under the concentration versus time curve during the dosing interval
BQL	below the lower limit of quantification
$C_{predose}$	Predose observed drug concentration
C_{max}	Maximum observed drug concentration
CI	Confidence interval
CL/F	apparent total body clearance of drug calculated after extra-vascular administration
CL_R	renal clearance
C_{last}	last predicted concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
f_e(t1-t2)	percentage of dose excreted in urine, by interval and cumulative
ICH	International Conference on Harmonisation

MAD	Multiple-Ascending Dose
MedDRA	Medical Dictionary for Regulatory Activities
MR_{AUC}	metabolic ratio based upon AUC(0-24)/AUCτ
MR_{Cmax}	metabolic ratio based upon C_{max}
MTD	Maximum tolerated dose
OGTT	oral glucose tolerance test
PG	Plasma glucose
PK	Pharmacokinetic
QD	Once daily
QTcF	the QT interval corrected using Fridericia's formula
R_A(AUC)	Accumulation ratio based upon AUC(0-24)/AUCτ
SAP	Statistical Analysis Plan
SD	Standard deviation
TBL	Total bilirubin
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
$t_{1/2}$	half-life associated with the terminal rate constant (λz) in non-compartmental analysis
ULN	Upper limit of normal
VAS	Visual analog scale
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 2019), amendment (a) (dated 23 July 2019), amendment (b) (dated 26 August 2019), amendment (c) (dated 14 October 2019), amendment (d) (dated 11 December 2019), amendment (e) (dated 02 March 2020), and amendment (f) (dated 17 April 2020), SAP version 1 (dated 11 June 2019), and SAP version 2 (dated 29 October 2019).

This SAP describes the planned analysis of the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical and PK analyses of data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement between Eli Lilly and Company and Covance Early Clinical (EC) Biometrics. 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 signed off prior to first subject administration for this study. 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 between Eli Lilly and Company and Covance EC Biometrics 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

4.1 Primary Objective

To investigate the safety and tolerability of single and multiple oral doses of LY3502970 in healthy subjects

4.2 Secondary Objective

To characterize the PK of LY3502970 after single and multiple oral doses in healthy subjects (Parts A and B)

4.3 Exploratory Objectives

- To evaluate the effect of a meal on the PK of a single oral dose of LY3502970 (Part C)

- To evaluate the PK of a single dose of LY3502970 controlled-release prototype (Part D)
- To investigate LY3502970 effects on markers of OATP function following single and multiple oral doses of LY3502970 in healthy subjects (Parts A, B, C, and D)
- To investigate potential DDIs of LY3502970 following multiple oral doses of LY3502970 in healthy subjects (Part B)
- To investigate the PD effects of LY3502970 following single oral doses administered to healthy subjects (Part A)
- To investigate the PD effects of LY3502970 following multiple oral doses administered to healthy subjects (Part B)
- To investigate the PD effects of LY3502970 following single oral doses administered to healthy subjects following a meal (Part C)
- To investigate the PD effects of LY3502970 controlled-release prototype following single oral doses administered to healthy subjects (Part D)
- To investigate the PK of 2 different formulations of LY3502970 following multiple oral doses of LY3502970 in healthy subjects (Part E)

5. STUDY DESIGN

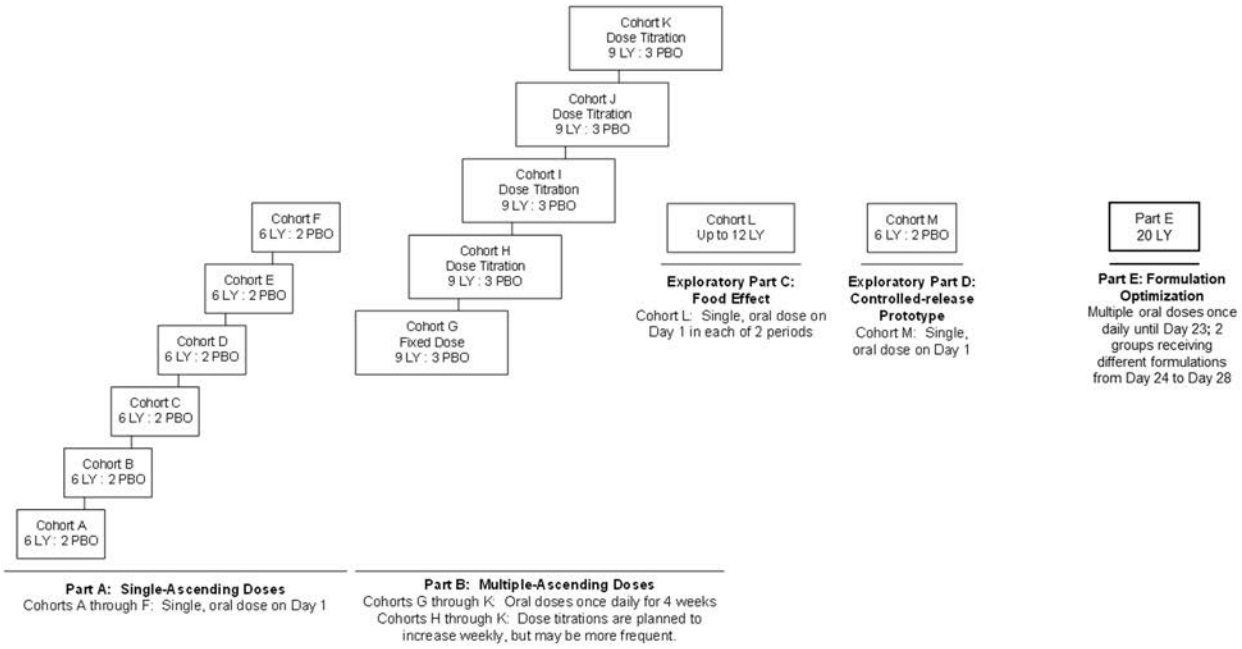
Study GZGA is a Phase 1, single site, 5-part study in healthy subjects. The study design includes:

- Part A: randomized, placebo-controlled, investigator- and subject-blind, single-ascending dose (SAD)
- Part B: randomized, placebo-controlled, investigator- and subject-blind, 4-week, multiple-ascending dose (MAD) with or without dose titration
- Exploratory Part C: single-dose, randomized, 2-treatment arm, 2-period, open-label, crossover to evaluate food effects
- Exploratory Part D: randomized, placebo-controlled, investigator- and subject-blind, single dose to evaluate the LY3502970 controlled-release prototype
- Exploratory Part E: randomized, investigator- and subject-blind, multiple dose to evaluate 2 different formulations of LY3502970 with dose titration

Figure GZGA.1 shows the general schematic of the planned study design.

In all parts of the study, safety and tolerability assessments will include the monitoring of adverse events (AEs), vital signs, body temperature, blood glucose levels, safety laboratory tests,

liver panel tests, medical assessments, body weight, concomitant medication, triplicate ECGs, and telemetry.



Abbreviations: LY=LY3502970; PBO = placebo.

This is a general schematic of the study design. Dose levels may be repeated. Each new dose level will be initiated after evaluation of preliminary safety, tolerability, and available pharmacokinetic and pharmacodynamic data through Day 5 for Part A or Day 15 for Part B for at least 5 subjects receiving LY3502970 in the preceding dose level.

Part B may be initiated after review of safety, tolerability, and available pharmacokinetic and pharmacodynamic data collected up to Day 5 for Cohort C. Part B may be initiated earlier if approximately 10 to 20 mg/dL glucose-lowering effect is observed at a tolerated dose after reviewing interim data.

Maximum tolerated dose needs to be determined in Part A before exploratory Parts C, D, and E may be initiated.

Figure GZGA.1. Illustration of planned study design

5.1 Single- and Multiple-Ascending Dose Studies (Parts A and B)

5.1.1 Single-Ascending Dose Study in Healthy Subjects (Part A)

Part A will consist of up to 6 escalating single-dose levels of LY3502970 or placebo. Approximately 48 subjects will be randomized into 6 groups (Cohorts A through F). For each cohort it is planned that approximately 8 subjects will be randomly assigned to either LY3502970 (6 subjects) or placebo (2 subjects).

Dose escalations will be based on the evaluation of safety, tolerability, and available PK and PD data through Day 5 from at least 5 subjects receiving LY3502970 in the preceding SAD dose level.

Eligible subjects will be admitted to the CRU on Day -1. On the morning of Day 1, a single oral dose of LY3502970 or placebo will be administered, according to randomization, after an overnight fast (at least 8 hours). The PK, PD, and coproporphyrin biomarker sampling and safety assessments will be performed. The PK or PD sampling schedules may be modified based on the available safety and PK data.

Subjects will be discharged from the study after the review of all final safety assessments from the follow-up visit is completed by the investigator.

5.1.2 Multiple-Ascending Dose Study in Healthy Subjects (Part B)

The MAD portion of the study may be initiated, at the earliest, after review of safety, tolerability, and available PK and PD data collected up to Day 5 for Cohort C in Part A. Part B may be initiated if data from Part A indicates an approximately 10 to 20 mg/dL glucose-lowering effect at a tolerated dose.

Part B will consist of up to 5 escalating multiple-dose levels of LY3502970 or placebo. Approximately 60 subjects will be randomized into 5 groups (Cohorts G through K). For each cohort it is planned that approximately 12 subjects will be randomly assigned to LY3502970 (9 subjects) or placebo (3 subjects). In Cohort J, subjects will be administered atorvastatin and midazolam on Days -2 and 27. In Cohort K, subjects will be administered simvastatin on Days -2 and 27. Cohorts J and K may be initiated after Cohort G (does not have to follow completion of Cohorts G through I).

The dose levels in Part B will be determined on the basis of safety, tolerability, and available PK and PD data from Part A. A fixed dose may be administered to subjects in Cohort G. In Cohorts H through K, LY3502970 dose regimens may be evaluated via dose titration. Dose escalations will be based on the evaluation of safety, tolerability, and available PK and PD data from at least 5 subjects receiving LY3502970 through Day 15 in the preceding MAD dose level.

Eligible subjects will be admitted to the CRU on Day -2 for Cohorts G through I and on Day -3 for Cohorts J and K. A baseline PK profile will be collected on Day -2 for midazolam and atorvastatin in Cohort J and for simvastatin in Cohort K. A baseline PD profile, including oral glucose tolerance test (OGTT) and gastric emptying, will be collected on Day -1 for all cohorts in Part B. Beginning on the morning of Day 1 through Day 28, subjects will be administered either once daily (QD) or twice daily (BID) oral dose of LY3502970 or placebo, according to randomization. In case of BID dosing, the 2 doses will be separated by approximately 12 hours. On Day 27, midazolam will be coadministered with the morning dose of LY3502970 or placebo and atorvastatin administered 4 hours after midazolam in Cohort J. In Cohort K, simvastatin will be coadministered with the morning dose of LY3502970 or placebo on Day 27. The PK or PD sampling schedules may be modified based on the available safety and PK data.

Subjects will be discharged from the study after the review of all final safety assessments from the follow-up visit is completed by the investigator.

5.2 Exploratory Food Effect Study in Healthy Subjects (Part C)

Part C may be initiated after the maximum tolerated dose (MTD) is determined in Part A (SAD). Up to 12 subjects may be enrolled into 1 group (Cohort L). Subjects will receive a single oral dose of LY3502970 at the MTD level in each of 2 treatment periods. Subject will be randomized to 1 of 2 treatment sequences which comprised of 2 treatment arms

- Fasted treatment: Dose administered with approximately 240 mL water following an overnight fast of at least 10 hours
- Food-effect treatment: Dose administered with approximately 240 mL water following a meal consumed after an overnight fast of at least 10 hours.

Table GZGA.1. Treatment Sequences for Food Effect Study (Part C)

Sequence	Period 1	Period 2
1	Fasted	Meal
2	Meal	Fasted

Subject eligibility will be determined at a screening visit. Eligible subjects will be admitted to the CRU on Day -1 in each period. On the morning of Day 1 in each period, a single oral LY3502970 dose will be administered, according to randomization, in either the fasted state or 30 minutes after the start of a meal. The PK or PD sampling schedules may be modified based on the available safety and PK data.

There will be a washout period of at least 5 days between each dose. In each period, subjects will remain in the CRU at least until completion of assessments on Day 4 and return for an outpatient visit on Day 5.

5.3 Exploratory LY3502970 Controlled-release Prototype Study in Healthy Subjects (Part D)

Part D may be initiated after the MTD is determined in Part A (SAD). It is planned that approximately 8 subjects may be enrolled into 1 group (Cohort M) and randomly assigned to LY3502970 controlled-release prototype (6 subjects) or placebo (2 subjects).

Subject eligibility will be determined at a screening visit. Eligible subjects will be admitted to the CRU on Day -1. On the morning of Day 1, a single oral dose at the MTD level will be administered, according to randomization, after an overnight fast (at least 8 hours). The PK, PD, and coproporphyrin biomarker sampling and safety assessments will be performed. The PK or PD sampling schedules may be modified based on the available safety and PK data.

Subjects will be discharged from the study after the review of all final safety assessments from the follow-up visit is completed by the investigator.

5.4 Formulation Optimization (Part E)

Part E of the study may be initiated, at the earliest, after review of safety, tolerability, and available PK and PD data collected for Cohort K in Part B.

Approximately 20 subjects will be enrolled into Part E of the study to target 18 completers. All the subjects will receive LY3502970 once daily for 28 days. Dose titration will be every 6 days and will reach a maximum dose on Day 19. This dose will be no higher than the maximum dose tolerated in Part B.

At screening, subjects will be administered a Heidelberg pH capsule with approximately 240 mL of room temperature water to permit pH testing of the gastric environment. On the PK sampling days (Days 23 and 28), the Heidelberg pH capsule will be administered at least 30 minutes prior to LY3502970 dosing to allow stabilization. On Day 24, subjects will be randomized into 2 equal groups and assigned 2 different formulations of LY3502970. From Day 24 to Day 28, the subjects will be administered the respective formulation of LY3502970 as per their randomization. The PK, PD, biomarker sampling, and safety assessments will be performed according to the Schedule of Activities in the protocol. The PK or PD sampling schedules may be modified based on the available safety and PK data.

Subjects will remain at the CRU for the entire 4-week treatment period. On Day 29, the investigator or qualified designee will review all available inpatient safety data before discharging subjects from the CRU after the morning procedures are completed, provided they are deemed medically fit by the investigator. Subjects may be required to remain at the CRU as needed for safety follow-up based on clinical judgment of the investigator.

Subjects will be discharged from the study after the review of all final safety assessments from the follow-up visit is completed by the investigator.

6. TREATMENTS

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

Study Part	Study Treatment Name	Treatment order in TFL
A	Placebo	1
	A mg LY3502970	2
	B mg LY3502970	3
	C mg LY3502970	4
	D mg LY3502970	5
	E mg LY3502970	6
	F mg LY3502970	7
B	Placebo QD	1
	G mg LY3502970 QD	2
	H mg LY3502970 QD	3
	I mg LY3502970 QD	4
	200 µg Midazolam	5
	200 µg Midazolam + 40 mg Atorvastatin	6
	J mg LY3502970 QD	7
	J mg LY3502970 QD + 200 µg Midazolam	8
	J mg LY3502970 QD + 200 µg Midazolam + 40 mg Atorvastatin	9
	20 mg Simvastatin	10
	K mg LY3502970 QD	11
	K mg LY3502970 QD + 20 mg Simvastatin	12
C	L mg LY3502970 Fasted	1
	L mg LY3502970 Fed	2
D	Placebo	1
	M mg LY3502970	2
E	2 mg LY3502970	1
	5 mg LY3502970	2
	12 mg LY3502970	3
	N mg LY3502970	4
	N mg LY3502970 Formulation 1	5
	N mg LY3502970 Formulation 2	6

Within Parts A and B separately, placebo data will be pooled. The above dose levels will be updated on the TFLs for the actual dose received. In Part B, dose levels may increase weekly in the dose titration cohorts (Cohorts H through K) meaning summary tables may be presented by dose regimen in the TFLs and not by treatment. This is also applicable to Part E due to the use of dose titration.

7. SAMPLE SIZE JUSTIFICATION

The sample size for Parts A through E of the study was chosen to provide sufficient data for evaluating safety, PK, and/or PD parameters, as well as primary objectives of this study.

Approximately 180 healthy subjects may be enrolled so that up to 146 subjects complete the study (48 in Part A, 60 in Part B, up to 12 in Part C, 8 in Part D, and 18 in Part E).

In Part B, subjects discontinued from the study prior to Day 16 or receiving the planned third titration dose within a given cohort may be replaced. Subjects who discontinue after Day 16 or receiving the planned third titration dose within a given cohort will not be replaced.

Subjects withdrawn from the study due to safety reasons will not be replaced.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all enrolled subjects, whether or not they completed all protocol requirements.

The "Pharmacokinetic" population will consist of all subjects who received at least one dose of LY3502970 and have evaluable PK data.

The "Pharmacodynamic" population will consist of all subjects who received at least one dose of LY3502970 and have evaluable PD data.

All protocol deviations including those related to COVID-19 that occur during the study will be considered for their severity/impact and will be taken into consideration when subjects are assigned to analysis populations.

9. STATISTICAL METHODOLOGY

9.1 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, min, max and N; for log-normal data (e.g. the PK parameters: Area under the concentration versus time curve (AUCs) and maximum observed drug concentration [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 subjects up to the point of withdrawal, with any subjects excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for subjects included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Mean change from baseline is the mean of all individual subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The individual subject's change from baseline

values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

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

9.2 Demographics and Subject Disposition

Subject disposition will be listed. The demographic variables age, sex, race, ethnicity, country of enrolment, body weight, height and body mass index will be summarized and listed. All other demographic variables will be listed only.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

The PK parameter estimates will be determined using non-compartmental methods in validated software program, Phoenix WinNonlin (Certara, Version 8.1 or later):

Parts A to E

Plasma concentrations of coproporphyrin (1 and 3) will be used to determine the following pharmacokinetic parameters, when possible:

Parameter	Definition
$AUC(0\text{-}t_{last})$	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
C_{max}	maximum observed drug concentration
t_{max}	time of maximum observed drug concentration

Parts A, C and D

Plasma concentrations of LY3502970 will be used to determine the following pharmacokinetic parameters, when possible:

Parameter	Definition
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-∞)	area under the concentration versus time curve from time zero to infinity
C_{max}	maximum observed drug concentration
t_{max}	time of maximum observed drug concentration
$t_{1/2}$	half-life associated with the terminal rate constant (λz) in non-compartmental analysis
CL/F	apparent total body clearance of drug calculated after extra-vascular administration
V_Z/F	apparent volume of distribution during the terminal phase after extra-vascular administration
V_{SS}/F	apparent volume of distribution at steady state after extra-vascular administration

Following oral administration of LY3502970 in Part A, urine concentrations of LY3502970 will be used to determine the following PK parameters where possible.

Parameter	Definition
A_e(t1-t2)	amount excreted in urine, by interval and cumulative
f_e(t1-t2)	percentage of dose excreted in urine, by interval and cumulative
CL_R	renal clearance $CL_R = \frac{Ae(0-\infty)}{AUC(0-tlast)}$

Unbound glomerular filtration rate will be estimated using creatinine. The renal clearance of LY3502970 may be compared to the unbound glomerular filtration rate with the use of figures or tables.

Parts B and E

Plasma concentrations of LY3502970 (Parts B and E only), midazolam, atorvastatin, simvastatin and their metabolites, and acetaminophen (where applicable) will be used to determine the following pharmacokinetic parameters, when possible:

Parameter	Definition
$AUC(0\text{-}t_{last})$	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(0-24)	area under the concentration versus time curve from time zero to 24h postdose
AUCτ	area under the concentration versus time curve during the dosing interval
$C_{predose}$	predose observed drug concentration
C_{max}	maximum observed drug concentration
t_{max}	time of maximum observed drug concentration
$t_{1/2}$	half-life associated with the terminal rate constant (λz) in non-compartmental analysis
CL/F	apparent total body clearance of drug calculated after extra-vascular administration
V_Z/F	apparent volume of distribution during the terminal phase after extra-vascular administration (for midazolam, atorvastatin, simvastatin and acetaminophen only)
V_{SS}/F	apparent volume of distribution at steady state after extra-vascular administration (for midazolam, atorvastatin, simvastatin and acetaminophen only – Day 1 only)
MR_{AUC}	metabolic ratio based upon AUC(0-24)/AUCτ $$\text{MRAUC} = \frac{Metabolite\ AUC}{Parent\ AUC}$$
MR_{Cmax}	metabolic ratio based upon C_{max} $$\text{MRCmax} = \frac{Metabolite\ Cmax}{Parent\ Cmax}$$
$R_A(AUC)$	Accumulation ratio based upon AUC(0-24)/AUCτ (Part B: LY3502970 only) $$\text{RA(AUC)} = \frac{AUC(Day\ x)}{AUC(Day\ 1)}$$

Day x = Day 15, Day 28

Additional pharmacokinetic parameters may be calculated, as appropriate.

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

Urine PK analysis will be calculated using nominal sample collection times.

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.

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

- AUC parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}.

- 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 subject 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 last predicted concentration (C_{last}) will be reported.

Individual PK Parameter Rules

- Only quantifiable concentrations will be used to calculate pharmacokinetic parameters with the exception of special handling of certain concentrations reported below the lower limit of quantification (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 subject 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.
- Urine concentrations reported as BQL will be set to a value of zero.

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 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.

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

Reporting of Excluded Values

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

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

The PK parameters for acetaminophen, coproporphyrin, midazolam, atorvastatin, simvastatin, and their metabolites will also be analyzed using standard noncompartmental methods of analysis.

9.3.2 Pharmacokinetic Statistical Methodology

9.3.2.1 Parts A (SAD) and B (MAD)

For single- and multiple-dose parts of the study, PK dose proportionality will be assessed separately. For Part B, the analyses will be performed for Days 15 and 28. Log-transformed C_{max} and AUC estimates will be evaluated using a power model (where log-dose acts as an explanatory variable) to estimate ratios of dose-normalized geometric means and corresponding 90% confidence intervals (CIs).

The estimated ratio of dose-normalized geometric means of PK parameters between the highest and lowest doses will be used to assess dose proportionality. The parameter t_{max} will be analyzed using a nonparametric method (Kruskal-Wallis test). Between subject variability estimates (and within subject variability estimates for Part B) will also be provided.

Example SAS code for the analysis:

```
proc mixed data=xxx;
model log_pk = log_dose / alpha=0.1 cl solution outpred=resids ddfm=kr;
estimate 'xx mg' intercept 1 log_dose yy / alpha=0.1 cl; /*Log value of xx*/
estimate 'zz mg - xx mg' log_dose pp / alpha=0.1 cl; /*Difference in log
values of zz and xx*/
ods output solutionf=est;
ods output estimates=estims;
run;

proc npar1way data=tmax;
class treatc;
var pk;
output out=kruskall;
run;
```

9.3.2.2 Exploratory Part B (DDI)

The primary PK parameter estimates for midazolam, atorvastatin, and simvastatin and their metabolites will be compared between Day -2 (baseline) and Day 27 (presence of LY3502970). Log-transformed C_{max} and AUC estimates will be evaluated in a linear mixed-effects model with treatment as a fixed effect and subject as a random effect. The treatment differences will be back-transformed to present the ratios of geometric least squares means and the corresponding 90% CIs. The metabolite ratio for midazolam (AUC_midazolam M1 / AUC_midazolam) will also be calculated and compared between Day -2 and Day 27.

Example SAS code for the analysis:

```
proc mixed data=xxx;
class subject trtmnt;
model log_pk = trtmnt / ddfm=kr;
random subject;
lsmeans trtmnt / pdiff cl alpha=0.1;
ods output lsmeans=lsmeans diffs=diffs;
run;
```

The parameter t_{max} will be analysed non-parametrically with medians, the median of the differences and corresponding 90% CI presented alongside the p-value from the Wilcoxon signed-rank test.

9.3.2.3 Exploratory Part C (food effect)

The primary PK parameter estimates will be compared between the reference fasted treatment and food-effect treatment. Log-transformed C_{max} and AUC estimates will be evaluated in a linear mixed-effects model with treatment, sequence and period as fixed effects and subject as a random effect. The treatment differences will be back-transformed to present the ratios of geometric least squares means and the corresponding 90% CIs.

Example SAS code for the analysis:

```
proc mixed data=xxx;
class sequence subject period trtmnt;
model log_pk = sequence period trtmnt / ddfm=kr;
random subject;
lsmeans trtmnt / pdiff cl alpha=0.1;
ods output lsmeans=lsmeans diffs=diffs;
run;
```

The parameter t_{max} will be analysed non-parametrically with medians, the median of the differences and corresponding 90% CI presented alongside the p-value from the Wilcoxon signed-rank test.

9.3.2.4 Exploratory Part D (controlled-release)

The primary PK parameter estimates will be compared between the controlled-release prototype formulation (Part D) and the corresponding dose level from Part A. Log-transformed C_{max} and AUC estimates will be evaluated in a linear fixed effects model with treatment as a fixed effect. The treatment differences will be back-transformed to present the ratios of geometric least squares means and the corresponding 90% CIs.

Example SAS code for the analysis:

```
proc mixed data=xxx;
class trtmnt;
model log_pk = trtmnt / ddfm=kr;
lsmeans treatment / pdiff cl alpha=0.1;
ods output lsmeans=lsmeans diffs=diffs;
run;
```

The parameter t_{max} will be analysed non-parametrically with medians, the median of the differences and corresponding 90% CI presented alongside the p-value from the Wilcoxon rank sum test.

9.3.2.5 Exploratory Part E (formulation optimization)

The primary PK parameter estimates will be compared between reference formulation, and test formulations 1 and 2. Log-transformed C_{max} and AUC estimates will be evaluated in a linear mixed-effects model with treatment as a fixed effect and subject as a random effect. The treatment differences will be back-transformed to present the ratios of geometric least squares means and the corresponding 90% CIs.

Example SAS code for the analysis:

```
proc mixed data=xxx alpha=0.1;
by param;
class trtmnt;
model log_pk = trtmnt / ddfm=kr;
random subject;
lsmeans treatment / pdiff=control(reference) cl alpha=0.1;
ods output lsmeans=lsmeans diffs=diffs;
run;
```

The parameter t_{max} will be analysed non-parametrically with medians, the median of the differences and corresponding 90% CI presented alongside the p-value from the Wilcoxon signed rank test.

9.3.3 Coproporphyrin Analysis

Plasma concentrations of coproporphyrin 1 and coproporphyrin 3 will be listed and summarized by part and treatment, using standard descriptive statistics. Parameter estimates for coproporphyrin 1 and coproporphyrin 3 will be calculated by standard noncompartmental methods. Parameters, including predose observed drug concentration ($C_{predose}$), C_{max}, t_{max}, and AUC, will be summarized using descriptive statistics.

In addition, a comparison between log-transformed $C_{predose}$ and C_{max} of coproporphyrin 1 and coproporphyrin 3 will be produced using a linear mixed effects model with treatment, timepoint (variable indicating whether the concentration value is either predose or postdose), and subject as a random effect. The difference between postdose and predose will be calculated for each treatment and will be back-transformed to present the ratios of geometric least squares means and the corresponding 90% CIs.

The following comparisons will be calculated from the model (including associated p-values):

- Postdose versus predose for each treatment group and placebo
- At the postdose timepoint, comparisons between each treatment group and placebo

For the Part B analysis, an additional fixed effect for week will be added to the model so that comparisons can be performed for each week. This will be a repeated measures analysis similar to section 9.4.1 above.

Example SAS code for the analysis (Part A):

```
proc mixed data=xxx;
class trtmnt timepoint subject;
model conc = trtmnt timepoint / ddfm=kr;
random subject;
lsmeans trtmnt / pdiff cl alpha=0.1;
lsmeans timepoint / pdiff cl alpha=0.1;
ods output lsmeans=lsmeans diffs=diffs;
run;
```

For example, SAS code for Part B, refer to section 9.4.1 above.

Plasma concentrations of coproporphyrin 1 and coproporphyrin 3 will also be plotted against dose for both individual and mean data. The plot will be produced separately by dose level and repeated to include all dose levels on one plot. A scatterplot will also be produced for coproporphyrin 1 and coproporphyrin 3 versus time-matched LY3502970 concentrations.

Additional analysis may be performed, if warranted, upon review of the data.

9.4 Pharmacodynamic Assessment

9.4.1 Pharmacodynamic Analysis

Preliminary assessment of LY3502970 PD will be evaluated based on

- fasting glucose and fasting insulin
- change from baseline (Day 1) fasting glucose and fasting insulin
- AUC for glucose and insulin during an OGTT (calculated using the trapezoidal rule) (in Parts A, B and D)
- change from baseline (Day -1 AUC) AUC for glucose and insulin during an OGTT
- body weight and change from baseline (Day 1 predose) body weight
- lipids (including fasting triglycerides, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol) (in Parts A and B).

If for a scheduled timepoint weight has been taken twice within a few minutes then the mean of the 2 values will be used for the analysis.

Untransformed absolute values as well as change from baseline in each parameter will be analysed, separately for each appropriate part, using a mixed-model repeated-measure model to evaluate treatment effects as well as treatment comparisons. The model will include treatment, day and treatment-by-day interaction as fixed effects, subject as a random effect and baseline as a covariate (for the change from baseline analysis). For the analysis of Part C, treatment sequence and period will be included as fixed effects. An unstructured covariance structure will be used and a compound symmetric structure will be used if the model fails to converge. The analysis will compare each dose of LY3502970 against placebo at each day. Least squares means as well as 90% CIs will be reported.

Example of SAS code as follows.

```
proc mixed data=xxx;
class treatment day subject;
model result = treatment day treatment*day /residual ddfm=kr;
repeated day / subject=subject type=UN;
lsmeans treatment*day / cl pdiff alpha=0.1;
ods output lsmeans=lsm diffs=estims;
run;
```

The above code will include baseline as a covariate for the change from baseline parameters.

All PD parameters, including baseline-corrected parameters, will be summarized and tabulated by part, treatment and day. Summary statistics will be provided. The individual observed and mean time profile of the postdose PD parameters will be plotted by treatment group.

9.4.2 Gastric Emptying Analysis (Part B)

Acetaminophen will be used to assess the effect of LY3502970 on gastric emptying. The concentration-time profiles of acetaminophen will be presented for Days -1, 1, and 28. Acetaminophen PK parameter estimates will be calculated by standard noncompartmental analysis methods and summarized using descriptive statistics. Key parameters for analysis will include C_{max}, AUC, and t_{max} of acetaminophen. Other parameters, such as half-life, apparent clearance, and apparent volume of distribution, may be reported.

Log-transformed AUC and C_{max} will be analyzed using a mixed-model repeated-measure model to evaluate treatment effects as well as treatment comparisons. The model will include treatment, day and treatment-by-day interaction as fixed effects, and subject as a random effect. An unstructured covariance structure will be used and a compound symmetric structure will be used if the model fails to converge. The analysis will compare each dose of LY3502970 against placebo at each day. Least squares means as well as 90% CIs will be reported.

Example of SAS code as follows.

```
proc mixed data=xxx;
class treatment day subject;
model logpk = treatment day treatment*day /residual ddfm=kr;
repeated day / subject=subject type=UN;
lsmeans treatment*day / cl pdiff alpha=0.1;
ods output lsmeans=lsm diffs=estims;
```

```
run;
```

In addition to the comparison to placebo, comparisons will occur between Day 1 or Day 28, and Day -1 for each dose level.

The parameter t_{max} of acetaminophen will be analysed non-parametrically with medians and the median of the differences alongside the 90% confidence interval presented.

9.4.3 Appetite Analysis (Parts B and E)

To explore the effects of LY3502970 on meal intake and appetite sensation, subjects will be asked to rate their appetite sensations using a 100-mm visual analog scale (VAS) for parameters of hunger, fullness, satiety, and prospective food consumption.

The VAS is presented as a 10-cm (100-mm) line, anchored by verbal descriptors, usually "extremely" and "not at all". Subjects are required to rate their subjective sensations on four 100 mm scales combined with questions similar to the following:

1. "How hungry do you feel?"

2. "How satisfied do you feel?"

3. "How full do you feel?"

4. "How much do you think you could eat?"

A staff member will use a caliper to measure the distance from 0 to the mark that the subject placed on the VAS and record the measurement in the source document. Overall appetite score is calculated as the average of the 4 individual scores: satiety + fullness + (100-prospective food consumption) + (100-hunger) / 4. The higher overall appetite score indicates less appetite, and the lower score indicates more appetite.

The individual VAS measurements and overall appetite score will be listed and summarized by treatment and timepoint.

9.5 Safety and Tolerability Assessments

9.5.1 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 an AE that starts before the subject has provided written informed consent and is ongoing at consent. A non-treatment emergent AE is defined as an AE which starts after informed consent but prior to dosing. A 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. Treatment-emergent AEs will be summarized by part, treatment, severity and relationship to the study drug. The frequency (the number of AEs, the number of subjects

experiencing an AE and the percentage of subjects experiencing an AE) of treatment-emergent AEs will be summarized by part, treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 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. Any serious AEs will be listed. AEs by day of onset will be presented for Parts B and E.

9.5.2 Concomitant medication

Concomitant medication will be coded using the World Health Organization (WHO) drug dictionary (Version September 2018). Concomitant medication will be listed.

9.5.3 Clinical laboratory parameters

All clinical chemistry, liver panel and hematology data will be summarized by part, parameter and treatment, together with changes from baseline, where baseline is defined as the scheduled assessment immediately prior to dosing (or first dose in Parts B and E), and listed. Urinalysis data will be listed. Additionally, clinical chemistry, liver panel, hematology and urinalysis data outside the reference ranges will be listed.

Values for any clinical chemistry, liver panel, hematology and urinalysis values outside the reference ranges will be flagged on the individual subject data listings.

For lab results that are below the lower limit of quantification then a value of half of the lower limit of quantification will be used for the summary statistics. If a lab result is above the upper limit of quantification then the upper limit of quantification will be used for the summaries.

9.5.4 Vital signs

Vital signs data will be summarized by part and treatment 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 part and treatment.

Furthermore, values for individual subjects will be listed.

For change-from-baseline values, a mixed-model repeated-measure model with treatment, time (of measurement), and treatment-by-time interaction as fixed effects, subject as random effect, and baseline as covariate will be used to determine the effects of LY3502970, separately for Parts A and B. An unstructured covariance structure will be used and a compound symmetric structure will be used if the model fails to converge. The analysis will compare each dose of LY3502970 against placebo at each timepoint. Least-squares means as well as 90% CIs for the difference of LY3502970 compared with placebo will be reported.

Example of SAS code as follows.

```
proc mixed data=xxx;
class treatment time subject;
model chg = base treatment time treatment*time /residual ddfm=kr;
repeated time / subject=subject type=UN;
lsmeans treatment*time / cl pdiff alpha=0.1;
```

```
ods output lsmeans=lsm diffs=estims;
run;
```

9.5.5 Electrocardiogram (ECG)

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the PR, QT, QRS duration and heart rate. In addition, QTcF (the QT interval corrected using Fridericia's formula) will be calculated as follows:

$$QTcF = \frac{QT}{\sqrt[3]{\left(60/HR\right)}}$$

The ECG data (mean of triplicate data) for Parts A, B, and E will be summarized by part and treatment together with changes from baseline, where baseline is defined as the mean of the triplicate Day 1 predose assessment. Figures of mean ECG data and mean changes from baseline will be presented by part and treatment. The frequency of subjects with a maximum increase from baseline in QTcF interval will be summarized for each part and treatment according to the following categories: >30 ms and >60 ms. In addition, the frequency of subjects with QTcF postdose values, according to the following categories: >450 ms, >480 ms and >500 ms, will be summarized by part and treatment.

The relationship between the time-matched LY3502970 concentrations and changes from baseline and time-matched placebo in QTcF interval will be explored graphically using a scatter plot. Three plots will be shown, the first will combine data from Parts A and B in which baseline is the subject's Day 1 predose value, the second in which the baseline is the subject's Day 28 predose, and will only use data from Part B, a third figure will contain Part E data with Day 1 predose as the baseline. A regression analysis using a linear mixed-effects model will be performed. A plasma LY3502970 concentration-QT analysis will be performed to assess the changes from baseline (Day 1 predose in the first plot and Day 28 predose in the second) and time-matched mean placebo in the QTcF interval relative to plasma LY3502970 concentrations across all dose levels. The change from baseline adjustment will be based on individual subject's Day 1 (Parts A and B) or 28 (Part B) predose value, and an additional placebo adjustment will be based on mean time-matched placebo values. The analysis will be performed by plotting double delta QTcF against LY3502970 concentrations, including all post dosing timepoints. A linear mixed-effects model will be performed on the double delta QTcF values and will include LY3502970 concentration as a covariate and subject as a random effect. The estimated regression line and associated 90% CI will be fitted on the plot and the p-value for the slope reported. Estimated delta QTcF and 90% CI at the geometric mean C_{max} of the highest dose level will also be presented. This analysis will also be repeated for PR and RR interval.

Example of SAS code as follows.

```
proc mixed data=xxx;
  class vol;
  model DDchg = concentration / solution cl alpha=0.1 ddfm=kr;
  random vol;
  ods output estimates=est solutionf=sol;
```

```
run;
```

If collected, telemetry data will be summarized and listed in the same way as ECGs.

9.5.6 Hepatic Monitoring

If a subject experiences elevated alanine aminotransferase (ALT) ≥3× upper limit of normal (ULN), alkaline phosphatase (ALP) ≥2× ULN, or elevated total bilirubin (TBL) ≥2× ULN, liver tests should be repeated within 3 to 5 days 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 subjects' liver disease history data will be listed. Any concomitant medication of acetaminophen/paracetamol will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography (MRE) scan, and a biopsy assessment will be listed, if performed.

Hepatic risk factor assessment data will be listed. Liver related signs and symptoms data will be summarized by treatment 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 subject data listings.

9.5.7 Glucose Monitoring and Hypoglycemia

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

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 part and treatment. Hypoglycemia is defined as follows:

- **Documented Glucose Alert Level (Level 1), plasma glucose (PG) ≤70 mg/dL (3.9 mmol/L):**

  – Symptomatic hypoglycemia: an event during which typical symptoms of hypoglycemia are accompanied by PG ≤70 mg/dL (3.9 mmol/L)
  – Asymptomatic hypoglycemia: an event not accompanied by typical symptoms of hypoglycemia but with PG ≤70 mg/dL (3.9 mmol/L)
  – Unspecified hypoglycemia: an event during which PG ≤70 mg/dL (3.9 mmol/L) but no information relative to symptoms of hypoglycaemia
- **Documented Clinically Significant Hypoglycemia (Level 2) PG ≤54 mg/dL (3.0 mmol/L):**

  – Symptomatic hypoglycemia: an event during which typical symptoms of hypoglycemia are accompanied by PG ≤54 mg/dL (3.0 mmol/L)

– Asymptomatic hypoglycemia: an event not accompanied by typical symptoms of hypoglycemia but with PG ≤54 mg/dL (3.0 mmol/L)
– Unspecified hypoglycemia: an event during which PG ≤54 mg/dL (3.0 mmol/L) but no information relative to symptoms of hypoglycemia was recorded.

- **Severe hypoglycemia (Level 3):** an event requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. During these episodes, the subject has an altered mental status and cannot assist in their care, is semiconscious or unconscious, or experienced coma with or without seizures and may require parenteral therapy. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of blood glucose concentration to normal is considered sufficient evidence that the event was induced by a low PG concentration (≤70 mg/dL [3.9 mmol/L]).

- **Severe hypoglycemia requiring medical attention**: a severe hypoglycemic event when subjects require therapy by health care providers (emergency medical technicians, emergency room personnel, etc.).

Other Hypoglycemia:

- **Nocturnal hypoglycemia:** any hypoglycemic event (documented symptomatic, asymptomatic, probable symptomatic, or severe hypoglycemia) that occurs between bedtime and waking
- **Relative hypoglycemia:** an event during which typical symptoms of hypoglycemia, which do not require the assistance of another person, are accompanied by PG >70 mg/dL (3.9 mmol/L), but these levels may be quickly approaching the 70 mg/dL (3.9 mmol/L) threshold
- **Overall (or total) hypoglycemia:** this optional category combines all cases of hypoglycemia. If an event of hypoglycemia falls into multiple subcategories, the event is counted only once in this category
- **Probable symptomatic hypoglycemia:** an event during which symptoms of hypoglycemia are not accompanied by a PG measurement but that was presumably caused by PG ≤70 mg/dL (3.9 mmol/L).

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

10. INTERIM ANALYSES

No interim statistical analyses are planned.

Access to the data is scheduled to occur after every dosing session during Parts A and B of the study. The purpose of these reviews is to guide SAD and MAD escalation decisions; initiation of the MAD portion of the study; dose selections; and PK and PD sample collection schemes. The investigator will remain blinded and the Lilly sponsor team will be unblinded throughout the study.

For SAD and MAD escalation decisions, the review will include data collected through Day 5 for Part A or Day 15 for Part B for at least 5 subjects receiving LY3502970 in the preceding dose level. The investigator and sponsor will make the determination regarding dose escalation based

upon their review of the safety and tolerability data. Although not mandated, available PK and PD data may also be reviewed.

For the decision to initiate Part B (MAD), the review will include safety, tolerability, and available PK and PD data collected, at the earliest, up to Day 5 for Cohort C in Part A. Part B may be initiated if data from Part A indicates an approximately 10 to 20 mg/dL glucose-lowering effect at a tolerated dose.

11. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

12. 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.

13. DATA PRESENTATION

13.1 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. N 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.

13.2 Missing Data

Missing data will not be displayed in listings.

13.3 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the centre of the table, such as, “No serious adverse events occurred for this study.”

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