J2M-MC-GZKA Statistical Analysis Plan Final Version 2

A Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study of Single- and Multiple-Ascending Doses of LY3478045 in Healthy Subjects

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STATISTICAL ANALYSIS PLAN

A Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study of Single- and Multiple- Ascending Doses of LY3478045 in Healthy Subjects

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Clinical Phase I

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1. TABLE OF CONTENTS

2. ABBREVIATIONS

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

%AUC(t_{last}-∞)	Percentage of AUC that is due to extrapolation from the last measurable concentration to infinity
ADA	Anti-drug antibody
AE	Adverse event
A_e	Amount excreted in urine
AUC	Area under the concentration versus time curve
AUC(0-6)	Area under the concentration versus time curve from time zero to 6 h.
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 24 hours postdose
AUC(6-12)	Area under the concentration versus time curve from time 6 h to 12 h.
AUC(12-24)	Area under the concentration versus time curve from time 12 h to 24 h.
AUCτ	Area under the concentration versus time curve during one dosing interval
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
CL_R	Renal clearance
C_{max}	Maximum observed drug concentration
$C_{predose}$	Predose observed drug concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
ECG	Electrocardiogram
f_e	Percentage of dose excreted in urine
FTT	Fructose Tolerance Test

ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
MR(AUC)	Metabolite ratio based upon AUC(0-∞)
MR (C_{max})	Metabolite ratio based upon C_{max}
PD	Pharmacodynamic
PK	Pharmacokinetic
QTcF	QT interval corrected using Fridericia's formula
R_A(AUC)	Accumulation ratio based upon AUC(0-24)
R_A (C_{max})	Accumulation ratio based upon C_{max}
SAP	Statistical Analysis Plan
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
ULN	Upper limit of normal
V_{ss}/F	Apparent volume of distribution at steady state after extra-vascular administration
V_z/F	Apparent volume of distribution during the terminal phase after extra-vascular administration
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 15 January 2020), protocol amendment (a) (final version dated 04 March 2020), protocol amendment (b) (final version 09 December 2020), protocol amendment (c) (final version dated 11 August 2021), and SAP Version 1 (final version dated 29 April 2020).

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 analyses of data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Eli Lilly and Company. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon with Eli Lilly and Company and identified in the CSR. Any minor deviations from the TFLs may not be documented in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials[1] and the ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports[2].

4. STUDY OBJECTIVES

4.1 Primary Objective

To investigate the safety and tolerability of single and multiple oral doses of LY3478045 in healthy subjects.

4.2 Secondary Objective

To determine the PK of LY3478045 following single and multiple doses in healthy subjects.

4.3 Exploratory Objectives

- To determine the PD effects of LY3478045 following single and multiple doses in healthy subjects.
- To investigate the effect of LY3478045 on the PK of CCI following multiple doses in healthy subjects.

- CCI [redacted]

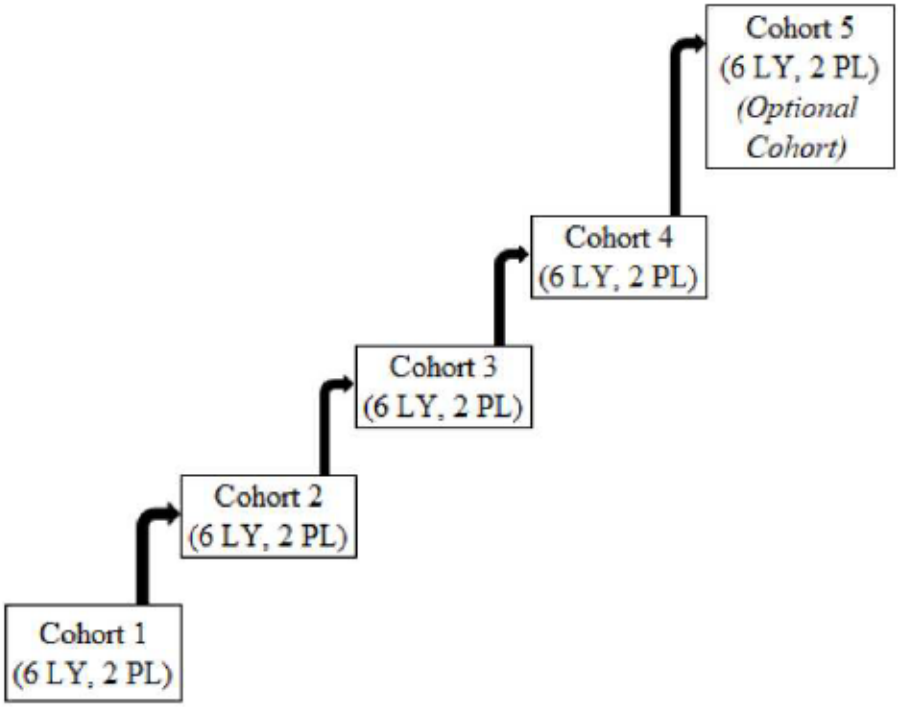
5. STUDY DESIGN

Study GZKA is a Phase 1, single site, randomized, double-blind, placebo-controlled, 2-part study of LY3478045 in healthy subjects.

5.1 Part A

Single-ascending oral doses of either LY3478045 or placebo will be administered in up to 5 cohorts. Each cohort will consist of 8 subjects. Cohort 5 is an optional cohort that may be assessed based on the available safety and PK data from the previous cohorts. In each cohort, 6 subjects will be randomized to receive LY3478045 and 2 subjects to receive placebo.

A sentinel dosing strategy will be utilized for Cohorts 3, 4, and 5. Two subjects (1 LY3478045 and 1 placebo) in each cohort will receive a sentinel dose on the same day. After at least 48 hours after dose, the remaining subjects in each cohort may be dosed based on the available safety data.



Abbreviations: LY = LY3478045; PL = placebo.

Figure GZKA.1 Illustration of study design for Part A

5.2 Part B

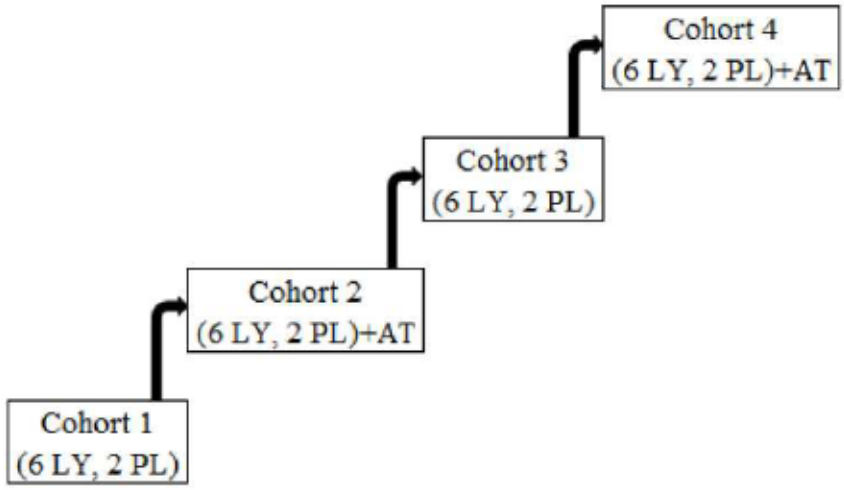
Part B will be initiated after assessing safety, tolerability, PK, and PD data through Cohort 3 in Part A.

Multiple-ascending oral doses of LY3478045 will be administered once daily (QD) for 14 days in up to 4 cohorts. Each cohort will consist of 8 subjects. In Cohorts 1 and 3, six subjects will receive LY3478045 and 2 subjects will receive placebo. In Cohorts 2 and 4, six subjects will receive LY3478045 co-administered with a single dose of CCI and 2 subjects will receive placebo with a single dose of CCI. The maximum dose in males and females will be determined based on the PK analyses from previous cohorts.

A sentinel dosing strategy will be utilized in Cohorts 3 and 4, for which the mean AUC(0-24) is predicted to exceed CCI µg·hr/mL. Two subjects (1 LY3478045 and 1 placebo) in the cohorts for which the mean AUC0-24 is predicted to exceed CCI µg·hr/mL will receive a sentinel dose on the same day. At least 48 hours after dose, the remaining subjects in each cohort may be dosed based on the available safety data.

Male subjects are allowed in Part B in the cohorts for which the predicted mean exposure AUC0-24 levels for the dose will not exceed CCI µg·hr/mL, 1/10th exposure level observed at CCI mg/kg in dogs, which is the lowest dose tested in dogs with no testicular findings, as determined from PK data in Parts A and B.

Female subjects are allowed in Part B in every cohort. The predicted mean exposure AUC0-24 levels for the doses investigated in Part B will not exceed CCI µg·hr/mL, 1/12th exposure level observed at CCI mg/kg in dogs, as determined from PK data in Parts A and B.



Abbreviations: AT = atorvastatin; LY = LY3478045; PL = placebo.

Figure GZKA.2 Illustration of study design for Part B

6. TREATMENTS

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

Part	Study Treatment	Treatment order in TFL

A	Placebo	1
	AA mg LY3478045	2
	BB mg LY3478045	3
	CC mg LY3478045	4
	DD mg LY3478045	5
	EE mg LY3478045	6
B	Placebo QD	1
	Placebo QD +CCI	2
	FF mg LY3478045 QD	3
	GG mg LY3478045 QD +CCI	4
	HH mg LY3478045 QD	5
	II mg LY3478045 QD +CCI	6

7. SAMPLE SIZE JUSTIFICATION

Up to 50 subjects may be enrolled in Part A to ensure that at least 40 subjects complete the study (depending on whether subjects will be enrolled in optional Cohort 5). Up to 40 subjects may be enrolled in Part B to ensure that at least 32 subjects complete the study.

The sample size for Parts A and B 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. Subjects who are randomized but not administered treatment, and who are discontinued from the study (providing that discontinuation was not as a result of a safety finding) may be replaced to ensure that enough subjects may complete the study.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all enrolled subjects, whether they completed all protocol requirements.

The "Pharmacokinetic" population will consist of all subjects who received at least one dose of study drug and have evaluable PK data. If a subject has an AE of vomiting that occurs before 2 times the median t_{max} after dosing, then that subject may be excluded from the PK summary statistics and statistical analysis.

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

All protocol deviations 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, 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.

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, body weight, height and body mass index will be summarized and listed. All other demographic variables will be listed only.

9.3 Pharmacokinetic Assessment

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

Pharmacokinetics of LY3470845

Following oral administration of LY3478045 (alone or with atorvastatin) in Part A and Part B, plasma concentrations of LY3478045 will be used to determine the following PK parameters where possible.

Parameter	Units	Definition
AUC(0-∞)	ng.h/mL	Area under the concentration versus time curve from time zero to infinity (Part A, Part B on Day 1 and 14 only)
AUC(0-t_{last})	ng.h/mL	Area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration (Part A, Part B on Day 1 only)
AUC(0-6)	ng.h/mL	Area under the concentration versus time curve from time zero to 6h postdose
AUC(0-24)	ng.h/mL	Area under the concentration versus time curve from time zero to 24h postdose
AUC(6-12)	ng.h/mL	Area under the concentration versus time curve from time 6h to 12h postdose
AUC(12-24)	ng.h/mL	Area under the concentration versus time curve from time 12h to 24h postdose
AUCτ	ng.h/mL	Area under the concentration versus time curve during the dosing interval (Part B only)
%AUC(t_{last}-∞)	%	Percentage of AUC that is due to extrapolation from the last measurable concentration to infinity (Part A, Part B on Day 1 only)
C_{max}	ng/mL	Maximum observed drug concentration
t_{max}	h	Time of maximum observed drug concentration
$t_{1/2}$	h	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
CL/F	L/h	Apparent total body clearance of drug calculated after extra-vascular administration
V_{ss}/F	L	Apparent volume of distribution at steady state after extra-vascular administration (Part A only)
V_z/F	L	Apparent volume of distribution during the terminal phase after extra-vascular administration
R_A(AUC)	NA	Accumulation ratio based upon AUC(0-24)

$$\text{RA(AUC)} = \frac{AUC(Day\ 14)}{AUC(Day\ 1)}$$

R_A (C_{max})	NA	Accumulation ratio based upon C_{max}

$$\text{RA (Cmax)} = \frac{C_{max}(Day\ 14)}{C_{max}(Day\ 1)}$$

NA: Not applicable

In addition, dose normalised parameters will be calculated for AUC(0-∞), AUC(0-t_{last}), AUC(0-24) and C_{max} by dividing the calculated parameter by the dose of LY3478045.

Following oral administration of LY3478045 in Part A, urine concentrations of LY3478045 will be used to determine the following PK parameters where possible.

Parameter	Units	Definition
A_e(t1-t2)	mg	Amount excreted in urine, by interval and cumulative
f_e(t1-t2)	%	Percentage of dose excreted in urine, by interval and cumulative
CL_R	L/h	Renal clearance $CL_R = \frac{Ae(0-\infty)}{AUC(0-\infty)}$

Pharmacokinetics of CCI [redacted]

Following oral administration of CCI [redacted] with either LY3478045 or placebo, plasma concentrations of CCI [redacted] will be used to determine the following PK parameters where possible.

Parameter	Units	Definition
AUC(0-∞)	ng.h/mL	Area under the concentration versus time curve from time zero to infinity
AUC(0-t_{last})	ng.h/mL	Area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
%AUC(t_{last}-∞)	%	Percentage of AUC that is due to extrapolation from the last measurable concentration to infinity
C_{max}	ng/mL	Maximum observed drug concentration
t_{max}	h	Time of maximum observed drug concentration
$t_{1/2}$	h	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
CL/F	L/h	Apparent total body clearance of drug calculated after extra-vascular administration (atorvastatin only)
V_{ss}/F	L	Apparent volume of distribution at steady state after extra-vascular administration (atorvastatin only)
V_z/F	L	Apparent volume of distribution during the terminal phase after extra-vascular administration (atorvastatin only)
MR(AUC)	NA	Metabolite ratio based upon AUC(0-∞) (metabolites only)
MR (Cmax)	NA	Metabolite ratio based upon C_{max} (metabolites only)

NA: Not applicable

Pharmacokinetics of Fructose for Pharmacodynamic Evaluation

Following administration of a fructose beverage the following parameter will be calculated.

Parameter	Units	Definition
AUC(0-6)	ng.h/mL	Area under the concentration versus time curve from time zero to 6h postdose
AUC(0-24)	ng.h/mL	Area under the concentration versus time curve from time zero to 24h postdose
AUC(6-12)	ng.h/mL	Area under the concentration versus time curve from time 6h to 12h postdose
AUC(12-24)	ng.h/mL	Area under the concentration versus time curve from time 12h to 24h postdose

Pharmacokinetics of CCI for Pharmacodynamic Evaluation

The following PK parameters will be calculated for for CCI

Parameter	Units	Definition
AUC(0-t_{last})	ng.h/mL	Area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
AUC(0-24)	ng.h/mL	Area under the concentration versus time curve from time zero to 24 hours postdose
C_{max}	ng/mL	Maximum observed drug concentration
$C_{predose}$	ng/mL	Predose observed drug concentration
t_{max}	h	Time of maximum observed drug concentration

Additional PK parameters may be calculated where appropriate.

The software and version used for the final analysis will be specified in the clinical study report. Any exceptions or special handling of data will be clearly documented within the final study report.

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

Interim plasma PK analysis will be performed by Lilly for the decision regarding dose escalation.

Urine PK analysis will be calculated using nominal sample collection times

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}.

- AUC(0-∞) values where the percentage of the total area extrapolated is more than 20% will be flagged. Any AUC(0-∞) value excluded from summary statistics will be noted in the footnote of the summary table. If AUC(0-∞) cannot be determined for all subjects an alternative AUC measure, such as AUC to a fixed time point, may be used in the assessment exposure between dose groups and metabolite ratios.

- 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 the last predicted quantifiable drug concentration (C_{last}) will be reported.

Individual PK Parameter Rules

- Only quantifiable concentrations will be used to calculate PK parameters with the exception of special handling of certain concentrations reported below the lower limit of quantitation (BQL). Plasma concentrations reported as BQL will be set to a value of zero when all of the following conditions are met:

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

Data within an Individual Profile

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

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

Data between Individual Profiles

1. If $n<6$, then the dataset is too small to conduct a reliable range test. Data will be analyzed with and without the atypical value, and both sets of results will be reported.
2. If $n\geq6$, 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.

9.3.1 Pharmacokinetic Statistical Methodology

All PK parameters will be summarized using descriptive statistics.

PK dose proportionality will be assessed separately for Parts A and B (on Day 14 for Part B). Log-transformed C_{max}, AUCτ (Part B only), and AUC(0-∞) of LY3478045 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. A subinterval within the highest and lowest doses may also be considered for assessment of dose proportionality using the same approach. The dose proportionality analysis for Part B will only be conducted if there are at least 3 different LY3478045 dose levels available for analysis.

Examples of the SAS code that will be used are as follows:

```
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;
```

In Part B, the PK parameters, AUCτ, AUC(0-∞), and C_{max}, will be log-transformed prior to analysis. A linear mixed effects model will be fitted to the data. The model will include Subject as a random effect, and Day as a fixed effect. For each PK parameter, the difference in least-square treatment means (Day 14 – Day 1) along with the 90% CIs will be back-transformed to produce the ratio of geometric means and the CIs comparing Day 14 to Day 1.

Example of SAS code as follows:

```
proc mixed data=xxx;
by treatment;
class day subject;
model log_pk = day /residual ddfm=kr;
random subject;
lsmeans day / cl pdiff alpha=0.1;
ods output lsmeans=lsm diffs=estims;
run;
```

To assess the effect that LY3478045 has on the primary CCI PK parameters, AUC(0-∞) and C_{max}, a linear fixed effect model on the parameters will be used. The response of the model will be the logged ratio of observations on Day 7 to Day-2. The model will include Treatment and the log of the baseline (Day -2) observation as fixed effects. For the Day 7 observations in Cohorts 2 and 4, the difference in least-square treatment means ([LY3478045 + CCI] –

[Placebo + CCI) along with the 90% CIs will be back-transformed to produce the ratio of geometric means and the CIs comparing (LY3478045 + CCI) to (Placebo + CCI).

Example of SAS code as follows:

```
proc mixed data=xxx;
class treatment baseline;
model log_ratioPK = treatment log_baseline /residual ddfm=kr;
lsmeans treatment / cl pdiff alpha=0.1;
ods output lsmeans=lsm diffs=estims;
run;
```

9.4 Pharmacodynamic Assessment

9.4.1 CCI

Plasma concentrations of CCI will be listed and summarized by part and treatment, using standard descriptive statistics. Parameters, including predose observed drug concentration ($C_{predose}$), C_{max}, t_{max}, AUC(0-t_{last}), and AUC(0-24), will be summarized using descriptive statistics.

In addition, a comparison between log-transformed $C_{predose}$ and C_{max} of CCI will be produced using a linear mixed effects model with treatment, concentration phase , and subject as a random effect, where the variable concentration phase will be a variable which indicates whether the concentration value is predose ($C_{predose}$) or postdose (C_{max}). 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 95% 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 Part A, the data will be those samples collected from the Day 1 timepoint. For the Part B analysis, an additional fixed effect for day will be added to the model so that comparisons can be performed for each day. For all cohorts in Part B, the data collected from the Day 1 and Day 7 samples will be used. This will be a repeated measures model with an unstructured covariance structure and a compound symmetric structure will be used if the model fails to converge.

Example SAS code for the analysis (Part A):

```
proc mixed data=xxx;
class trtmnt concphase subject;
model conc = trtmnt concphase / ddfm=kr;
random subject;
lsmeans trtmnt / pdiff cl alpha=0.05;
lsmeans concphase / pdiff cl alpha=0.05;
ods output lsmeans=lsmeans diffs=diffs;
```

```
run;
```

Example SAS code for the analysis (Part B):

```
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=0.05;
ods output lsmeans=lsm diffs=estims;
run;
```

Plasma concentrations of CCI [redacted] will also be plotted against dose. The plot will be produced separately by dose level and repeated to include all dose levels on one plot.

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

9.4.2 Biomarkers

Biomarkers including fasting insulin, adiponectin, low- and high-density lipoproteins, cholesterol, and triglycerides will be listed and summarized by Part, treatment and timepoint.

Untransformed absolute values as well as change from baseline in each parameter will be analyzed, separately for each Part, using a mixed-model repeated-measure model to evaluate treatment effects as well as treatment comparisons. The model will include treatment, timepoint and treatment-by-day interaction as fixed effects, subject as a random effect and baseline as a covariate (for the change from baseline analysis). 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 LY3478045 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 timepoint subject;
model result = treatment timepoint treatment*timepoint /residual ddfm=kr;
repeated timepoint / subject=subject type=UN;
lsmeans treatment*timepoint / 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.

9.4.3 Fructose Tolerance Test

Fructose Tolerance Test (FTT): Three meals (breakfast, lunch, and dinner) will be served at approximately 20 minutes, 6 hours, and 12 hours after dose with low fructose content. A beverage containing mixture of fructose CCI [redacted] CCI [redacted] in approximately 300 to 500 mL of non-caloric solution) will be served with each of the

3 meals on Day 1 in Part A, and Days 1 and 14 in Part B. AUC(0-24), AUC(0-6), AUC(6-12), and AUC(12-24) for FTT will be calculated using trapezoid methods.

In Part A, the AUC(0-24), AUC(0-6), AUC(6-12), and AUC(12-24) from the FTT will be log-transformed prior to analysis. A linear fixed effects model will be fitted to the fructose data. The model will include Treatment as a fixed effect. The difference in least-square treatment means (LY3478045– Placebo) along with the 90% CIs will be back-transformed to produce the ratio of geometric means and the CIs comparing LY3478045 to Placebo.

Example of SAS code as follows:

```
proc mixed data=xxx;
class treatment;
model log_AUC = treatment /residual ddfm=kr;
lsmeans treatment / cl pdiff alpha=0.1;
ods output lsmeans=lsm diffs=estims;
run;
```

In Part B, the AUC(0-24), AUC(0-6), AUC(6-12), and AUC(12-24) from the FTT will be log-transformed prior to analysis. A linear mixed effects model will be fitted to the data. The model will include treatment, day and the interaction between treatment and day as fixed effects and subject as a random effect. The difference in least-square treatment means (LY3478045- Placebo) along with the 90% CIs will be back-transformed to produce the ratio of geometric means and the CIs comparing LY3478045 to Placebo. Similar comparisons will be calculated between Day 14 and Day 1 for LY3478045.

Example of SAS code as follows:

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

9.5 Pharmacokinetic/Pharmacodynamic Assessment

PK/PD modelling may be employed to characterize the exposure-response relationships between LY3478045 concentrations and various PD endpoints, provided enough data are available.

9.6 Safety and Tolerability Assessments

9.6.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the adverse event (AE) will be reported in the listings, only the most severe will be used in the

summary tables. A pre-existing condition is defined as 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 22.1 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 by the investigator. Any serious AEs will be listed.

Discontinuations due to AEs will be listed.

9.6.2 Concomitant medication

Concomitant medication will be coded using the World Health Organization (WHO) drug dictionary (Version March 2019). Concomitant medication will be listed.

9.6.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by parameter and treatment group together with changes from baseline, where baseline is defined as the Day 1 predose assessment, and listed. Urinalysis data will be listed. Additionally, clinical chemistry, hematology and urinalysis data outside the reference ranges will be listed and flagged on individual subject data listings.

9.6.4 Vital signs

Vital signs data will be summarized by Part and treatment group 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.

Values for individual subjects will be listed.

9.6.5 Electrocardiogram (ECG)

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

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

The mean of triplicate data will be used for reporting. The ECG data will be summarized by Part and treatment group together with changes from baseline, where baseline is defined as the mean of the triplicate Day 1 predose assessments (-1.5, -1 and 0.5 hours). 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 treatment according to the following categories: >30 ms and >60 ms. In addition, the frequency of subjects QTcF postdose values, according to the following categories: >450 ms, >480 ms and >500 ms, will be summarized by Part and treatment.

Plasma PK Concentration versus delta and double delta ECG parameter analysis

A plasma LY3478045 concentration-ECG parameter analysis will be performed to assess the relationship between changes from baseline (mean of Day 1 predose triplicate assessments) in ECG parameters (QTc, PR, and RR intervals, QRS duration, and heart rate) and plasma LY3478045 concentrations across all treatments. The change from baseline adjustment will be based on individual subject's Day 1 predose value. Further details on how these will be calculated:

- Calculate the baseline ECG value for each subject, which is the mean of ECG parameter values of each individual subject over 3 predose time points at day 1.
- Calculate the change from baseline at each timepoint for each individual subject.

The relationship between LY3478045 concentrations and ECG parameters will be explored graphically by plotting delta ECG parameter values against LY3478045 concentrations, including all post dosing timepoints.

A mixed effects analysis model will be employed with change from baseline in ECG parameter as the dependent variable, LY3478045 concentration and baseline ECG parameter value as continuous covariates, treatment and time as categorical factors, and a random intercept and slope per subject. Treatment will be fitted as a binary variable (Placebo, or LY3478045). The model will have the form

$$\Delta ECG_{ijk} = (\theta_0 + \eta_{0,i}) + \theta_1 TRT_j + (\theta_2 + \eta_{2,i}) C_{ijk} + \theta_3 TIME_j + \theta_4 (ECG_{i,j=0} - \overline{ECG_0}) + \varepsilon_{ijk},$$

where ΔECG_{ijk} is the change from baseline in ECG parameter for subject i in treatment j at time k, θ_0 is the population mean intercept in the absence of treatment effect, $\eta_{0,i}$ is the random effect associated with the intercept term θ_0, θ_1 is the fixed effect categorical variable associated with treatment TRT_j , θ_2 is the population mean slope of the assumed linear association between concentration and ΔECG_{ijk}, $\eta_{2,i}$ is the random effect associated with the slope θ_2, C_{ijk} is the concentration for subject i in treatment j and time k, θ_3 is the fixed effect associated with time, θ_4 is the fixed effect associated with baseline $ECG_{i,j=0}$, $\overline{ECG_0}$ is the overall mean of $ECG_{i,j0}$ (the mean of all the baseline ECG parameter values, at time 0), and ε_{ijk} is the residual error. It will be assumed the random effects are multivariate Gaussian distributed with mean vector 0 and an unstructured covariance matrix G, whereas the residuals, ε_{ijk}, are Gaussian distributed with mean 0 and variance r.

The predicted mean change from baseline and placebo-corrected change from baseline in ECG parameter (ΔECG and ΔΔECG respectively) at the observed geometric mean C_{max} of each treatment (slope estimate * C_{max} + treatment effect) and two-sided 90% CI at different dose levels will be calculated. Residual plots will be produced to assess the adequacy of the model.

Example of SAS code as follows:

```
proc mixed data=xxx;
by param;
class treat time subject;
model ΔECG = treat time baseline_ECG PKconc / solution cl alpha=0.1 ddfm=kr;
random intercept PKconc / type=un subject=subject;
estimate 'XX mg LY3478045' intercept 1 treat 0 1 PKconc [cmax XXmg] / CL
alpha=0.1;
estimate 'YY mg LY3478045' intercept 1 treat 0 1 PKconc [cmax YYmg] / CL
alpha=0.1;
ods output solutionF=sol;
ods output estimates=estim;
run;
```

Similar code will be used for the analysis of ΔΔECG.

9.6.6 Immunogenicity Assessments

The frequency and percentage of subjects with pre-existing antidrug antibody (ADA) and with treatment-emergent ADAs (TE ADA) to LY3478045 may be tabulated and listed if available.

For subjects who are ADA negative at baseline, TE ADAs are defined as those with a signal increase, greater than assay variability, compared to baseline. The frequency of cross-reactive binding to native GIP, GLP-1 or neutralizing antibodies may also be tabulated in TE ADA+ participants, when available.

9.6.7 Body Weight

Body weight data will be listed. In Part B, it will also be summarized by treatment group, together with changes from baseline (Day -1 [Cohorts 1 and 3], Day -3 [Cohorts 2 and 4]).

9.6.8 Hepatic Monitoring

If a subject experiences elevated alanine aminotransferase ≥3× upper limit of normal (ULN), alkaline phosphatase ≥2× ULN, or elevated total bilirubin ≥2× ULN, liver tests will be performed to confirm the abnormality. Additional safety data may be collected if required, as defined in the protocol. Where applicable, the following will be presented.

The subjects' liver disease history and associated person liver disease history data will be listed. Any concomitant medications that have potential for hepatotoxicity, including acetaminophen will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography scan, and biopsy assessments will be listed, if performed.

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

9.6.9 Testicular Safety assessment

Observations of total testosterone, follicle-stimulating hormone, and luteinizing hormone will be listed. Values outside the reference range will be flagged in Cohorts 1 and 2 for Part B on the individual subject data listings.

9.6.10 Other assessments

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

10. INTERIM ANALYSES

No interim analyses are planned for this study except the interim access to safety, tolerability, and other PK/PD data to guide dose selection for the next dosing.

If an unplanned interim analysis is deemed necessary, the Lilly clinical pharmacologist, clinical research physician/investigator, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

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 center of the table, such as, “No serious adverse events occurred for this study.”

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