Statistical Analysis Plan J3F-MC-EZCB (e)

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of LY3561774 in Adults With Mixed Dyslipidemia

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Statistical Analysis Plan (J3F-MC-EZCB): A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of LY3561774 in Adults with Mixed Dyslipidemia

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Compound Number: LY3561774

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[Acronym: PROLONG-ANG3]

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Version history

This statistical analysis plan (SAP) for Study J3F-MC-EZCB is based on protocol amendment (e) dated 24 August 2022.

Table EZCB.1.1 SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	See date on Page 1	Not Applicable	Original version

1. Introduction

1.1. Objectives, Endpoints, and Estimands

This table describes the objectives and endpoints related to Study EZCB.

Objectives	Endpoints
Primary	
To evaluate if LY3561774 is superior to placebo for the treatment of mixed dyslipidemia in adults.	Percent change from baseline at Day 180 for ApoB.
Secondary	
To compare the clinical response of LY3561774 to placebo.	Percent change from baseline at Day 180 for • ANGPTL3 • LDL-C • HDL-C • non-HDL-C, and • TG.
	Percent change from baseline at Day 270 for • ANGPTL3 • Non-HDL-C • LDL-C • HDL-C • ApoB, and • TG.

To characterize the pharmacokinetics of LY3561774.	Plasma concentrations of LY3561774.
To compare the effect of LY3561774 to placebo on safety endpoints.	Frequency of treatment-emergent adverse events.
To describe the safety of LY3561774 in participants with mixed dyslipidemia.	Summary of safety data, including number and incidence of • TEAEs, • SAEs, and • discontinuations due to AEs.
Exploratory	
To assess the relationship between LY3561774 dose and clinical endpoints, and potential participant factors that may influence these relationships.	Dose-response analyses for key efficacy and safety parameters.
To assess the relationship between LY3561774 exposure and clinical endpoints, and potential participant factors that may influence these relationships.	Exposure-response analyses for key efficacy and safety parameters.
Evaluation of immunogenicity.	Incidence of treatment-emergent ADA.
To compare the effect of LY3561774 to placebo on clinical endpoints or biomarkers.	Percent change from baseline at Day 180 for • hsCRP • ApoA-I • ApoC-III • VLDL-C • UACR

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	• HbA1c, and • FG.
To compare the effect of LY3561774 to placebo for key efficacy parameters.	Absolute change from baseline at Day 180 for • Non-HDL-C • LDL-C • HDL-C • ApoB, and • TG.
	Percent change from baseline in time-averaged parameters over Days 30 to 180 and Days 120 to 270 for • ApoB • LDL-C • HDL-C • Non-HDL-C • TG.
• To compare the effect of LY3561774 to placebo on hepatic fat fraction.	Percent and absolute change from baseline for MRI hepatic fat fraction at Day 180.

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; ANGPTL3 = angiopoietin-like protein 3; Apo = apolipoprotein; ApoA-I = apolipoprotein A-I; ApoB = apolipoprotein B; ApoC-III = apolipoprotein C-III; FG = fasting glucose; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein-cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein-cholesterol; MRI = magnetic resonance imaging; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TG = triglycerides; UACR = urinary albumin/creatinine ratio; VLDL-C = very-low-density lipoprotein-cholesterol.

Primary estimand

The primary clinical question of interest is: what is the treatment difference in the apolipoprotein B (ApoB) percent change from baseline after 180 days of treatment in participants who meet the inclusion criteria and who would have completed the Study EZCB treatment period?

The "efficacy estimand" is described by

- population: participants who meet the inclusion criteria; further details can be found in Sections 5 and 9 of the Study EZCB protocol
- endpoint: percent change from baseline in ApoB at Day 180, and
- treatment condition: the randomized treatment, without any excluded medications or additional lipid-lowering drugs.

The intercurrent events for Study EZCB are permanent discontinuation of intervention, initiation of excluded medications taken during the study, and new initiation of any lipid-lowering drug required to be on a stable regimen prior to treatment per the protocol inclusion criteria. These are handled by a hypothetical strategy wherein the potential outcome of interest is the participant's response in the efficacy measurement, if participants had adhered to the randomized treatment.

The potential outcomes related to the efficacy estimand are summarized at the population level using the difference in mean percent changes in ApoB at Day 180 between each dose of LY3561774 and placebo.

The rationale for this estimand is to study the efficacy of LY3561774 under the ideal condition that all participants adhere to the randomized treatment.

Estimand(s) for secondary objectives

The same estimand for the primary objective will be used for the efficacy endpoints for the secondary objective of comparing the clinical response of each dose of LY3561774 to placebo.

Secondary estimand: treatment-regimen estimand

The clinical question of interest is: what is the treatment difference in key lipid parameters after 180 days of treatment in participants who meet the inclusion criteria regardless of treatment discontinuation?

The treatment-regimen estimand is described by the attributes

- population: participants who were randomized and had at least one dose of study medication; further details can be found in Sections 5 and 9 of the Study EZCB protocol
- endpoint: percent change from baseline in key lipid parameters (low-density lipoprotein-cholesterol [LDL-C], non-high-density lipoprotein-cholesterol [non-HDL-C], high-density lipoprotein-cholesterol [HDL-C], triglycerides [TG], and ApoB) at Day 180, and
- treatment condition: the randomized treatment, regardless of treatment discontinuation.

The intercurrent events are handled by the treatment policy strategy where the potential outcome of interest is the response in the efficacy measurement regardless of treatment adherence.

The potential outcomes related to the treatment-regimen estimand are summarized at the population level using the difference in mean percent changes in key lipid parameters at Day 180 between each dose of LY3561774 and placebo.

The rationale for this estimand is to facilitate analysis based on the real-world scenario (that is, the intention-to-treat principle) for key lipid parameters (LDL-C, non-HDL-C, HDL-C, TG, and ApoB).

Unless otherwise specified, safety assessments will be guided by an estimand comparing the safety of LY3561774 doses with placebo irrespective of adherence to study intervention, including data collected during the treatment period and safety follow-up (that is, the treatment-regimen estimand).

1.2. Study Design

Study EZCB is a Phase 2, randomized, double-blind, placebo-controlled, parallel-arm study to investigate the efficacy and safety of LY3561774 in adults with mixed dyslipidemia.

Participants will be randomly assigned in a 2:1:2:2 ratio to placebo: LY3561774 100 mg:400 mg:800 mg. Placebo participants will be randomly assigned such that each dose cohort will have a matching placebo cohort that receives the same dose volume to maintain the study blind.

Participants will be stratified according to the Visit 1 TG level of less than 250 mg/dL and 250 mg/dL or greater.

Study intervention administration is by subcutaneous injection. Dosing will occur twice during the study, on Day 0 and Day 90 ± 5 days.

If a participant's ApoB levels do not return to 80% of baseline or higher on Day 270, then the participant will continue to the follow-up visit at Day 360.

If a participant's ApoB levels return to ≥80% of baseline or higher on Day 270, then Day 270 is the participant's last study visit.

Figure EZCB.1.1 illustrates the study schema.


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2. Statistical Hypotheses

The Study EZCB hypothesis for the primary objective is that at least one dose of LY3561774 100 mg, 400 mg, or 800 mg is superior in percent change from baseline for ApoB relative to placebo at Day 180 in participants with mixed dyslipidemia.

Thus, the null hypothesis to be tested in relation to the primary estimand is that LY3561774 100 mg, 400 mg and 800 mg are not different from placebo with respect to percent change in ApoB from baseline to Day 180.

2.1. Multiplicity Adjustment

All treatment comparisons will be performed at the full significance level of 0.05. No adjustment for multiplicity will be performed.

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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 signed informed consent.
Randomized	All participants who are randomly assigned to a treatment arm.
EAS	Data obtained during the treatment period from all randomly assigned participants who are exposed to at least 1 dose of the study intervention and are not discontinued due to inadvertent enrollment. Excludes data after any of • permanent discontinuation of intervention • initiation of excluded medications taken during the study, and • new initiation of any lipid-lowering drug required to be on a stable regimen prior to treatment per the protocol inclusion criteria. Participants will be included in the treatment group to which they were randomly assigned.
FAS	Data obtained during the treatment period from all randomly assigned participants who are exposed to at least 1 dose of study intervention, regardless of adherence to intervention, and are not discontinued due to inadvertent enrollment. Participants will be included in the treatment group to which they were randomly assigned.
SAS	Data obtained during the treatment period plus safety follow-up from all randomly assigned participants who are exposed to at least 1 dose of the study intervention, regardless of adherence to the intervention, and are not discontinued due to inadvertent enrollment. Participants will be included in the treatment group to which they were randomly assigned.

Abbreviations: EAS = efficacy analysis set; FAS = full analysis set; SAS = safety analysis set.

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4. Statistical Analyses

4.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (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 exploratory analyses of the data may be conducted as deemed appropriate.

Unless otherwise noted, all tests of treatment effects 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 the planned randomized treatment groups: placebo, LY 100 mg, LY 400 mg, and LY 800 mg.

The primary estimand (a precise definition of the treatment effect to be estimated) of interest in comparing the efficacy of LY3561774 doses with placebo is the efficacy estimand (Section 1.1). The primary efficacy assessment, guided by the efficacy estimand, will be conducted using the efficacy analysis set (EAS) (Section 3). Subjects who received only the first dose of LY3561774 will be considered "on-treatment" during Day 1 to Day 90, whereas subjects who received both doses will be considered "on-treatment" during the entire treatment and assessment period.

Unless otherwise specified, safety assessments will be guided by an estimand comparing the safety of LY3561774 doses with placebo, irrespective of adherence to the study intervention. Thus, safety analyses will be conducted using the safety analysis set (SAS) (Section 3).

For continuous measures, summary statistics will include sample size, mean, standard deviation (SD), median, minimum, and maximum for both the actual and the change from baseline measurements. Least squares (LS) means and standard errors derived from the analysis models, mixed model repeated measures (MMRM) and analysis of covariance (ANCOVA) will also be displayed for the change from baseline measurements. Treatment comparisons will be displayed showing LS means and 95% CIs for treatment differences, along with p-values for 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 analyses of efficacy parameters involving an ANCOVA model, missing data will be imputed using the multiple imputation method under the missing at random assumption. Such an approach is valid when the propensity for a data point to be missing is not related to the missing data, but is related to some of the observed data. Estimates and standard errors from multiple imputed datasets will be combined using Rubin's rules.

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 EZCB.4.1, where Z_b is the baseline of the log of the response.

Table EZCB.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	$\left[\exp\left(\hat{\mu}_{\Delta Z,k}\right)-\exp\left(\hat{\mu}_{\Delta Z,R}\right)\right]\cdot\exp(\bar{Z}_{b\cdot})$	$\left(\exp\left(\hat{\mu}_{\Delta Z,k\ vs\ R}\right)-1\right)\times 100$
	SE	$e^{\bar{Z}_{b\cdot}}\sqrt{e^{2\hat{\mu}_{\Delta Z,k}}\cdot\left(\widehat{SE}_{\Delta Z,k}\right)^2+e^{2\hat{\mu}_{\Delta Z,R}}\cdot\left(\widehat{SE}_{\Delta Z,R}\right)}$	$\exp\left(\hat{\mu}_{\Delta Z,k\ vs\ R}\right)\cdot\widehat{SE}_{\Delta Z,k\ vs\ R}\times 100$
	P-value	NR	$p_{\Delta Z,k\ vs\ R}$
	95% CI	Estimate $\pm\ \Phi^{-1}(1-\frac{\alpha}{2})$*SE	$\left(\left[\exp\left(L_{\Delta Z,k\ vs\ R}\right)-1\right]\times 100, \left[\exp\left(U_{\Delta Z,k\ vs\ R}\right)-1\right]\times 100\right)$

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

In general, a time-averaged parameter will refer to the area under the curve (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 30 to 180 will equal $AUC/150$, where AUC represents the AUC constructed by the trapezoidal rule.

Unless otherwise specified, baseline is defined as the last non-missing measurement recorded on or before the randomization visit, prior to first dose of intervention.

When considering treatment-emergent abnormal safety laboratory values and vital signs, baseline observation will start from the screening visit and end prior to, or at, the randomization visit, wherein all scheduled and unscheduled measurements will be included. The baseline for the treatment-emergent safety analysis will be the maximum/minimum from all measurements taken during the baseline period. For postbaseline measurements, all scheduled and unscheduled measurements in the analysis period will be included. The maximum/minimum from all measurements taken during the analysis period will be used in the treatment-emergent safety analysis. The end of Study EZCB participation for a participant will be the earliest of date of death, the date of withdrawal from further participation in the study, or the date of the safety follow-up visit (Visit 801). For participants considered to be lost to follow-up, end of Study EZCB participation will be the date participant is lost to follow-up as reported by the investigator. Participant data included in the database after the last date of Study EZCB participation (including the safety follow-up period) will be excluded from statistical analysis.

Statistical treatment comparisons will only be performed between LY3561774 doses and placebo. Since the trial is not adequately powered to detect differences among LY3561774 doses, comparisons across LY3561774 doses will not be performed unless otherwise specified. Not all analyses described in this SAP will necessarily be included in the clinical study reports. Any analysis described in this SAP and not provided in the clinical study reports will be available upon request.

4.2. Participant Dispositions

A listing and summary of Study EZCB participant disposition for all randomly assigned participants will be provided at the primary and final database locks, respectively. Frequency counts and percentages of all participants screened, randomly assigned, and receiving at least 1 dose of study drug will be presented by treatment groups. A listing and summary of randomly assigned participants not receiving the study drug will be provided. All participants who discontinue Study EZCB and/or the study drug will be identified, and the extent of their participation in Study EZCB 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 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 efficacy assessment, guided by the efficacy estimand, will be conducted using the efficacy analysis set (EAS) for the primary endpoint (percent change from baseline at Day 180 for ApoB).

The hypothetical strategy defined relative to the efficacy estimand – had participants adhered to the randomized treatment – will be used to handle the intercurrent events of permanent discontinuation of intervention, initiation of excluded medications taken during the study, and new initiation of any lipid-lowering drug required to be on a stable regimen prior to treatment per the protocol inclusion criteria. Only data collected before the occurrence of any intercurrent events will be used in the MMRM analysis. The MMRM analysis will then implicitly impute the potential efficacy measures (after the intercurrent events) if participants had not had intercurrent events.

See Section 10.7.3 of the Study EZCB protocol for a list of prohibited concomitant medications. Excluded medication and lipid lowering drugs are listed in Table EZCB.4.2.

Table EZCB.4.2 List of Medications

Prohibited Concomitant Medications and Procedures for Study EZCB	
Drug Class/Procedure	**Comments**
Lipid lowering therapy including, but not limited to • triglyceride-lowering medication ○ example: Vascepa® (icosapent ethyl)	Prohibited within 4 weeks prior to screening and during the study.
• simvastatin 80 mg per day • fibrates • bile acid sequestrants	Prohibited within 6 weeks prior to screening and during the study.
• over-the-counter and health food preparations ○ examples: red yeast rice, fish oil, omega-3 fatty acid >100 mg/day • niacin >250 to <1000 mg/day or other nicotinic acid derivatives • probucol	Prohibited within 8 weeks prior to screening and during the study.
• niacin >1000 mg per day	Prohibited within 16 weeks prior to screening and during the study.
• inclisiran or any other small interfering ribonucleic acid	Prohibited within 12 months prior to screening and during the study.
Warfarin or other coumarins	Prohibited within 1 month prior to screening and during the study.
Direct thrombin inhibitors	Prohibited within 1 month prior to screening and during the study.
Factor Xa inhibitors	Prohibited within 1 month prior to screening and during the study.
Heparins or heparinoids	Prohibited within 1 month prior to screening and during the study.
Systemic corticosteroids, cyclosporine, isotretinoin, or anabolic agents **Exceptions:** local, topical, intra-articular, inhalation, or nasal corticosteroids	Prohibited within 3 months prior to screening and during the study.
Anti-sense oligonucleotides **Exception:** mRNA vaccines	Prohibited within 6 months prior to screening and during the study.
Tamoxifen	Prohibited.
HIV protease inhibitors, cyclophosphamide or systemic retinoids	Prohibited.
Medications associated with weight gain or loss **Exception:** if participant is on a stable dose for at least 3 months prior to screening and will continue taking a stable dose during the study.	Prohibited.

4.3.1. Definition of Endpoint

The primary efficacy comparison will be based on the contrast between each treatment group of LY3561774 and placebo for the mean percent change of ApoB between randomization at Visit 2 and Day 180.

4.3.2. Main Analytical Approach

Mean percent change of ApoB will be analyzed using the MMRM model for the efficacy estimand. As described in Section 4.1, the response variable will be log-transformed.

A restricted maximum likelihood-based MMRM analysis will be used to analyze continuous longitudinal variables. All longitudinal observations taken at each scheduled postbaseline visit will be included in the analysis. The model for the analysis of the primary efficacy endpoint of percent change from baseline in ApoB will include the fixed class effects of treatment group (placebo, LY3561774 100 mg, LY3561774 400 mg, and LY3561774 800 mg), visit, treatment-by-visit interaction, Visit 1 TG stratum (lower than 250 mg/dL, 250 mg/dL or greater) as well as the continuous baseline value of the log-transformed dependent variable.

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, these covariance structures will be tested in order

- Toeplitz with heterogeneity
- autoregressive with heterogeneity
- compound symmetry with heterogeneous variances
- Toeplitz
- autoregressive, and
- 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.

4.4. Secondary Endpoints Analysis

4.4.1. Analyses Using the Efficacy Analysis Set

The secondary study objectives will be analyzed with the efficacy estimand using the data in the EAS. The clinical measures for secondary endpoints may be log-transformed before statistical analyses, if deemed necessary.

Percent change from baseline at Day 180 for

- angiopoietin-like protein 3 (ANGPTL3)
- LDL-C
- HDL-C
- non-HDL-C, and
- TG.

Percent change from baseline at Day 270 for

- ANGPTL3
- ApoB
- LDL-C
- HDL-C

- non-HDL-C, and
- TG.

Mean percent change of the above endpoints will be analyzed using the MMRM model for the efficacy estimand as described in Section 4.3.2.

4.5. Exploratory Endpoints Analysis

Unless otherwise specified, exploratory analyses will be conducted for the EAS using the general methods detailed in Section 4.1.

4.5.1. Analyses using the Efficacy Analysis Set

These two exploratory study objectives will be analyzed using the EAS and the associated efficacy estimand.

Percent change from baseline at Day 180 for

- high-sensitivity C-reactive protein (hsCRP)
- apolipoprotein A-I (ApoA-I)
- apolipoprotein C-III (ApoC-III)
- VLDL-C
- urine albumin/creatinine ratio (UACR)
- hemoglobin A1c (HbA1c), and
- fasting glucose (FG).

Percent change from baseline in time-averaged parameters over Days 30 to 180 and Days 120 to 270 for

- non-HDL-C
- LDL-C
- HDL-C
- ApoB, and
- TG.

These endpoints will be analyzed using the MMRM modeling strategy as detailed in Section 4.3.2. 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

$$\hat{\theta}_{\Delta k} = \hat{\mu}_{1k} - \hat{\mu}_{1R} + \sum_t w_t \left(\hat{\beta}_{k:t} - \hat{\beta}_{R:t} \right),$$

where $\hat{\mu}_{1k}$ is the coefficient corresponding to treatment group k, $\hat{\beta}_{k:t}$ corresponds to the treatment-time interaction coefficient, 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. An overall test of significance will be conducted using the F-test under the null hypothesis that $\theta_{\Delta k} = 0$ for all LY3561774 arms simultaneously.

4.5.2. Analyses using the Full Analysis Set

These two exploratory study objectives will be analyzed using the full analysis set (FAS) and the associated treatment-regimen estimand.

Absolute change from baseline at Day 180 for

- non-HDL-C
- LDL-C
- HDL-C
- ApoB, and
- TG.

Percent change from baseline at Day 180 for

- non-HDL-C
- LDL-C
- HDL-C
- ApoB, and
- TG.

Missing data for the dependent variables at each time point will be imputed using multiple imputation as detailed in Section 4.1.

4.5.3. 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 LY3561774 concentration data.

Exposure-response analysis between LY3561774 concentration and safety, pharmacology, and efficacy may be performed using population PK and 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 liver function on PK and PD parameters may be examined as needed.

If anti-drug antibody (ADA) titers are detected from immunogenicity testing, then the impact of immunogenicity titers on LY3561774 PK, or any other relevant efficacy parameters, may also be examined. Additional analyses may be conducted if deemed appropriate.

4.5.4. Bayesian Analyses for Dose-Response

A Bayesian dose-response analysis will be performed on the percent change from baseline at Day 180 and the percent change from baseline for time-averaged parameters from Day 30 to Day180 and from Day 120 to Day 270 for the parameters

- ApoB, and
- non-HDL-C.

The longitudinal model, a proportional discrete time model (PDT), will be used to estimate Bayesian dose response. The PDT model assumes that the efficacy of the modelled treatment plateaus after some time point, Q. Let $y_{it}(d)$ represent the change from baseline ApoB at time t for participant i receiving dose d. Then the PDT can be written as

$$y_{it}(d) = \mu(t_l, d, \theta) + g(t) * s_i + \epsilon_{it}$$

with the mean function

$$\mu(t_l, d, \theta) = \lambda(d)\{p_l * I(t_l < t_Q) + I(t_l \geq t_Q)\}$$

where $s_i \sim N(0, \sigma_s^2)$ and $\epsilon_{it} \sim N(0, \sigma^2)$, $\theta = (\lambda(d), p_1, \ldots, p_{Q-1})'$, and p_l represents the proportion of the efficacy of dose level d, $\lambda(d)$, at time t_l, for $t_l < t_Q$. Based on the data from the above, we may assume $t_Q =$ Day 30. The function, $g(t)$, may be specified to allow the errors to be proportional to the time trend of the mean response. An example of such a function that also incorporates a plateau in efficacy (Qu et al. 2019) is

$$g(t) = \{p_l * I(t_l < t_Q) + I(t_l \geq t_Q)\}.$$

A simple normal dynamic linear model may be assumed for the dose-response function, $\lambda(d)$:

$$\lambda(1) \sim N(0, \sigma_\lambda^2)$$

$$\lambda(d) \sim N(\lambda(d-1), \sigma_\lambda^2) \text{ for } d > 1$$

The estimation of the parameters will be carried out in a Bayesian framework, assuming non-informative priors for the hyperparameters:

$$p_l \sim U(0,1)$$

$$1/\sigma^2, 1/\sigma_s^2, 1/\sigma_\lambda^2 \sim Gamma(0.01, 0.01)$$

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

Alternative dose-response models, including the three-parameter logistic regression or power model, may also be considered for $\lambda(d)$, if the dose-response model does not fit the data well. Some alternative dose-response models are

- Three-parameter logistic model

$$\lambda(\mathrm{d}) = \alpha_0 + \frac{\alpha_1 \mathrm{d}^*}{\alpha_2 + \mathrm{d}^*},$$

where parameters α_0, α_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 (ED_{50}), respectively. Here, d^*, represents the actual dose (for example, in mg) versus dose level (1, 2, 3, and so on).

- Power model

$$\lambda(\mathrm{d}) = \alpha_0 * \alpha_1 \mathrm{d}^{*\gamma}$$

where α_0 and α_1 represent the basal effect for the placebo group and the slope, respectively, and γ is a sigmoidicity parameter indicating shape or steepness of the dose response. Here, d^*, represents the actual dose (for example, in mg) versus dose level (1, 2, 3, and so on).

Furthermore, if the PDT model, or any related longitudinal model, does not fit the data well, these or other dose-response models may be fitted to the percent change from change from baseline at Day 180, and the percent change from baseline for time-averaged parameters from Day 30 to Day 180 and from Day 120 to Day 270 for the parameters, excluding the intermediate timepoints.

The same dose-response models may be fitted to the percent absolute change from baseline for magnetic resonance imaging (MRI) hepatic fat fraction at Day 180 and the time-averaged endpoints. These models will not require additional longitudinal modeling, and will take place after imputation for missing data according to the efficacy estimand for the time-averaged analysis and the treatment policy estimand for the hepatic fat fraction analysis.

4.5.5. Immunogenicity Assessments

If data from validated immunogenicity assays are available, treatment-emergent-ADAs may be assessed.

Treatment-emergent ADAs are defined as participants

- with a 2-fold (1 dilution) increase in titer than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA), or
- with a 4-fold (2 dilutions) increase in titer compared with baseline if ADAs were detected at baseline (treatment-boosted ADA).

The frequency and percentage of participants with preexisting ADA and who are treatment-emergent-ADA positive (TE-ADA+) to LY3561774 will be tabulated.

The distribution of titers and frequency of neutralizing antibodies (if assessed) for the treatment-emergent-ADA+ participants may also be tabulated.

The relationship between the presence of antibodies and PK parameters, efficacy response, or safety to LY3561774 may also be assessed.

4.6. (Other) Safety Analyses

Unless otherwise specified, safety will be assessed by comparing safety of LY3561774 doses with placebo irrespective of adherence to study drug. Thus, safety analyses will be conducted using the SAS.

4.6.1. Extent of Exposure

Duration of exposure will be calculated as number of days participant was on-treatment, as defined in Section 4.1. Summary of duration of exposure will be provided by treatment group using data from the SAS. The descriptive statistics n, mean, SD, median, minimum, maximum, and sum (that is, total participant-years of follow-up) will be provided. In addition, the number of participants who received 1 or 2 doses will be summarized by counts and percentages.

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4.6.2. 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) 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 the 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 (AE), death, discontinued from study treatment or study due to an AE, and TEAE 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 contain patient level data and a summary paragraph. Patient narratives will be provided for participants in the randomized population with at least one notable event. Notable events include death, serious adverse events, and permanent discontinuation of study treatment due to an adverse event.

4.6.4. Vital Signs

If multiple records of a participant'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 4.3.2

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. Counts and percentages of participants with treatment-emergent abnormal sitting systolic blood pressure (BP), sitting diastolic BP, and pulse will be presented by treatment for participants who have both baseline and at least 1 postbaseline result. A treatment-emergent high result is defined as a change from a value less than or equal to the high limit at baseline, to a value greater than the high limit at any time, that meets the specified change criteria during the postbaseline period. A treatment-emergent low result is defined as a change from a value greater than or equal to the low limit at baseline, to a value less than the low limit at any time, that meets the specified change criteria during the postbaseline period. To assess decreases, change from the minimum value during the baseline period to the minimum value during the postbaseline period will be used. To assess increases, changes from the maximum value during the baseline period to the maximum value during the postbaseline period will be used. 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 EZCB.4.3.

Table EZCB.4.3 Categorical Criteria for Abnormal Treatment-Emergent Blood Pressure and Pulse Measurements

Parameter	Low	High
Systolic BP (mm Hg) (supine or sitting)	≤90 and decrease from baseline ≥20	≥129 and increase from baseline ≥20
Diastolic BP (mm Hg) (supine or sitting)	≤50 and decrease from baseline ≥10	≥90 and increase from baseline ≥10
Pulse (bpm) (supine or sitting)	<50 and decrease from baseline ≥15	>100 and increase from baseline ≥15
Weight (kg)	(Loss) Decrease ≥7%	(Gain) Increase ≥7%

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

Counts and percentages of participants with maximum systolic blood pressure and diastolic blood pressure will be summarized by treatment groups for the categories listed in Table EZCB 4.4, using the SAS.

Table EZCB 4.4 Categorical Criteria for Summaries of Maximum Blood Pressure

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

Abbreviation: BP = blood pressure.

4.6.5. Electrocardiograms

Treatment-emergent qualitative electrocardiogram (ECG) abnormalities are defined as qualitative abnormalities that first occurred after the first dose of study intervention. Qualitative abnormal ECGs will be recorded as AEs. A listing of qualitative ECGs may be produced.

4.6.6. Clinical Laboratory Evaluation

All laboratory data will be reported in SI units. Selected laboratory measures will also be reported using conventional 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 the 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 number and percentage 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.

Using the SAS, the MMRM model as described in Section 4.3.2 will be used for the analysis during the treatment period for the continuous measurements for selected lab tests. Alternatively, ANCOVA will be used if the MMRM model is not applicable due to unavailability of multiple postbaseline measurements.

Detailed analyses can be found in Appendix 7 (Section 6.7).

4.6.7. Additional Safety Assessments

4.6.7.1. Hepatic Safety

4.6.7.1.1. Hepatic Fat Fraction

The endpoint labeled "percent and absolute change from baseline for MRI hepatic fat fraction at Day 180," will be analyzed using the SAS.

ANCOVA will be used for the analysis of both percent and absolute change.

4.6.7.1.2. Hepatic Disorders

The counts and percentages of participants with TE, potentially drug-related hepatic disorders, will be summarized by treatment using the MedDRA PTs. Detailed search criteria can be found in Appendix 6 (Section 6.6)

4.6.7.1.3. 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-glutamyltransferase (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 forms (eCRFs).

Table EZCB.4.5 describes the planned summary tables related to hepatic safety.

Table EZCB.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 1X, 3X, 5X, 10X, and 20X 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 1X, 3X, 5X, 10X, and 20X 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 2X and 3X 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 2X, 5X, and 8X 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 2X and 5X 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 2X the performing lab ULN during the treatment period will be summarized for all participants with a postbaseline value.	SAS
Hepatocellular Drug-Induced Liver Injury Screening Plot (TBL vs ALT or AST)	SAS
Hepatocellular Drug-Induced Liver Injury Screening Table	SAS
Cholestatic Drug-Induced Liver Injury Screening Plot (TBL vs ALP)	SAS
Cholestatic Drug-Induced Liver Injury Screening Table	SAS
Participant profiles will be created for participants meeting criteria for a comprehensive hepatic evaluation (as defined in the protocol).	SAS

Analysis	Population or Analysis Set
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.	

Abbreviations: 1X = one time the ULN; 2X = two times the ULN; 3X = three times the ULN; 4X = four times the ULN; 5X = five times the ULN; 10X = ten times the ULN; 20X = twenty times the ULN; 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 in the analyses listed in Table EZCB.4.5. The measurements do not need to be taken at the same blood draw. The 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. This 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 may have been missed by focusing only on the maximum values when determining 30-day time associations.

4.6.7.1.4. Gallbladder and biliary tract disorders

The counts and percentages of participants with treatment-emergent, potentially drug-related gallbladder and biliary tract disorders will be summarized by treatment using the MedDRA PTs. Detailed search criteria can be found in Appendix 6 (Section 6.6).

4.6.7.2. Hypersensitivity Events

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

Two main analyses will be performed:

- Potential Immediate Hypersensitivity: analysis of TEAEs occurring from the start of study drug administration up to 24 hours after the end of study drug administration. For events without the hypersensitivity eCRF, only date (no time) information is collected, and any events occurring on the same date as the study drug injection date will be included.
- Potential Non-Immediate Hypersensitivity: analysis of TEAEs occurring more than 24 hours after the end of study drug administration but prior to subsequent study drug administration.

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

4.6.7.3. Injection Site Reactions

Injection site reactions, incidence, and related information reported in the eCRF 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. Such characteristics include erythema, induration, pain, pruritus, and edema.

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 the summary by treatment within each HLT category.

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

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: under 65 years versus 65 years and over
- race
- sex: female versus male
- ethnicity
- BMI (kg/m^2) group: less than 30 versus 30 or higher, and less than 35 versus 35 or higher
- Visit 1 TG level less than 250 mg/dL versus 250 mg/dL or higher
- Visit 1 TG and LDL-C levels: TG 250 mg/dL or higher and LDL-C 100 mg/dL or higher, versus TG less than 250 mg/dL and LDL-C less than100 mg/dL, and
- diabetic vs non-diabetic.

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For each subgroup analysis, 2 models will be conducted:

- MMRM model: conduct MMRM model as described in Section 4.3.2 on the subgroup only, and
- MMRM model with interactions: the MMRM model as described in Section 4.3.2, adding interactions between subgroup and visit, between subgroup and treatment, and between subgroup, treatment and visit as fixed effects.

Separate MMRMs may be conducted on participants meeting the inclusion/exclusion criteria for the Study EZCB protocol both before and after amendment (e): Visit 1 lipid levels of TG greater than 200 mg/dL and LDL-C greater than 100 mg/dL versus TG greater than150 mg/dL and LDL greater than 70 mg/dL and non-HDL-C greater than130 mg/dL. If less than 10% of participants differ between these two subgroups, this analysis will not be produced.

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. Additional subgroup analyses may also be performed.

For the purposes of the subgroup analysis, diabetic status will be defined using the criteria described in Appendix 8 (Section 6.8).

Subgroup analyses may be done for the Japanese population to support local regulatory interactions.

4.8. Interim Analyses

A first-planned interim analysis may be conducted when at least 50% of participants complete Day 120 (Visit 7) or discontinue treatment. There may be 2 more interim analyses after the first interim analysis and before final analysis (100% of patients complete 180 days of study or discontinue treatment). These 3 interim analyses will be for the purpose of internal planning and decision making and may assess safety, PK, or efficacy measures.

If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the Study EZCB protocol must be amended.

An interim assessment committee (IAC) will be formed to review the interim analyses for totality of data including the safety and efficacy reports in an unblinded manner.

The IAC will be fully independent from the study team and will include, at a minimum, a Lilly medical physician and a statistician. Details about IAC membership, purpose, responsibilities, and operation will be described in an IAC charter, which will be approved prior to the first unblinding.

Details on the timing of the interim analyses, operational support, and unblinding will be specified in the IAC charter and in the Study EZCB unblinding plan. Since the endpoints for interim analysis are a subset of the endpoints in Section 1.1, the analysis methods for these endpoints should be consistent with those methods described in this SAP. The time points of at which certain endpoints are assessed may be amended to reflect data availability at the interim. Such changes will be specified in the IAC charter.

Information that may unblind Study EZCB during the analyses will not be reported to study sites or blinded study team members before the study has been unblinded until final database lock. Study sites will receive information about interim results only if deemed necessary for the safety of the participants. Study EZCB will not be stopped based on the superiority of LY3561774 versus placebo. Therefore, there will be no inflation of the type I error rate and no need to employ an alpha spending function or multiplicity adjustment.

4.9. Changes to Protocol-Planned Analyses

The description of the EAS was amended to exclude participants who experienced permanent discontinuation of intervention, initiation of excluded medications taken during the study, and new initiation of any lipid-lowering drug required to be on a stable regimen prior to treatment per the Study EZCB protocol inclusion criteria. In the Study EZCB protocol, the EAS was described as only excluding measurements based on permanent discontinuation of intervention. This change is intended to align the analyses based on the EAS with the description of the primary estimand, based on the hypothetical strategy.

For the exploratory analysis of time-averaged endpoints, the days of time-averaging have been augmented from Day 120 to Day 180 to Day 30 to Day 180, and from Day 210 to Day 270 to Day 120 to Day 270. The purpose of this change is to capture a broader measure of effectiveness over time to accompany our other analyses at specific time points.

5. Sample Size Determination

The sample size calculation is based on the primary efficacy estimand and its endpoint, percent change, from baseline at Day 180 in ApoB.

Approximately 175 participants will be randomly assigned in a 2:1:2:2 ratio to placebo: LY3561774 100 mg:400 mg:800 mg. Assuming a CCI dropout rate, this results in approximately 20 completers for the 100 mg group and 40 completers per arm for the rest of the groups.

Assuming a standard deviation of 15%, and a 2-sided alpha level of 0.05, the completers for each treatment arm will provide greater than 99% power to detect a treatment difference of -30% for the primary endpoint.

6. Supporting Documentation

6.1. Appendix 1: Demographic and Baseline Characteristics

A listing of participant demographics for all randomly assigned participants will be provided. All demographic and baseline clinical characteristics will be summarized by treatment groups for all randomly assigned 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)
- body mass index (BMI [kg/m^2])
- age group (less than 65 years, 65 years or over)
- BMI group (less than 30, 30 or greater and less than 35, 35 or greater)
- LDL-C
- HDL-C
- VLDL-C
- TGs
- ANGPTL3
- non-HDL-C
- ApoB, and
- Visit 1 TG stratum (less than 250 mg/dL, 250 mg/dL or greater).

6.2. Appendix 2: Historical Illnesses and Preexisting 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 SOCs. The SOCs will be in alphabetical order. Conditions (that is, PTs) will be ordered by decreasing frequency within the SOC. This will be summarized for all randomly assigned 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 in the LY3561774 100 mg group.

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 EZCB for all randomly assigned 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 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).

Gallbladder and biliary tract disorders

Treatment-emergent gallbladder and biliary tract disorders will be summarized by treatment using the MedDRA PTs contained in any of the SMQs

- 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 reactions 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

The hypersensitivity TEAE are characterized as follows

- Anaphylactic reaction SMQ (20000021; narrow, algorithm per SMQ guide, and broad)
- Hypersensitivity SMQ (20000214; narrow and broad)
- Angioedema SMQ (20000024; narrow and broad), and
- Event maps to PT of Injection related reaction (10071152).

Using these four SMQs, the number and percentage of participants who experienced a TEAE for the following will be analyzed for each of the two study intervention time periods (Day 0 to Day 90 and Day 90 to either Day 180 or Day 270 depending on safety follow-up):

- any narrow or algorithmic term from any one of the 4 indicated SMQs (that is, combined search across narrow and algorithmic portions of all 4 SMQs)
- any narrow scope term within each SMQ, separately (that is, narrow SMQ search), and
- any term within each SMQ, separately (that is, broad SMQ search).

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6.7. Appendix 7: Clinical Laboratory Evaluation

Table 6.1 Tables and Figures Produced to Support Clinical Laboratory Evaluations

Analysis Type	Analysis Details	Population/Analysis Set
Box plots and mean/SD plots for observed values by visit	Includes participants who have both a baseline and at least 1 postbaseline measurement from a planned visit. Unplanned measurements will be excluded. Last baseline will be used. Original-scale data will be used. Both SI and conventional units will be provided in the axis within a single plot. No inferential statistics. See also: Figure 6.1 from the Analyses and displays Associated with Laboratory Analyte Measurements in Phase 2-4 Clinical Trials and Integrated Submission Documents – Update to Recommendations white paper[a].	FAS
Box plots and mean/SD plots for change from baseline values by visit	Includes participants who have both a baseline and at least 1 postbaseline measurement from a planned visit. Unplanned measurements will be excluded. Last baseline will be used. No inferential statistics. See also: Figure 6.2 from the Analyses and Displays Associated with Laboratory Analyte Measurements in Phase 2-4 Clinical Trials and Integrated Submission Documents – Update to Recommendations white paper[a].	FAS
Maximum, minimum, and last observed and change values	Includes all participants who have both a baseline and at least 1 postbaseline measurement.	FAS

Analysis Type	Analysis Details	Population/Analysis Set
	The following will be summarized: o last baseline, last postbaseline, change from last baseline to last postbaseline (last postbaseline minus last baseline) o minimum baseline, minimum postbaseline, change from minimum baseline to the minimum postbaseline (minimum postbaseline minus minimum baseline), and o maximum baseline, maximum postbaseline, change from maximum baseline to the maximum postbaseline (maximum postbaseline minus maximum baseline) P-values using the MMRM or ANCOVA models will be included. See also: Table 6.2 from the Analyses and Displays Associated with Laboratory Analyte Measurements in Phase 2-4 Clinical Trials and Integrated Submission Documents – Update to Recommendations for Labs white paper[a].	
Participants with elevated or low values meeting specified levels	Excludes analytes collected qualitatively. Definitions provided in Table 59 and 60 from FDA's Standard Safety Tables and Figures Integrated Guide will be used for the numerator[b]. . Includes participants with at least 1 postbaseline measurement. For initial controlled analysis sets, maximum baseline is used for elevated assessments and minimum baseline is used for low assessments. For LY-treated analysis sets (all participants receiving at least 1 dose of LY3561774), participants randomly assigned to placebo or active comparator in the initial period, last baseline is used for any change calculations. For controlled analysis sets, statistical comparisons (using methods described in Section 4.3.2) will be included. See Table 24 from FDA's Standard Safety Tables and Figures Integrated Guide (FDA 2022).	FAS
Listing of abnormal laboratory findings	Includes laboratory analytes collected quantitatively (high or low during postbaseline using Level 2 definitions) and qualitatively (abnormal during postbaseline).	FAS

Analysis Type	Analysis Details	Population/Analysis Set
	Includes participant identification, treatment group, laboratory analyte collection day (that is, days from start of study intervention), analyte name, and analyte finding.	

Abbreviations: ANCOVA = analysis of covariance; FAS = full analysis set; MMRM = mixed model repeated measures; SD = standard deviation.

[a] [PHUSE]. Safety Analytics Working Group. Analyses and displays associated with laboratory analyte measurements in phase 2-4 clinical trials and integrated submission documents – update to recommendations. Accessed March 05, 2023. https://phuse.s3.eu-central-1.amazonaws.com/Deliverables/Safety+Analytics/WP068.pdf

[b] [FDA] United States Food and Drug Administration. Standard safety tables and figures: integrated guide. August 2022. Accessed May 31, 2023. https://downloads.regulations.gov/FDA-2022-N-1961-0046/attachment_1.pdf

6.8. Appendix 8: 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*, or
- medical history classified under the MedDRA LLT *Diabetes Mellitus*.

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7. References

Qu Y, Liu Z, Fu H, et al. Modeling the impact of preplanned dose titration on delayed response. *J Biopharm Stat*. 2019;29(2):287-305. https://doi.org/10.1080/10543406.2018.1535499

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