Statistical Analysis Plan

Sponsor:	Eli Lilly and Company
Protocol No:	J2O-MC-EKBA(c)
Protocol Title:	A Safety, Tolerability, and Pharmacokinetic Study of Single – and Multiple-Ascending Doses of LY3473329 in Healthy Subjects
PRA Project ID:	ELL19958-19958X
Version Date:	14-Oct-2021 (SAP) V2

1.0 Approvals

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

Name of Sponsor Representative / Title:	PPD
Signature of Sponsor Representative / Date:	
Name of Author / Title:	
Signature of Author / Date:	

2.0 Table of Contents

3.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical methods that will be used during the analysis and reporting of data collected under Eli Lilly and Company Protocol J2O-MC-EKBA(c).

This SAP should be read in conjunction with the study protocol and electronic case report form (eCRF). This version of the SAP has been developed using the amended protocol (Version c) approved 19-Jan-2021 (including all amendments up to this protocol date) and the final eCRF(s) dated 12-Aug-2020 (SAD), 25-Sep-2020 (MAD), 10-Mar-2021 (SAD and MAD protocol Version c).

An approved and signed SAP is a requirement for database lock. An approved SAP is also required for unblinding of the study treatments.

This SAP only covers the results that will be processed by the PRA Early Development Services (EDS) Biostatistics Department. PRA EDS will perform the pharmacokinetic (PK), pharmacodynamic (PD), and safety and tolerability evaluation.

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

4.0 Changes from Previous Version of Approved SAP

This is the first version of the SAP.

5.0 Study Objectives

The study objectives are given in Table 1 below.

Table 1 Objectives and Endpoints

Objectives	Endpoints
Primary (Part A – SAD)	
To evaluate safety and tolerability of LY3473329 in healthy subjects following a single oral dose	• AEs • SAEs
Primary (Part B – MAD)	
To evaluate safety and tolerability of LY3473329 in otherwise healthy subjects with elevated Lp(a) (≥75 nmol/L or 30 mg/dL) following multiple once-daily oral doses	• AEs • SAEs
Secondary (Part A – SAD)	
To evaluate the pharmacokinetics of LY3473329 in healthy subjects following a single oral dose	• AUC • C_{max} • t_{max}
Secondary (Part B – MAD)	
To evaluate the pharmacokinetics of LY3473329 in otherwise healthy subjects with elevated Lp(a) (≥75 nmol/L or 30 mg/dL) following multiple once-daily oral doses	• AUC • C_{max} • t_{max}
Exploratory (Part A – SAD)	
To explore the mechanism of action of LY3473329 based on safety and efficacy biomarkers following a single oral dose	• Lp(a) concentration • Plasminogen activity • Plasminogen concentration • hs-CRP • tPA • PAI • α_2-antiplasmin
Exploratory (Part B – MAD)	
To explore the mechanism of action of LY3473329 based on safety and efficacy biomarkers following multiple once-daily oral doses	• Lp(a) concentration • Plasminogen activity • Plasminogen concentration • hs-CRP • tPA • PAI • α_2-antiplasmin

Abbreviations: AE = adverse event; AUC = area under the concentration versus time curve; C_{max} = maximum observed drug concentration; hs-CRP = high-sensitivity C-reactive protein; Lp(a) = lipoprotein (a); MAD = multiple-ascending dose; PAI = plasminogen activator inhibitor; SAD = single-ascending dose; SAE = serious adverse event; t_{max} = time of C_{max}; tPA = tissue plasminogen activator.

6.0 Study Design

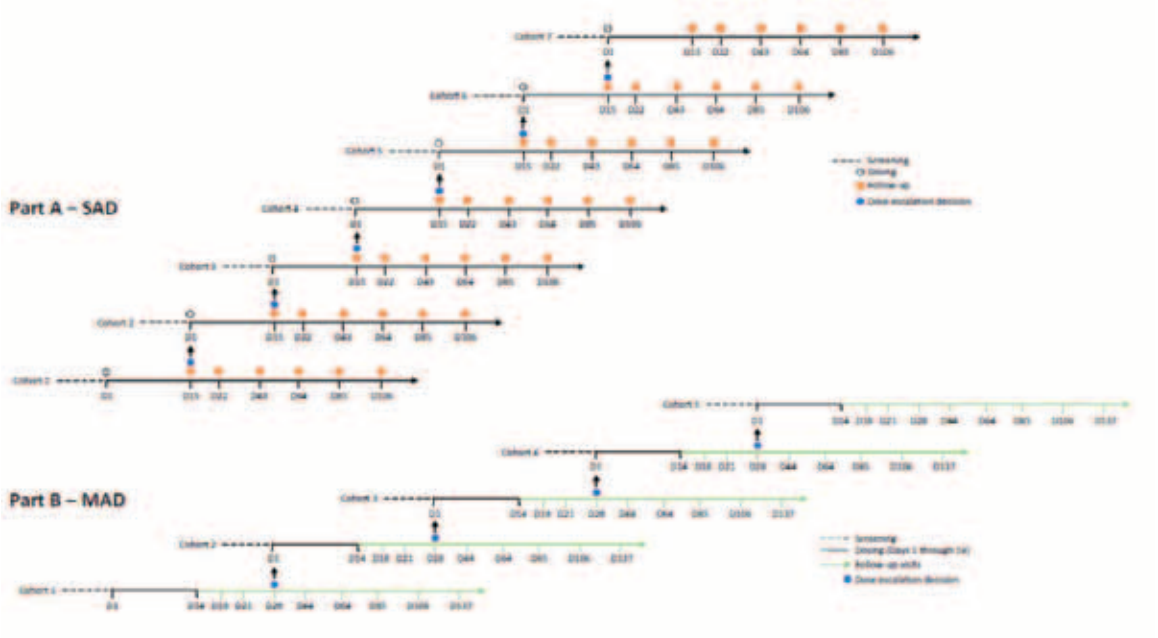
This is a Phase 1, randomized, investigator- and subject-blinded, placebo-controlled study of LY3473329 in healthy subjects (SAD; Part A) and in otherwise healthy subjects with elevated Lp(a) (≥75 nmol/L or 30 mg/dL; MAD; Part B).

In Part A, single-ascending doses of LY3473329 will be administered in up to 7 cohorts of 8 subjects each. Subjects will be randomly assigned to receive either LY3473329 or placebo in a 6:2 ratio. For the first cohort, 2 subjects will receive a sentinel dose (1 each with LY3473329 and placebo) with subsequent dosing of the remaining cohort after review of the safety data through 24 hours postdose. Dose escalation may occur as outlined in Section 7.4 of the protocol. All subjects will be confined to the clinical research unit (CRU) a day prior to Day 1 until all assessments are complete on Day 4. All subjects will be followed up for approximately 106 days following administration of the study drug. The follow-up period may be altered based on review of available data.

In Part B, multiple ascending doses of LY3473329 will be administered in up to 5 cohorts, with up to 10 evaluable subjects in the first 4 cohorts and 17 evaluable subjects in the last cohort. Subjects will be randomly assigned to receive either LY3473329 or placebo in a 8:2 ratio in all but the last cohort and in a 15:2 ratio in the last cohort. Subjects will receive either LY3473329 or placebo once daily (QD) for 14 days. Dose escalation may occur as outlined in Section 7.4 of the protocol. All subjects will be confined to the CRU a day prior to Day 1 and until all assessments are complete on Day 15. All subjects will be followed up for approximately 123 days following administration of the last dose of study drug. The follow-up period may be altered based on review of available data.

In both parts, the proposed doses may be adjusted after a review of available safety, PK, and additional data such as exploratory biomarkers that may include but are not limited to Lp(a) and plasminogen.

Figure 1 illustrates the study design.



Abbreviations: D = Day; MAD = multiple-ascending dose; SAD = single-ascending dose.
Overall timelines may be adjusted by 1 to 3 days to accommodate logistics across countries.

Figure 1 Study Design

6.1 Sample Size Considerations

Part A: The sample size for each cohort is customary for the first-in-human study in which formal power analyses are not necessary to address the objectives associated with safety, tolerability, PK, and/or other assessments.

Part B: The sample size for each cohort, except the final cohort, is customary for a first multiple-dose study. The sample size for the final cohort of Part B has been shown, through simulations, to be optimal for detecting a clinically meaningful decrease in Lp(a) with confidence appropriate for this Phase 1 study.

6.2 Randomization

In Part A and Part B, subjects who meet all criteria for enrollment will be randomly assigned to receive either LY3473329 or placebo. For the first cohort in Part A, 2 subjects will receive a sentinel dose (1 each with LY3473329 and placebo), with subsequent dosing of the remaining cohort in a 5:1 ratio. The other cohorts in Part A will be randomized in a 6:2 ratio. For Part B, subjects will be randomly assigned to treatment in a 8:2 ratio in all but the last cohort and in a 15:2 ratio in the last cohort. A randomization table will be created using a computer software program. The randomization list will be provided to the designated unblinded CRU staff for subject randomization and dispensing purposes and kept in a secure location, accessible to the designated unblinded CRU staff only.
Subjects who withdraw from the study before completion of all study activities may be replaced at the discretion of the Sponsor.

7.0 Overview of Planned Analysis

7.1 Changes from Protocol

There are no changes from the protocol.

7.2 Interim Analysis and Key Results

Blinded interim reports will be provided for each dose escalation meeting in Parts A and B by an unblinded PRA statistician. The blinded interim reports will contain the PK data and available data for Lp(a) and plasminogen.

PK data will include Tables 12.4.2.x, 12.4.3.x and Figures 12.4.5.x, 12.4.7.x. Lp(a) data will include Table 12.5.1.2.x and Figures 12.5.1.3.x and 12.5.1.4.x. Plasminogen data will include Table 12.5.2.2.x and Figures 12.5.2.3.x and 12.5.2.4.x. An overview of the tables and figures can be found in Appendix 4. Tables and figures may be updated for future dose escalation meetings as needed.

Topline tables, figures and listings (TFLs) will be provided at a time to be determined and will include:

- Lp(a) absolute and percentage change from individual baseline and also relative to placebo control
- Plasminogen activity (absolute and percentage change from baseline)
- Adverse events (AEs)
  - Listing 12.3.1.3 and
  - Table 12.3.1.4

7.3 Final Analysis

Draft TFLs will be provided with the draft CSR. After Sponsor comments have been incorporated, the TFLs will be finalized and incorporated in the final CSR.

8.0 Data Review

8.1 Data Management

Data handling and transfer will take place under the PRA Data Management Plan for the study.

8.2 Acceptance of Data for Summarization

Programming of analysis datasets and TFLs may be ongoing during the data management of the study. However, programming of analysis datasets and TFLs will be completed and quality controlled (QC'd) after database lock. Only quality assured (QA'd) results released by the Safety Laboratory, Bioanalytical Laboratory, or other external data source will be used for the programming of analysis datasets and TFLs for the final report. Any data values requiring investigation or corrections that are identified while programming the analysis datasets and TFLs will be sent to the project Data Manager. If the issue affects the TFLs, the Programmer or Statistician who identified the issue will follow it to resolution.

9.0 Definitions and General Analysis Methods

9.1 Analysis Data Presentation

9.1.1 Rounding

In listings, data will be presented with the same precision as the original data. Derived data will be rounded for presentation purposes.

For all summaries, except PK data summaries, descriptive statistics will be presented with the same precision (same number of decimals or significant figures) as the data they are calculated from. Frequency percentages will be presented as integers.

For all PK data (i.e. concentrations and derived parameters) summaries, descriptive statistics will be presented as integers when values are ≥100 or presented with 3 significant digits when values are < 100. Ratios will be presented with 2 decimals. The t_{max} values and descriptive statistics thereof will be reported with 2 decimals. The coefficient of variation (CV%) will be reported with 1 decimal.
Any p-values will be reported to four decimal places; p-value less than 0.0001 will be reported as p<0.0001.

9.1.2 Imputation

Unless otherwise noted, data will not be imputed.

9.1.3 Descriptive Statistics

Unless otherwise indicated, continuous variables will be summarized with the following descriptive statistics: n (number of observations), (arithmetic) mean, standard deviation (SD), minimum value, median, and maximum value.

Categorical data will be summarized with frequencies and percentages. Percentages by categories will be based on the number of subjects exposed within a treatment.

For categorical data the categories will be presented in the tables exactly as they appear in the eCRF / Database.

9.1.4 Pooling

Summary statistics will be calculated by treatment (and time point, if applicable). Placebo data will be pooled for Parts A (SAD) and B (MAD) separately.

9.1.5 Unscheduled Measurements

Unscheduled measurements will be included in the listings. Except for unscheduled measurements used for baseline, unscheduled measurements will be excluded from the descriptive statistics and statistical analysis.

9.2 Analysis Data Definitions

9.2.1 Baseline Definition

Unless otherwise stated, baseline for post-dose evaluations is defined as the last observation recorded before the first study drug administration. The last observation can be an unscheduled / repeated measurement.

Only for electrocardiogram (ECG) data, baseline is defined as the mean of the last recorded triplicate before the first study drug administration. If no triplicate is available before the first study drug administration, the mean of the last recorded duplicate closest to the first study drug administration will be considered as baseline. If no triplicate or duplicate is available, the last single ECG recorded before the first study drug administration will be considered as baseline.

9.2.2 Treatment/Subject Grouping

In summary tables, data will be presented by part and treatment.

Label	Grouping
Part	Part A (SAD) Part B (MAD)
Cohort	A1-A6, B1-B5
Treatment*	Part A (SAD): - Placebo - 1 mg LY3473329 - 10 mg LY3473329 - 30 mg LY3473329 - 100 mg LY3473329 - 200 mg LY3473329 - 400 mg LY3473329 - 800 mg LY3473329 Part B (MAD): - Placebo qd - 30 mg LY3473329 qd - 100 mg LY3473329 qd - 300 mg LY3473329 qd - 500 mg LY3473329 qd - 800 mg LY3473329 qd

qd = once daily

* the proposed doses may be adjusted after a review of available safety, PK, and additional data such as exploratory biomarkers that may include but are not limited to Lp(a) and plasminogen.

9.2.3 Common Variable Derivations

Variable	Definition/Calculation	Variable Name (CDISC ADaM)
Change from Baseline	Post-dose observation minus baseline observation	CHG
Percentage change from Baseline	Post-dose observation minus baseline observation / baseline observation *100	PCHG
Analysis Study Day	Prior to first day of dosing: Date of measurement minus date of dosing On or after first day of dosing: date of measurement minus date of dosing +1	ADY
Scheduled time	Planned time of the assessment. Time in hours of the assessment relative to the planned time of the first drug administration.	ATPT/ATPTN
Actual Time	Actual time in hours calculated as the sampling data/time minus the date/time of the first drug administration.	ARELTM

9.2.4 QC

The analysis datasets and the TFLs will be QC'ed according to the general PRA EDS QC plan.

9.2.4.1 Critical Data

The QC plan requires datasets be classified as critical or non-critical. As the primary end-point of this study are AEs and SAEs the analysis datasets considered critical are subject level analysis dataset (ADSL) and the AE analysis dataset (ADAE). As these are related to the primary objectives, these datasets will be double programmed per the QC plan. The Lp(a) and plasminogen activity data included in the laboratory analysis dataset (ADLB) will also be considered critical and will be QC'd by double programming.

9.2.5 ADaM Datasets and Metadata

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

ADaM compliant datasets will be delivered to the sponsor. A define.xml file Version 2 with the corresponding metadata will be included. Analysis results metadata are excluded.

The following datasets will be generated:

- ADSL
- ADAE
- ADLB
- Vital Signs Analysis Dataset (ADVS)
- ECG Analysis Dataset (ADEG)
- PK Concentrations Analysis Dataset (ADPC)
- PD Concentrations Analysis Dataset (ADPD)
- PK Parameter Analysis Dataset (ADPP)

9.3 Software

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

PK parameter calculations will primarily be done using Phoenix® WinNonlin® Version 8.1 or higher (Certara, L.P.). Additional PK and/or PD computations may be performed in SAS®.

9.4 Statistical Methods

9.4.1 Statistical Outlier Determination

No statistical outlier analysis is planned.

9.4.2 Predetermined Covariates and Prognostic Factors

There are no predetermined covariates or prognostic factors.

9.4.3 Hypothesis Testing

No formal hypothesis testing will be done.

9.5 TFL Layout

Report layout will be according to the PRA EDS Abbreviated CSR Template. The layout of TFLs will be according to the PRA EDS standards.

No table shells will be provided. The TFLs will be provided in Adobe PDF format.

Format:

- Page size: A4
- Data in listings will be sorted by part, subject number and time point.
- Data in tables will be sorted by part, treatment and time point.
- Column titles will be in title case letters.
- All tables and listings will be in landscape format.
- The treatment labels used in TFLs will be as outlined in Section 9.2.2

10.0 Analysis Sets

Analyses	Randomized Set	Safety Set	Pharmacokinetic Set	Pharmacodynamic Set
Disposition Summaries	✓			
Safety Assessments		✓		
Baseline Characteristics		✓		
PK Concentrations			✓	
PK Parameters			✓	
Lipoprotein(a)				✓
Other PD Markers				✓

PD = pharmacodynamic; PK = pharmacokinetic

10.1 Randomized Set

The all subjects randomized set will consist of subjects who are assigned a randomization number in the study. This set will be used for disposition summaries.

10.2 Safety Set

The safety analysis set will consist of subjects randomized who received at least 1 dose of study drug regardless of whether or not they completed all protocol requirements. This set will be used for the safety data summaries and baseline characteristic summaries.

10.3 Pharmacokinetic Set

The PK analysis set will consist of all subjects who received at least 1 dose of LY3473329 and have sufficient concentration-time data to calculate valid estimates of the (primary) PK parameters.

10.4 Pharmacodynamic Set

The PD analysis set will consist of all subjects who received at least 1 dose of LY3473329 or placebo and have evaluable PD data.

11.0 Subject Disposition

The number and percentage of subjects randomized, dosed, and members of each analysis set will be presented. The number and percentage of subjects who withdrew from the study prematurely and a breakdown of the corresponding reasons for withdrawal will also be presented.

Individual disposition data will be listed.

12.0 Protocol Deviations and Violations

Protocol deviations/violations will be included in the CSR.

13.0 Demographic and Baseline Characteristics

13.1 Demographics

All demographic data as collected during the screening visit will be listed by subject.

Subject demographics will be summarized descriptively for all subjects by part and treatment. The summary will include the subjects' age (in years), gender, race, ethnicity, weight (in kg), height (in cm), and body mass index (BMI; in kg/m^2). Subjects' age will also be presented in categories (18-64 years and >=65 years). Demographics will be summarized for the safety and PK analysis set.

13.2 Medical History

Medical history will be listed.

13.3 Other Baseline Characteristics

The results of serology tests, pregnancy tests and drug and alcohol screen will be listed.

14.0 Concomitant Medications

Concomitant medication will be listed by subject. Medications with an end date prior to the first dose of study drug will be considered prior medications and will be identified as such in the listing. If a partial date allows a medication to be considered concomitant it will be categorized as such.

Concomitant medications will be coded according to the WHODrug dictionary (Version Global B3 Sep2020).

15.0 Treatment Compliance and Exposure

Exposure data will be listed by subject.

16.0 Pharmacokinetic Analyses

16.1 Pharmacokinetic Variables

16.1.1 Plasma Variables

16.1.1.1 Concentrations

- Plasma concentrations of LY3473329

16.1.1.2 Parameters

- PK Parameters for LY3473329 as defined in Table 2

Table 2: Plasma PK Parameters

Parameter*	Description	SAD	MAD Day 1	MAD Day 14	SAS Programming Notes
C_{max}	Maximum plasma concentration. Observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units	✓	✓	✓	Cmax from WNL
t_{max}	Time to maximum plasma concentration. First observed time to reach peak analyte concentration obtained directly from the experimental data without interpolation, expressed in time units.	✓	✓	✓	Tmax from WNL
$AUC_{0\text{-last}}$	Area under the concentration-time curve (time 0 to time of last quantifiable concentration).	✓			AUClast from WNL
$AUC_{0\text{-inf}}$	Area under the plasma concentration-time curve (time 0 to infinity). Percent extrapolation less than or equal to 20% is required to obtain a reliable $AUC_{0\text{-inf}}$.	✓			AUCINF_obs from WNL If AUC_%Extrap_obs >20% then parameter is flagged
$AUC_{0\text{-tau}}$	Area under the plasma concentration-time curve over the dosing interval (time 0 to 24 hours)		✓	✓	AUCtau from WNL
λ_z	Terminal phase rate constant calculated by linear regression of the terminal log-linear portion of the concentration vs. time curve. Linear regression of at least 3 points and an adjusted r^2 greater than 0.80 are required to obtain a reliable λ_z.	✓		✓	Lambda_z from WNL If Rsq adjusted ≤ .80 then parameter is flagged
$t_{1/2}$	Terminal phase half-life expressed in time units. Percent extrapolation less than or equal to 20% and adjusted r^2 greater than 0.80 is required to obtain a reliable $t_{1/2}$.	✓		✓	HL_Lambda_z from WNL If Rsq adjusted ≤ .80 then parameter is flagged
CL/F	Apparent oral clearance, calculated as Dose/$AUC_{0\text{-inf}}$ for the SAD regimens or Dose/$AUC_{0\text{-tau}}$ for the MAD regimens on Day 14	✓		✓	CL_F_obs or CLss_F from WNL respectively. If AUC_%Extrap_obs >20% or Rsq adjusted ≤ 0.80 then parameter is flagged

Parameter*	Description	SAD	MAD Day 1	MAD Day 14	SAS Programming Notes
V_z/F	Apparent volume of distribution calculated as $((CL/F)/\lambda_z$	✓		✓	Vz_F_obs from WNL
Vss/F	Apparent volume of distribution at steady state, calculated as CL/F*MRTINF			✓	Vss_F_obs
AR_{AUC}	Accumulation ratio AUC_{tau}			✓	AUCtau (Day 14)/AUCtau (Day 1), calculated in SAS

Note: AUCs will be calculated using linear up / log down, expressed in units of concentration x time.
WNL = WinNonlin; *) In end-of-text TFLs, subscript will not be used.

16.2 Pharmacokinetic Summaries

16.2.1 Pharmacokinetic Concentrations

Plasma concentrations for LY3473329 below the quantifiable limit (BQL) will be set to ½ lower limit of quantification (LLOQ) in the computation of descriptive statistics of concentration values. Descriptive statistics (number of subjects, arithmetic mean, SD, CV%, median, minimum value, maximum value, geometric mean, and geometric CV%) will be used to summarize the plasma concentrations by part and treatment at each scheduled time point. If over ½ the subjects in a given cell have values BQL then the descriptive statistics will not be presented and will instead display as BQL for the mean and minimum value. With the exception of maximum all other statistics will be missing.

Linear and semi-logarithmic plots of the geometric mean plasma concentration by scheduled sampling time will be presented by part and treatment. These plots will show time in hours. The SAD treatments will be presented in 1 plot. The full profile of the MAD treatments will be presented in 1 plot. In addition, overlay plots for the MAD treatments will be presented showing Day 1 and Day 14 in 1 plot. The plots will match the summary table results and will not have an observation at a given time point if more than half of the subjects have values BQL.

Linear and semi-logarithmic plots of combined individual plasma concentrations by actual sampling time will be provided by part and treatment. For Part B, the full profiles will be presented. These plots will show time in hours. Individual plots will use the BQL handling procedure described below for “Pharmacokinetic Parameters”.

In addition, similar plots may be presented to a specific time point in order to improve readability.

Linear and semi-logarithmic plots of the individual plasma concentrations by actual sampling time will be provided by subject (1 subject per plot, 6 plots per page). For Part B, the plots will be presented as overlay plots (Day 1 and Day 14). These plots will show time in hours. The semi-logarithmic plots will indicate the time points that were included in the terminal phase range (λ_z range). Individual plots will use the BQL handling procedure described below for “Pharmacokinetic Parameters”.

Individual plasma concentration data will be presented together with descriptive statistics by treatment. Individual sampling times, time deviations and comments will be listed.

Linear and semi-logarithmic plots of the mean trough (pre-dose Day 2 – Day 15) plasma LY3473329 concentrations will be provided by treatment to visually assess steady state by study day for each cohort in Part B.

16.2.2 Pharmacokinetic Parameters

PK parameters for LY3473329 will be estimated using non-compartmental methods with WinNonlin®.

The plasma PK parameters will be estimated from the concentration-time profiles. In estimating the PK parameters, BQL values at the beginning of the profile will be set to zero. BQL values that occur after the first quantifiable point will be considered missing. Values that are embedded between BQLs, or quantifiable values occurring after 2 or more BQLs, will be set to missing at the discretion of the pharmacokineticist. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If the actual time or dose time is missing, the scheduled time may be substituted in order to calculate the PK parameter.

Descriptive statistics (number of subjects, arithmetic mean, SD, CV%, median, minimum value, maximum value, geometric mean, and geometric CV%) will be used to summarize the calculated PK parameters by treatment. For t_{max}, only median, min and max will be presented.

The points to be included in the λz range will be determined by the pharmacokineticist after inspection of the semi-logarithmic concentration-time profiles. At least 3 points will be required to be used. The C_{max} data point will not be included.

Parameters based on adjusted $r^2 \leq 0.80$ or $\%AUC_{extra}$ above 20% will be flagged but not excluded from descriptive statistics.

16.2.2.1 Dose-Proportionality

Dose proportionality will be explored for C_{max} and $AUC_{0\text{-}inf}$ (for SAD) or $AUC_{0\text{-}tau}$ (for MAD) using the power model as described by Smith et al, 2000. If $AUC_{0\text{-}inf}$ cannot be calculated in many profiles rendering the relationship suspect, $AUC_{0\text{-}last}$ may be used instead. In the power model, the $\log_e$-transformed parameters (Y) are assumed to be linearly related to the $\log_e$-transformed Dose:

$$\log_e = \beta_0 + \beta_1 * \log_e(\text{Dose})$$

Results will be presented in a table. The table will show the results of the dose proportionality assessment as shown in Table 2 in Smith et al, 2000. If the 90% confidence Intervals (CIs) for the dose-normalized ratio of PK geometric mean values (over the full range of doses tested) is included in the interval (0.8, 1.25) dose proportionality can be assumed. The maximum fold dose range in which dose proportionality can be concluded will also be reported.

16.2.2.2 PK/PD Relationship

The relationship between LY3473329 PK and Lp(a) will be graphically explored (e.g. scatterplots). Relationships between PK and other biomarkers and/or QT may be graphically explored, if indicated by the data obtained.

17.0 Pharmacodynamic Analysis

17.1 Pharmacodynamic Variables

17.1.1 Lipoprotein(a)

17.1.1.1 Serum Concentrations

- Lipoprotein(a)
- High-density lipoprotein-cholesterol (HDL-C)
- Low-density lipoprotein-cholesterol (LDL-C)
- Triglycerides

- Total cholesterol
- Apolipoprotein B (ApoB)

17.1.2 Other Pharmacodynamic Markers

17.1.2.1 Serum Concentrations

- high-sensitivity C-reactive protein (hs-CRP)
- Plasminogen concentration
- Plasminogen activity
- Plasminogen activator inhibitor (PAI)
- Tissue plasminogen activator (tPA)
- α2-antiplasmin

17.2 Pharmacodynamic Summaries

17.2.1 Lipoprotein(a)

All individual concentration data will be listed by subject.

Individual values and descriptive statistics (number of subjects, arithmetic mean, SD, CV%, median, minimum value, maximum value, geometric mean, and geometric CV%) summarizing the lipoprotein panel data (absolute observed values, derived percentage change from baseline, and percentage change relative to placebo) by part, treatment and at each scheduled day will be presented. The percentage change relative to placebo will be calculated as the individual percentage change from baseline minus pooled placebo change from baseline per timepoint.

Linear plots of the arithmetic mean serum concentrations with error bars (absolute observed values and derived percentage change from baseline) by scheduled day will be presented by part and treatment. The SAD treatments will be presented in 1 plot. The full profile of the MAD treatments will be presented in 1 plot. In addition, similar plots may be presented to a specific day in order to improve readability. Linear plots of combined individual serum concentrations (absolute observed values, derived percentage change from baseline, and percentage change relative to placebo) by actual day will be provided by part and treatment.

17.2.2 Other Pharmacodynamic Markers

All individual data will be listed by subject.

Biomarker endpoints will be summarized using descriptive statistics of absolute observed values and derived percentage change from baseline and presented together with the individual values by part, treatment and at each scheduled day.

Linear plots of the arithmetic mean serum concentrations with error bars (absolute observed values and derived percentage change from baseline) by scheduled day will be presented by part and treatment for each endpoint. The SAD treatments will be presented in 1 plot. The full profile of the MAD treatments will be presented in 1 plot. In addition, similar plots may be presented to a specific day in order to improve readability. Linear plots of combined individual serum concentrations (absolute observed values and derived percentage change from baseline) by actual day will be provided by part and treatment.

If a relevant change in one or more of the above mentioned PD markers is observed after treatment, then an exploratory analysis of the relationship between these PD markers may be conducted (e.g. scatterplots of plasminogen activity versus tPA). The endpoints to be tested will be determined in consultation with Eli Lilly and Company.

18.0 Safety Analyses

18.1 Safety Variables

The following safety variables will be summarized:

- AEs
- Vital Signs
  - Supine Blood Pressure
    - Systolic Blood Pressure
    - Diastolic Blood Pressure
  - Pulse Rate
  - Oral Body Temperature
  - Body Weight
- ECG
  - Heart Rate
  - PR Interval
  - QRS- Duration
  - QT Interval
  - QTc (Friderica) Interval
- Clinical Laboratory Evaluations
  - Clinical Chemistry
  - Hematology
  - Urinalysis

18.1.1 Adverse Events

Treatment-emergent adverse events (TEAEs) are those which occur or worsen after the first dose of study drug.

All AEs (including non-treatment-emergent events) will be listed, including the AE description (verbatim term), Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT), start date and time, end date and time, severity, relation to study drug, seriousness, action taken, and outcome.

All AE summaries will include only TEAEs. TEAEs occurring following dosing will be attributed to the treatment that was received.

A breakdown of the number of events, number and percentage of subjects reporting each TEAE, categorized by SOC and PT coded according to MedDRA (Version 23.1), will be presented by treatment and overall for each part, in descending order of total number of events by SOC and PT. Subjects will only be counted once within each SOC or PT.

One table will be presented for all TEAEs and 1 table will be presented for TEAEs considered to be related to the study drug. Additionally, a summary table with TEAEs by severity and relationship to study drug will be presented by part and treatment.
TEAEs of which the relationship to study drug will be classified as ‘possibly’, ‘’likely’, or ‘definitely’ will be regarded as related, while TEAEs that are classified as ‘none’, or ‘unlikely’ will be regarded as not related in the tables.

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

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

The following missing data will be imputed as defined (for calculations only / will not be presented):

- Missing AE start and / or end times for the calculation of onset and duration will be assumed to be at 00:01 for a start time and 23:59 for end times
- Missing AE severity or relationship will be assumed to be severe or related, respectively

- Missing AE start times for the determination of treatment emergence will be assumed to occur after treatment unless partial date documents the AE as happening prior to treatment
- Missing AE start times for the determination of treatment assignment will be assumed to occur after treatment on the recorded date
- Missing AE start date will be assumed to be after treatment for the determination of TEAE

For the US Clinical Trials Registry (CTR), a CTRAE summary table and the CTRAESUMM SAS dataset will be provided separately from the TFL created for CSR. The table and corresponding dataset will be created according to the specifications provided by the Sponsor.

18.1.2 Deaths and Serious Adverse Events

A listing of deaths and other serious adverse events (SAE) will be provided by subject.

18.1.3 Laboratory Data

Clinical laboratory data will be presented using standard units from the study data tabulation model (SDTM) Controlled Terminology.

All laboratory data will be listed by subject, including laboratory variables not listed in the protocol. A separate listing, including out-of-range values will also be provided. Normal ranges will be used directly from the clinical laboratory.

Descriptive statistics summarizing continuous laboratory results of clinical chemistry and hematology (absolute observed and derived changes from baseline) by treatment and scheduled time will be presented.

18.1.4 Vital Signs

All vital signs data will be listed by subject.

Descriptive statistics will be provided to summarize vital signs (absolute observed and derived changes from baseline) by treatment and scheduled time.

18.1.5 Electrocardiograms

The observed measurements for all ECG parameters and any corresponding abnormalities and Investigator's conclusion will be listed for all timepoints. The means of triplicate measurements for continuous parameters and the corresponding changes from baseline of the mean triplicate measurements at each scheduled timepoint will be listed by subject.

Descriptive statistics will be provided to summarize mean ECG parameters (absolute observed and changes from baseline) by treatment and scheduled time.

18.1.6 Physical Examinations

The physical examination findings (abnormalities) at screening and changes from/new findings during study or at follow-up will be listed.

19.0 References

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

Clinical Study Protocol. A Safety, Tolerability, and Pharmacokinetic Study of Single – and Multiple-Ascending Doses of LY3473329 in Healthy Subjects. Amendment (b), Final, 07 Aug 2020.

Smith BP, Vandenhende FR, DeSante KA, Farid NA, Welch PA, Callaghan JT, Forgue ST. Confidence interval criteria for assessment of dose proportionality. Pharm Res. 2000 Oct; 17(10):1278-83.

Appendix 1: Glossary of Abbreviations

Glossary of Abbreviations:	
ADAE	AE analysis dataset
ADaM	Analysis data model
ADEG	ECG analysis dataset
ADLB	Laboratory analysis dataset
ADPC	PK concentrations analysis dataset
ADPD	PD concentrations analysis dataset
ADPP	PK parameters analysis dataset
ADSL	Subject level analysis dataset
ADVS	Vital signs analysis dataset
AE	Adverse event
ApoB	Apolipoprotein B
AUC	Area under the concentration time curve
BMI	Body mass index
BQL	Below the quantifiable limit
CDISC	Clinical Data Interchange Standard Consortium
CI	Confidence interval
CRU	Clinical research unit
CSR	Clinical study report
CTR	Clinical Trials Registry
CV%	Coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic case report form
EDS	Early Development Services
HDL-C	High-density lipoprotein-cholesterol
hs-CRP	high-sensitivity C-reactive protein
LDL-C	Low-density lipoprotein - cholesterol
LLOQ	Lower limit of quantification
Lp(a)	Lipoprotein(a)
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
PAI	Plasminogen activator inhibitor
PD	Pharmacodynamic
PK	Pharmacokinetic

PT	Preferred term
QA'd	Quality assured
QC'd	Quality controlled
QD	Once daily
SAD	Single-ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDTM	Study data tabulation model
SOC	System organ class
TEAE	Treatment-emergent adverse event
TFL(s)	Tables, figures and listings
tPA	Tissue plasminogen activator
WHO-DD	World Health Organization – Drug Dictionary
WNL	WinNonlin

A detailed description of the PK parameters can be found in Table 2 Plasma PK Parameters.

Appendix 2: Schedule of Assessments Single-Ascending Dose (SAD) – Part A

	S	Treatment and Follow Up												ED[a]
Study Day	-28	-1	1	2	3	4	8	15	22	43	64	85	106	-
Visit Window	-		-	-	-	-	±1	±1	±3	±3	±3	±3	±3	-
Visit	1[b]	2[c]					3	4	5	6	7	8	9	-
CRU admission		X												
CRU discharge						X[d]								
Informed consent	X													
Medical history	X													
Height	X													
Weight	X	X					X	X						X
Physical examination (complete [C] or directed [D])	C	D	D	D	D	D	D	C	D	D	D	D	D	C
Urine drug screen and ethanol test	X	X					X	X						X
Vital signs including temperature	X		P	X	X	X	X	X	X	X	X	X	X	X
Hematology and clinical chemistry	X[j]	X				X	X	X						X
Urinalysis[e]	X	X							X	X	X	X	X	
ECG[f]	X		X	X	X			X						X
β-hCG pregnancy test	X	X				X							X	X
HIV, HCV, HBsAg	X													
Eligibility review	X	X												
Randomization			X											
Study drug administration[g]			X											
Adverse event		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK blood sampling[h]			X	X	X	X	X	X	X	X	X	X	X	X
hs-CRP	X			X	X									
Lipoprotein panel blood sample[i]	X		P	X	X	X	X	X						X
Plasminogen concentration			P	X	X		X	X	X	X	X	X	X	X
Plasminogen activity			P	X	X		X	X	X	X	X	X	X	X
PAI			P	X	X		X	X						X
tPA			P	X	X		X	X						X
α_2-antiplasmin			P	X	X		X	X						X

Abbreviations: β-hCG = beta subunit of human chorionic gonadotropin; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HDL-C = high-density lipoprotein-cholesterol; HIV = human immunodeficiency virus; hs-

Appendix 2: Schedule of Assessments Single-Ascending Dose (SAD) – Part A (Cont.)

CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein-cholesterol; Lp(a) = lipoprotein (a); P = pre-dose; PAI = plasminogen activator inhibitor; PK = pharmacokinetics; S = screening; SOP = standard operating procedure; t_{max} = time to reach the maximum observed drug concentration; tPA = tissue plasminogen activator.

[a] Subjects who discontinue prior to study completion will complete the ED visit procedures.

[b] Screening will be performed within 28 days prior to the study drug administration (Day 1).

[c] All subjects will be confined to the CRU a day prior to Day 1 until assessments are complete on Day 4.

[d] Subjects will be discharged after completing all activities on Day 4.

[e] A standard urine dipstick may be used.

[f] 12-Lead ECGs will be recorded in the supine position after 5 minutes rest. A single ECG will be recorded at screening and triplicate ECGs will be recorded at all other indicated time points. Triplicate ECGs will be recorded prior to blood draws when the time points coincide with blood draws; ECG recording will not exceed 5 minutes (for all 3 ECGs). On Day 1, ECG will be recorded pre-dose and at approximately 2, 4, and 6 hours after dosing.

[g] Study drug will be administered in a fasting state. Fasting is considered as approximately 8 hours prior to the dose and 4 hours after the morning dose. The exact time of study drug administration will be recorded.

[h] PK samples will be collected according to the PK Sampling Schedule (Appendix 6). Timing of PK sample collection may be adjusted based on clinical needs. The exact sample collection dates and times must be recorded.

[i] Lipoprotein panel blood sample will include Lp(a), HDL-C, LDL-C, triglycerides, total cholesterol, and ApoB.

[j] Screening laboratory tests should be done under fasting conditions.

* All local requirements with regard to COVID-19 will be followed according to local/site SOP.

Appendix 3: Schedule of Assessments Multiple-Ascending Dose (MAD) – Part B

	S1	S2	Treatment Period															FU								ED [a]
Study Day	-60	-28	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	18	22	29	43	64	85	106	137	
Visit Window																			±1	±1	±1	±4	±3	±3	±3	±3	
Visit	1[b]	2[b]	3																4	5	6	7	8	9	10	11	
CRU admission			X																								
CRU discharge																		X									
Informed consent	X																										
Medical history		X																									
Height		X																									
Weight		X	X															X									
Physical examination (complete [C] or direct [D])		C		D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	C	D	D	D	D	C
Urine drug screen and ethanol test		X	X															X	X	X		X					X
Vital signs including temperature		X	X	P	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology and clinical chemistry[j]		X	X		X						X						X		X	X		X					X
Urinalysis[c]		X	X																X	X	X	X	X	X	X	X	X
ECG[d]		X		X	X						X						X	X				X					X
β-hCG pregnancy test		X	X															X								X	X
HIV, HCV, HBsAg		X																									
Eligibility review		X	X																								
Randomization				X																							
Study drug administration[k]				X	X	X	X	X	X	X	X	X	X	X	X	X	X										
Adverse event			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK blood sampling[f]				X	X			X			X			X			X	X	X	X	X	X	X	X	X	X	X
hs-CRP		X									X						X										
Lipoprotein panel blood sample	X			P	P			P		P	P			P			P	X	X	X	X	X	X	X	X	X	X

Appendix 3: Schedule of Assessments Multiple-Ascending Dose (MAD) – Part B (Cont.)

	S1	S2	Treatment Period															FU								ED [a]
Study Day	-60	-28	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	18	22	29	43	64	85	106	137	
Visit Window																			±1	±1	±1	±4	±3	±3	±3	±3	
Visit	1[b]	2[b]	3																4	5	6	7	8	9	10	11	
Plasminogen concentration [f]	X			P	P	P	P			P							P	X	X	X	X	X	X	X	X	X
Plasminogen activity[f,h]	X			P	P	P	P			P							P	X	X	X	X	X	X	X	X	X
PAI[g]				P	P					P							P				X					X
tPA[g]				P	P					P							P				X					X
α2-antiplasmin[g]				P	P					P							P				X					X
Storage sample[i]				P			X			P							P				X					

Abbreviations: AE = adverse event; β-hCG = beta subunit of human chorionic gonadotropin;; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; FU = safety follow-up; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hs-CRP = high-sensitivity C-reactive protein; Lp(a) = lipoprotein (a); P = pre-dose; PAI = plasminogen activator inhibitor; PK = pharmacokinetics; S1 = screening visit 1; S2 = screening visit 2; SOP = standard operating procedure; tPA = tissue plasminogen activator.

[a] Subjects who discontinue the study prior to study completion will complete the ED visit procedures. The follow-up period may be altered based on review of available data such as PK, Lp(a) concentration, and plasminogen such that follow-up may cease for an individual once any AEs are resolved and Lp(a) levels and plasminogen activity return to at least 90% of baseline.

[b] Each subject will undergo 2 screening visits. Screening Visit 1 (S1) will be performed within 60 days before the first dose of study drug and screening Visit 2 (S2) will be performed within 28 days before the first dose of study drug. S1 must be completed at least 3 days before the first dose of study drug.

[c] A standard urine dipstick may be used.

[d] 12-Lead ECGs will be obtained in the supine position after 5 minutes rest. A single ECG will be recorded at screening and triplicate ECGs will be recorded at all other indicated time points. Triplicate ECGs will be recorded prior to blood draws when the time points coincide with blood draws; ECG recording will not exceed 5 minutes (for all 3 ECGs). On Day 1, ECGs will be collected at pre-dose and at 2, 4, and 6 hours after the dosing.

[e] Study drug will be administered in a fasting state, preferably at the same time every day at the CRU. Fasting is considered as approximately 8 hours prior to the dose and 4 hours after the dose. The exact time of study drug administration will be recorded.

[f] PK samples will be collected according to the PK Sampling Schedule (Appendix 6). If applicable, a PK sample will be obtained at the ED visit. Timing of PK sample collection may be adjusted based on clinical needs. The exact collection dates and times must be recorded.

[g] Biomarker samples will be collected prior to the morning dose.

[h] Investigator may order additional plasminogen activity samples if needed. This sampling schedule designed based on expectation of timing of the potential effect of LY3473329 on plasminogen activity

[i] Storage sample to be collected according to Section 9.8.

[j] Screening laboratory tests should be done under fasting conditions.

* All local requirements with regard to COVID-19 will be followed according to local site SOP

Appendix 4: List of End of Text Outputs

The planned TFLs for the CSR are listed below. The placement and numbering presented is for tracking/development purpose and may deviate from the placement order and numbering listed in the CSR.

This list defines the tables to be produced by programming. The medical writer can decide to insert any of the figures or create more tables in the CSR text independently of this SAP.

List of End of Text Tables, Figures and Listings:		
Output	**Title**	**Population Set used in Tables/Figures***
Section 12.1 – Demographic and Other Baseline Data		
Section 12.1.1 Demographic Data		
Listing 12.1.1.1	Subject Randomization and Treatment Assignment	
Table 12.1.1.2	Summary of Subject Disposition	Safety
Table 12.1.1.3	Summary of Demographics	Safety
Table 12.1.1.4	Summary of Demographics	PK
Listing 12.1.1.5	Subject Demographics	
Listing 12.1.1.6	Analysis Sets	
Section 12.1.2 Other Baseline Data		
Listing 12.1.2.1	Medical History	
Listing 12.1.2.2	Prior and Concomitant Medications	
Listing 12.1.2.3	Results of Serology Tests	
Listing 12.1.2.4	Results of Pregnancy Tests	
Listing 12.1.2.5	Results SARS-CoV-2 Tests	
Section 12.2 – Compliance Data		
Listing 12.2.1	Study Dates	
Listing 12.2.2	Subject Disposition	
Listing 12.2.3	Study Drug Administration	
Section 12.3 – Safety Data		
Section 12.3.1 – Adverse Events		
Table 12.3.1.1	Table of Deaths and Other Serious Adverse Events	Safety
Listing 12.3.1.2	Adverse Events Leading to Withdrawal	
Listing 12.3.1.3	Adverse Events	
Table 12.3.1.4	Summary of All Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Treatment	Safety
Table 12.3.1.5	Summary of Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Treatment	Safety

Table 12.3.1.6	Summary of Treatment-Emergent Adverse Events by Treatment, Relationship and Severity	Safety
Section 12.3.2 – Clinical Laboratory Data		
Listing 12.3.2.1	Clinical Laboratory Results - Clinical Chemistry	
Listing 12.3.2.2	Clinical Laboratory Results - Hematology	
Listing 12.3.2.3	Clinical Laboratory Results - Urinalysis	
Listing 12.3.2.4	Clinical Laboratory Results - Alcohol and Drug Screen	
Listing 12.3.2.5	Clinical Laboratory Results - Comments	
Table 12.3.2.6	Summary of Clinical Laboratory Data - Clinical Chemistry	Safety
Table 12.3.2.7	Summary of Clinical Laboratory Data - Hematology	Safety
Table 12.3.2.8	Abnormal Laboratory Values by Subject	Safety
Section 12.3.3 Vital Signs Data		
Listing 12.3.3.1	Vital Signs	
Table 12.3.3.2	Summary of Vital Signs	Safety
Section 12.3.4 ECG Data		
Listing 12.3.4.1	12-Lead Electrocardiogram Results – Individual Parameters	
Listing 12.3.4.2	12-Lead Electrocardiogram Results – Investigator's Interpretation and Specification of Abnormalities	
Table 12.3.4.3	Summary of 12-Lead Electrocardiogram	Safety
Section 12.3.5 Other Safety Data		
Listing 12.3.5.1	Physical Examination Findings and Changes	
Listing 12.3.5.2	Body Weight	
Section 12.4 – Pharmacokinetic Data		
Listing 12.4.1	LY3473329 Plasma Concentrations, Sampling Time Deviations and Comments	
Table 12.4.2.1	Individual Values and Descriptive Statistics of LY3473329 Plasma Concentrations by Treatment, Part A (SAD)	PK
Table 12.4.2.2	Individual Values and Descriptive Statistics of LY3473329 Plasma Concentrations by Treatment, Part B (MAD)	PK
Table 12.4.3.1	Individual Values and Descriptive Statistics of LY3473329 Plasma PK Parameters by Treatment, Part A (SAD)	PK
Table 12.4.3.2	Individual Values and Descriptive Statistics of LY3473329 Plasma PK Parameters by Treatment, Part B (MAD)	PK
Table 12.4.4	Dose Proportionality and Prediction of Exposure for LY3473329, Part A (SAD) and Part B (MAD)	PK
Figure 12.4.5.1	Geometric Mean LY3473329 Plasma Concentrations versus Time Profiles on Linear and Semi-Logarithmic Scale, Part A (SAD)	PK

Figure 12.4.5.2	Geometric Mean LY3473329 Plasma Concentrations versus Time Profiles on Linear and Semi-Logarithmic Scale, Part B (MAD) Full profiles	PK
Figure 12.4.5.3	Geometric Mean LY3473329 Plasma Concentrations versus Time Profiles on Linear and Semi-Logarithmic Scale, Part B (MAD) Overlay Day 1 and Day 14	PK
Figure 12.4.6	Geometric Mean LY3473329 Trough Plasma Concentrations versus Time Profiles on Linear and Semi-Logarithmic Scale, Part B (MAD)	PK
Figure 12.4.7.1	Combined Individual LY3473329 Plasma Concentrations versus Time Profiles on Linear and Semi-Logarithmic Scale, Part A (SAD)	Safety
Figure 12.4.7.2	Combined Individual LY3473329 Plasma Concentrations versus Time Profiles on Linear and Semi-Logarithmic Scale, Part B (MAD)	Safety
Figure 12.4.8	Individual LY3473329 Plasma Concentrations versus Time Profiles on Linear and Semi-Logarithmic Scale	Safety
Section 12.5 – Pharmacodynamic Data		
Section 12.5.1 Lipoprotein Panel		
Listing 12.5.1.1	Lipoprotein Panel Concentrations and Comments	
Table 12.5.1.2.1	Individual Values and Descriptive Statistics of Lipoprotein Panel Data (Absolute Values, Percentage Change from Baseline, and percent change relative to placebo) by Treatment, Part A (SAD)	PD
Table 12.5.1.2.2	Individual Values and Descriptive Statistics of Lipoprotein Panel Data (Absolute Values, Percentage Change from Baseline, and percent change relative to placebo) by Treatment, Part B (MAD)	PD
Figure 12.5.1.3.1	Arithmetic Mean ± SE Lipoprotein Panel Concentrations (Absolute Values and Percentage Change from Baseline) versus Day Profiles on Linear Scale, Part A (SAD)	PD
Figure 12.5.1.3.2	Arithmetic Mean ± SE Lipoprotein Panel Concentrations (Absolute Values and Percentage Change from Baseline) versus Day Profiles on Linear Scale, Part B (MAD)	PD
Figure 12.5.1.4.1	Combined Individual Lipoprotein Panel Concentrations (Absolute Values, Percentage Change from Baseline, and percent change relative to placebo) versus Day Profiles on Linear Scale, Part A (SAD)	PD
Figure 12.5.1.4.2	Combined Individual Lipoprotein Panel Concentrations (Absolute Values, Percentage Change from Baseline, and percent change relative to placebo) versus Day Profiles on Linear Scale, Part B (MAD)	PD
Section 12.5.2 Other Pharmacodynamic Biomarkers		
Listing 12.5.2.1	Other Biomarker Concentrations and Comments	

Table 12.5.2.2.1	Individual Values and Descriptive Statistics of Other Biomarkers (Absolute Values and Percentage Change from Baseline) by Treatment, Part A (SAD)	PD
Table 12.5.2.2.2	Individual Values and Descriptive Statistics of Other Biomarkers (Absolute Values and Percentage Change from Baseline) by Treatment, Part B (MAD)	PD
Figure 12.5.2.3.1	Arithmetic Mean ± SE Other Biomarker Concentrations (Absolute Values and Percentage Change from Baseline) versus Day Profiles on Linear Scale, Part A (SAD)	PD
Figure 12.5.2.3.2	Arithmetic Mean ± SE Other Biomarker Concentrations (Absolute Values and Percentage Change from Baseline) versus Day Profiles on Linear Scale, Part B (MAD)	PD
Figure 12.5.2.4.1	Combined Individual Other Biomarker Concentrations (Absolute Values and Percentage Change from Baseline) versus Day Profiles on Linear Scale, Part A (SAD)	PD
Figure 12.5.2.4.2	Combined Individual Other Biomarker Concentrations (Absolute Values and Percentage Change from Baseline) versus Day Profiles on Linear Scale, Part B (MAD)	PD
Section 12.6 – Exploratory Analysis		
Section 12.6.1 PK/PD Relationship		
	Exploratory analysis of the relationship between LY3473329 PK and Lp(a) and other biomarkers and/or QT; to be determined in consultation with Eli Lilly and Company.	
Section 12.6.2 PD Relationships		
	Exploratory analysis of the relationship between PD markers; to be determined in consultation with Eli Lilly and Company.	

* The safety set will be used for all listings.

Document History

Version Date	Modified/Reviewed By	Brief Summary of Changes (if created from a template, include template code)
18-Aug-2020	PPD	Internal review version
09-Sep-2020		Internal review comments incorporated.
16-Oct-2020		Sponsor comments incorporated
17-Nov-2020		Sponsor comments incorporated
03-Dec-2020		Final SAP for approval
07-Dec-2020		SAP Finalized V1
16-Apr-2021		Version 1.1 due to protocol amendment
30-Sep-2021		Version 2 sponsor comments
14-Oct-2021		Version 2 sponsor comments

PPD

Electronic Record and Signature Disclosure:
Not Offered via DocuSign

In Person Signer Events	Signature	Timestamp
Editor Delivery Events	**Status**	**Timestamp**
Agent Delivery Events	**Status**	**Timestamp**
Intermediary Delivery Events	**Status**	**Timestamp**
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**

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Electronic Record and Signature Disclosure:

Carbon Copy Events	Status	Timestamp
Not Offered via DocuSign		

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	10/15/2021 6:29:27 AM
Certified Delivered	Security Checked	10/15/2021 8:23:48 AM
Signing Complete	Security Checked	10/15/2021 8:24:58 AM
Completed	Security Checked	10/15/2021 8:24:58 AM

Payment Events	Status	Timestamps