Statistical Analysis Plan J3L-MC-EZEB Version 3

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of LY3819469 in Adults With Elevated Lipoprotein(a)

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Statistical Analysis Plan (J3L-MC-EZEB): A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of LY3819469 in Adults with Elevated Lipoprotein(a)

Protocol Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of LY3819469 in Adults with Elevated Lipoprotein(a)

Protocol Number: J3L-MC-EZEB

Compound Number: LY3819469

Brief Title: Efficacy and safety of LY3819469 compared with placebo in adults with elevated Lp(a)

[Acronym: ALPACA]

Study Phase: 2

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Version history

This statistical analysis plan (SAP) for Study J3L-MC-EZEB (EZEB) is based on the protocol dated 19 July 2022.

Table 1. SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	04 Apr 2023	Not Applicable	Original version
2	30 June 2023	• Added acronym for the study in front page. • Clarified the definition of full analysis set (FAS) in Section 3. • Updated analysis method for time-averaged endpoint in Section 4.3.2. Changed language in Section 4.1 and Section 4.4.2 to reflect updates. • Updated analysis for hypersensitivity events in Section 4.8.7.2. • Updated the renal safety analysis in Section 4.8.7.4. • Removed Appendix 7. Adjusted formatting of Table 4.7. • Removed KM plot in Section 4.2. • Adjusted subgroup analyses in Section 4.9.	• Added acronym for the study in front page. • Clarified the definition of FAS in Section 3. • Instead of original approach using multiple imputation, MMRM approach is applied to analyze time-averaged endpoint. • Updated analysis for hypersensitivity events in Section 4.8.7.2 per Phase 1 results. • Updated the unit for UACR. The slope analysis is not required for the non-CKD population. • Safety analyses defined in Appendix 7 are not needed for Phase 2 studies. • KM plots for patients' disposition are not required for this study because there are only 2 injections in total. • Redefined the subgroup analyses because the number of participants is too small (less than 10%) within a subgroup.

SAP Version	Approval Date	Change	Rationale
		• Added more time averaged endpoints for the first secondary objective in Section 1.1	• Percent change from baseline on time averaged Lp(a) over Days 30-180, and Days 30-360 were put in incorrect cell.
3	See data on Page 1	• Modified the error for time averaged Lp(a) analysis in Table 4.2 and Table 4.5. Removed "ANCOVA" from footnote. • Updated the searching criteria for TEAE hypersensitivity events in Section 6.6 Appendix 6. • Reworded the model in Section 4.3.2 • Removed the publication not cited in the document from "References"	• Revised the text in the table and made it consistent with the SAP body. • The original searching criteria are not accurate. Updated per team discussion. • The expression was updated with re-defining betas as least-squares means which make the wording less confusing. • Two publications in "References" were not cited in the text.

Abbreviations: ANCOVA = analysis of covariance; CKD = chronic kidney disease; KM = Kaplan-Meier; Lp(a) = lipoprotein(a); MMRM = mixed model repeated measures; SAP = statistical analysis plan; TEAE = treatment-emergent adverse event; UACR = urine albumin-to-creatinine ratio.

1. Introduction

1.1. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
• To evaluate if LY3819469 is superior to placebo in percent Lp(a) reduction	• Percent change from baseline in time-averaged Lp(a) over Days 60-180
Secondary	
• To evaluate if LY3819469 is superior to placebo in percent Lp(a) reduction over Days 240-360, Days 30-180, and Days 30-360	• Percent change from baseline in time-averaged Lp(a) over Days 240-360, Days 30-180, and Days 30-360
• Compare proportion of participants on LY3819469 versus placebo achieving Lp(a) threshold levels	• Proportion of participants achieving Lp(a) <125 and <75 nmol/L at Days 60, 180, 240, 360, and 540
• Compare the effect of LY3819469 to placebo on cardiovascular biomarkers	• Percent change from baseline and absolute change from baseline to Days 60, 180, 240, 360, and 540 for o Lp(a) o ApoB o hsCRP
• Characterize the PK of LY3819469	• Population PK parameters
Exploratory	
• To evaluate if LY3819469 is superior to placebo in absolute change from baseline	• Absolute change from baseline in Lp(a) at Days 60, 180, 240, 360, and 540
• Compare proportion of participants on LY3819469 versus placebo achieving absolute lowering of Lp(a) threshold	• Proportion of participants achieving Lp(a) lowering of at least 150 nmol/L at Days 60, 180, 240, 360, and 540
• Compare the lipid profile in response to LY3819469 versus placebo	• Percent change from baseline and absolute change from baseline for lipid profile o LDL-C o total cholesterol o HDL-C o triglycerides
• Evaluation of immunogenicity	• Incidence of treatment-emergent ADAs

Abbreviations: ADA = antidrug antibody; ApoB = apolipoprotein B; HDL-C = high-density lipoprotein-cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein-cholesterol; Lp(a) = lipoprotein(a); PK = pharmacokinetics.

Primary estimand

The primary clinical question of interest is: What is the intervention difference in percent change from baseline in time-averaged lipoprotein(a) (Lp[a]) over Days 60 to 180 of study intervention in participants who meet the inclusion criteria regardless of treatment discontinuation or initiation of excluded medications and Lp(a) modifying medication for any reason?

The primary estimand characterizes the treatment effect regardless of intercurrent events (ICEs) and is named the “treatment-regimen estimand.”

The treatment-regimen estimand is described by the following attributes:

- Population: participants who meet the enrollment criteria. Further details can be found in Section 5 and Section 9 of the study protocol EZEB.
- Endpoint: percent change from baseline in time-averaged Lp(a) over Days 60 to 180, which will be calculated by area under the curve (AUC) between Day 60 to Day 180 divided by 120.
- Treatment condition: the randomized treatment. Further details on study interventions, and concomitant interventions can be found in Section 6 of the study protocol EZEB.

There are no ICEs, because treatment discontinuation and initiation of medications that are known to impact Lp(a) level are part of the treatment condition.

Population-level summary: percent change from baseline in time-averaged Lp(a) over Days 60 to 180.

Treatment contrast of interest: difference in percent change from baseline in time-averaged Lp(a) over Days 60 to 180 between each dose of LY3819469 and placebo.

Rationale for estimand: this estimand aims to study the efficacy of LY3819469 that reflects the real-life behavior of the target population.

Safety

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of LY3819469 doses with placebo irrespective of adherence to study intervention.

Efficacy estimand

The efficacy estimand answers the question: What is the treatment difference in percent change from baseline in time-averaged Lp(a) over Days 60 to 180 after a single dose of LY in participants who meet the inclusion criteria and would have completed the treatment period without initiation of medications that are known to impact Lp(a) levels?

The “efficacy estimand” is described by the following attributes:

- Population: participants who meet the enrollment criteria. Further details can be found in Section 5 and Section 9 of the Study Protocol J3L-MC-EZEB.
- Endpoint: percent change from baseline in time-averaged Lp(a) over Days 60 to 180, which will be calculated by AUC between Day 60 to Day 180 divided by 120, and
- Treatment condition: the randomized treatment.

The ICEs “permanent discontinuation of intervention” and “initiation of excluded medications taken during the study or new initiation of any Lp(a) modifying medication per the protocol inclusion criteria” are handled by the hypothetical strategy where the potential outcome of interest is the response in the efficacy measurement if participants had adhered to the randomized treatment without using such medication. Analyses post–Day 180 will also consider the ICE of “treatment discontinuation”. There are no other defined ICEs. Switching medications within a class (for example, from one statin to another) is not considered an ICE for the definition of estimand in this study.

Population-level summary: percent change from baseline in time-averaged Lp(a) over Days 60 to 180.

Treatment contrast of interest: difference in percent change from baseline in time-averaged Lp(a) over Days 60 to 180 between each dose of LY3819469 and placebo.

Rationale for estimand: this estimand aims to study the efficacy of LY3819469 under the ideal condition that all participants adhere to their randomly assigned treatment without being confounded by the initiation of other medication that are known to impact Lp(a) levels.

1.2. Study Design

Study J3L-MC-EZEB is a parallel, double-blinded, placebo-controlled, dose-finding, Phase 2 study of LY3819469 in participants with elevated Lp(a). The purpose of this study is to measure difference in percent change from baseline in time-averaged Lp(a) over Days 60 to 180 with LY3819469 versus placebo in participants with elevated Lp(a). The duration of the study will be up to 20 months. The study will consist of an optional prescreening period, an approximately 21-day screening period followed by a 540-day treatment and assessment period.

Participants will be randomly assigned in a 1:2:2:2:2 ratio to one of the following arms:

- Arm A: 16-mg LY3819469, dosed at randomization and Day 180
- Arm B: 96-mg LY3819469, dosed at randomization and Day 180
- Arm C: 400-mg LY3819469, dosed at randomization and Day 180
- Arm D: 400-mg LY3819469, dosed at randomization, placebo at Day 180, and
- Arm E: placebo, dosed at randomization and Day 180.

This is a double-blind study in which participants are blinded to study intervention. Placebo participants will be randomly assigned so that each dose cohort will have a matching placebo cohort that receives the same dose volume to maintain the study blind. The matching placebo-treated patients will be pooled for all statistical analysis.

Participants will be stratified by high risk for cardiovascular events (yes/no) and baseline Lp(a) (<275 nmol/L, ≥275 nmol/L). High risk for cardiovascular events will be defined as coronary artery disease (including coronary artery disease, coronary artery bypass graft, myocardial infarction, percutaneous coronary intervention, and unstable angina), stroke (cerebrovascular accident), or peripheral artery disease, or atherosclerotic cardiovascular disease (ASCVD) risk equivalents (familial hypercholesterolemia or type 2 diabetes).

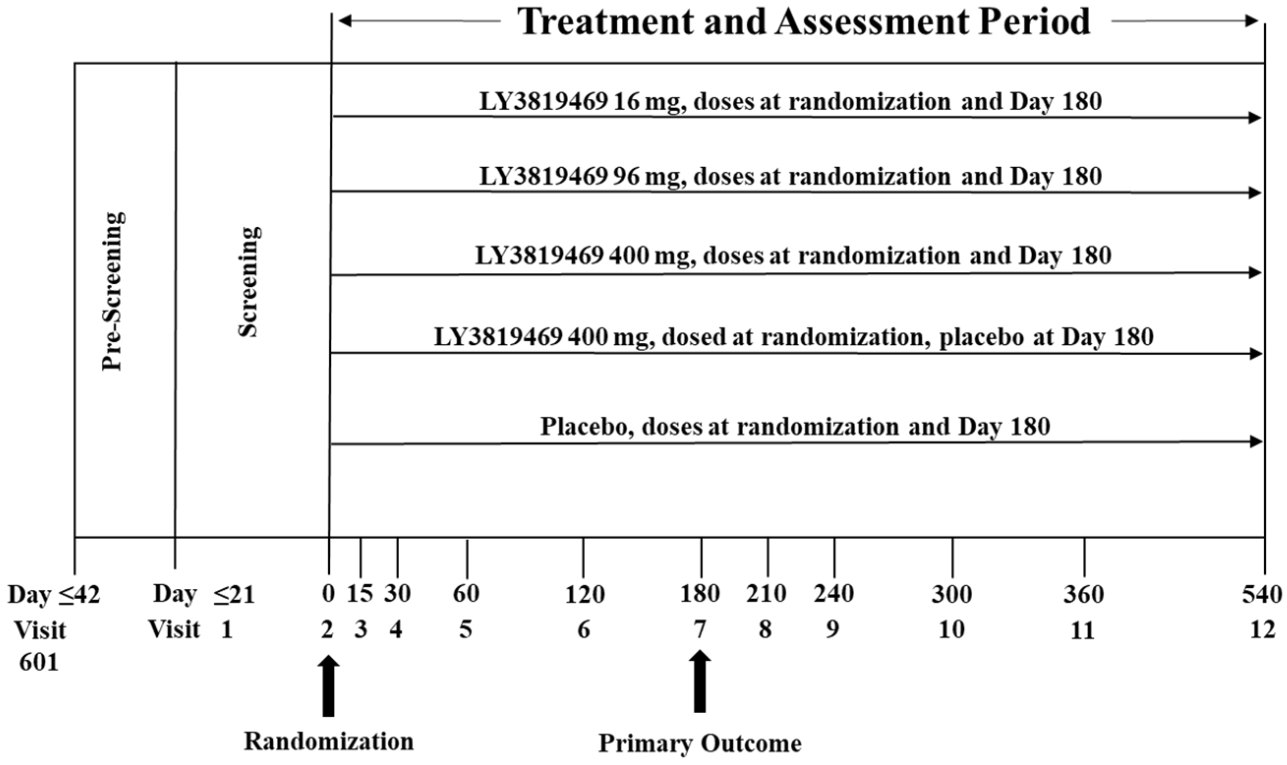

Figure 1.1 Illustration of study design for clinical protocol J3L-MC-EZEB.

2. Statistical Hypotheses

The null hypothesis to be tested in relation to the primary estimand is as follows:

- LY3819469 16 mg, 96 mg, or 400 mg is not different from placebo with respect to percent change in Lp(a) from baseline in time-averaged Lp(a) over Days 60 to 180.

2.1. Multiplicity Adjustment

Treatment comparisons will be performed for the primary objective at the full significance level of 0.05. No multiplicity adjustments will be made for the analysis of secondary and exploratory objectives.

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3. Analysis Sets

This table defines the analysis population and datasets for the purposes of analysis.

Population	Description
Screened	All participants who sign the ICF.
Randomized	All participants who are randomly assigned to a treatment arm.
Full Analysis Set (FAS)	All data for patients who are randomized, take at least 1 dose of study medication, and are not discontinued from the study due to inadvertent enrollment. Participants will be analyzed according to the treatment they were assigned.
Efficacy Analysis Set (EAS)	Data for patients who are randomized, take at least 1 dose of study medication, and are not discontinued due to inadvertent enrollment. Excludes data after permanent discontinuation of study drug (for analysis post–Day 180 participants will be analyzed according to the treatment they were assigned) or after new initiation of medications that are known to impact Lp(a) levels.

Abbreviation: ICF = informed consent form.

4. Statistical Analyses

4.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. Some analyses and summaries described in this analysis plan may not be conducted if not warranted by data (for example, too few events to justify conducting an analysis). Additional analyses of the data may be conducted as deemed appropriate.

Unless otherwise noted, all tests will be conducted at a 2-sided alpha level of 0.05, and confidence intervals (CIs) will be calculated at 95%, 2-sided. All tests of interactions between treatment groups and other factors will be conducted at a 2-sided alpha level of 0.10.

Unless stated otherwise, statistical summaries and analyses will be conducted based on planned randomized treatment group (LY 16 mg 2 doses, LY 96 mg 2 doses, LY 400 mg 2 doses, 400 mg 1 dose plus placebo 1 dose, and placebo 2 doses), regardless of the actual treatment(s) received by the participant. Assessment at or before Day 180 will pool data from both treatment arms assigned to the 400-mg dose.

The primary efficacy assessment, guided by the "treatment-regimen" estimand, which represents the efficacy regardless of treatment discontinuation, will be conducted using the full analysis set (FAS) (Section 3). A restricted maximum likelihood-based, mixed-effect model repeated measures (MMRM) analysis will be used to analyze continuous longitudinal variables. All the longitudinal observations at each scheduled postbaseline visit will be included in the analysis. The model for primary efficacy endpoint of percent change from baseline in Lp(a) will include log(Lp[a])-log(Baseline of Lp[a]) as the dependent variable and the fixed class effects of treatment group (LY 16 mg 2 doses, LY 96 mg 2 doses, LY 400 mg 2 doses, LY 400 mg 1 dose and placebo 1 dose, placebo 2 doses), strata (high risk of cardiovascular events for Lp[a] analysis; high risk of cardiovascular events and Lp[a] strata for non-Lp[a] biomarkers analyses), visit, and treatment-by-visit interaction, as well as the continuous, fixed covariate of baseline Lp(a). An unstructured covariance structure will be used to model the within-participant errors. Significance tests will be based on least squares (LS) means and Type III tests. SAS PROC MIXED will be used to perform the analysis. If this analysis fails to converge, the following covariance structures will be tested in order:

1. Toeplitz with heterogeneity
2. autoregressive with heterogeneity
3. compound symmetry with heterogeneous variances
4. Toeplitz
5. autoregressive, and
6. compound symmetry without heterogeneous variances.

The first covariance structure that converges will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Comparisons of difference in time-averaged response from baseline for each treatment group of LY3819469 versus placebo reference group will be made by using contrasts of LS means.

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Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of LY3819469 doses with placebo irrespective of adherence to intervention. Thus, safety analyses will be conducted using the FAS (Section 3).

Baseline is defined as the last nonmissing measurement recorded on or before the randomization visit, prior to the first dose of intervention, unless otherwise specified. Data may exist at visits where the variable was not scheduled to be collected. In these situations, data from the early discontinuation visit that does not correspond to the planned collection schedule will be excluded from the MMRM, analysis of covariance (ANCOVA), or logistic regression analysis.

Multiple imputation will be used to impute corresponding missing potential outcome according to the missingness pattern. Table EZEB.4.2 summarizes the strategy to handle ICEs and the imputation method to handle missing values for efficacy endpoints.

For continuous measures, summary statistics will include sample size, mean, standard deviation (SD), median, minimum, and maximum for the actual, the change from baseline and percent change from baseline measurements. LS means and standard errors derived from the analysis (MMRM or ANCOVA) models will also be displayed for the change from baseline measurements. Treatment comparisons will be displayed showing the treatment difference LS means and the 95% CIs for the treatment differences, along with the p-values for the treatment comparisons. For categorical measures, summary statistics will include sample size, frequency, and percentages. A logistic regression model will be used to examine the treatment difference in binary efficacy outcomes with missing endpoints imputed. Fisher's exact test or Pearson's chi-square test will be used for treatment comparisons in other categorical outcomes.

For Lp(a), only nmol/L will be reported because there is no direct conversion to conventional (CN) units. For other laboratory values, both CN and the International System of Units (SI) units will be presented.

Endpoints that compare treatment groups based on percent change from baseline will be conducted by log-transformation of the dependent variables. Standard errors and 95% CIs will be constructed using the delta method. The LS means and standard error for each treatment, difference in LS means between arms, and corresponding 95% CIs will be calculated as shown in Table EZEB.4.1, where Z_b is the baseline of the log of the response.

Table EZEB.4.1. Summary of Reported Quantities for Variables Requiring Log-Transformation

Quantity		Change from Baseline	Percent Change from Baseline
Within Treatment	Estimate	$[\exp(\hat{\mu}_{\Delta Z,k}) - 1]\exp(\bar{Z}_{b\cdot})$	$[\exp(\hat{\mu}_{\Delta Z,k}) - 1] \times 100$
	SE	$\exp(\bar{Z}_{b\cdot})\exp(\hat{\mu}_{\Delta Z,k}) \cdot \widehat{SE}_{\Delta Z,k}$	$\exp(\hat{\mu}_{\Delta Z,k}) \cdot \widehat{SE}_{\Delta Z,k} \times 100$
	p-value	NR	p_k
	Estimate	$[\exp(\hat{\mu}_{\Delta Z,k}) - \exp(\hat{\mu}_{\Delta Z,R})] \cdot \exp(\bar{Z}_{b\cdot})$	$(\exp(\hat{\mu}_{\Delta Z,k\ vs\ R}) - 1) \times 100$

Quantity		Change from Baseline	Percent Change from Baseline
Between-Treatment Difference (Treatment k vs. Reference Arm)	SE	$e^{\bar{z}_b \cdot}\sqrt{e^{2\hat{\mu}_{\Delta Z,k}} \cdot \left(\widehat{SE}_{\Delta Z,k}\right)^2 + e^{2\hat{\mu}_{\Delta Z,R}} \cdot \left(\widehat{SE}_{\Delta Z,R}\right)}$	$\exp(\hat{\mu}_{\Delta Z,k\ vs\ R}) \cdot \widehat{SE}_{\Delta Z,k\ vs\ R} \times 100$
	p-value	NR	$p_{\Delta Z,k\ vs\ R}$
	95% CI	Estimate ± $\Phi^{-1}(1-\frac{\alpha}{2})$*SE	$([\exp(L_{\Delta Z,k\ vs\ R}) - 1] \times 100, [\exp(U_{\Delta Z,k\ vs\ R}) - 1] \times 100)$

Abbreviations: CI = confidence interval; NR = not reported; SE = standard error.

In general, a time-averaged parameter will refer to the AUC constructed using the trapezoidal rule, applied to the parameter according to the scheduled time, divided by the length of observation. For example, a time-averaged dependent variable for Days 60 to 180 will equal $AUC/120$, where AUC represents the AUC constructed by the trapezoidal rule.

Details about the analyses regarding demographic and baseline characteristics, historical illnesses, and preexisting conditions, treatment compliance, concomitant medications, and important protocol deviations can be found in Appendices 1 through 5 (Section 6.1 through Section 6.5, respectively.

While considering treatment-emergent abnormal safety laboratory values and vital signs, the baseline observation period starts from the screening visit and ends prior to or at the randomization visit, wherein all scheduled and unscheduled measurements will be included. Baseline for the corresponding safety analysis will be the maximum/minimum (that is, the most extreme/abnormal) from all these measurements during the baseline period. For postbaseline measurements, all scheduled and unscheduled measurements in the analysis period will be included. Table EZEB.4.3 summarizes the definition of baseline, postbaseline, and patient population for different safety endpoints.

End of study participation for a participant will be the earliest of date of death or date of withdrawal from further participation in the study. For participants considered to be lost-to-follow-up, end of study participation will be the date of lost-to-follow-up reported by the investigator. Participant data included in the database after the last date of study participation will be excluded from statistical analysis.

Statistical treatment comparisons will only be performed between LY3819469 and placebo. Because the trial is not adequately powered to detect differences among LY3819469 doses, comparisons across LY3819469 doses will not be performed unless otherwise specified.

Not all analyses described in this SAP will necessarily be included in the clinical study report (CSR). Any analysis described in this SAP and not provided in the CSR will be available upon request.

4.2. Participant Dispositions

A listing and summary of study disposition for all randomized participants will be provided at the primary database lock and final database lock, respectively. Frequency counts and percentages of all participants screened, randomized, and receiving at least 1 dose of study drug will be presented by treatment groups. A listing and summary of randomized participants not receiving study drug will be provided. All participants who discontinue the study and/or study drug will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given. The primary reasons for discontinuation will be listed and summarized by treatment groups.

Details about the demographic and baseline characteristics, historical illnesses, and preexisting conditions, treatment compliance, concomitant medications, and important protocol deviations can be found in Appendices 1 through 5 (Section 6.1 through Section 6.5, respectively).

Table EZEB.4.2. Strategy to Handle ICE and Missingness for Efficacy Endpoints

Analysis Type (Analysis Set)	ICE	Strategy to Handle ICE	Assumption for Missingness	Methods to Handle Missing Values at Endpoints
Time-averaged Lp(a) over Day 60-180 Analysis (FAS)	None	Treatment policy	MAR	There are no ICEs. Missing values will be imputed using all nonmissing data from the same treatment arm.
Time-averaged Lp(a) over Day 30-180, Day 60-180, Day 30-360, and Day 240-360 Analysis (EAS)	"Permanent discontinuation of intervention" and initiation of excluded medications taken during the study or new initiation of Lp(a) modifying medication required to be on a stable regimen prior to treatment per protocol inclusion criteria.	Hypothetical	MAR	Data collected after the ICE will be set to missing. Missing values will be imputed using all nonmissing data (excluding data collected after ICEs) from the same treatment arm.
Lp(a), ApoB, and hsCRP MMRM (EAS)	"Permanent discontinuation of intervention" and initiation of excluded medications taken during the study or new initiation of Lp(a) modifying medication required to be on a stable regimen prior to treatment per protocol inclusion criteria.	Hypothetical	MAR	Data collected after the ICE will be set to missing. Missing values will be imputed using all nonmissing data (excluding data collected after ICEs) from the same treatment arm.

Analysis Type (Analysis Set)	ICE	Strategy to Handle ICE	Assumption for Missingness	Methods to Handle Missing Values at Endpoints
Lipids parameter MMRM (EAS)	"Permanent discontinuation of intervention" and initiation of excluded medications taken during the study or new initiation of Lp(a) modifying medication required to be on a stable regimen prior to treatment per protocol inclusion criteria.	Hypothetical	MAR	Data collected after the ICE will be set to missing. Missing values will be imputed using all nonmissing data (excluding data collected after ICEs) from the same treatment arm.
Lp(a) categorical analyses logistic regression (EAS)	"Permanent discontinuation of intervention" and initiation of excluded medications taken during the study or new initiation of Lp(a) modifying medication required to be on a stable regimen prior to treatment per protocol inclusion criteria.	Hypothetical	MAR	Data collected after the ICE will be set to missing. Missing values will be imputed using all nonmissing data (excluding data collected after ICEs) from the same treatment arm.

Abbreviations: ApoB = apolipoprotein B; EAS = efficacy analysis set; FAS = full analysis set; hsCRP= high-sensitivity C-reactive protein; ICE = intercurrent event; Lp(a)= lipoprotein(a); MAR = missing at random; MMRM = mixed model repeated measures.

Note: For the continuous analysis of clinical laboratory tests, unscheduled measurements are excluded from analysis to reduce bias. The early discontinuation visits are considered scheduled visits.

Table EZEB.4.3. Baseline and Postbaseline Definitions for Safety Analyses

Study Period/Analysis Type	Participant Population	Baseline Observations	Postbaseline Observations
540 Days Study Period			
1.1) Treatment-Emergent Adverse Events (FAS)	All randomized participants who are exposed to at least 1 dose of study drug	The baseline period is defined as the start of screening and ends prior to the first dose of study drug (Visit 2).	Starts after the first dose of study drug and end of the study period.
1.2) Treatment-Emergent Abnormal Labs and Vital Signs (FAS)	All randomized participants who are exposed to at least 1 dose of study drug who have a normal baseline (with respect to the direction being analyzed) and a postbaseline observation	Baseline will be all scheduled and unscheduled measurements recorded during the baseline period as defined above (1.1).	Postbaseline will be defined as above (1.1). All scheduled and unscheduled measurements will be included.
1.3) Change from Last Baseline for Labs, Vital Signs (FAS)	All randomized participants who are exposed to at least 1 dose of study drug and have a baseline and at least 1 postbaseline observation	The last scheduled nonmissing assessment recorded prior to the date of first dose of study treatment during the baseline period defined above (1.1).	Postbaseline will be defined as above (1.1). Only scheduled visits will be included. The early discontinuation visits are considered scheduled visits.
Immunogenicity (FAS)	All randomized participants who are exposed to at least 1 dose of study drug and have a baseline and at least 1 postbaseline observation	Baseline is defined as predose collection at Visit 2.	Postbaseline will be defined as above (1.1). Only scheduled visits will be included. The early discontinuation visits are considered scheduled visits.

Abbreviation: FAS = full analysis set.

Note: For the continuous analysis of clinical laboratory tests, unscheduled measurements are excluded from analysis to reduce bias. The early discontinuation visits are considered scheduled visits.

4.3. Primary Estimand Analysis

The primary estimand (a precise definition of the treatment effect to be estimated) of interest in comparing efficacy of LY3819469 doses with placebo is the “treatment-regimen estimand” (Section 1.1). Because each patient can only take 1 dose for the first 6 months, there are no ICEs of treatment discontinuation. The primary efficacy assessment, guided by the “treatment regimen estimand”, will be conducted using the FAS.

4.3.1. Definition of Endpoint(s)

The primary efficacy measure will be based on the contrast between each treatment group of LY3819469 and placebo for the percent change from baseline in time-averaged Lp(a) over Days 60 to 180 in participants with elevated Lp(a). The Lp(a) over Days 60 to 180 is defined as AUC between Day 60 to Day 180 divided by 120.

4.3.2. Main Analytical Approach

Percent change from baseline in time-averaged Lp(a) over Days 60 to 180 will be analyzed using MMRM modeling strategy for the treatment regimen estimand as detailed in Section 4.1. For the primary analysis (up to Day 180), the 2 LY3819469 treatment groups assigned to 400 mg will be pooled into 1 treatment group because participants are receiving the same study intervention in the first 180 days. Patients without any postbaseline measurement will be excluded from this analysis.

Comparisons of difference in time-averaged response from baseline for treatment group k versus placebo reference group, indexed by R, will be made by using contrasts of LS means to calculate

$$\hat{\theta}_{\Delta k} = \sum_{t} w_t \left(\hat{\beta}_{k:t} - \hat{\beta}_{R:t} \right),$$

where $\hat{\beta}_{k:t}$ corresponds to the LS mean of treatment group k at time t, R represents the placebo reference group, and w_t is the weight at time t informed by the trapezoidal rule. Estimates and CIs will be constructed from the model-based versions using the delta method.

Mean (SD) percent change over time in fasting Lp(a) will be plotted by LY3819469 treatment group and pooled placebo group, until there are fewer than 10% of the FAS population at a given visit. Waterfall plots of by-patient percent changes from baseline to Days 30, 60, 180, 360, and 540 time point will also be provided.

4.4. Efficacy Estimand Analysis

The efficacy endpoints assessment, guided by the "efficacy estimand," will be conducted using the EAS. For the "efficacy estimand," the hypothetical strategy is used to handle the ICEs, so only data collected before the occurrence of any such ICEs will be used in the estimation. Subjects who received only the first dose will be considered to be "on-treatment" during Day 1 to Day 180, whereas subjects who received both doses will be considered to be on-dose during the entire treatment and assessment period (Day 1 to Day 540).

The ICEs considered in the analysis, which are "permanent discontinuation of intervention" and "initiation of excluded medications taken during the study and new initiation of Lp(a) altering therapies per the protocol inclusion criteria", will be handled by the hypothetical strategy, and the potential outcome of interest is the response in the efficacy measurement if participants had adhered to the randomized treatment without using such medication (medication list in Table EZEB.4.4 based on known impact on Lp[a]). Analyses post–Day 180 will also consider the ICE of "treatment discontinuation." There are no other defined ICEs. Switching medications within a class (for example, from 1 statin to another) is not considered as an ICE for the definition of estimand in this study.

Table EZEB.4.4. List of Medication

Category	Medication
Lp(a)-Altering Therapies	• statins • PCSK9 inhibitors • prescription-dose niacin • mipomersen • testosterone, estrogens, antiestrogens, progestins, selective estrogen receptor modulators, or growth hormone
Excluded Treatment Medical Devices, and/or Procedures	• lipid apheresis • any investigational drug, biological agent, or device other than study provided investigational product

Abbreviation: Lp(a)= lipoprotein(a).

4.4.1. Definition of Endpoint(s)

The following endpoints will be analyzed with the "efficacy estimand" using the data in the EAS:

- percent change from baseline in time-averaged Lp(a) over Days 60 to 180, Days 240 to 360, Days 30 to 180, and Days 30 to 360
- proportion of participants achieving Lp(a) <125 and <75 nmol/L at Days 60, 180, 240, 360, and 540
- proportion of participants achieving time-averaged Lp(a) <125 and <75 nmol/L over Days 30 to 180 and Days 30 to 360
- percent change from baseline and absolute change from baseline to Days 60, 180, 240, 360, and 540 for
  - Lp(a)
  - apolipoprotein B (ApoB), and
  - high-sensitivity C-reactive protein (hsCRP)
- proportion of participants achieving Lp(a) lowering of at least 150 nmol/L at Days 60, 180, 240, 360, and 540
- proportion of participants achieving time-averaged Lp(a) lowering of at least 150 nmol/L over Days 30 to 180 and Days 30 to 360
- percent change from baseline and absolute change from baseline in low-density lipoprotein-cholesterol (LDL-C), total cholesterol, high-density lipoprotein-cholesterol (HDL-C), and triglyceride (TG)

The Day 60 and Day 180 analyses may also pool the 2 LY3819469 400-mg treatment groups, where appropriate.

4.4.2. Main Analytical Approach

The time-averaged endpoints will be analyzed using the MMRM in a manner similar to method in Section 4.3.2 for the "efficacy estimand" as described in Section 1.1.

The following 2 study objectives will be analyzed using MMRM and the associated efficacy estimand:

- percent change from baseline and absolute change from baseline to Days 60, 180, 240, 360, and 540 for
  - Lp(a)
  - ApoB, and
  - hsCRP
- percent change from baseline and absolute change from baseline in
  - LDL-C
  - total cholesterol
  - HDL-C, and
  - TG.

Binary endpoints with missing values imputed by categorizing (Yes, No) the imputed values for the corresponding continuous endpoints as described in Table EZEB.4.2 will be analyzed using a logistic regression model with treatment and high-risk cardiovascular disease strata as fixed effects and the continuous baseline value as a covariate.

Table EZEB.4.5 summarizes the objective, endpoints, analysis approaches, and additional information for the efficacy estimand analyses.

Table EZEB.4.5. Efficacy Estimand Analysis

Objectives	Relative to the Efficacy Measure	Analysis Conducted in a Manner Similar to	Additional Information
To evaluate if LY3819469 is superior to placebo in percent Lp(a) reduction over • Days 60-180 • Days 240-360 • Days 30-180, and • Days 30-360	Percent change from baseline in time-averaged Lp(a) over • Days 60-180 • Days 240-360 • Days 30-180, and • Days 30-360	MMRM model in Section 4.3.2	
Compare the effect of LY3819469 to placebo on cardiovascular biomarkers	Percent change from baseline and absolute change from baseline to Days 60, 180, 240, 360, and 540 for • Lp(a) • ApoB • hsCRP	MMRM model described in Section 4.4.2	The continuous clinical measures, including Lp(a), ApoB, and hsCRP, may be log transformed before statistical analyses. LSM estimates will be plotted by treatment through Day 540.
Compare the lipid profile in response to LY3819469 versus placebo	Percent change from baseline and absolute change from baseline in lipid profile • LDL-C	MMRM model described in Section 4.4.2	The lipid biomarkers may be log transformed before statistical analyses.

Objectives	Relative to the Efficacy Measure	Analysis Conducted in a Manner Similar to	Additional Information
	• total cholesterol • HDL-C • triglycerides		LSM estimates will be plotted by treatment through Day 540.
Compare proportion of participants on LY3819469 versus placebo achieving Lp(a) threshold levels	• Proportion of participants achieving Lp(a) <125 and <75 nmol/L at Days 60, 180, 240, 360, and 540 • Proportion of participants achieving time-averaged Lp(a) <125 and <75 nmol/L over Days 30-180 and Days 30-360	Logistic regression model with multiple imputation with log-transformed baseline Lp(a) as a covariate	Use treatment group, stratification strata and continuous baseline value as covariates. Missing postbaseline continuous-valued Lp(a) data are imputed first within each treatment arm before deriving the binary outcome. Plot of proportion of patients achieving Lp(a) <125 and <75 nmol/L reduction at different timepoints will also be provided. Kaplan-Meier plots of time to initially achieve Lp(a) <125 and <75 nmol/L will be provided.
Compare proportion of participants on LY3819469 versus placebo achieving absolute lowering of Lp(a) threshold	• Proportion of participants achieving Lp(a) lowering of at least 150 nmol/L at Days 60, 180, 240, 360, and 540 • Proportion of participants achieving time-averaged Lp(a) lowering of at least 150 nmol/L over Days 30-180 and Days 30-360	Logistic regression model with log-transformed baseline Lp(a) as a covariate	Similar to the binary endpoint above.

Abbreviations: ApoB = apolipoprotein B; HDL-C = high-density lipoprotein-cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); LSM = least squares mean; MMRM = mixed model for repeated measures.

4.5. Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Methods

Pharmacokinetic (PK), pharmacodynamic (PD), and PK/PD analysis are the responsibility of Lilly's PK/PD group.

A population PK approach using nonlinear mixed-effects modeling will be used to analyze LY3819469 concentration data.

Exposure-response analysis between LY3819469 concentration and Lp(a) levels may be performed using population PK/PD nonlinear mixed-effects modeling techniques implemented on Nonlinear Mixed Effects Modeling (NONMEM) software.

Additionally, the impact of intrinsic and extrinsic factors, such as age, weight, gender, and renal function, on PK and PD parameters, may be examined as needed.

If antidrug antibody (ADA) titers are detected from immunogenicity testing, then the impact of immunogenicity titers on LY3819469 PK or any relevant efficacy parameters may also be examined. Additional analyses may be conducted if they are deemed appropriate.

4.6. Immunogenicity

At the visits and times specified in the protocol schedule of activities (Section 1.3), venous blood samples will be collected (if local regulations and ethical review boards allow) and stored for potential future analysis to determine antibody production against LY3819469. If the data is available at the time of final database lock, the following analysis will be conducted.

Treatment-emergent antidrug antibodies (TE ADAs) are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA). A patient is evaluable for TE ADA if the patient has a nonmissing baseline ADA result, and at least 1 nonmissing postbaseline ADA result.

A listing of ADA results and TE ADA status at each visit will be provided, including ADA screening test result (detected/not detected) and the titer for detected samples.

The frequency and percentage of patients with preexisting ADA and with TE ADA will be tabulated by dose (if data warrant), where proportions are relative to the number of patients who are TE ADA evaluable. The frequency and percentage of patients with hypersensitivity and injection site reaction treatment-emergent adverse events (TEAEs) by TE ADA status will be tabulated if data warrant.

4.7. Tertiary/Exploratory Endpoints Analysis

4.7.1. Bayesian Analyses for Dose-Response

The longitudinal Nonmonotone Exponential Time (NEXT) model will be applied to model the longitudinal dose-response following a single dose of LY3819469. The model is appropriate for a situation when the response reaches the maximum effect and starts to deteriorate. It can be used to evaluate the durability of the treatment after a single dose of a potent and durable treatment such as LY3819469. The 2-component prediction (ITP) model proposed in Fu et al. (2010) and Qu et al. (2019) can be considered a special case of the NEXT model. The model is as follows:

$$Y_{dit} = \beta_0 Baseline + f(t;\beta_1,\beta_2)(\lambda(d) + \delta_{di}) + \epsilon_{dit},$$

where Y_{dit} represents the observation for subject i at time t when taking dose d, $\lambda(d)$ is the mean dose response function for dose d, δ_{di} is the between-subject random error term, ϵ_{dit} is the within-subject random error term. The mean response function $f(t;\beta_1,\beta_2)$ is modeled as

$$f(t;\beta_1,\beta_2) = \frac{1-e^{-\beta_1 t}}{1+\beta_2 t},$$

where β_1 controls the rate of change of the response curve and β_2 controls the time to maximum treatment effect.

A 3-parameter logistic regression model may be assumed for the dose response function, $\lambda(d)$. Let α_0, α_1, and α_2 represent the basal effect when the dose level is 0 (placebo), the maximum effect that can be achieved by any dose level on top of placebo, and the dose level that produces half of the maximum improvement, respectively. Then, the mean function of the parameter of interest is modeled by

$$\lambda(d) = \alpha_0 + \frac{\alpha_1 d}{\alpha_2 + d}.$$

The estimation of the parameters will be carried out in a Bayesian framework assuming noninformative priors for the hyperparameters in the model as follows:

$$\begin{cases} \alpha_0, \alpha_1 \sim N(0, 100^2), \\ \alpha_2 \sim U(0, 400), \\ \frac{1}{\sigma^2} \sim Gamma(0.01, 0.01), \\ \beta_0, \beta_1, \beta_2 \sim N(0, 100^2). \end{cases}$$

Posterior inference will be drawn for the dose-response of clinical interest and the 95% credible intervals will also be plotted.

Other dose-response models for $f(d)$ may be explored if the aforementioned dose-response models do not fit the data well, for example, Simple Normal Dynamic Linear Modeling (NDLM) described below

$$\begin{cases} f(d_1) \sim N(0, \tau) \\ f(d_{i+1}) \sim N(f(d_1), \tau), i = 1,2 \ldots \end{cases}$$

where 1,2,... are the indexes of each ith dose level. The first dose level prior takes on a normal distribution with a mean of 0 and a precision of τ. τ is drawn from either a normal or gamma distribution. Subsequent dose levels take on a normal distribution with the mean of the previous dose level and precision τ.

Variations of the NEXT model may be explored to model the longitudinal dose-response following a second dose of LY3819469.

4.8. Safety Analyses

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of LY3819469 doses with placebo irrespective of adherence to intervention. Thus, safety analyses will be conducted using the FAS. Safety assessments may also pool the 2 LY3819469 400-mg treatment groups, where appropriate.

4.8.1. Extent of Exposure

Duration of exposure will be calculated as number of days subject was "on-treatment" as defined in Section 4.1. Summary of duration of exposure (defined as time in days from date of randomization to the date of the last study visit) will be provided by treatment group using data from FAS. The following descriptive statistics will be provided: n, mean, SD, median, minimum, maximum, and sum (that is, total participant-years of follow-up). In addition, the number of subjects who received 1 or 2 doses will be summarized by counts and percentages.

4.8.2. Adverse Events

A TEAE is defined as an event that first occurred or worsened in severity after first dose. The Medical Dictionary for Regulatory Activities (MedDRA) low level term (LLT) will be used in the treatment-emergent derivation. The maximum severity for each LLT during the baseline period including ongoing medical history will be used as baseline severity. Events with a missing baseline severity will be treated as "mild" in severity for determining treatment-emergence. Events with a missing severity during the postbaseline period will be treated as "severe" and treatment-emergence will be determined by comparing to baseline severity.

For events occurring on the day of first taking study medication, the case report form collected information (for example, treatment emergent flag, start time of study treatment and event) will be used to determine whether the event was pre- versus post-treatment if available. If the relevant information is not available, then the events will be counted as posttreatment.

The counts and percentages of participants with TEAEs will be summarized by treatment using MedDRA preferred terms (PTs) nested within system organ class (SOC). Statistical comparisons will be applied at both the SOC and PT levels. Events will be ordered by decreasing frequency within SOC. The SOC will be in alphabetical order. For events that are sex-specific, the denominator and computation of the percentage will include only participants from the given sex.

An overview of the number and percentage of participants who experienced a TEAE, a serious adverse event (SAE), or death, participants who discontinued from study treatment or study due to an AE, and relationship to study drug will be summarized by treatment.

The counts and percentages of patients with TEAEs by maximum severity will be summarized by treatment using MedDRA PT. For each participant and TEAE, the maximum severity for the MedDRA PT is the maximum postbaseline severity observed from all associated LLTs mapping to the MedDRA PT. The maximum severity will be determined based on the nonmissing severities. If all severities are missing for the defined postbaseline period of interest, it will show as missing in the table.

4.8.3. Patient Narratives

Patient narratives will be provided for all participants who experience any of the following "notable" events:

- death
- serious AE, or
- permanent discontinuation of study treatment due to AEs.

Patient narratives (patient level data and summary paragraph) will be provided for participants in the randomized population with at least 1 notable event.

4.8.4. Vital Signs

If multiple records of an individual's vital signs are collected at the same visit, they will be averaged prior to being used for data summaries and analyses.

Descriptive summaries by treatment and by nominal visit will be provided for baseline and postbaseline values as well as change from baseline values.

Treatment differences in mean change will be analyzed using the MMRM model as described in Section 4.4.2 for the FAS.

Counts and percentages of participants with treatment-emergent abnormal sitting systolic blood pressure (BP), sitting diastolic BP, and pulse rate will be presented by treatment group. Both planned and unplanned measurements will be included in the analysis. The criteria for identifying patients with treatment-emergent vital sign abnormalities are stated in Table EZEB.4.6.

Table EZEB.4.6. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressure and Pulse Measurements

Parameter	Low	High
Systolic BP (mm Hg) (sitting)	≤90 and decrease from baseline ≥20	≥129 and increase from baseline ≥20
Diastolic BP (mm Hg) (sitting)	≤50 and decrease from baseline ≥10	≥90 and increase from baseline ≥10
Pulse (bpm) (sitting)	<50 and decrease from baseline ≥15	>100 and increase from baseline ≥15

Abbreviation: BP = blood pressure.

Counts and percentages of participants with maximum systolic BP and diastolic BP will be summarized by treatment groups for the following categories using safety participants.

Systolic BP (mm Hg)	Diastolic BP (mm Hg)
<90	<60
≥90	>60
≥120	>90
≥140	>110
≥160	≥120
≥180	

Abbreviation: BP = blood pressure.

4.8.5. Electrocardiograms

Treatment-emergent qualitative electrocardiogram (ECG) abnormalities are defined as qualitative abnormalities that first occurred after baseline. Qualitative abnormal ECGs will be recorded as an AE. A listing of abnormal qualitative ECGs will be created.

4.8.6. Clinical Laboratory Evaluation

For Lp(a), only nmol/L will be reported. All other laboratory data will be reported in both CN and SI units. Limits from the performing lab will be used to define low and high. Descriptive summaries by treatment and by nominal visit will be provided for the baseline and postbaseline values as well as the change from baseline values.

Observed and change from baseline values for each visit may be displayed in plots for participants who have both a baseline and at least 1 postbaseline planned measurement. Baseline will be the last nonmissing observation prior to taking first study drug. Unplanned measurements will be excluded from plots.

A shift table will be provided including unplanned measurements. The shift table will include the number and percentage of participants within each baseline category (low, normal, high, or missing) versus each postbaseline category (low, normal, high, or missing) by treatment. The proportion of participants shifted will be compared between treatments using Fisher's exact test.

For qualitative laboratory analytes, the counts and percentages of participants with normal and abnormal values will be summarized by treatment.

A listing of abnormal findings will be created for laboratory analyte measurements, including qualitative measures. The listing will include participant identification, treatment group, laboratory collection date, study day, analyte name, and analyte finding.

The MMRM model as described in Section 4.4.2 or ANCOVA (if MMRM model is not applicable due to single postbaseline measurement) will be used for the analysis during the treatment period for the continuous measurements for selected lab tests.

4.8.7. Additional Safety Assessments

4.8.7.1. Hepatobiliary Disorders

The counts and percentages of participants with treatment-emergent potentially drug-related hepatobiliary disorders will be summarized by treatment using the PTs nested within Standardized MedDRA Queries (SMQs). Detailed search criteria can be found in Appendix 6 (Section 6.6).

4.8.7.1.1. Liver Enzymes

Analyses for laboratory analyte measurements are described in Section 4.8.6. This section describes additional analyses of liver enzymes.

Hepatic labs include alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBL), direct bilirubin (DBL), serum alkaline phosphatase (ALP), international normalized ratio (INR), and gamma-glutamyl transferase (GGT). When criteria are met for hepatic evaluations, investigators will conduct close monitoring of hepatic symptoms and liver tests, perform a comprehensive evaluation for alternative causes of abnormal liver tests, and complete follow-up hepatic safety electronic case report form (eCRFs).

The following will be analyzed for hepatic safety (Table EZEB.4.7):

Table EZEB.4.7. Summary Tables and Figures Related to Hepatic Safety

Analysis	Population or Analysis Set
Abnormal Postbaseline Categories – Hepatic Safety Parameters ALT • The number and percentage of participants with a measurement greater than or equal to 1×, 3×, 5×, 10×, and 20× the performing lab ULN during the treatment period for all participants with a postbaseline value. AST • The number and percentage of participants with a measurement greater than or equal to 1×, 3×, 5×, 10×, and 20× the performing lab ULN during the treatment period for all participants with a postbaseline value. ALP • The number and percentage of participants with a measurement greater than or equal to 2× and 3× the performing lab ULN during the treatment period will be summarized for all participants with a postbaseline. TBL • The number and percentage of participants with a measurement greater than or equal to 2×, 5×, and 8× the performing lab ULN during the treatment period will be summarized for all participants with a postbaseline value. DBL • The number and percentage of participants with a measurement greater than or equal to 2× and 5× the performing lab ULN during the treatment period will be summarized for all participants with a postbaseline value. GGT • The number and percentage of participants with a measurement greater than or equal to 2× the performing lab ULN during the treatment period will be summarized for all participants with a postbaseline value.	FAS
Hepatocellular Drug-Induced Liver Injury Screening Plot (TBL vs. ALT or AST)	FAS
Hepatocellular Drug-Induced Liver Injury Screening Table	FAS
Cholestatic Drug-Induced Liver Injury Screening Plot (TBL vs. ALP)	FAS
Cholestatic Drug-Induced Liver Injury Screening Table	FAS
Participant profiles will be created for participants meeting criteria for a comprehensive hepatic evaluation (as defined in the protocol). Participant profiles will include demographics, disposition, information collected on the hepatic safety CRFs (where applicable) and a display of study drug exposure, adverse events, medications, blood pressure, heart rate, and the liver-related measurements over time.	FAS

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRF = case report form; DBL = direct bilirubin; FAS = full analysis set; GGT = gamma-glutamyl transferase; TBL = total bilirubin; ULN = upper limit of normal.

Planned and unplanned measurements will be included. The measurements do not need to be taken at the same blood draw. Maximum baseline will be the maximum nonmissing observation in the baseline period. The maximum value will be the maximum nonmissing value from the postbaseline period. Planned and unplanned measurements will be included.

The primary purpose of the screening plots is to identify participants whose data warrant further review. For these plots, symbols will be used to indicate the randomized treatment.

For individual participants of interest, participant profiles will be reviewed. The review will include which treatment the participant was taking over time, the changes in hepatic labs over time, and the temporal association with potential causes. The review of participant profiles will also include the identification of any potential Hy's law case or potential cholestatic liver injury case that could have been missed by focusing only on the maximum values when determining 30-day time associations.

4.8.7.2. Hypersensitivity Events

Hypersensitivity reactions and related information reported in eCRF will be listed and summarized by treatment.

Summaries of all potential hypersensitivity reactions will be generated by PT with decreasing frequency by treatment. The AE database will be searched using predefined SMQs to identify events consistent with hypersensitivity events. Detailed search criteria can be found in Appendix 6 (Section 6.6).

4.8.7.3. Injection Site Reactions

Injection site reactions, incidence, and related information reported in eCRFs will be summarized by treatment. Information to be summarized includes the timing of the reaction relative to study drug administration, and characteristics of the injection site reaction: erythema, induration, pain, pruritus, and edema.

Additionally, potential injection site reactions will be searched by predefined MedDRA high level terms (HLTs) of injection site reactions, administration site reactions, and infusion-related reactions. Detailed searching criteria for injection site reaction events can be found in Appendix 6 (Section 6.6). The PT will be used for summary by treatment within each HLT category.

4.8.7.4. Renal Safety

Two shift tables examining renal function will be created: i) a min-to-min shift table of estimated glomerular filtration rate (eGFR) estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation with unit mL/min/1.73 m^2, using categories (<30, ≥30 to <45, ≥45 to <60, ≥60 to <90, and ≥90 mL/min/1.73 m^2), and ii) max-to-max shift table of urine albumin-to-creatinine ratio (UACR), using the categories UACR <30 g/kg, 30 g/kg ≤ UACR

≤300 g/kg, and UACR >300 g/kg (respectively, these represent normal, microalbuminuria, and macroalbuminuria).

Mixed model repeated measure analyses for eGFR and UACR will be provided. Log transformation will be performed for UACR.

4.8.7.5. Major Adverse Cardiovascular Events

Death and nonfatal cardiovascular AEs (NCAE) reported by investigators will be adjudicated by an independent clinical endpoint committee (CEC) that consists of a group of physicians external to Lilly with cardiology expertise. This committee will be blinded to treatment assignment.

The NCAEs to be adjudicated include

- myocardial infarction
- hospitalization for unstable angina
- hospitalization for heart failure
- coronary interventions, such as coronary artery bypass graft or percutaneous coronary intervention, and
- cerebrovascular events, including cerebrovascular accident (stroke) and transient ischemic attack.

The counts and percentages of participants with adjudicated NCAEs and death may be summarized by treatment.

In addition, NCAEs reported by investigator may also be summarized. Death reported by investigator may be listing in a separate table.

A listing of participants reporting NCAE events, either reported by investigators or identified by the aforementioned committee, will be provided. The listing will include treatment, participants' identification, including the site number, date of event, type of event as reported by the investigator, type of event as adjudicated by the physician committee, time from first dose of study drug to the event, and time from last dose to the event (if participant has discontinued study drug prior to the event).

4.9. Subgroup Analyses

Subgroup analyses of the primary endpoint will be conducted to assess the consistency of the intervention effect across the following subgroups:

- age group (<65 vs. ≥65 years old)
- race (white, nonwhite)
- gender: female vs. male
- baseline body mass index (BMI) (kg/m^2) (< median vs. ≥ median)
- baseline Lp(a) level (<275 nmol/L vs. ≥275 nmol/L)
- high risk of cardiovascular event (yes/no), and
- baseline eGFR(<60 and ≥60 mL/min/1.73 m^2).

For each subgroup analysis, the following model will be conducted:

- Time-averaged endpoints analysis in Lp(a) (percent change from baseline in time-averaged Lp[a] over Days 60 to 180)

If the number of participants within a subgroup is too small (less than 10%), then the subgroup categories may be redefined prior to unblinding the study or descriptive statistical analysis will be applied. Additional subgroup analyses may also be performed.

Additional subgroup analyses may be performed. For example, subgroup analyses may be done for Chinese and Japanese populations, respectively, to support local regulatory interactions.

4.10. Interim Analyses

An interim analysis may be conducted when at least 10% of the participants complete Day 180 at Visit 7 or discontinue the study. The primary database lock and primary data analysis for Study EZEB will occur when all participants have completed Day 180 (Visit 7). After primary analysis and before final analysis (all randomized participants have completed the study), additional efficacy and safety assessment may occur when at least 85% participants have completed 240 days (Visit 9) and 10% of participants have completed 360 days (Visit 11) of the treatment. These analyses will be for the purpose of internal planning and decision-making and may assess safety, PK, and/or efficacy measures.

An assessment committee (AC) will be formed to review the interim analyses in an unblinded manner. The details regarding the number of participants and type of analysis will be provided in the AC charter and in the unblinding plan. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team members before the study has been unblinded. Study sites will receive information about interim results only if deemed necessary for the safety of the participants. Participants and investigators will remain blinded until the completion of the study.

4.11. Changes to Protocol-Planned Analyses

Extend the time periods of interest for first secondary objective regarding time-averaged Lp(a) lowering.

5. Sample Size Determination

The sample size calculation is based on the primary estimand and its endpoint, and the percent change from baseline in time-averaged Lp(a) over Days 60 to 180.

Approximately 254 participants will be randomly assigned in a 1:2:2:2:2 ratio to LY3819469 16 mg 2 doses, 96 mg 2 doses, 400 mg 2 doses, 400 mg 1 dose plus placebo 1 dose, and placebo 2 doses. Assuming a 15% dropout rate, this results in approximately 24 completers for the 16-mg group and 48 completers per arm for the rest of the groups.

Assuming a SD of 20%, and a 2-sided alpha level of 0.05, the completers for each treatment arm will provide >99% power to detect a treatment difference of 70% reduction for the primary endpoint of LY3819469 versus placebo. The sample size was determined appropriate to provide a sufficient amount of safety data.

6. Supporting Documentation

6.1. Appendix 1: Demographic and Baseline Characteristics

A listing of participant demographics for all randomized participants will be provided. All demographic and baseline clinical characteristics will be summarized by treatment groups for all randomized participants.

Baseline demographic and clinical characteristics of special interest include but are not limited to: age (years), sex (female, male), race, ethnicity, height (cm), weight (kg), BMI (kg/m^2), age group (<65 years, ≥65 years), Lp(a), LDL-C, ApoB, hsCRP, total cholesterol, HDL-C, TGs and baseline Lp(a) strata, eGFR (CKD-EPI, mL/min/1.73m^2), eGFR groups (<30, ≥30 to <45, ≥45 to <60, ≥60 to <90, and ≥90 mL/min/1.73 m^2), high risk of cardiovascular event group (yes/no), and medical history group (including aortic valve stenosis, cerebrovascular accident, coronary artery bypass grift, coronary artery disease, familial hypercholesterolemia, heart failure, LDL apheresis, myocardial infarction, percutaneous coronary intervention, peripheral arterial disease, rheumatic aortic stenosis, transient ischemic attack, type 2 diabetes mellitus and unstable angina).

6.2. Appendix 2: Historical Illnesses and Pre-existing Conditions

The count and percentages of participants with historical illnesses and preexisting conditions will be summarized by treatment groups using the MedDRA PTs nested within SOC. The SOC will be in alphabetical order. Conditions (that is, PTs) will be ordered by decreasing frequency within SOC. This will be summarized for all randomized participants.

6.3. Appendix 3: Treatment Compliance

Listing and summary of prematurely discontinuing study treatment (including discontinuation reason) and discontinuing study will be provided by treatment groups.

6.4. Appendix 4: Concomitant Medications

Concomitant medications will be summarized by treatment group. The percentages of participants who took concomitant medication will be summarized by treatment using PTs nested within Anatomical Therapeutic Chemical (ATC) Level 3 codes. The concomitant medications will be ordered by decreasing frequency within each ATC level.

6.5. Appendix 5: Important Protocol Deviations

Important protocol deviations are identified in the Trial Issues Management Plan. A listing and summary of important protocol deviations by treatment groups will be provided at the end of study (for all randomized participants).

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6.6. Appendix 6: Searching Criteria for Additional Safety Assessments

Hepatic treatment-emergent adverse events

Treatment-emergent, potentially drug-related hepatic disorders will be summarized by treatment using the MedDRA PTs contained in any of the following SMQs:

- Broad and narrow terms in the Liver related investigations, signs and symptoms SMQ (20000008)
- Broad and narrow terms in the Cholestasis and jaundice of hepatic origin SMQ (20000009)
- Broad and narrow terms in the Hepatitis non-infections SMQ (20000010)
- Broad and narrow terms in the Hepatic failure, fibrosis and cirrhosis and other liver damage SMQ (20000013)
- Narrow terms in the Liver-related coagulation and bleeding disturbances SMQ (20000015)
- Narrow PTs in Gallbladder related disorders SMQ (20000124)
- Narrow PTs in Biliary tract disorders SMQ (20000125), and
- Narrow PTs in Gallstone related disorders SMQ (20000127).

Injection site reactions

Treatment emergent injection site reaction will be summarized by treatment using the MedDRA PT in any of the following MedDRA HLTs:

- Injection site reaction
- Administration site reaction, and
- Infusion site reactions.

Hypersensitivity events

Both analyses in Section 4.8.7.2 use the current standard MedDRA SMQs to search for relevant events.

The hypersensitivity TEAEs are characterized as follows:

- Narrow and algorithm terms in Anaphylactic reaction SMQ (20000021)
- Narrow terms in Angioedema SMQ (20000024)
- Narrow terms in Severe cutaneous adverse reactions SMQ (20000020), and
- Narrow terms in Hypersensitivity SMQ (20000214).

7. References

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