Statistical Analysis Plan I8Q-MC-GSEA

A Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Oral Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LY3202328

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ABBREVIATIONS/DEFINITIONS

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ApoB	apolipoprotein
AST	alanine aminotransferase
AUC	area under the curve
BMI	body mass index
bpm	beats per minute
CI	confidence interval
Cmax	maximum concentration
CRP	clinical research physician
CRU	clinical research unit
CSR	clinical study report
DDI	drug-drug interaction
DGAT2	Diacylglycerol acyltransferase 2
ECG	Electrocardiogram
eCRF	electronic case report form
FFA	free fatty acid
HDL-c	high-density lipoprotein cholesterol
LDL-c	low-density lipoprotein cholesterol
Lp(a)	lipoprotein (a)
LY	LY3202328
MAD	multiple ascending dose
MedDRA™	Medical Dictionary for Regulatory Activities
mmHg	millimeters of mercury
MMRM	Mixed-effects model repeated measures
non-HDL-c	total cholesterol – high-density lipoprotein cholesterol
PCSK9	proprotein convertase subtilisin/kexin type 9

Abbreviation	Definition
PD	pharmacodynamic
PK	pharmacokinetic
PT	preferred term
QD	quaque die (once a day)
QTc_f	Fridericia corrected QT interval
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical analysis plan
SDTM	Study Data Tabulation Model
SOC	system organ class
TEAE	treatment emergent adverse event
TC	total cholesterol
TG	triglycerides
WHODD	World Health Organization Drug Dictionary

1 INTRODUCTION AND OBJECTIVES

1.1 Introduction

The purpose of this statistical analysis plan (SAP) is to describe the analysis variables and statistical procedures that will be used to analyze and report the results from a Phase 1 study evaluating the safety and pharmacodynamics of LY3202328 (LY), a diacylglycerol acyltransferase 2 (DGAT2) inhibitor, in overweight, healthy subjects (Part A) and in dyslipidemic, statin-free, overweight, healthy subjects (Part B). This SAP addresses only the planned analyses based on amended Protocol I8Q-MC-GSEA(a) that was approved on 22 JUN 2016.

Changes to the protocol that impact the design, the data collected, or the statistical methods and that occur after the finalization of this SAP may require amendment of the approved SAP. Similarly, changes to the planned analysis variables and/or statistical methods described in the approved SAP may also require amendment of the SAP.

The formats for the tables, listings, and figures described in this SAP are provided in a companion documents. Changes to the formats of these reports that are decided after the finalization of the SAP will not require an amendment. In addition, any additional supportive or exploratory analyses requested after SAP approval will not require amendment of the SAP. These additional analyses will be described in the clinical study report (CSR).

Please see the study protocol for details about the study design, procedures, and schedule of assessments and see the electronic case report form (eCRF) for details about variables collected and their possible values.

1.2 Study Objectives

1.2.1 Primary Objective

The primary objective of this study is to explore safety and tolerability of single and multiple doses of LY in statin-free, overweight, healthy subjects.

1.2.2 Secondary Objectives

The secondary objectives of this study are:

- To assess the pharmacokinetic (PK) characteristics of LY in statin-free, overweight, healthy subjects after single and multiple doses.
- To evaluate the effect of food on the extent and rate of LY absorption.
- To determine the effects of LY upon multiple dose administration on:
  - Fasting lipid profiles
  - Simvastatin and atorvastatin exposure

1.2.3 Exploratory Objectives

The exploratory objective of this study is to explore the effects of LY on:

- Post-prandial lipid profiles.
- Fasting free fatty acids and β-hydroxybutyrate.
- Fasting apolipoprotein (Apo) B100, ApoC3, proprotein convertase subtilisin/kexin type 9 (PCSK9), lipoprotein (Lp [a]), and insulin.
- Body weight.

1.3 Study Design with Sample Size Justification

Study I8Q-MC-GSEA(a) (GSEA) is a first-in-man, Phase 1, randomized, double-blind, placebo-controlled, 2-part, ascending single- and multiple-oral dose study of LY in overweight, healthy subjects (Part A) and in dyslipidemic, statin-free, overweight, healthy subjects with a statin drug-drug interaction (DDI) assessments (Part B).

This study will be conducted in 2 parts: Part A, a single ascending dose (SAD) study design at a single site and Part B, a multiple ascending dose (MAD) study design conducted in multiple sites.

Eighteen statin-free, overweight, healthy males and female subjects may be enrolled in one of two 9-subject cohorts in Part A. Each subject is scheduled to receive 2 single doses of LY and 1 dose of placebo in ascending dose levels. This sample size is customary for Phase 1 studies evaluating safety, tolerability, and pharmacokinetic parameters, and is not powered on the basis of statistical hypothesis testing.

Forty statin-free, overweight, dyslipidemic subjects may be enrolled in Part B. Subjects will be enrolled in one of four dose-ascending 10-subject cohorts (8 subjects will receive LY and 2 subjects will receive placebo in each cohort). This sample size is a customary sample size for a Phase 1b MAD study evaluating safety, tolerability, and pharmacokinetic parameters.

2 General Statistical Methodology and Conventions

Chorus will designate a provider to generate the statistical analyses detailed in this SAP. All computations for statistical analyses will be performed using SAS® software, Version 9.3 or later. All SAS programs used in the production of statistical summary outputs will be validated with independent programming prior to finalization. In addition, all program outputs will be independently reviewed. The validation process will be used to confirm that all data manipulations and calculations were accurately done. Once validation is complete, a senior statistical reviewer will perform a final review of the documents to ensure the accuracy and consistency with this plan and consistency within tables. Upon completion of validation and quality review procedures, all documentation will be collected and filed by the project statistician or designee.

For the implementation of parametric methods of analysis, residual plots will be examined to determine if model assumptions are satisfied. Transformations or nonparametric methods of

analysis may be used if warranted. In some cases, nonparametric analysis may be the initially proposed method due to the expected distribution of response. Whenever alternative methods of analysis are required, the description of the new method along with the rationale for its use will be documented in the CSR.

The eCRF data for all subjects will be provided in Standard Data Tabulation Model (SDTM) datasets, and the production of the tables, figures and listings for the study will be generated from the SDTM datasets. Data listings supplied as part of the CSR will be sorted by investigative site and subject identification number, and subjects will be identified in the listings by the investigator number concatenated with the subject number.

2.1 Randomization Schedule and Unblinding Plan

Both Parts A and B are double-blinded so the subjects, investigator, and study site personnel will be blinded to treatment assignment – LY or Placebo. Simvastatin and atorvastin dosing in Part B will also be determined by random assignment, but the subjects, investigators, and study site personnel will be unblinded to the statin assignment since commercially available product will be used. PRA Health Sciences International will be responsible for generating the schedules for both parts of the study.

In Part A, the subjects in each of the 9-patient cohorts -- Cohort 1 (1mg, 10mg, 100mg) and Cohort 2 (3mg, 30mg, 300mg) – will be randomized in a 1:1:1 ratio to one of the treatment sequences (Placebo, LY, LY), (LY, Placebo, LY), or (LY, LY, Placebo). The 30 mg dose level treatment assignments for Cohort 2 will be repeated in Period 4 to evaluate food effects on exposure. One of the period's treatment assignments for Cohort 1 will be repeated in Period 4 to evaluate the 600 mg dose level, so a couple subjects in Cohort 1 may receive Placebo twice.

In Part B, the subjects in each of four planned 10-patient cohorts -- Cohort 3 (5mg QD), Cohort 4 (20mg QD), Cohort 5 (100mg QD), and Cohort 6 (300mg QD) -- will be randomized to receive LY with simvastatin assessment (4 subjects), LY with atorvastatin assessment (4 subjects), placebo with simvastatin assessment (1 subject), or placebo with atorvastatin assessment (1 subject).

PRA Health Sciences will provide emergency codes to the investigator and pharmacy. A code, which reveals the treatment for a specific study subject, may be opened during the study only if the subject's well-being requires knowledge of the subject's treatment assignment. The investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted for medical management of an event. However, if the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Chorus clinical research physician (CRP) prior to unblinding a study subject's treatment assignment unless this could delay emergency treatment of the subject. If a study subject's treatment assignment is unblinded for the investigator, Chorus must be notified immediately and the subject must be discontinued from the study, unless the investigator obtains specific approval from a Chorus CRP for the study participant to continue in the study. All cases of emergency unblinding, including who and why, will be documented in the CSR

To preserve the blinding of the study, only a minimum number of Chorus personnel will have access to the actual treatment assignments for a cohort before the dosing is completed for all patients in the cohort. The Chorus personnel with access to unblinded treatment information prior to the completion of dosing for a cohort will be limited to the Clinical Trial Supply Planner and potentially personnel monitoring ongoing safety of subjects in the study. All Chorus personnel can be unblinded to the actual treatment assignments for a cohort once dosing has been completed for the cohort. However, the blind for investigators, subjects and study personnel with direct contact with the sites will remain until the completion of the study.

After the last subject completes the study and all data management data activities have been completed – data entered, coding completed, and all queries resolved – the Chorus Asset Manager or designee will approve PRA Health Sciences to release the randomization schedule to the reporting team.

Upon completion of the study, all codes must be returned to Chorus or its designee.

2.2 Analysis Populations and Treatment Groups

The study population will consist of 18 statin-free, overweight, healthy male and female subjects in Part A and 40 statin-free, overweight, healthy male and female subjects with dyslipidemia in Part B, aged 18 to 70 years old inclusive for males, or 40 to 70 years old, inclusive for females. The number of subjects in the study population may increase if replacement subjects are treated in the study.

2.2.1 Analysis Populations

Two analysis populations will be used in this study:

- Safety data and baseline information will be analyzed using the **Safety Population**. The Safety Population is defined as all randomized subjects who received at least one dose of study treatment.
- Pharmacodynamics (PD) data will be analyzed using the **PD Population**. The PD Population is defined as all subjects who received at least one dose of LY and have both a baseline and post-baseline assessment of at least one PD parameter.

2.2.2 Treatment Groups

During Part A, subjects will be treated in multiple dosing periods with single doses of a subset of the treatments -- Placebo, and 1mg, 3mg, 10mg, 30mg, 100mg, 300mg, or 600mg of LY. Dosing will be performed in a fasted state, except in the fourth dosing period for Cohort 2 when subjects will be dosed with 30mg LY after a standard meal. The treatment groups for Part A will be the dose levels of LY, plus the group 30mg LY fed.

During Part B, subjects will be enrolled in one of four dose-ascending groups (5mg LY, 20mg LY, 100mg LY, and 300mg LY) where they will be randomized to receive LY or placebo. The treatment groups for Part B will be Placebo, 5mg LY, 20mg LY, 100mg LY, and 300mg LY.

2.3 Handling of Dropouts and Missing Data

Summaries are primarily based on the Safety population, and safety data will be reported for all available subjects. In situations where Subjects in Part A discontinue early from the study, replacement subjects may be included for subsequent dosing periods.

Analyses of the PD endpoints will be performed using mixed-effects model repeated measures (MMRM). This methodology mitigates the impact of missing data, which will be assumed to be missing at random during the study.

Imputation of missing or partial dates is not expected, but if a complete date is required for calculations, the following algorithms will be applied:

- For the start date:
  - If year, month, and day are missing then use the minimum of the subject's first visit date or the consent date.
  - If either only month or month and day are missing then use January 1.
  - If only day is missing, impute the first day of the month.
- For the end date:
  - If year, month, and day are missing then use the subject's last visit date.
  - If either only month or month and day are missing then use December 31.
  - If only day is missing then use the last day of the month.
  - Do not expand the record past the subject's last visit.

The original missing or partial date, the imputed complete date, and the indicator variable identifying dates that were imputed will be retained in the database.

2.4 Adjustment for Multiple Centers

Part A will be conducted in a single study center.

Part B will be conducted in multiple study centers, but PRA will centrally manage the randomization. No adjustment of multiple study centers will be incorporated into the statistical analyses for this study. This is common for early phase studies with limited enrollment.

2.5 Interim Analysis and Adjustment for Multiplicity

Not applicable.

2.6 Coding of Concomitant Medications and Adverse Events

Adverse events (AEs) will be coded using version 19.0 of the Medical Dictionary for Regulatory Activities (MedDRA™), and concomitant medications will be coded using the Mar-2016 version of the World Health Organization Drug Dictionary. The version of the dictionary used for reporting will be provided in the CSR.

2.7 Definition of Study Time Points

Study day is explicitly defined in the study protocol.

2.8 Reporting Conventions

This section details the general conventions to be used for the statistical analyses. Departures from these general conventions will be provided in the specific detailed sections of this analysis plan. The following conventions will be applied to all data presentations and analyses:

- Continuous variables will generally be summarized by the number of subjects, mean, standard deviation, median, minimum, and maximum.
- Categorical variables will be summarized by the number and percentage of subjects within each category.
- All mean and median values will be formatted to one more decimal place than the measured value.
- Standard deviation values will be formatted to two more decimal places than the measured value.
- Minimum and maximum values will be presented with the same number of decimal places as the measured value.
- The number and percent of responses will be presented in the form XX (XX %), where the percentage is in parentheses. Percentages will be rounded to the nearest percent. In the case of a frequency of zero, the frequency and percentage will be presented as 0 rather than 0 (0%).
- All summary tables will include the analysis population sample size (i.e., number of subjects) in each treatment group.
- Date variables will be formatted as ddMMMYY for presentation.

3 Subject Accounting and Disposition

3.1 Subject Accounting

The number of subjects in the Safety and PD populations will be presented by treatment group. For each treatment group the date of the first subject visit and the last subject visit will also be provided. These dates and subject totals will also be summarized by study site for Part B. In addition, the total number of subjects randomized and the number of subjects added as replacements will be presented by cohort for Part A

A list of protocol violations that could potentially impact the analysis of the study will be determined during the conduct of the study by study team members who are blinded to study treatment being received. The number and percentage of subjects with each violation will be tabulated overall and by randomized treatment assignment for Part B.

3.2 Study Disposition

The disposition of all randomized subjects will be presented. The number of subjects in the Safety Population will be presented overall and by treatment group. In addition, the reason for study discontinuation will be tabulated for the overall population and by treatment group using the list of reasons provided in the eCRF.

For Part A the disposition of all subjects in the Safety Population will be presented. Since subjects receive multiple treatments during the course of the study, the number (percent) of subjects who complete a treatment period will be presented. The number (percent) of subjects who discontinue from the study will be tabulated according to the most recently received treatment. The reason for study discontinuation will also be tabulated using the list of reasons provided in the eCRF. Denominators for all percentages in the table will be the number of subjects in the Safety Population who received the given treatment.

For Part B the disposition of all randomized subjects will be presented. Randomization of subjects for Part B occurs early, on Day -7, so that subjects can be allocated evenly to treatment with simvastatin or atorvastatin for the DDI component of the study. The number of subjects randomized, the number of subjects randomized but not treated with LY or placebo, and the number of subjects added as replacements will be summarized by treatment assignment and overall for each statin and the combined statin assignment. The reason for discontinuation for subjects who were randomized but not treated with LY or placebo will only be presented in data listings.

The number (percent) of subjects who complete Part B of the study, and the number (percent) of subject who discontinue, along with the reason for discontinuation, will be summarized by treatment group and overall. Denominators for all percentages in the table will be the number of subjects in the Safety Population.

4 Baseline Characteristics

Demographic data, baseline anthropometric measurements, and fasting lipids will be summarized at the subject level using descriptive statistics for the overall study population and by treatment group for both Parts A and B. These summaries will be based on the Safety population. Subjects who are missing measurements of the baseline variable being analyzed will not be included in the summary for that variable.

4.1 Demographics

Demographic variables collected prior to randomization include date of birth, sex, race, and Hispanic ethnicity. Age at study entry, age group, sex, and race will be summarized and reported. Age at study entry will be based on the age of the subject on the date the informed consent is signed. Age group will be defined using the median age group for the Safety population (Age <= Median age; Age > Median age). Subject race will be reported using the categories provided in the eCRF (i.e., American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, and White). The responses for Hispanic ethnicity are Hispanic or Latino and Non-Hispanic or Latino.

4.2 Baseline Anthropometrics

Subject height and weight will be collected prior to randomization for both Parts A and B. Both variables will be reported in metric units (height in cm and weight in kg) and will be summarized as continuous variables along with Body Mass Index (BMI; in kg/m^2). Body mass index will also be analyzed categorically using the categories overweight ($25 \leq BMI < 30\ kg/m^2$) and Class 1 Obese ($30 \leq BMI < 35\ kg/m^2$) that are provided by United States Center for Disease Control (http://www.cdc.gov/obesity/adult/defining.html).

In Part B the additional anthropometric variables waist, hip, and neck circumference (all in cm) will be collected on Day -1 of the study. These variables will also be summarized as continuous variables for each of the treatment groups and overall.

4.3 Baseline Lipids

For enrollment in Part B subjects are required to have screening triglyceride (TG) levels between 150 and 499 mg/dL, inclusive, and screening low-density lipoprotein cholesterol (LDL-c) levels between 100 and 200 mg/dL, inclusive. These lipids levels are allowed for enrollment in Part A but they are not required. During the Part B screening visit, fasting measurements of TG, total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-c) will be obtained from plasma samples. LDL-c and non-HDL-c will then be derived as follows:

$$\text{LDL-c} = \text{TC} - (\text{TG}/5 + \text{HDL-c}), \text{ and}$$

$$\text{non-HDL-c} = \text{TC} - \text{LDL-c}.$$

Descriptive statistics for these five lipid parameters for subjects enrolled in Part B will be provided for each of the treatment groups and overall.

5 Concomitant Medications

Concomitant medications will be defined as medications, other than simvastatin and atorvastatin, taken on or after the date of first dose of randomly assigned study treatment (LY or placebo). This includes all medications initially taken prior to the date of first dose of randomly assigned study medication but with a stop date that is either missing or after the date of first dose of randomly assigned study medication. Those medications where the stop date is documented as prior to the date of first dose of randomly assigned study medication will be classified as prior medications. The prior medications will not be included in any summary reports.

The number (percent) of subjects who receive each concomitant medication, based on the WHODD preferred drug name, will be tabulated for Part B, but it is not planned to summarize in table format the concomitant medication usage for Part A of the study. However, by-subject listings of all concomitant medications that includes WHODD preferred drug name will be prepared separately for Parts A and B.

6 Pharmacodynamics Analyses

Pharmacodynamics (PD) analyses for this study will be based on fasting and post-prandial lipid profiles, fasting free fatty acids (FFA), β-hydroxybutyrate, apolipoprotein (Apo) B100, ApoC3,

proprotein convertase subtilisin/kexin type 9 (PCSK9), lipoprotein (a) [Lp(a)] and insulin, and body weight. All of these assessments will be collected longitudinally during the study.

All PD analyses will be performed using the PD population. Presentations of PD analyses will include the number of subjects with data at each time point plus related statistics derived from the analysis. Subjects who received Placebo during more than 1 dosing period in Part A will have their data from different dosing periods reported separately. The following sections contain the planned analyses. If plots of the raw data or residuals suggest alternative analysis techniques, such as log-transformation or nonparametric methods, then additional analyses will also be performed. The rationale for and results of the alternatives techniques will be described in the CSR.

6.1 Fasting Lipid Profile Analyses

6.1.1 Fasting Lipid Profile Analyses in Part A

A fasting lipid profile will be collected from all subjects in each dosing period in Part A, except for dosing period 4 for Cohort 2 which prescribes dosing subjects in a fed state. Fasting measurements of TG, TC, and HDL-c will be obtained and fasting measurements of LDL-c and non-HDL-c will be derived from plasma samples collected just prior to dosing on the day of dosing, then at 24, 48 and 96 hours after dosing.

A last observation measurement will be derived for each subject using the last post-dose measurement of a lipid parameter. Change from baseline for each of the lipid parameters will be derived for each of the post-dosing time points (Day 1 [24 hours], Day 2 [48 hours], and Day 4 [96 hours]) and the last observation using the pre-dose measurement from the day of dosing as the baseline.

Descriptive statistics for the measurement at baseline and the measurement and change from baseline at each post-dose time point plus the last observation will be tabulated.

A mixed-effect repeated measures (MMRM) analyses will be conducted for each lipid parameter using the change from baseline values from Days 1, 2, and 4. The MMRM model for change from baseline will contain fixed effects for treatment, time, and their interaction, a random effect for subject, and the baseline measurement as a covariate. The covariance structure among the repeated measurements for a subject will be assumed to be common across subjects and modeled using an unstructured 3x3 matrix. Satterthwaite's approximation will be used to estimate denominator degrees of freedom. Any missing assessments will be assumed to be missing at random, so estimates of treatment effects from the model will be assumed to be unbiased. These analyses will be performed using the SAS procedure PROC MIXED. The tabular output for these MMRM analyses will present the least squares means, standard errors and 95% confidence intervals and Type 3 p-values for each main effect marginal. Pairwise contrasts of the least squares means between the LY dose levels and placebo along with the associated 95% confidence interval and Type 3 p-values will also be provided at each time point using LSMESTIMATE statements.

Plots of the least squares mean ± standard error estimates for each lipid parameter over time (pre-dose through Day 4 post-dose) will be provided by treatment group.

A last observation analysis will be performed for change from baseline using an analysis of covariance (ANCOVA) model with a fixed effect for treatment a random effect for subject and the baseline value as a covariate. Tabular output for these ANCOVA analyses will present the least squares means, standard errors and 90% confidence intervals and Type 3 p-values for each main effect marginal. Pairwise contrasts of the least squares means between each LY dose level and placebo along with the associated 95% confidence interval and Type 3 p-values will also be provided.

6.1.2 Fasting Lipid Profile Analyses in Part B

Fasting lipid profiles will be collected from all subjects in Part B just prior to dosing on the day of dosing, Day 7, Day 14, Day 21, and Day 28, and 7 (Day 35) days after stopping dosing of the randomized treatment. An additional follow-up assessment will be collected 14 (Day42) or 28 (Day 56) days after stopping dosing of the randomized treatment for Cohort 3 (5mg QD) and Cohorts 4 through 6, respectively.

A last on-treatment observation measurement will be derived for each subject using the last post-dose measurement for a lipid parameter taken while the subject is taking study medication during the 28-day treatment period. Change from baseline for each of the lipid parameters will be derived for each of the post-dosing time points (Days 7, 14, 21, 28, 35, and 42 or 56) and the last on-treatment observation using the pre-dose measurement from the first day of dosing as the baseline.

Descriptive statistics for the measurement at baseline and the measurement and change from baseline at each post-baseline time point plus the last observation will be tabulated.

An MMRM analysis will be conducted for each lipid parameter using the change from baseline values from Days 7, 14, 21, 28, 35, and 42. The MMRM model for change from baseline will contain fixed effects for treatment, time, and their interaction, a random effect for subject, and the baseline measurement as a covariate. Since the time points are evenly spaced the covariance structure among the repeated measurements for a subject will be assumed to be common across subjects and modeled using a autoregressive(1) 7x7 matrix. Satterthwaite's approximation will be used to estimate denominator degrees of freedom. Any missing assessments will be assumed to be missing at random, so estimates of treatment effects from the model will be unbiased. These analyses will be performed using the SAS procedure PROC MIXED. The tabular output for these MMRM analyses will present the least squares means, standard errors and 95% confidence intervals and Type 3 p-values for each main effect marginal. Pairwise contrasts of the least squares means between the LY dose levels and placebo along with the associated 95% confidence interval and Type 3 p-values will also be provided at each time point using LSMESTIMATE statements.

Plots of the least squares mean ± standard error estimates for each lipid parameter over time (baseline through Day 56) will be provided by treatment group.

A last on-treatment observation analysis will be performed for change from baseline using an analysis of covariance (ANCOVA) model with a fixed effect for treatment a random effect for subject and the baseline value as a covariate. Tabular output for these ANCOVA analyses will present the least squares means, standard errors and 95% confidence intervals and Type 3 p-values for each main effect marginal. Pairwise contrasts of the least squares means between each

LY dose level and placebo along with the associated 95% confidence interval and Type 3 p-values will also be provided.

6.2 Post-prandial Lipid Profile Analyses

6.2.1 Post-prandial Lipid Profile Analyses in Part A

Measurement of the lipids TC, TG, HDL-c, LDL-c, and non-HDL-c will be obtained just prior to the midday meal on the day of dosing and again at 0.5, 1, 2, and 4 hours post-meal for all subjects in each dosing period in Part A.

Change from baseline for each of the lipid parameters will be derived for each of the post-meal time points using the pre-meal measurement as the baseline, and the level of excursion within the 4-hour post-meal period will be determined using a post-meal area under the curve (AUC). The areas of the trapezoidal region for change from baseline between successive planned collection time points will be calculated, and these areas will be summed to obtain the AUC value.

Descriptive statistics for the post-meal AUC will be tabulated by treatment group.

An ANOVA will be conducted for each lipid parameter using post-meal AUC values. The ANOVA model will have a fixed effect for treatment and a random effect for subject. Subjects treated with Placebo for the second time during the fourth dosing period will be handled as 'new' subjects in the analysis.

Boxplots of the lipid values at pre-meal and each planned post-meal time point (0.5, 1, 2, and 4 hours post-meal) will be presented for each treatment group.

6.2.2 Post-prandial Lipid Profile Analyses in Part B

Measurement of the lipids TC, TG, HDL-c, LDL-c, and non-HDL-c will be obtained just prior to the midday meal on Days -1 and 28 of dosing. Post-meal measurements will be collected on both days at 0.5, 1, 2, and 4 hours after the meal for all subjects in Part B.

Change from baseline for each of the lipid parameters will be derived for each of the post-meal time points using the pre-meal measurement as the baseline, and the level of excursion within the 4-hour post-meal period will be determined using the post-meal AUC, as described in Section 6.2.1.

Descriptive statistics for the post-meal AUC at Days -1 and 28 as well as the difference between Days -1 and 28 will be presented by treatment group.

An ANCOVA will be conducted for each lipid parameter using the difference in post-meal AUC values from Day -1 to Day 28. The ANCOVA model will have a fixed effect for treatment, a random effect for subject, and the Day -1 post-meal AUC as a covariate.

Boxplots of the lipid values at pre-meal and each planned post-meal time point (0.5, 1, 2, and 4 hours post-meal) will be presented for each treatment group for both Day -1 and Day 28.

6.3 Exploratory Biomarkers

The exploratory biomarkers FFA, β-hydroxybutyrate, and ApoB100 will be assessed from samples collected from all subjects in Part B on Day -1, Day 7, Day 14, Day 21, and Day 28,

plus 7 (Day 35) and 14 (Day 42) or 28 (Day 56) days after stopping dosing of the randomized treatment, while the biomarkers ApoC3, PCSK9, Lp(a) and insulin will only be collected on Day -1, Day 14, Day 28, Day 35, and Day 42 or 56. While the subjects are receiving randomized study medication samples will be collected just prior to dosing.

For each parameter a last on-treatment observation measurement will be derived for each subject using the last post-dose measurement for a parameter taken while the subject is taking study medication during the 28-day treatment period. Change from baseline for each parameter will be derived for each of the post-dosing time points (Days 7, 14, 21, 28, 35, and 42 or 56) and the last on-treatment observation using the Day -1 measurement as the baseline.

Descriptive statistics for the measurement at baseline and the measurement and change from baseline at each post-baseline time point plus the last observation will be tabulated.

An MMRM analysis will be conducted for each parameter using the change from baseline values. The MMRM model for change from baseline will contain fixed effects for treatment, time, and their interaction, a random effect for subject, and the baseline measurement as a covariate. Since the time points are evenly spaced the covariance structure among the repeated measurements for a subject will be assumed to be common across subjects and modeled using an autoregressive matrix. The analyses will be conducted and tabulated as described in Section 6.1.2.

Plots of the least squares mean ± standard error estimates for each parameter over time (baseline through Day 56) will be provided by treatment group.

A last on-treatment observation analysis will be performed for change from baseline using an ANCOVA model with a fixed effect for treatment, a random effect for subject and the baseline value as a covariate. The analyses will be conducted and tabulated as described in Section 6.1.2.

Sufficient biomarker samples will be collected during Part B to allow for the determination of ApoB48, lathosterol, lanosterol, demosterol, and potentially other biomarkers of interest. No analyses for these biomarkers are currently planned. If analyses for these biomarkers are subsequently added, the description of the analysis will be documented in the CSR.

7 Safety Analyses

All analyses of safety including the extent of exposure to study medication will be performed using the Safety population. Summaries will be presented at the subject level, and subjects who received Placebo for the second time during the fourth dosing period will be presented as separate subjects in the summaries.

7.1 Study Medication Exposure and Treatment Compliance

7.1.1 Extent of Exposure

In Part A, the single dose of LY or placebo will be administered at the clinical research unit (CRU) under the supervision of the investigator. As a result, subject compliance will be ensured. A by-subject listing of the treatment received by each subject for each dosing period in Part A will be provided.

In Part B, the daily dose of LY or placebo will be administered at the CRU on Days 1, 2, 7, 14, 21, 28, and 29, while doses on the intermittent days will be administered by the subject while at home. Each subject will document in a daily diary the administration of each daily dose along with the time of dosing and the time of the first meal of the day. From the daily diaries and the Medication Dosing pages of the CRF, the total number of doses received and date of last dose of study medication can be determined. The extent of exposure can be derived as:

Extent of Exposure = Date of last dose of study drug – Date of 1st dose of study drug + 1.

Extent of exposure will be reported as a continuous variable by treatment group. In addition, extent of exposure will be reported as a categorical variable using the categories: 1 to <7 days, 7 to <14 days, 14 to <21 days, 21 to <29 days, and 29 days.

7.1.2 Treatment Compliance

Compliance for the study will be derived as:

Compliance = Total number of doses received / Extent of Exposure.

Each subject in Part B is supposed to take ≥80% of the intended dose to be deemed compliant with study drug administration. Compliance with study medication will be reported by treatment group using the categories: < 80% compliance, 80% to < 100% compliances, and 100% or greater compliance.

A by-subject listing of each subject's daily dose will be provided for the subjects in Part B.

7.2 Adverse Events

Investigators will monitor the safety of subjects and will be responsible for their medical care during the study. The investigator will interpret and document adverse advents and will indicate whether each event is serious and the strength of causality to the study medication. The subject will be followed until adverse events are resolved.

Only those adverse events (AE) that emerge or worsen after the date of first dose of study medication, i.e. treatment emergent adverse events (TEAE), will be summarized. Adverse events with a missing start date will also be classified as TEAE.

Summaries of TEAE will include the number of subjects with at least one TEAE for each treatment group. When reporting by system organ class (SOC) and preferred term (PT), the reports will present the SOC in alphabetical order; while PTs within the SOC will be presented in order of overall decreasing frequency of occurrence in the combined LY treatment groups. A subject with multiple TEAEs (different PTs) coded to the same SOC will be counted only once for that SOC, but will be counted each time for different PTs within that SOC. A subject with separate events of the same PT (different start/stop dates) will be counted only once in the frequency tables for that PT.

In Part A, TEAEs will be reported using the treatment that the subject most recently received. Adverse events that occur on the first day of a dosing period will be assigned to the treatment received on that day.

No statistical testing will be performed for comparisons of TEAEs.

An overview of all TEAEs for both Parts A and B will also be provided by treatment group using the types of TEAEs defined in the following subsections.

7.2.1 Treatment-Emergent Adverse Events

For both Parts A and B, TEAEs will be summarized by SOC and PT for each treatment group. These reports will also present the total number of TEAE for each SOC and PT, since this information is needed for reporting on clinicaltrials.gov. In addition, a presentation of TEAE preferred terms by decreasing frequency will be provided. The sort order for the table will based on the number of subjects in the combined LY treatment groups who had the TEAE.

7.2.2 Serious Treatment-Emergent Adverse Events

A serious TEAE (SAE) is a TEAE that met one or more of the following criteria:

- Is fatal
- Is life-threatening
- Requires or prolongs hospitalization
- Is significantly or permanently disabling or incapacitating
- Constitutes a congenital anomaly or a birth defect or
- Jeopardizes the subject and may require medical or surgical intervention to prevent one of the above outcomes

For both Parts A and B, SAEs will be summarized for each treatment arm by SOC and PT for the Safety population. These reports will also include the total number of SAE for each SOC and PT. A listing of all SAE will also be provided. The listing will include the criteria that a TEAE met to be declared an SAE.

7.2.3 TEAE Resulting in Death

If there are any TEAE that result in death for either part of the study, then a listing of all deaths will be provided for that part of the study.

7.2.4 TEAE Leading to Study Discontinuation

For Part A subjects receive only a single dose of study medication which precludes drug withdrawal in response to an adverse event. ‘Drug Withdrawn’. The subjects who experience adverse events leading to study discontinuation during Part A will be captured in the disposition listing.

For Part B, adverse events for resulting in drug discontinuation (designated as ‘Drug Withdrawn’) will be classified as a TEAE leading to study drug discontinuation. TEAEs that lead to study drug discontinuation will be summarized for each treatment group by SOC and PT for the Safety population. A by-subject listing of the TEAE that lead to study drug discontinuation will also be provided.

7.2.5 Treatment-Related TEAE

Every AE will be assessed by the investigator for its relationship to study medication. The TEAEs either assessed by the investigator to be possibly, probably, or definitely related to study treatment or that are missing the investigator's assessment will be categorized as treatment-related TEAEs.

The tabled results for all TEAE, serious TEAE, and TEAE that lead to study discontinuation will be repeated for Parts A and B using the subset of TEAE that are classified as treatment-related.

7.2.6 TEAE by Maximal Severity

Every AE will be graded by the investigator as mild, moderate, or severe, so for each subject the greatest severity observed can be obtained by comparing the severity of all of a subject's TEAE that share the same SOC or PT. A table of TEAE by maximal severity will be prepared for each treatment arm by SOC and PT for the Safety population. This report will be generated for both Parts A and B.

7.2.7 Treatment-Emergent (not including Serious) Adverse Events

To meet the requirements for reporting on clinicaltrials.gov, the most common non-serious TEAE will be reported for both Parts A and B. All PT that occur in at least 5% of the Safety Population subjects in any treatment group, when not counting the serious TEAE, will be tabulated by SOC and PT for each treatment group. These reports will also present the total number of TEAE for each SOC and PT

7.3 Clinical Laboratory Analyses

Blood samples for hematology and clinical chemistry and urine samples for urinalysis will be collected in both Parts A and B. Profiles for the hematology, clinical chemistry and the numeric urinalysis parameters will be summarized for both Parts A and B.

7.3.1 Clinical Laboratory Analyses in Part A

For Part A, blood samples will be collected pre-dose on Day 1 and at 24, 48 and 96 hours post-dose for all subjects in each dosing period in Part A. The measurements from dosing period 4 for Cohort 2 will not be included in this analysis since dosing of study medication occurred in a fed state.

7.3.1.1 Clinical Laboratory over time in Part A

Change from baseline for each of the hematology, clinical chemistry and the numeric urinalysis parameters will be derived for each of the post-dose time points using the pre-dose measurement as the baseline. Descriptive statistics for the measurement at baseline and the measurement and change from baseline at each post-dose time point will be tabulated.

Plots of the least squares mean ± standard error estimates for each parameter over time (pre-dose through 96 hours post-dose) will be provided by treatment group.

7.3.1.2 Clinical Laboratory Shift Tables in Part A

Each laboratory parameter will be classified as low, normal or high relative to the central laboratory's normal range. For each treatment group shift tables will be generated from the pre-dose category to the category 96 hours post-dose for each laboratory parameter. The shift tables will present the number (percent) of subjects who started in a category (low, normal, high) at baseline and ended in a category at the end of the study. A missing category will be included for both pre-dose and 96-hours post-dose, so that all subjects in the Safety population will be represented in the table. The percentages will be calculated using number of subjects in the Safety population who have measurements at pre-dose and 96-hours post-dose.

Shift tables comparing pre-dose to the other time points in the study may be generated if warranted after data review.

Similar shift tables for the categorical urinalysis parameter will also be produced using all categories reported for a parameter during the study.

7.3.2 Clinical Laboratory Analyses in Part B

For Part B, blood samples will be collected on Day -1 then pre-dose on Days 2, 7, 14, 21, and 29 and during follow-up on Days 35 and 42 or 56 for all subjects in Part B.

7.3.2.1 Clinical Laboratory over time in Part B

Change from baseline for each of the hematology, clinical chemistry and the numeric urinalysis parameters will be derived for each of the post-baseline time points using the Day -1 measurement as the baseline. Descriptive statistics for the measurement at baseline and the measurement and change from baseline at each post-baseline time point will be tabulated.

Plots of the least squares mean ± standard error estimates for each lipid parameter over time (baseline through Day 56) will be provided by treatment group.

7.3.2.2 Clinical Laboratory Shift Tables in Part B

For each treatment group shift tables will be generated from the baseline category to the category at Day 42 or 56 for each laboratory parameter. The shift tables will present the number (percent) of subjects who started in a category (low, normal, high) at baseline and ended in a category at the end of the study. A missing category will be included for both baseline and Day 42 or 56, so that all subjects in the Safety population will be represented in the table. The percentages will be calculated using number of subjects in the Safety population who have measurements at baseline and at Day 42 or 56.

Additional shift tables may be generated if warranted after data review.

Shift tables for the categorical urinalysis parameter will also be produced.

7.4 Vital Signs and Weight

7.4.1 Vital Signs in Part A

On the Day -1 for each dosing period the blood pressure, pulse rate, and temperature for each subject in Part A will be collected. At each collection time point all vital signs are to be collected after the subject has been supine for at least 5 minutes. Then, to assess orthostatic hypertension, measurements of blood pressure and pulse rate will to be collected in triplicate at 1, 2, and 3 minutes after rising to a standing position, Vital signs will be similarly assessed at 2, 4, and 8, 24, 48, and 96 hours after dosing for each subject. At each time point, the maximum value among the triplicate standing measurements will be obtained, and the change from the supine measurement will be derived for the triplicate maximum.

Descriptive statistics for the supine measurement and triplicate maximum along with the change from supine for the triplicate maximum will be tabulated for each treatment group, except the 30mg fed treatment group, at each time point.

Subjects will be determined to have orthostatic hypotension if either of the following occur after the subject rises from a supine to standing position.

- Systolic blood pressure decreases ≥ 20 mmHg, or
- Diastolic blood pressure decreases ≥ 10 mmHg.

In addition, subjects with the following increases in the pulse rate after rising from a supine to standing position will be tabulated.

- Pulse rate increases ≥ 20 beats per minute (bpm),

The number (percent) of subjects having orthostatic hypotension and pulse rate increases will be tabulated by treatment group. The percentage will be calculated using the number of subjects in the Safety population with data at the time point as the denominator.

Change from baseline statistics will also be defined for the supine measurements of blood pressure, pulse rate and temperature using the pre-dose values as baseline. Descriptive statistics for the supine measurement of temperature will also be provided by treatment group.

Plots of the mean ± standard error for each vital sign, collected while supine, over time (baseline through Day 4 [96 hours]) will be provided by treatment group.

7.4.2 Vital Signs in Part B

Orthostatic blood pressure and pulse rate along with temperature will be collected pre-dose on Days 1, 2, 7, 14, 21, and 29, at 4 hours post-dose on Days 1 and 28, and as follow-up assessments on Days 35 and 42. Data summaries will be created using the pre-dose and follow-up assessments, and a separate summary will examine the 4-hour post-dose measurements. The orthostatic blood pressure and pulse rate measurements collected on Days -6, -2, -1 and 27 along with all unscheduled vital sign assessments will be provided in the listings but will not be included in the summary tables or figures.

7.4.2.1 Vital Signs over time in Part B

For the pre-dose and follow-up assessments on Days 1, 2, 7, 14, 21, and 29 and Days 35 and 42, respectively, the maximum value among the triplicate standing measurement will be obtained, and the change from the supine measurement will be derived for the triplicate maximum.

Descriptive statistics for the supine measurement and triplicate maximum along with the change from supine for the triplicate maximum will be tabulated for each treatment group at each time point.

Subjects will be determined to have orthostatic hypotension using the criteria provided in Section 7.4.1. The number (percent) of subjects having orthostatic hypotension will be tabulated by treatment group. The percentage will be calculated using the number of subjects in the Safety population with data at the time point as the denominator.

Change from baseline statistics will also be defined for the supine measurements of blood pressure, pulse rate and temperature using the Day 1 values as baseline. Descriptive statistics for the supine measurement of temperature will also be provided by treatment group.

Plots of the mean ± standard error for each vital sign, collected while supine, over time (baseline through Day 4 [96 hours]) will be provided by treatment group.

7.4.2.2 Post-dose (4-hour) Vital Signs in Part B

For the 4-hour post-dose assessments on Days 1 and 28 the maximum value among the triplicate standing measurement will be obtained, and the change from the supine measurement will be derived for the triplicate maximum.

Descriptive statistics for the supine measurement and triplicate maximum along with the change from supine for the triplicate maximum will be tabulated for each treatment group at each time point. Subjects will be determined to have orthostatic hypotension using the criteria provided in Section 7.4.1. The number (percent) of subjects having orthostatic hypotension will be tabulated by treatment group. The percentage will be calculated using the number of subjects in the Safety population with data at the time point as the denominator. Descriptive statistics for the supine measurement of temperature will also be provided by treatment group.

7.4.2.3 Clinically Significant Vital Sign Change in Part B

The number (percent) of subjects who experience either orthostatic hypotension or a clinically significant deviation in vital signs while on-treatment will be tabulated by treatment group. Vital sign normal are defined as follows:

- Pulse rate < 50 bpm or > 100 bpm,
- Systolic blood pressure either ≤ 90 mmHg or ≥ 160 mmHg,
- Diastolic blood pressure either ≤ 50 mmHg or ≥ 100 mmHg.

All on-treatment values, including unscheduled assessments, will be considered, and the denominator for the percentages will be the number of subjects in the Safety Population.

All subjects who have a clinically significant change in vital signs or orthostatic hypotension will be documented in a by-subject listing. The listing will include all of the vital sign measurements

from the study for the subject, and abnormal values will be flagged. A similar listing for the data from Part A will also be produced, but no a summary table of the results as are planned for Part A.

7.4.3 Anthropometric variables in Part B

Weight plus waist, hip and neck circumference will be collected on Days -1, 7, 14, 21, and 29, and at the follow-up assessments times on Days 35 and 42 or 56.

Change from baseline statistics will be defined for each parameter using the Day -1 values as baseline; descriptive statistics for each parameter will also be tabulated by treatment group.

Plots of the mean ± standard error for weight over time (baseline through Day 56) will be provided by treatment group.

7.5 Electrocardiograms

Subjects must be supine for at least 5 minutes prior to and remain awake during each 12-lead, digital, triplicate electrocardiogram (ECG) collection. ECGs will be read by a qualified physician at the site to document parameter measurements and to determine any clinically relevant findings. The triplicate numeric measurements will be averaged at each time point to obtain the value that will be used for analyses, while the most severe interpretation (Normal; Abnormal, not Clinically Significant; Abnormal, Clinically Significant) among the triplicate measurements will be used for analyses. However, all abnormalities documented on any of the triplicate measurements will be reported in the listings. The investigator, or qualified designee, will report any new clinically relevant finding from any of the triplicate measurements as an AE.

7.5.1 ECGs in Part A

In Part A, triplicate ECGs will be collected during each dosing period at pre-dose and at 2, 4, 6, 8, 12, 24, 48, and 96 hours post-dose. The parameters heart rate, PR interval, QRS duration, QT interval, RR interval, QTc Bazett, and QTc Fridericia (QTc_f) will be obtained as the mean of the triplicate measurements for each ECG collection, plus the investigator will provide an overall ECG evaluation.

7.5.1.1 Descriptive Summary of ECGs

At each time point, the change from baseline will be derived for each numeric parameter using the pre-dose value as baseline. Descriptive statistics for the value of each parameter at each time point and the change from baseline for each parameter at each post-dose time point will be provided by treatment group.

Plots of the mean ± standard error for the changes from baseline in each parameter over time will be provided by treatment group.

The single tracing collected at Screening and the triplicate measurements collected on the Day -1 for each dosing interval will be included in by-subject listings but will not be included in any summary tables.

7.5.1.2 Exposure Response Analysis for QTc_f

To evaluate the effect of LY3202328 on QTc prolongation, QTc_f will be assessed across a range of concentrations using concentration response modeling. The changes in QTc_f at the time points 2, 4, 6, 8, 12, and 24 post-dose, where PK blood samples are also collected, will be modeled with drug concentration as a continuous covariate, treatment (LY3202328 or placebo) and time as fixed effects, and a random effect for subject within dosing period. This random effect introduces correlation among a subject's QTc_f measurements with a dosing period, but the measurements from different dosing intervals will be treated as independent. Estimates of the regression coefficient and the treatment effect along with their associated 90% confidence intervals (CIs) will be obtained from the model.

The predicted mean placebo-adjusted change from baseline in QTc_f will be obtained by multiplying the estimated regression coefficient and the observed geometric mean Cmax and adding the estimate of the treatment effect (LY3202328 – Placebo). An estimate of the 90% CI for the predicted mean placebo-adjusted change from baseline in QTc_f will be bootstrapped using 5000 resamples with subject within dosing interval as the resampling unit. For each resample the model will be fitted and the predicted estimate obtained using the geometric mean Cmax based on the resample. The CI will be determined from the distribution of the resampled predicted values.

If the upper bound of the 90% CI does not exceed 10 ms then a clinically relevant QT effect can be excluded.

7.5.2 ECGs in Part B

In Part B, ECGs will be collected on Day -1, at pre-dose on Days 2, 7, 14, 21, and 29, at post-dose on Day 1 (4 hours) and Day 28 (1, 4, and 8 hours), during follow-up on Days 35 and 42 or 56. The same parameters reported in Part A will also be reported for Part B.

7.5.2.1 ECGs over time in Part B

At each time point, the change from baseline will be derived for each numeric parameter using the Day -1 value as baseline. Descriptive statistics for the value of each parameter at each time point and the change from baseline for each parameter at each post-dose time point will be provided by treatment group.

Plots of the mean ± standard error for each vital sign, collected while supine, over time (baseline through Day 56) will be provided by treatment group.

The single tracing collected on the Day -2 will be included in by-subject listings but will not be included in any summary tables.

7.5.2.2 Clinically Significant ECGs in Part B

The number (percent) of subjects who either had an abnormal ECG (regardless whether clinically significant or not) or had a clinically significant change in the QTc_f value while on-treatment will be tabulated by treatment group. Abnormal QTc_f values will be determined using the following criteria:

- $QTc_f \geq 480$ msec
- $QTc_f \geq 500$ msec
- $QTc_f \geq 550$ msec
- Change from baseline in $QTc_f \geq 30$ msec
- Change from baseline in $QTc_f \geq 60$ msec.

All on-treatment values, including unscheduled assessments, will be considered, and the denominator for the percentages will be the number of subjects in the Safety Population.

All subjects who have an extreme QTc_f value or orthostatic value will be documented in a by-subject listing. The listing will include all of the ECG measurements from the study for the subject, and the noteworthy values will be flagged. A similar listing for the Part A will also be produced, but no summary table of the results is planned for Part A.

8 Pharmacokinetic Analyses

The PK analysis for the study will be detailed in a separate PK SAP.

9 Exploratory PK/PD and PK/Biomarker Analyses

The exploratory PK/PD and PK/biomarker analyses for the study will be detailed in a separate SAP.

10 Additional, non-PK, Analyses for the DDI study

Any additional non-PK analyses for the DDI study will be detailed in a separate SAP.