Statistical Analysis Plan J2O-MC-EKBC Version 1

KRAKEN: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Oral Once-Daily LY3473329 in Adults With Elevated Lipoprotein(a) at High Risk for Cardiovascular Events

NCT05563246

Approval Date: 20-Sep-2023

Statistical Analysis Plan for KRAKEN Study (J2O-MC-EKBC)

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Oral Once-Daily Muvalaplin (LY3473329) in Adults with Elevated Lipoprotein(a) at High Risk for Cardiovascular Events

Protocol Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Oral Once-Daily Muvalaplin (LY3473329) in Adults with Elevated Lipoprotein(a) at High Risk for Cardiovascular Events

Protocol Number: J2O-MC-EKBC

Compound Number: LY3473329

Short Title: Efficacy and safety of muvalaplin (LY3473329) compared with placebo in adults with elevated Lp(a) at high risk for cardiovascular events

Acronym: KRAKEN

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

Registry	ID
	IND: 155551
	EU trial number: 2022-501466-21-00

Document ID: VV-CLIN-076972

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Version history

Table 1.1. SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	6 Sept 2023	Not Applicable	Original version

1. Introduction

There are no changes to the analyses described in the protocol.

1.1. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
• To evaluate if muvalaplin is superior to placebo in percent Lp(a) reduction	• Percent change in Lp(a) from baseline to Week 12
Secondary	
• Compare proportion of participants on muvalaplin versus placebo achieving Lp(a) threshold levels	• Proportion of participants achieving Lp(a) <125 nmol/L at Week 12
• Compare the effect of LY3473329 to placebo on cardiovascular biomarkers	• Percent change from baseline to Week 12 for o ApoB o hsCRP
• Characterize the PK of LY3473329	• Population PK parameters
Exploratory	
• Compare proportion of participants on LY3473329 versus placebo achieving absolute lowering of Lp(a) threshold	• Proportion of participants achieving Lp(a) lowering of at least 150 nmol/L at Week 12
• To compare the effect of LY3473329 versus placebo on plasminogen	• Change in plasminogen activity
• Compare the lipid profile in response to LY3473329 versus placebo	• Lipid profile o LDL o total cholesterol o HDL o triglycerides
• Health-related quality of life	• SF-36v2 acute form domain scores

Abbreviations: ApoB = apolipoprotein B; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; 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 Lp(a) after 12 weeks of study intervention in participants who meet the

inclusion criteria and would have completed the treatment period without initiating other medications that are known to impact Lp(a) levels?

This question is addressed using the efficacy estimand, which is described by the following attributes:

- Population: participants who meet the enrollment criteria. Further details can be found in Section 5 of the study protocol of EKBC.
- Endpoint: percent change from baseline to Week 12 in Lp(a).
- Treatment condition: the randomized treatment. Further details on study interventions and concomitant interventions can be found in Section 6 of the study protocol of EKBC.

The intercurrent event*s (ICEs) "intervention discontinuation for any reason" and "new initiation of any Lp(a) modifying medication" are addressed 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.*

Population-level summary: mean *percent changes in Lp(a).*

Treatment contrast of interest*: difference in mean percent changes in Lp(a) between LY3473329 and placebo.*

Rationale for estimand: *This Phase 2 study aims to study the efficacy of LY3473329 under the ideal condition that all participants adhere to the randomized treatment without initiating other medications known to impact Lp(a) levels*.

A similar efficacy estimand will be used for the secondary and exploratory objectives.

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of LY3473329 doses with placebo irrespective of adherence to study intervention or initiation of new Lp(a) modifying medication, including data collected during the treatment period and safety follow-up.

Secondary estimand

For the primary endpoint, a secondary clinical question of interest is: What is the intervention difference in percent change from baseline in Lp(a) after 12 weeks of study intervention in participants who meet the inclusion criteria regardless of treatment discontinuation for any reason or initiation of other medications known to impact Lp(a) levels?

This question is addressed using the treatment-regimen estimand, which is described by the following attributes:

Population: participants who meet the enrollment criteria. Further details can be found in Section 5 of the study protocol of EKBC.

Endpoint: percent change from baseline to Week 12 in Lp(a).

Treatment condition: the randomized treatment. Further details on study interventions, and concomitant interventions can be found in Section 6 of the study protocol of EKBC.

The intercurrent events "intervention discontinuation for any reason" and "new initiation of any Lp(a) modifying medication" are addressed by the treatment-regimen strategy, and the potential

outcome of interest is the response in the efficacy measurement regardless of whether participants had adhered to the randomized treatment without using such medication.

Population-level summary: mean percent changes in Lp(a).

Treatment contrast of interest: difference in mean percent changes in Lp(a) between LY3473329 and placebo.

Rationale for estimand: this estimand aims to study the efficacy of LY3473329 that reflects the real-life behavior of the target population.

1.2. Study Design

Study EKBC is a parallel, double-blinded, placebo-controlled, dose-finding, Phase 2 study of LY3473329 in participants with elevated Lp(a) and at high risk for cardiovascular events.

The purpose of this study is to measure difference in percent change in Lp(a) from baseline to 12 weeks with LY3473329 versus placebo in participants with elevated Lp(a) and high risk for cardiovascular events.

Study details include:

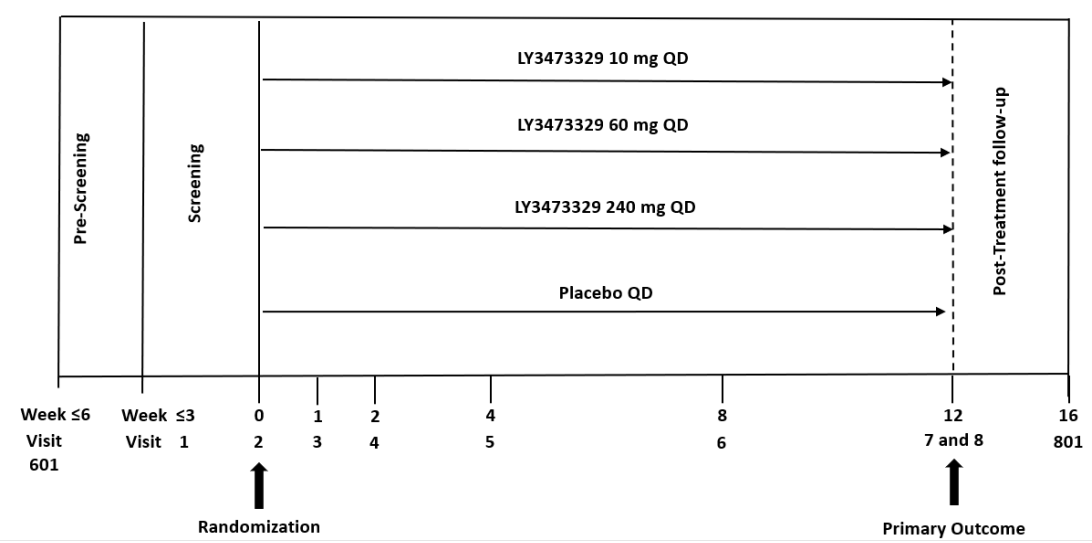
- The study duration will be up to 22 weeks.
- The treatment duration will be up to 12 weeks.

All participants will be required to take 4 tablets by mouth every day for 12 weeks to ensure blinding.

Approximately 233 participants will be randomized in a 1:2:2:2 ratio to 1 of the following arms with daily oral dosing for a 12-week treatment period:

- Arm A: 10 mg LY3473329
- Arm B: 60 mg LY3473329
- Arm C: 240 mg LY3473329
- Arm D: placebo

Participants will be stratified by country and baseline Lp(a) (<275 nmol/L, ≥275 nmol/L as measured by the apo(a) assay defined in Section 4.1).



2. Statistical Hypotheses

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

- LY3473329 10 mg, 60 mg, and 240 mg are not different from placebo with respect to percent change from baseline in Lp(a)

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.

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.
Efficacy Analysis Set (EAS)	Data obtained during treatment period from all randomly assigned participants who are exposed to at least 1 dose of double-blind study treatment. Excludes data after discontinuation of study drug or initiation of Lp(a) modifying medication.
Full Analysis Set (FAS)	Data obtained during the treatment period from all randomly assigned participants who are exposed to at least 1 dose of intervention, regardless of adherence to intervention or initiation of Lp(a) modifying medication.
Safety Analysis Set (SS)	Data obtained during the treatment period plus safety follow-up from all randomly assigned participants who are exposed to at least 1 dose of intervention, regardless of adherence to intervention or initiation of Lp(a) modifying medication.

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.

Change from baseline will be calculated as the value of interest at the visit minus the baseline value. In general, percent change from baseline will be calculated as the value of change from baseline divided by the baseline value in 100% scale. Some specific predefined parameters may be log-transformed before statistical analysis, if deemed necessary. If the baseline value is missing for a particular variable, then the change from baseline and percent change from baseline will not be calculated.

Unless stated otherwise, statistical summaries and analyses will be conducted based on planned randomized treatment group (LY 10 mg, LY 60 mg, LY 240 mg, and placebo), regardless of the actual treatment(s) received by the participant.

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 the percent change from baseline measurements. Measures that are log-transformed will be summarized by geometric mean rather than arithmetic mean and coefficient of variation rather than standard deviation. Least squares (LS) means and standard errors derived from the analysis models will also be displayed for the change from baseline measurements. For analysis of log-transformed parameters, model estimated means and standard errors on the original scale will be derived through back-transformation using the delta method from the LS means and standard errors on the natural log-scale. All baseline measures will be analyzed using an analysis of variance (ANOVA) model that has treatment group as the fixed effect. 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.

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 mixed model repeated measures (MMRM), analysis of covariance (ANCOVA), or logistic regression analysis, unless otherwise specified.

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 EKBC.4.1, where $\bar{Z}_{b\cdot}$ is the arithmetic mean of the baseline of the log of the response, $\hat{\mu}_{\Delta Z,k}$ and $\widehat{SE}_{\Delta Z,k}$ are the estimates and standard errors of change from baseline on the log scale for treatment group k, and $\hat{\mu}_{\Delta Z,k\ vs\ R}$, $\widehat{SE}_{\Delta Z,k\ vs\ R}$, $L_{\Delta Z,k\ vs\ R}$, and $U_{\Delta Z,k\ vs\ R}$ are the estimates, standard errors, lower and upper confidence limits for the comparison of treatment group k versus placebo.

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

Quantity		Change from Baseline	Percent Change from Baseline
Within Treatment	Estimate	$\left[\exp\left(\hat{\mu}_{\Delta Z,k}\right)-1\right]\exp(\bar{Z}_{b\cdot})$	$\left[\exp\left(\hat{\mu}_{\Delta Z,k}\right)-1\right]\times 100$
	SE	$\exp(\bar{Z}_{b\cdot})\exp\left(\hat{\mu}_{\Delta Z,k}\right)\cdot\widehat{SE}_{\Delta Z,k}$	$\exp\left(\hat{\mu}_{\Delta Z,k}\right)\cdot\widehat{SE}_{\Delta Z,k}\times 100$
	P-value	NR	p_k
Between-Treatment Difference (Treatment k vs. Reference Arm)	Estimate	$\left[\exp\left(\hat{\mu}_{\Delta Z,k}\right)-\exp\left(\hat{\mu}_{\Delta Z,R}\right)\right]\cdot\exp(\bar{Z}_{b\cdot})$	$\left(\exp(\hat{\mu}_{\Delta Z,k\ vs\ R})-1\right)\times 100$
	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	$([\exp(L_{\Delta Z,k\ vs\ R})-1]\times 100, [\exp(U_{\Delta Z,k\ vs\ R})-1]\times 100)$

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

Lp(a) is a form of low-density lipoprotein that features apolipoprotein(a) (apo(a)) bound to apolipoprotein B (apoB). The mechanism of action of the drug substance is to inhibit apo(a) binding to apoB, thereby decreasing the formation of intact Lp(a) particles. In this study, Lp(a) is assessed using two distinct assays. The "apo(a) assay" assesses Lp(a) by measuring total apo(a). Apo(a) assay measurements are collected for all participants and are used to determine the Lp(a) stratification factor (<275 nmol/L, ≥275 nmol/L). The "intact Lp(a) assay" assesses Lp(a) by measuring intact Lp(a) particles. Intact Lp(a) assay measurements are collected for all participants except those at Chinese sites.

Unless otherwise specified, all analyses conducted for primary, secondary, and exploratory endpoints involving Lp(a) will be conducted twice, once using data from the apo(a) assay and once using data from the intact Lp(a) assay. Because intact Lp(a) assay measurements are not

collected for participants at Chinese sites, such participants will be excluded from the intact Lp(a) assay analyses.

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

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).

Statistical treatment comparisons will only be performed between LY3473329 and placebo. Since the trial is not adequately powered to detect differences among LY3473329 doses, comparisons across LY3473329 doses will not be performed unless otherwise specified.

4.1.1. Definition of Baseline

Unless specified otherwise, baseline is defined as the last non-missing measurement recorded on or before the randomization visit (Visit 2), prior to the first dose of intervention, which in most cases will be the measurement recorded at Week 0 (Visit 2). For the safety related parameters, the definition of baseline and postbaseline are specified in Table EKBC.4.2.

Table EKBC.4.2. Baseline and Postbaseline Definitions for Safety Analyses

Study Period/ Analysis Type	Participant Population	Baseline Observations	Postbaseline Observations
1.1) Treatment-Emergent Adverse Events (SS)	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.	Starts at or after the first dose of study drug and ends at the conclusion of the study period.
1.2) Treatment-Emergent Abnormal Labs and Vital Signs (SS)	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 post-baseline 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 to each postbaseline week and to last postbaseline for Labs, Vital Signs (SS)	All randomized participants who are exposed to at least 1 dose of study drug and have a baseline and at least 1 post-baseline observation	The last scheduled non-missing assessment recorded prior to the 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.

Abbreviations: ED = early discontinuation; SS = safety 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.

4.1.2. Analysis methods

4.1.2.1. Analysis method for efficacy estimand

Unless otherwise specified, the primary endpoint, secondary endpoints, and exploratory endpoints will be analyzed according to the efficacy estimand, which represents the efficacy had participants adhered to the randomized treatment without initiating Lp(a) modifying medications. Considered Lp(a) modifying medications are listed in Table EKBC.4.3. The assessment of efficacy measurements guided by the efficacy estimand will be conducted using the EAS (Section 3).

Table EKBC.4.3. Lp(a) Modifying Medications

Category	Medication
Lp(a)-Altering therapies	• statins • PCSK9 inhibitors • prescription-dose niacin • mipomersen • testosterone, estrogens, anti-estrogens, 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

A restricted maximum likelihood-based, mixed-effect model repeated measures (MMRM) analysis will be used to analyze continuous longitudinal endpoints. All the longitudinal observations at each scheduled postbaseline visit will be included in the analysis. The MMRM model will include the fixed class effects of treatment group (LY 10 mg, LY 60 mg, LY 240 mg, and placebo), strata (country and baseline Lp(a) stratum [<275 nmol/L, ≥275 nmol/L as measured by the apo(a) assay]), visit, and treatment-by-visit interaction, as well as the continuous baseline value. An unstructured covariance structure will be used to model the within-participant errors. Significance tests will be based on LS means and Type III tests. 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.

If the data does not warrant the MMRM model, then an ANCOVA model with treatment group, strata, and the continuous baseline value will be used to analyze the continuous endpoint. Data for participants with missing values at Week 12 will be imputed using the multiple imputation

method under the MAR assumption. Estimates and standard errors from multiple imputed datasets will be combined using Rubin's rules.

For binary endpoints derived from a continuous variable, the missing value in the underlying continuous variable will be imputed first based on the missing at random assumption (MAR), and then the corresponding binary variable will be derived.

A logistic regression model with treatment group and strata as fixed effects and the continuous baseline value as a covariate will be used to examine the treatment difference with missing endpoints imputed. The unconditional treatment group effect will be assessed by risk difference and relative risk using the marginal standardization method, where the treatment group-specific risk will be derived from the counterfactual risks for each participant that are predicted with the fitted logistic model (Ye et al. 2023). The estimated treatment group-specific risk, risk difference, relative risk, p-value and 95% CI will be presented.

For endpoints involving Lp(a), the Lp(a) strata class effects will be excluded from the above models.

4.1.2.1.1. Multiple Imputation Based Tipping-Point Analysis

A multiple imputation-based tipping-point (MI-TP) analysis is planned as a sensitivity analysis to explore how different patterns of Lp(a) percent change post treatment discontinuation by different treatment groups could impact the treatment comparisons.

To start with, missing Lp(a) percent change from baseline data are imputed through multiple imputation using all non-missing data (excluding data collected after ICEs) from the same treatment group under the MAR assumption. A fixed percentage penalty is then added to these imputed values at the Week 12 visit before analysing treatment differences with the ANCOVA model. In the analysis, the magnitude of the penalties added for both treatment groups under comparison is varied, and the impact that these variations would have on the study conclusion is evaluated. A 2-dimentional space of penalties will be assessed for each dose of LY3473329 and placebo ranging from -30% to 30%. MI-TP aims to evaluate the robustness of the superiority claim to the assumptions of using the observed data to impute the missing Lp(a) level in all treatment groups.

4.1.2.2. Analysis method for treatment-regimen estimand

The primary endpoint will also be analyzed according to the treatment-regimen estimand, which represents the efficacy regardless of discontinuation of intervention or initiation of Lp(a) modifying medications. The assessment of efficacy measures guided by the treatment regimen estimand will be conducted using the FAS (Section 3), and an ANCOVA model will be used to analyze the measures as described in Section 4.1.2.1.

4.1.2.3. Analysis method for safety

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of LY3473329 doses with placebo irrespective of adherence to intervention or initiation of Lp(a) modifying medications. Thus, safety analyses will be conducted using the SS (Section 3).

While considering treatment-emergent abnormal safety laboratory values and vital signs, the baseline observation period starts from the screening visit and ends prior to the first dose of study

intervention, wherein all scheduled and unscheduled measurements will be included. Baseline for the corresponding safety analysis will be the maximum/minimum (i.e., 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 EKBC.4.2 the definition of baseline, postbaseline, and patient population for different safety endpoints.

4.2. Participant Dispositions

A listing and summary of study disposition for all randomized participants will be provided at the final database lock. 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. Kaplan-Meier plots of time to study discontinuation, study treatment discontinuation, and study treatment discontinuation due to adverse event (AE) will be provided based on the all randomized population. Time-to-event analyses of study discontinuation, study treatment discontinuation, and study treatment discontinuation due to AE may be conducted.

Details about participant dispositions are included in the appendices: the demographic and baseline characteristics (Appendix 1, Section 6.1), historical illnesses and preexisting conditions (Appendix 2, Section 6.2), treatment compliance (Appendix 3, Section 6.3), concomitant medications (Appendix 4, Section 6.4), and important protocol deviations (Appendix 5, Section 6.5).

4.3. Primary Endpoint Analysis

The primary objective of the study is to demonstrate that LY3473329 10 mg, 60 mg, or 240 mg are superior to placebo with respect to percentage change from baseline in Lp(a) at Week 12.

4.3.1. Definition of endpoint(s)

The primary efficacy measure is percentage change from baseline in Lp(a) at Week 12, where baseline is defined as in Section 4.1.1.

4.3.2. Main analytical approach

The analytical approaches are specified for the efficacy estimand in Section 4.1.2.1 (MMRM) and for the treatment regimen estimand in Section 4.1.2.2 (ANCOVA). The primary efficacy measure will be log-transformed prior to statistical analyses.

For each estimand, LY3473329 will be declared superior to placebo in controlling Lp(a) if the p-value is less than 0.05 for both the analysis conducted with the apo(a) assay data and the analysis conducted with the intact Lp(a) assay data.

4.3.3. Sensitivity Analyses

A multiple imputation-based tipping-point sensitivity analysis is specified in Section 4.1.2.1.1 (MI-TP).

Additionally, the primary efficacy measure analyses specified in Section 4.3.2 that are conducted using the apo(a) assay data will be repeated, excluding participants at Chinese sites. This sensitivity analysis aims to evaluate the impact on the results from excluding participants at Chinese sites from the primary efficacy analyses conducted using the intact Lp(a) assay data.

4.4. Secondary Endpoints Analysis

4.4.1. Definition of endpoint(s)

The secondary study objectives are listed in Section 1.1.

4.4.2. Main analytical approach

The secondary study objectives will be analyzed with the efficacy estimand using the analytical approaches specified in Section 4.1.2.1. The clinical measures for secondary endpoints may be log-transformed before statistical analyses, if deemed necessary. Specifically, percent change from baseline to Week 12 for Apo(B) and hsCRP will be analyzed by MMRM model. The proportion of participants achieving Lp(a) <125 nmol/L at Week 12 will be analyzed by logistic regression model.

For each hypothesis, LY3473329 will be declared superior to placebo if the p-value is less than 0.05.

LY3473329 concentration data will be analyzed using a population PK approach via nonlinear mixed-effects modeling with the NONMEM software. The relationships between LY3473329 dose and/or concentration and efficacy, tolerability, and safety endpoints may be characterized. Additionally, the impact of intrinsic and extrinsic participant factors, such as age, weight, gender, and renal function on PK and/or PD parameters, may be examined as needed.

4.5. Tertiary/Exploratory Endpoints Analysis

Unless otherwise specified, exploratory analyses will be conducted with the efficacy estimand using the analytical approaches specified in Section 4.1.2.1. Percent change in lipid profile and change in plasminogen activity will be analyzed by the MMRM. Analyses for proportion of participants achieving Lp(a) lowering of at least 150 nmol/L at Week 12 will be conducted using the logistic regression model. Change in SF-36v2 acute form domain scores will be analyzed by the ANCOVA model specified in Section 4.1.2.1, with last observation carried forward (LOCF) used for imputation of missing values at Week 12.

4.5.1. Bayesian Analyses for Dose-Response

A Bayesian dose-response analysis will be performed on the percent change from baseline at Week 12 for Lp(a).

The two-component prediction (ITP) model proposed in Fu et al. (2010) and Qu et al. (2019) will be used to estimate Bayesian dose response. The model is as follows:

$$Y_{dit} = f(t;d)(\lambda(d) + s_i) + \epsilon_{it},$$

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, s_i is the between-subject random error term, and ϵ_{it} is the within-subject random error term. The mean response function $f(t;d)$ is modeled as

$$f(t;d) = \frac{1-e^{-k(d)t}}{1-e^{-k(d)t_{max}}},$$

where t_{max} is the maximum duration of treatment period and $k(d)$ is the shape parameter for dose d. $s_i \sim N(0, \sigma_s^2)$ and $\epsilon_{it} \sim N(0, \sigma^2)$ are independent, denoting between-subject variation and within-subject variation respectively. Given s_i, $Y_{dit} \sim N(f(t;d)(\lambda(d) + s_i), \sigma^2)$.

A three-parameter logistic regression model may be assumed for the dose response function, $\lambda(d)$. Let $\alpha_0, \alpha_1,$ and α_2 represent the basal effect when the dose level is zero (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:

$$\begin{cases} k(d) \sim \text{Uniform}(0,1), \\ \alpha_0, \alpha_1, \alpha_2 \sim N(0, 100^2), \\ \frac{1}{\sigma^2}, \frac{1}{\sigma_s^2} \sim Gamma(0.01, 0.01). \end{cases}$$

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 $\lambda(d)$ may be explored if the aforementioned dose-response model does not fit the data well, for example, Simple Normal Dynamic Linear Modeling (NDLM) described below.

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

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.

4.6. Safety Analyses

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of LY3473329 doses with placebo irrespective of adherence to intervention or initiation of Lp(a) modifying medications. Thus, safety analyses will be conducted using the SS (Section 3).

4.6.1. Extent of Exposure

Duration of exposure to study intervention will be summarized by treatment group. Exposure will be summarized and calculated for the treatment period being considered as the date of last dose of study intervention minus the date of first dose of study intervention plus 1 day using safety participants. Duration on study (date of end of study participation – date of randomization + 1) will also be summarized by treatment group.

Descriptive statistics (including n, mean, SD, minimum, first quartile, median, third quartile, and maximum) will be provided.

4.6.2. Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after first dose. The Medical Dictionary for Regulatory Activities (MedDRA) Lowest 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 Term (PT) 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, serious adverse event, death, 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 non-missing severities. If all severities are missing for the defined postbaseline period of interest, it will show as missing in the table.

4.6.3. Patient Narratives

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

- death
- serious adverse event, 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.

4.6.4. 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 4.1.2.1.

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 EKBC.4.4.

Table EKBC.4.4. 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

Abbreviations: BP = blood pressure; bpm = beats per minute.

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 Blood Pressure (mm Hg)	Diastolic Blood Pressure (mm Hg)
<90	<60
≥90	>60
≥120	>90
≥140	>110
≥160	≥120
≥180	

4.6.5. Electrocardiograms

Treatment-emergent qualitative ECG abnormalities are defined as qualitative abnormalities that first occurred after baseline. Qualitative abnormal ECGs will be recorded as adverse events. A listing of abnormal qualitative ECGs will be created.

4.6.6. 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 (L) and high (H). 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 non-missing 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 4.1.2.1 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.

4.6.7. Additional Safety Assessments

4.6.7.1. 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).

4.6.7.1.1. Liver Enzymes

Analyses for laboratory analyte measurements are described in Section 4.6.6. 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 EKBC.4.5):

Table EKBC.4.5. 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.	SS
Hepatocellular Drug-Induced Liver Injury Screening Plot (TBL vs. ALT or AST)	SS
Hepatocellular Drug-Induced Liver Injury Screening Table	SS
Cholestatic Drug-Induced Liver Injury Screening Plot (TBL vs. ALP)	SS
Cholestatic Drug-Induced Liver Injury Screening Table	SS
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.	SS

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRF = case report form; DBL = direct bilirubin; INR = international normalized ratio, 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 non-missing observation in the baseline period. The maximum value will be the maximum non-missing value from the postbaseline period.

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.

4.6.7.2. 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).

4.6.7.3. Major Adverse Cardiovascular Events

Death and nonfatal cardiovascular AEs (NCAEs) will be adjudicated by a committee of physicians external to Lilly with cardiology expertise. This committee will be blinded to treatment assignment.

The NCAEs to be adjudicated include:

- myocardial infarction
- cardiogenic shock
- hospitalization for unstable angina
- hospitalization for heart failure
- coronary interventions (such as coronary artery bypass graft or percutaneous coronary intervention)
- resuscitated sudden death,
- cerebrovascular events, including cerebrovascular accident (stroke) and transient ischemic attack,
- peripheral revascularization procedure, and
- peripheral arterial event

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

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

A listing of participants reporting NCAEs, either reported by an investigator or identified by the clinical endpoint committee (CEC), will be provided. This listing will include treatment, participant identification including the site number, date of event, type of event as reported by the investigator, type of event as adjudicated by the CEC, 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).

4.7. Other 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, non-white)
- gender: female versus male
- ethnicity
- baseline body mass index (BMI) (kg/m^2) (< median vs. ≥ median)
- baseline Lp(a) level (<275 nmol/L vs. ≥275 nmol/L)
- baseline eGFR(<60 and ≥60 mL/min/1.73 m^2)
- diabetic vs non-diabetic.

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

- Percent change in Lp(a) from baseline to Week 12.

For the purposes of the subgroup analysis, diabetic status will be defined using the criteria described in Appendix 7 (Section 6.7).

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

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

4.8. Interim Analyses

A planned interim analysis will be conducted when at least 50% enrollment has been completed. The interim analysis will consist of a subset of the primary efficacy estimand analyses specified in the SAP for the primary endpoint, such as the descriptive summaries described in Section 4.1, the MMRM model described in Section 4.1.2.1, and the Bayesian dose-response model described in Section 4.5.1.

Additionally, a planned interim analysis may be conducted when at least 50% of the participants complete Week 12 at Visit 7 or discontinue the study. The details regarding the number of participants and type of analysis will be provided in the assessment committee (AC) charter and in the unblinding plan.

All interims will be for the purpose of internal planning and decision-making and may assess safety, PK, and/or efficacy measures. Additional details related to statistical methods will be described in the SAP. An assessment committee (AC) will be formed to review the interim analyses in an unblinded manner. Only blinded study team members will have contact with the sites. 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. The study will not be stopped based on the efficacy of LY3473329 versus placebo. Therefore, there will be no inflation of the type 1 error rate, and no need to employ an alpha spending function or multiplicity adjustment.

The database lock and primary data analysis for Study EKBC may occur when all participants have completed the study. Unblinded data and results will not be shared with the study sites to maintain blinding at the sites while the study is still ongoing. Details will be specified in the blinding or unblinding plan.

4.9. Changes to Protocol-Planned Analyses

There are no changes to the analyses described in the protocol.

5. Sample Size Determination

The sample size calculation is based on the primary efficacy estimand and its endpoint, percent change from baseline at Week 12 in Lp(a).

Approximately 233 participants will be randomly assigned in a 1:2:2:2 ratio to LY3473329 10 mg:60 mg:240 mg:placebo. Assuming a 10% dropout rate, this results in approximately 30 completers for the 10-mg group and 60 completers per arm for the rest of the groups.

Assuming a standard deviation 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 60% reduction for the primary endpoint of LY3473329 verses 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) measured by apo(a) assay, Lp(a) measured by intact Lp(a) assay, plasminogen, LDL-C, ApoB, hsCRP, total cholesterol, HDL-C, triglycerides, baseline Lp(a) strata by apo(a) assay, eGFR (CKD-EPI, mL/min/1.73m^2), and eGFR groups (<30, ≥30 to <45, ≥45 to <60, ≥60 to <90, and ≥90 mL/min/1.73 m^2).

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

The count and percentages of participants with historical illnesses and pre-existing 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 discontinuing study treatment (including discontinuation reason) and discontinuing study will be provided by treatment groups.

If data warrant, counts and percentages of participants who have missed tablets of study drug (eCRF data) ≥ 7 days will be summarized for each treatment group. Listings of such participants will also be provided. Additionally, non-compliance, defined as having ≥75% of missed tablets before permanent study drug discontinuation, will be summarized by treatment group.

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).

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), and
- 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).

Hypersensitivity Events

The hypersensitivity TEAE 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)
- Narrow terms in Hypersensitivity SMQ (20000214), and
- Narrow terms in Vasculitis SMQ (20000174)

For the Anaphylactic reaction SMQ, the algorithmic query (per the MedDRA Maintenance and Support Services Organization SMQ guide) will be performed. An algorithmic case must include either:

- A narrow term from the SMQ (Category A of the SMQ);
- Multiple terms from the SMQ, from the same administration of study drug, comprising terms from at least 2 of the following categories from the SMQ:
    - Category B - (Upper Airway/Respiratory)
    - Category C - (Angioedema/Urticaria/Pruritus/Flush)
    - Category D - (Cardiovascular/Hypotension)

The counts and percentages of participants who experienced a TEAE for the following will be analyzed:

- Any narrow or algorithm term from any 1 of the 5 SMQs indicated above (i.e., combined search across narrow and algorithmic portions of all 5 SMQs)
- Any narrow or algorithm term within each SMQ, separately (i.e., narrow SMQ search).

Within query, individual PTs that satisfied the queries will be summarized, and the Anaphylactic reaction SMQ algorithm will be summarized. A single event may satisfy multiple SMQs, in which case the event contributes to every applicable SMQ.

6.7. Appendix 7: Definition of Diabetic Status

For the purposes of the subgroup analysis on diabetic status, participants will be defined as diabetic if, prior to being randomly assigned, they possess ANY of

- baseline hemoglobin A1c levels greater than 6.5%
- concomitant medications classified as a *drug used in diabetes* according to the Anatomical Therapeutic Chemical (ATC) level 2 code A10.
- medical history classified under the MedDRA PT *Diabetes Mellitus*,
- medical history classified under the MedDRA LLT *Diabetes Mellitus*, or
- medical history of Type 2 Diabetes Mellitus reported on the clinical report form.

7. References

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