Protocol 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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Approval date: 14-Feb-2023

Title Page

Protocol Title:

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

Protocol Number: J3F-MC-EZCB

Amendment Number: e

Compound: LY3561774

Brief Title:

Efficacy and Safety of LY3561774 Compared with Placebo in Adults with Mixed Dyslipidemia

Study Phase: 2

Acronym: PROLONG-ANG3

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

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Approval Date: Protocol amendment (e) Electronically Signed and Approved by Lilly on date provided below.

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (d)	24-Aug-2022
Amendment (c)	03-Aug-2022
Amendment (b)	09-May-2022
Amendment (a)	08-Dec-2021
Original Protocol	18-Nov-2021

Amendment [e]

This amendment is considered to be substantial.

Overall Rationale for the Amendment:

The rationale for the amendment is to modify some of the inclusion and exclusion criteria to include a broader population who may benefit from the therapy, as well as to incorporate other minor changes.

Section # and Name	Description of Change	Brief Rationale
Section 1.1. Synopsis	Added the safety-related secondary objective and endpoints Modified to state that the dosing will occur twice on Day 0 and Day 90 (-5 to +10 days)	Changes to study design and for clarification
Section 1.3. Schedule of Activities (SoA)	Changed the visit tolerance interval from ±5 to "-5 to +10" for Visit 6 Changed the follow-up visit V801 to on-site for all sites including the US Clarified that the second PK sample will be taken 4-12 hr post-dose (minimum 2 hr)	To give more flexibility to participants with COVID infection Since ECG is required at V801, an on-site ECG is preferable Clarified the timing of the second PK sample
Section 3 Objectives, Endpoints, and Estimands	Added the safety-related secondary objective and endpoint For intercurrent events, added language to indicate that the excluded medications or new initiation of any lipid-lowering drugs are handled by hypothetical strategies	Added safety objective to align with trial title Clarification for the estimand
Section 4.1. Overall Design	Modified dosing at Day 90 (-5 to +10 days)	To give more flexibility to participants with COVID infection

Section 5.1 Inclusion Criteria	Modified age limit from 40 to 18 years of age for IC #1 Modified the lower limit of fasting TG to 150 mg/dL (1.69 mmol/L) for IC #2 Modified the cut-off for fasting LDL-C to 70 mg/dL (1.81 mmol/L) for IC #3 Added non-HDL-C $\geq$130 mg/dL (3.36 mmol/L) as IC #51	To include a broader population that could benefit from this therapy
Section 5.2. Exclusion Criteria	Modified EC #31 so that anemia will need to be clinically relevant at the discretion of the investigator for the participant to be excluded Deleted the word “supine” from EC #34	To limit exclusion only to clinically relevant anemia. For consistency with protocol Section 8.2.2
Section 6.1. Study Intervention(s) Administered	Modified to state that each injection should be delivered into separate quadrants when multiple injections are needed	To provide general advice in case of multiple injections
Section 10.2.1. Laboratory Samples Obtained at the Time of as Systemic Hypersensitivity Event	Only plasma samples will be collected to test the LY3561774 concentrations	Correction of the sample type
Throughout the document	Minor editorial and format changes	For clarity

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title:

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

Brief Title:

Efficacy and Safety of LY3561774 Compared with Placebo in Adults with Mixed Dyslipidemia

Rationale:

Residual cardiovascular risk is still high, despite the current standard of care that includes maximally tolerated statin. Studies show that a reduction in circulating biomarkers, such as non-HDL-C and apolipoprotein B (ApoB), are associated with a reduction in major cardiovascular events.

This study aims to investigate the impact of LY3561774 on surrogate biomarkers of major cardiovascular events in participants with mixed dyslipidemia. This is the first Phase 2 study and data from this study will inform dose decisions for the clinical development of LY3561774.

Overall design:

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

The duration of the study is 270 days with a follow-up visit for some participants at Day 360.

Brief Summary:

Screening

Interested participants will sign the appropriate informed consent document(s) prior to completion of any procedures.

The investigator will review symptoms, risk factors, medical history, concomitant medications and other inclusion and exclusion criteria prior to any diagnostic procedures. If the participant is eligible after this review, then the site will perform the diagnostic procedures to confirm eligibility.

Double-blind treatment and assessment period

This part of the study has 11 visits. The two visits after randomization will occur about 15 days apart and the remaining visits occur about 30 days apart.

This is the general flow during the treatment and assessment period:

- Complete MRI at any date prior to randomization
- Complete baseline procedures and sample collection
- Participants are randomly assigned to an intervention group, and
- Participants complete all visit procedures including efficacy assessments, safety monitoring, study intervention dosing, and post-dosing sample collection.

Safety follow-up

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

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

Objectives, Endpoints, and Estimands:

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	
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 • Triglycerides.
	Percent change from baseline at Day 270 for • ANGPTL3 • Non-HDL-C • LDL-C • HDL-C • ApoB, and • Triglycerides.
Characterize the pharmacokinetics (PK) of LY3561774.	Plasma concentrations of LY3561774.
Compare the effect of LY3561774 to placebo on safety endpoints.	Frequency of treatment-emergent adverse events.

Objectives	Endpoints
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.

Abbreviations: AE = adverse event; ANGPTL = angiopoietin-like; Apo = apolipoprotein; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein cholesterol; SAE = serious adverse event; and TEAE = treatment emergent adverse event.

Estimands

The primary clinical question of interest is

> What is the treatment difference in ApoB percent change from baseline after 180 days of treatment in participants who meet the inclusion criteria and would have completed the treatment period?

The same estimand for the primary objective will be used for the secondary clinical response endpoints.
Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of LY3561774 doses with placebo irrespective of adherence to study intervention, including data collected during the treatment period and safety follow-up.

Number of Participants:

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 20% dropout rate, this results in approximately 20 completers for 100 mg group and 40 completers per arm for the rest of the groups.

Intervention Groups and Duration:

The planned treatment arms are

- 100 mg LY3561774 or placebo
- 400 mg LY3561774 or placebo, and
- 800 mg LY3561774 or placebo.

Intervention administration is by subcutaneous injection.

Dosing will occur twice during the study on Day 0 and Day 90 (-5 to +10 days).

Data Monitoring Committee: No

1.2. Schema

1.3. Schedule of Activities (SoA)

Screening

If screening takes longer or shorter than 45 days to complete, it will not be considered a protocol deviation.

Remote visits

Visits noted in the SoA are eligible to be conducted remotely at the direction of the sponsor, according to local laws and regulations. Remote visits may be by telephone, IT-assisted virtual visit, mobile healthcare, at a local laboratory, or a combination thereof.

Safety follow-up

If a participant's ApoB levels do not return to ≥80% of baseline 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 on Day 270, then Day 270 is their last study visit.

Study J3F-MC-EZCB(e)	**Screening**	**Double-Blind Treatment and Assessment**												**Follow-up**	**Comments**
Remote Visits			**X**	**X**	**X**		**X**	**X**		**X**	**X**				V801 on-site for all sites including the US
Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**ED**	**801**	ED = early discontinuation.
Days from randomization	**-45**	**0**	**15**	**30**	**60**	**90**	**120**	**150**	**180**	**210**	**240**	**270**	**—**	**360**	
Visit interval tolerance (days)		—	±3	±3	±3	-5 to +10	±7	±7	±7	±7	±7	±7	—	±7	Visit 1 procedures may be conducted over more than 1 day if all activities are completed within the allowable visit tolerance.
Fasting Visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Participants should not eat or drink anything but water for 8 hours before the visit. If a participant arrives not fasted, schedule the laboratory draw for another date.
Procedures															
Informed consent	X														The ICF must be signed before any protocol-specific tests/procedures are performed. See Section 10.1.3, for additional details.

Study J3F-MC-EZCB(e)	**Screening**	**Double-Blind Treatment and Assessment**												**Follow-up**	**Comments**
Remote Visits			**X**	**X**	**X**		**X**	**X**		**X**	**X**				V801 on-site for all sites including the US
Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**ED**	**801**	ED = early discontinuation.
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Fasting Visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Participants should not eat or drink anything but water for 8 hours before the visit. If a participant arrives not fasted, schedule the laboratory draw for another date.
Inclusion and exclusion criteria, review and confirm	X	X													Confirm inclusion and exclusion criteria prior to randomization and administration of first dose of study intervention.
Demographics	X														Includes ethnicity (where permissible), year of birth, sex, and race.
Preexisting conditions and medical history	X														Collect all ongoing conditions and relevant past surgical and medical history including history of premature CV disease.
Prespecified medical history (indication and history of interest)	X														Additional data for the indication and comorbidities of interest.
Substance use (alcohol)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

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Remote Visits			**X**	**X**	**X**		**X**	**X**		**X**	**X**				V801 on-site for all sites including the US
Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**ED**	**801**	ED = early discontinuation.
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Fasting Visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Participants should not eat or drink anything but water for 8 hours before the visit. If a participant arrives not fasted, schedule the laboratory draw for another date.
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Any events that occur after signing the informed consent are considered AEs as defined in Section 10.3. If an injection-site reaction occurs, collect an additional unscheduled immunogenicity and PK sample (Section 8.3.4).
Physical Evaluations															
Height	X														Participant should remove shoes.
Weight	X					X			X			X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Includes blood pressure and pulse rate. May repeat measure once. Measure after participant has been sitting at least 5 minutes and before ECG tracing and collection of blood samples for laboratory testing.
Physical examination	X											X	X		See Section 8.2.1. The complete physical examination excludes pelvic, rectal, and breast examinations, unless clinically indicated.

Study J3F-MC-EZCB(e)	**Screening**	**Double-Blind Treatment and Assessment**												**Follow-up**	**Comments**
Remote Visits			**X**	**X**	**X**		**X**	**X**		**X**	**X**				V801 on-site for all sites including the US
Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**ED**	**801**	ED = early discontinuation.
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Visit interval tolerance (days)		—	±3	±3	±3	-5 to +10	±7	±7	±7	±7	±7	±7	—	±7	Visit 1 procedures may be conducted over more than 1 day if all activities are completed within the allowable visit tolerance.
Fasting Visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Participants should not eat or drink anything but water for 8 hours before the visit. If a participant arrives not fasted, schedule the laboratory draw for another date.
Symptom-directed physical assessment		X		X	X	X	X	X	X	X	X			X	Performed by qualified personnel per local regulations based on participant status and standard of care.
Single 12-lead ECG (local)	X					X			X			X	X	X	Collect at least 30 minutes prior to collection of blood samples for laboratory testing, including PK samples. Participants should be supine for approximately 5 to 10 minutes before ECG collections and remain supine but awake during the ECG collection. ECGs may be repeated at the investigator's discretion at any visit.
Schedule MRI	X														Schedule MRI prior to randomization for applicable participants who meet screening inclusion and exclusion criteria.
MRI		X							X				X		Performed for the quantification of hepatic fat. See Section 8.2.4. The participant must fast for at least 6 hours prior to the MRI. If they did not fast, schedule MRI for another date prior to randomization.

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Remote Visits			**X**	**X**	**X**		**X**	**X**		**X**	**X**				V801 on-site for all sites including the US
Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**ED**	**801**	ED = early discontinuation.
Days from randomization	**-45**	**0**	**15**	**30**	**60**	**90**	**120**	**150**	**180**	**210**	**240**	**270**	**—**	**360**	
Visit interval tolerance (days)		—	±3	±3	±3	-5 to +10	±7	±7	±7	±7	±7	±7	—	±7	Visit 1 procedures may be conducted over more than 1 day if all activities are completed within the allowable visit tolerance.
Fasting Visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Participants should not eat or drink anything but water for 8 hours before the visit. If a participant arrives not fasted, schedule the laboratory draw for another date.
															Visit 2: Perform MRI at any day prior to randomization. **ED Visit:** if ED Visit is prior to Visit 9, then conduct MRI. If ED Visit is after Visit 9, do not conduct MRI.
Laboratory Tests and Sample Collections															On dosing days, collect samples before dosing.
Hematology	X					X			X			X	X	X	
Clinical Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Lipid panel	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Includes non-HDL-C.
Coagulation panel	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ApoB, ApoA-I, ApoC-III	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ANGPTL3 and ANGPTL3/8	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
TSH	X														
HbA1c	X	X				X			X			X	X		
Insulin		X				X			X			X	X		
Urinalysis	X					X			X			X	X	X	
UACR	X					X			X			X	X	X	Urinary albumin/creatinine ratio calculation.

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Remote Visits			**X**	**X**	**X**		**X**	**X**		**X**	**X**				V801 on-site for all sites including the US
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Fasting Visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Participants should not eat or drink anything but water for 8 hours before the visit. If a participant arrives not fasted, schedule the laboratory draw for another date.
Serum pregnancy	X														Only for WOCBP and women with a history of tubal ligation. See Section 10.4.
Urine pregnancy (local)		X				X			X			X	X		Collect for WOCBP only. This test must be performed at Visits 2, 6, 9, and end of study with the result available prior to first dose of intervention. Perform additional pregnancy tests if a menstrual period is missed, if there is clinical suspicion of pregnancy, or as required by local law or regulation.
FSH	X														Optional. Perform as needed to confirm postmenopausal status. See Section 10.4.
Hepatitis B virus (HBV)	X														
Hepatitis C virus (HCV)	X														
HIV	X														
Estimated glomerular filtration rate (eGFR)	X	X		X		X			X			X	X	X	Calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) method.

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Remote Visits			**X**	**X**	**X**		**X**	**X**		**X**	**X**				V801 on-site for all sites including the US
Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**ED**	**801**	ED = early discontinuation.
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Fasting Visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Participants should not eat or drink anything but water for 8 hours before the visit. If a participant arrives not fasted, schedule the laboratory draw for another date.
Pharmacokinetic (PK) samples		X				X									**Visit 2:** Collect 2 samples. First sample at 0.5 hr post-dose, and Second sample: 4-12 hr post-dose (minimum 2 hr). **Visit 6:** Collect 1 sample any time on the next day after 2nd injection, 24-48 hrs post-dose. This may require a PK-specific visit.
Immunogenicity (ADA)		X	X	X		X			X			X	X	X	Collect samples before dosing. If an immediate or nonimmediate systemic drug hypersensitivity reaction occurs, collect an additional unscheduled sample as detailed in Section 10.2.1.
PK sample for immunogenicity		X	X	X		X			X			X	X	X	Collect a time-matched PK sample for all scheduled and unscheduled immunogenicity samples. Collect samples before dosing.
High-sensitivity C-reactive protein (hsCRP)		X				X			X			X	X	X	
Stored Samples															On dosing days, collect samples before dosing.
Genetic sample		X													

Study J3F-MC-EZCB(e)	**Screening**	**Double-Blind Treatment and Assessment**												**Follow-up**	**Comments**
Remote Visits			**X**	**X**	**X**		**X**	**X**		**X**	**X**				V801 on-site for all sites including the US
Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**ED**	**801**	ED = early discontinuation.
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Visit interval tolerance (days)		—	±3	±3	±3	-5 to +10	±7	±7	±7	±7	±7	±7	—	±7	Visit 1 procedures may be conducted over more than 1 day if all activities are completed within the allowable visit tolerance.
Fasting Visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Participants should not eat or drink anything but water for 8 hours before the visit. If a participant arrives not fasted, schedule the laboratory draw for another date.
Exploratory biomarker samples		X		X		X			X			X	X		
Randomization and Dosing using IWRS															
Register visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization		X													
Dispense in IWRS		X				X									
Dispense intervention		X				X									
Administer intervention		X				X									

Abbreviations: ANGPTL = angiopoietin-like; Apo = apolipoprotein; CV = cardiovascular; ECG = electrocardiogram; FSH = follicle-stimulating hormone; ICF = informed consent form; IWRS = interactive web-response system; MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

2. Introduction

LY3561774

LY3561774 is a novel Dicer-substrate siRNA oligonucleotide designed to reduce the levels of ANGPTL3 protein expression.

How blocking ANGPTL3 reduces lipid levels

Blocking ANGPTL3 activity or preventing its expression is a potential therapeutic approach to reducing ApoB-containing lipoprotein particles that are contributing risk factors for ASCVD (Graham et al. 2017; Stitziel et al. 2017).

Loss-of-function mutations in the ANGPTL3 gene are associated with decreased plasma TGs, LDL-C, and HDL-C levels (Graham et al. 2017; Stitziel et al. 2017). In turn, the reduction of these atherogenic lipids is expected to result in decreased risk of primary and secondary MACE.

LY3561774 clinical development

LY3561774 is being developed as a treatment for patients with mixed dyslipidemia to ultimately reduce the risk of MACE.

2.1. Study Rationale

Residual cardiovascular risk is still high, despite the current standard of care that includes maximally tolerated statin. Studies show that a reduction in circulating biomarkers, such as non-HDL-C and ApoB, are associated with a reduction in MACE (Bowman et al. 2017; Ference et al. 2019).

This study aims to investigate the impact of LY3561774 on surrogate biomarkers of MACE in participants with mixed dyslipidemia. This is the first Phase 2 study and data from this study will inform dose decisions for the clinical development of LY3561774.

2.2. Background

A detailed description of the chemistry, pharmacology, efficacy, and safety of LY3561774 is provided in the IB.

Clinical Study EZCA preliminary results

Study J3F-MC-EZCA (EZCA) is a first-in-human study of LY3561774, assessing the safety, tolerability, PK, and PD of single-ascending subcutaneous and repeat subcutaneous doses of LY3561774 in participants with dyslipidemia. The study had 3 parts that are described in this table.

Study EZCA Part	Subcutaneous dosing frequency	Dose levels	Number of participants at data cut-off date for preliminary results
A	Single	24, 72, 208, 480 and 960 mg	40
B	2 doses given 28 days apart	208 or 480 mg	16
C	Single	208 or 480 mg	18 Japanese participants[a]

[a] Part C was a cohort of only Japanese participants.

Safety

Preliminary results suggest LY3561774 is generally well tolerated when administered as single doses up to 960 mg and as 2 doses of either 208 or 480 mg.

Treatment emergent adverse events were mostly mild in severity.

Part A

Treatment emergent adverse events reported by at least 2 participants included headache, increased blood creatine phosphokinase, and rash.

After single doses, transient elevations of liver enzymes (AST or ALT >2x ULN) and/or creatine kinase (>5x ULN) were observed. These were not associated with any clinical signs or symptoms.

All ISRs resolved spontaneously and there was no apparent relationship of the frequency or severity with the dose.

Part B

Treatment emergent adverse events reported by at least 2 participants included headache, increased hepatic enzymes, and rash.

No clinically relevant changes in laboratory values were observed.

Injection-site reactions were reported after administration of 1 dose or repeat dosing, and they spontaneously resolved with no apparent relationship to dose.

Part C

Treatment emergent adverse events reported by at least 2 participants included ecchymosis.

One participant had ALT >2x ULN, but less than 3x ULN with no associated clinical signs or symptoms.

Injection-site reactions were reported by 4 participants.

Pharmacokinetics

Part A

After single doses, LY3561774 PK across the tested dose range exhibited

- linear PK
- median t_{max} between 7.5 and 12.5 hours, and
- mean terminal half-life from 5.5 to 12.9 hours.

Part B

After 2 doses, LY3561774 PK exhibited

- approximate dose proportionality across the dose range tested
- consistent PK with single-ascending dose cohorts
- median t_{max} between 9 and 16 hours after the first dose
- median t_{max} between 9 and 10.5 hours after the 2nd dose on Day 29, and

- a mean $t_{½}$ of approximately 7 hours.

Pharmacodynamics

Dose-dependent decreases in ANGPTL3, TG, and LDL-C were observed after single doses and 2 doses across the tested dose range. The duration of effect continued up to the last collection time point after dosing at Day 169.

2.3. Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks and reasonably expected AEs of LY3561774 may be found in the IB.

2.3.1. Risk Assessment

Study EZCA clinical data

Preliminary results from Study EZCA in healthy participants suggest LY3561774 is generally well tolerated (See Section 2.2).

Nonclinical data

Based on the nonclinical data, LY3561774 is not considered to be a high-risk compound.

Potential risks

Based on the current clinical data, nonclinical safety pharmacology and toxicology studies, and considering the oligonucleotide class effects, potential risks for clinical study participants receiving LY3561774 are hepatobiliary events, systemic allergic or hypersensitivity reactions, or ISRs.

Mitigations for potential risks

Liver enzyme levels will be monitored at multiple time points and clinical events will be monitored closely throughout the study. Participants will also have 2 MRI scans to determine change in hepatic fat fraction (see Section 8.2.4).

Hypersensitivity reactions will be managed per Section 8.3.3.

Injection-site reaction assessments will occur throughout the study.

2.3.2. Benefit Assessment

The efficacy of LY3561774 for lowering lipids has not been established. Participants may benefit by receiving personal health information from the physical examinations and from other routine safety assessments performed in this study.

2.3.3. Overall Benefit Risk Conclusion

Considering the measures taken to minimize risk for the participants in this study, the potential risks identified in association with LY3561774 are justified by the anticipated benefits that may be afforded to participants with mixed dyslipidemia.

3. Objectives, Endpoints, and Estimands

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	
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 • Triglycerides.
	Percent change from baseline at Day 270 for • ANGPTL3 • Non-HDL-C • LDL-C • HDL-C • ApoB, and • Triglycerides.
Characterize the pharmacokinetics (PK) of LY3561774.	Plasma concentrations of LY3561774.
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	
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.

Objectives	Endpoints
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 anti-drug antibodies (ADA).
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 • HbA1c, and • FG.
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 • Triglycerides.
Compare the effect of LY3561774 to placebo on hepatic fat fraction.	Change from baseline for MRI hepatic fat fraction at Day 180.

Abbreviations: AE = adverse event; ANGPTL3 = angiopoietin-like protein 3; Apo = apolipoprotein; 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; UACR = urinary albumin/creatinine ratio; and VLDL-C = very-low-density lipoprotein-cholesterol.

Primary estimand

The primary clinical question of interest is

> What is the treatment difference in ApoB percent change from baseline after 180 days of treatment in participants who meet the inclusion criteria and would have completed the treatment period?

Efficacy estimand attributes

This table describes the efficacy estimand attributes.

Efficacy Estimand Attribute	Description
Population	Participants who meet the inclusion criteria. Further details can be found in Sections 5 and 9.
Endpoint	Percent change from baseline in ApoB at Day 180.
Treatment condition	The randomized treatment.
Population-level summary	Difference in mean percent changes in ApoB at Day 180 between LY3561774 and placebo.

Intercurrent events

The intercurrent events including the following are handled by the hypothetical strategy:

- Permanent discontinuation of intervention.
- Initiation of excluded medications taken during the study.
- New initiation of any lipid-lowering drug required to be on a stable regimen prior to treatment per the protocol inclusion criteria.

The potential outcome of interest is the response in the efficacy measurement if participants adhere to the randomized treatment.

Rationale for the efficacy estimand

This Phase 2 study aims 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 secondary clinical response endpoints.

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

4. Study Design

4.1. Overall Design

This 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.

The planned treatment arms are

- 100 mg LY3561774 or placebo
- 400 mg LY3561774 or placebo, and
- 800 mg LY3561774 or placebo.

Intervention administration is by subcutaneous injection.

Dosing will occur twice during the study, on Day 0 and Day 90 (-5 to +10 days).

4.1.1. Design Outline

Screening

Interested participants will sign the appropriate informed consent document(s) prior to completion of any procedures.

The investigator will review symptoms, risk factors, medical history, concomitant medications and other inclusion and exclusion criteria prior to any diagnostic procedures. If the participant is eligible after this review, then the site will perform the diagnostic procedures to confirm eligibility.

Double-blind treatment and assessment period

This is the general flow during the treatment and assessment period:

- Complete MRI at any date prior to randomization
- Complete baseline procedures and sample collection
- Participants are randomly assigned to an intervention group, and
- Participants complete all visit procedures including efficacy assessments, safety monitoring, study intervention dosing, and post-dosing sample collection.

Safety follow-up

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

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

4.2. Scientific Rationale for Study Design

Primary endpoint

The primary endpoint, ApoB, is considered the strongest surrogate biomarker and predictor of future cardiovascular events. Plasma ApoB levels reflect the number of circulating atherogenic ApoB-containing lipoproteins, namely VLDL, intermediate-density lipoprotein, remnants of TG-rich lipoproteins, LDL, and lipoprotein(a).

The clinical benefit of lowering both TG and LDL-C levels in patients with mixed dyslipidemia appears to be proportional to the absolute change in ApoB (Ference et al. 2019). Even though LDL-C and non-HDL-C are good predictors of cardiovascular risk (Puri et al. 2016), more recent studies suggest that ApoB may be the primary driver of atherosclerosis and that lowering the concentration of all ApoB-containing lipoproteins should be the focus of therapeutic strategies (Ference et al. 2020; Richardson et al. 2020; Sniderman et al. 2019; Marston et al. 2022).

Overall design

The 270-day duration of the treatment period is based on the demonstrated efficacy and prolonged activity of the intervention in the Phase 1 Study EZCA. This duration is also a reasonable timeframe to observe efficacy for the treatment of mixed dyslipidemia, which will inform the dose level and frequency in future clinical studies.

The follow-up visit after the last dose is designed to capture any additional safety signals and to quantitate the return to baseline for ApoB.

Placebo is chosen as the control treatment to assess whether any observed effects are treatment related or simply reflect the study conditions. The double-blind design minimizes bias on safety assessments and allows a more robust comparison among LY3561774 doses and placebo.

In this study, collection of demographic information includes ethnicity and race. The scientific rationale is based on the need to assess variable response in safety and/or efficacy based on race or ethnicity. This question can be answered only if all the relevant data are collected.

4.3. Justification for Dose

Planned dose levels and frequency for this study

In this study, the planned subcutaneous doses of 100 mg, 400 mg, and 800 mg will evaluate the effect of LY3561774 in participants with mixed dyslipidemia. Dosing will occur twice during the study approximately 90 days apart.

Justification for dose levels and frequency

The doses and frequency were selected based on human safety, tolerability, PK and PD from Phase 1 evaluations, and nonclinical toxicology. Detailed information on these studies may be found in the IB.

The selected dose levels and dosing frequency with prolonged post-dose evaluations of ApoB will support a robust dose-exposure-response analysis of multiple safety and efficacy measures.

Data from this study will support future clinical development of LY3561774.

Phase 1 clinical Study EZCA

The available clinical safety data from healthy participants after receiving LY3561774 treatment up to 960 mg supports continued clinical development in Phase 2.

LY3561774 treatment up to 960 mg appears to reduce ANGPTL3 and TG levels dose-dependently.

Based on a PK/PD model of Study EZCA interim data, the 800 mg dose given every 90 days is expected to provide optimal ApoB and non-HDL-C reduction. The 100 mg dose given every 90 days is chosen as a low efficacy dose to optimize dose-exposure-response analysis.

Nonclinical toxicology data

The margin of safety for the 800 mg maximum dose in this study is expected to have an exposure multiple of approximately 9.6 times the NOAEL level based on the 6-month, repeat-dose mouse toxicity study and 22 times the NOAEL based on the 9-month, repeat-dose monkey toxicity study.

4.4. End of Study Definition

The end of the study is defined as the date of last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the trial globally.

A participant is considered to have completed the study if the participant completes all applicable scheduled procedures as shown in the SoA (Section 1.3).

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Must be 18 years of age or older at the time of signing the informed consent.

Type of participant and disease characteristics

2. Have fasting TGs within the range of 150 to 499 mg/dL (1.69 to 5.64 mmol/L) at screening.
3. Have fasting LDL-C ≥70 mg/dL (1.81 mmol/L) at screening.
51. Have fasting non-HDL-C ≥130 mg/dL (3.36 mmol/L) at screening.
4. Must be on a stable moderate or high-intensity dose of a statin (See Section 10.7.1) for at least 2 months before screening and remain on the same medication and dose for the duration of the study.

Weight

5. Have a body mass index within the range of 18.5 to 40.0 kg/m^2, inclusive.

Sex and contraceptive/barrier requirements

6. Are WOCBP who agree to use contraception as outlined in Section 10.4 or
   Are WNOCBP as defined in Section 10.4 or
   Are men who agree to use contraception as outlined in Section 10.4.

   Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

   Definitions and contraception requirements for participants in this study are provided in Section 10.4.

Informed consent

7. Are capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Other inclusions

8. Have not started a structured weight loss program within 3 months of screening, or plan on starting a program during the study.
9. If taking hypertensive therapy, doses must be stable 30 days prior to screening.
10. Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.
11. Have an optimal MRI image quality at screening, as assessed by central laboratory.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Diabetes and cardiovascular medical conditions

12. Have, in the 6 months prior to screening, uncontrolled Type 1 or Type 2 diabetes, defined as an episode of ketoacidosis or hyperosmolar state requiring hospitalization, or have an HbA1c ≥8% at screening.
13. Have a history of nephrotic syndrome.
14. Have had within the past 3 months prior to screening
    a. Myocardial infarction
    b. Unstable angina
    c. Coronary artery bypass graft
    d. Percutaneous coronary intervention – diagnostic angiograms are permitted
    e. Peripheral artery disease
    f. Transient ischemic attack, or
    g. Cerebrovascular accident.
15. Have New York Health Association Class III or IV heart failure or last known left ventricular ejection fraction <30%.
16. Have undergone LDL apheresis within 12 months prior to screening.

Other medical conditions

17. Have a TSH outside of the 0.4 to 6.0 mIU/L range.
18. Have a history or presence of an underlying disease, or surgical, physical, or medical condition that, in the opinion of the investigator would potentially affect participant safety within the study or interfere with the interpretation of data.
19. Have, within 1 year prior to screening or plan on having during the study, surgical treatment for obesity.
20. Have within 5 years prior to screening a history of an active or untreated malignancy or are in remission from a clinically significant malignancy.
    Exceptions:
    - Basal or squamous cell skin cancer.
    - Cervical carcinoma in situ or prostate cancer in situ.
21. Have a history of or current significant psychiatric disorders considered clinically significant in the opinion of the investigator.
22. Have within 3 years prior to screening a history of chronic alcohol abuse, IV drug abuse, or other illicit drug abuse.
23. Have within 3 months prior to screening used marijuana or tetrahydrocannabinol containing products or are unwilling to abstain from use during the study.
24. Have 2 or more clinically significant or severe drug allergies, or severe post-treatment hypersensitivity reactions, including, but not limited to
    a. erythema multiforme major
    b. linear immunoglobulin A dermatosis
    c. toxic epidermal necrolysis, or

d. exfoliative dermatitis.

25. Have a history of acute or chronic pancreatitis.
26. Have active severe liver diseases, such as cirrhosis, active hepatitis, or biliary obstruction with hyperbilirubinemia.
27. Have a history of infection within 14 days before screening that, in the opinion of the investigator, would potentially affect participant safety within the study or interfere with the interpretation of data.
28. Have HIV infection or are positive for HIV antibodies.
29. Have current infection with hepatitis B virus or positive for hepatitis B surface antigen.
30. Have a current infection with hepatitis C virus or positive hepatitis C virus antibody.

Diagnostic assessments

31. Have clinically relevant anemia, as defined by the investigator.
32. Have laboratory values, in relation to the reference range,
    ALT >3.0X ULN or
    ALP >1.5X ULN or
    TBL >1.5X ULN, except for participants diagnosed with Gilbert's syndrome.
33. Have an eGFR <30 mL/min/1.73 m^2.
34. Have a pulse rate >100 bpm, a repeat measure is allowed.
35. Have uncontrolled hypertension with a resting blood pressure ≥180 mm Hg systolic and/or ≥100 mm Hg diastolic, a repeat measure is allowed.

Prior/concomitant therapy

36. Have used or are taking products for the purpose of lowering lipid levels. This includes lipid-regulating medication, over-the-counter products, or herbal therapies.
    See Section 10.7.3 for details on prohibited treatments and the timeframe relative to screening.

    Exceptions: Statins, PCSK9 inhibitors, bempedoic acid, and ezetimibe.

37. Have within 3 months of screening, initiated treatment with SERMs, estrogens, progestins, testosterone, or thyroid hormone therapy.
38. Have or are currently taking HIV protease inhibitors, cyclophosphamide, or systemic retinoids.
39. Have within 6 months of screening had treatment with any oligonucleotide, including small interfering ribonucleic acid.
    Exception: mRNA vaccines.
40. Have within 3 months of screening treatment with systemic corticosteroids, cyclosporine, isotretinoin, or anabolic agents.
    Exceptions: local, topical, intra-articular, inhalation, or nasal corticosteroids.
41. Have within 1 month prior to screening treatment with
    a. warfarin or other coumarins
    b. direct thrombin inhibitors
    c. Factor Xa inhibitors, or

d. Heparins or heparinoids.

42. Are currently using a medication associated with weight gain or weight loss.
    Exception: if the participant is on a stable dose for at least 3 months prior to screening and will continue the stable dose during the study.

Prior or concurrent clinical study experience

43. Are currently enrolled or have participated within the last 6 months in a clinical study involving an investigational intervention or any other type of medical research judged not to be scientifically or medically compatible with this study.
44. Have previously completed or withdrawn from this study.

Other exclusions

45. Are breastfeeding.
46. Have an average weekly alcohol intake more than 21 units per week for men and 14 units per week for women or are unwilling to stop alcohol consumption from 48 hours prior to each visit.
    1 unit of alcohol is equal to
    - 12 ounces or 360 mL of beer
    - 5 ounces or 150 mL of wine, or
    - 1.5 ounces or 45 mL of distilled spirits.
47. Are unwilling to have an MRI scan or have contraindications for MRI scanning
    a. have a cardiac pacemaker or implants made out of metal, for example, cochlea implants, nerve stimulators, magnetic vascular clips, or metallic heart valves
    b. Have extreme claustrophobia
    c. Weight or girth exceeds scanner capabilities, or
    d. In the opinion of the investigator, have any condition or circumstance that would interfere with completion of the MRI.
48. Are Lilly employees or are employees of any third party involved in the study who require exclusion of their employees.
49. Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
50. Are unsuitable for inclusion in the study in the opinion of the investigator.

5.3. Lifestyle Considerations

Participants must not donate blood for the duration of the study and for 8 weeks following the study.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to

respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time and require a new identification number. If initial MRI image needs to be resubmitted, it will not cause a new identification number to be submitted. If, in the opinion of the investigator, an ineligible laboratory test result is the result of an error or extenuating circumstance, then that parameter can be retested once without the participant having to be rescreened.

The interval between screenings should be at least 1 week.

5.5. Criteria for Temporarily Delaying Enrollment of a Participant

This section is not applicable for this study.

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to, or used by, a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Each participant will receive either placebo or LY3561774 via subcutaneous injection.

Intervention Name	**LY3561774**	**Placebo**
IMP and NIMP	IMP	IMP
Authorized as defined by EU Clinical Trial Regulation	No	No
Use	Experimental	Placebo-control
Dose Form	Solution	Solution
Unit Dose Strength(s)	200 mg/mL	Not applicable
Dosage Level(s)	100 mg 400 mg 800 mg	Not applicable
Route of Administration	Subcutaneous injection	Subcutaneous injection
Sourcing	Provided centrally by the sponsor	Commercially available 0.9% sodium chloride solution.
Labeling	Study intervention will be labeled as appropriate for country requirements.	

Abbreviations: IMP = investigational medicinal product; NIMP = non-investigational medicinal product.

This table describes the number of injections for the different intervention dose groups.

Intervention group	**Number of injections**
100 mg or matched placebo participants	1 injection
400 mg or matched placebo participants	1 injection
800 mg or matched placebo participants	2 injections

Location of subcutaneous injections

All SC injections will be administered into the SC tissue of the abdominal wall, 5 to 10 cm from the umbilicus.

If multiple injections are needed, they will be performed in quick succession and each injection should be delivered into separate quadrants in the anterior abdominal wall.

Record the package number and location of each injection.

6.2. Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.

The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).

Only authorized study personnel may supply, prepare, or administer study intervention.

Only participants enrolled in the study may receive study intervention.

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Randomization

All participants will be centrally assigned to randomized study intervention using an IWRS. Before the study is initiated, the log in information and directions for the IWRS will be provided to each site.

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 so 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 <250 mg/dL and ≥250 mg/dL.

Maintaining blinding

Investigators will remain blinded to each participant's assigned study intervention within each dose group, throughout the course of the study. To maintain this blind, an otherwise unblinded third party will be responsible for the receiving, registering, preparing, and administering of all study intervention. Although the participant and the investigator will know the injection volume, they will not know whether the participant is receiving LY3561774 or placebo. To mitigate the risk of unblinding due to color difference between IMPs, site will be trained on additional operational procedures. Unblinded personnel who administer IMP to participants at Visit 2 will have no other interaction, role, or responsibilities other than receiving, registering, preparing, and administering IMP at Visit 6 in the trial. Participants should be instructed to look away during IMP administration.

Emergency unblinding

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination.

If a participant's intervention assignment is unblinded, the sponsor must be notified immediately within 24 hours of this occurrence. The date and reason that the blind was broken must be recorded.

Discontinuation from the study in case of unblinding

If an investigator, study personnel performing assessments, or participant is unblinded, the participant must be discontinued from intervention and follow procedures outlined in Section 7.1. In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from a sponsor clinical research physician for the participant to continue in the study.

6.4. Study Intervention Compliance

Study intervention will be administered under medical supervision by the investigator or designee. The study intervention and study participant identification will be confirmed prior to the time of dosing. The date and time of each dose administered will be recorded in the source documents and in the CRF.

6.5. Dose Modification

This protocol does not allow dose adjustments.

6.6. Continued Access to Study Intervention after the End of the Study

Study intervention will not be available to participants after completion of the study.

6.7. Treatment of Overdose

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should

- contact the medical monitor immediately
- evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted, and
- closely monitor the participant for any AE/SAE and laboratory abnormalities until LY3561774 no longer has a clinical effect.

6.8. Concomitant Therapy

See Section 10.7 for lists of medications that are permitted or prohibited in this study.

Concomitant therapy regimens

All participants should maintain their usual medication regimens for concomitant conditions or diseases throughout the study, unless those medications are specifically excluded in the protocol.

Participants taking concomitant medications should be on stable dosages at the time of screening and should remain at stable dosages throughout the study, unless changes need to be made because of AEs.

Changing concomitant therapy

Participants should consult with authorized study personnel before taking any new medications or supplements during the study. Authorized study personnel should consult the sponsor's medical monitor if there are any questions about concomitant therapies during the study.

The investigator or the participant's usual diabetes care physician is responsible for changes in diabetic medications.

Concomitant therapy data collection

For therapy that the participant is receiving at the time of enrollment or receives during the study, authorized study personnel should collect

- the name of medication, vaccine or therapy
- the reason for use, and
- dates of administration, including start and end dates.

For diabetes and lipid modifying medications, such as statins and PCSK9 inhibitors, collect dosage information including dose and frequency.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.9.

7.1. Discontinuation of Study Intervention

When necessary, a participant may be permanently discontinued from study intervention.

Situations when discontinuation of study intervention may occur

A participant should be permanently discontinued from study intervention if

- the participant becomes pregnant during the study
- a prohibited treatment listed in Section 10.7.3 is initiated during the study, or
- in the opinion of the investigator, the participant should permanently discontinue the study intervention for safety reasons.

If the investigator determines that a systemic hypersensitivity reaction has occurred related to study intervention administration, the participant may be permanently discontinued from the study intervention, and the sponsor's designated medical monitor should be notified. If the investigator is uncertain about whether a systemic hypersensitivity reaction has occurred and whether discontinuation of study intervention is warranted, the investigator should consult the sponsor.

If study intervention is permanently discontinued, the participant will remain in the study and follow procedures for the remaining study visits as shown in the SoA.

7.1.1. Liver Chemistry Stopping Criteria

The study intervention should be interrupted or discontinued if 1 or more of these conditions occur.

Elevation	Exception
ALT or AST >8x ULN	
ALT or AST >5x ULN for more than 2 weeks	
ALT or AST >3x ULN and either TBL >2x ULN or INR >1.5	In participants with Gilbert's syndrome, doubling of direct bilirubin should be used for intervention interruption or discontinuation decisions rather than TBL >2x ULN.
ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >3x ULN, when the source of increased ALP is the liver	
ALP >2.5x ULN and TBL > 2x ULN	In participants with Gilbert's syndrome, doubling of direct bilirubin should be used for intervention interruption or discontinuation decisions rather than TBL >2x ULN.

ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	

Resumption of the study intervention can be considered only in consultation with the Lilly-designated medical monitor and only if the liver test results return to baseline and if a self-limited, non-intervention etiology is identified.

7.1.2. QTc Stopping Criteria

If a clinically significant finding is identified, including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

- at any time at the participant's own request
- at the request of the participant's designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

Discontinuation is expected to be uncommon.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation visit and safety follow-up, if applicable, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued from both the study intervention and the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel or designee are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

8.1.1. Primary Efficacy Assessment

Even though TGs, LDL-C, and non-HDL-C are routinely measured in clinical practices and commonly used as primary endpoints in clinical trials for mixed dyslipidemia, ApoB is considered the strongest predictor of future cardiovascular events.

8.1.2. Secondary Efficacy Assessments

At times specified in the SoA, blood samples will be collected to measure changes in levels of these markers for mixed dyslipidemia

- ANGPTL3
- LDL-C
- HDL-C
- Non-HDL-C, and
- TGs.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

Physical examination at screening

The complete physical examination will include assessments of these areas and body systems

- Skin
    - Head
    - Abdomen
    - Extremities
- Ears, eyes, nose, throat
- Lymph nodes
- Thyroid palpation

- Cardiovascular
- Respiratory
- Gastrointestinal, and
- Neurologic.

Height and weight will also be measured and recorded.

The complete physical examination excludes pelvic, rectal, and breast examinations, unless clinically indicated.

Symptom-directed physical assessments after screening

These assessments are performed based on participant status and standard of care.

8.2.2. Vital Signs

Blood pressure and pulse rate will be measured when specified in the SoA and as clinically indicated. Additional vital signs may be measured during study visits if warranted, as determined by the investigator.

Vital signs should be measured after participant has been sitting at least 5 minutes, before obtaining an ECG tracing, and before collection of blood samples for laboratory testing.

8.2.3. Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that preferably automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

Electrocardiograms will initially be interpreted by the investigator or qualified designee at the site as soon after the time of ECG collection as possible, and ideally while the participant is still present, to determine whether the participant meets entry criteria and for immediate participant management, should any clinically relevant findings be identified.

The investigator or qualified designee is responsible for determining if any change in participant management is needed and must document their review of the ECG printed at the time of evaluation.

8.2.4. Magnetic Resonance Imaging

Participants will undergo MRI evaluations as outlined in the SoA for the measurement of liver fat content.

Liver fat content will be determined using MRI – Proton Density Fat Fraction. The fat fraction is the proportion of mobile protons in liver tissue attributable to fat and is a noninvasive MRI-based biomarker of liver TG concentration.

MRI images will be transmitted to a central reader for evaluation of the MRI-based endpoints. For participant safety, images should also be over-read locally to assure there are no underlying liver pathologies.

For participants with claustrophobia in MRI machines, investigators may offer, at their discretion, a light sedative.

8.2.5. Clinical Safety Laboratory Tests

See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.

The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE.

The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration.

Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.

If laboratory values from non-protocol specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator (for example, SAE or AE or dose modification), then report the information as an AE.

8.2.6. Hepatic Monitoring

Close hepatic monitoring

Initiating laboratory and clinical monitoring for abnormal liver laboratory test results

Laboratory tests, including ALT, AST, ALP, TBL, direct bilirubin, GGT, and CK, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur. This table shows when to repeat laboratory tests.

If a participant with baseline results of ...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN
ALP <1.5x ULN	ALP ≥2x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥1.5x baseline (except for participants with Gilbert's syndrome)

What to do if the abnormal condition persists or worsens

If the abnormal liver test result persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including

- symptoms
- recent illnesses, for example, heart failure, systemic infection, hypotension, or seizures
- recent travel
- history of concomitant medications, including over-the-counter, herbal and dietary supplements, and
- history of alcohol drinking and other substance abuse.

Frequency of monitoring

Initially, monitoring of symptoms and liver tests should be done 1 to 3 times weekly, based on the participant's clinical condition and liver test results.

Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and laboratory results stabilize.

Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

When to perform a comprehensive evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if 1 or more of the conditions in this table occur.

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN with hepatic signs/symptoms[a], or ALT or AST ≥5x ULN
ALP <1.5x ULN	ALP ≥3x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline with hepatic signs/symptoms[a], or ALT or AST ≥3x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥2x baseline (except for participants with Gilbert's syndrome)

[a]Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

What a comprehensive evaluation should include

At a minimum, this evaluation should include

- physical examination and a thorough medical history, as outlined above
- tests for
    - PT-INR
    - viral hepatitis A, B, C, or E

    - autoimmune hepatitis, and
- an abdominal imaging study, for example, ultrasound or computed tomography scan.

Based on the patient's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for

- hepatitis D virus
- cytomegalovirus
- Epstein-Barr virus
- acetaminophen levels
- acetaminophen protein adducts
- urine toxicology screen
- Wilson's disease
- blood alcohol levels
- urinary ethyl glucuronide, and
- blood phosphatidylethanol.

Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.

Additional hepatic data collection (hepatic safety CRF) in study participants who have abnormal liver tests during the study

If a participant develops a hepatic event considered to be an SAE, or discontinues study intervention due to a hepatic event, then collect additional hepatic safety data collection in the hepatic safety CRFs.

This table shows when to collect additional hepatic safety data based on changes in laboratory results.

If a participant with baseline results of...	develops the following elevations…	Then…
Elevated serum ALT		Collect additional heaptic safety data in the hepatic safety CRF.
ALT <1.5x ULN	ALT to ≥5x ULN on 2 or more consecutive blood tests	
ALT ≥1.5x ULN	ALT ≥3x baseline on 2 or more consecutive blood tests	
Elevated TBL		
TBL <1.5x ULN	TBL ≥2x ULN (except for participants with Gilbert's syndrome)	
TBL ≥1.5x ULN	TBL ≥2x baseline	
Elevated ALP		
ALP <1.5x ULN	ALP ≥2x ULN on 2 or more consecutive blood tests	
ALP ≥1.5x ULN	ALP to ≥2x baseline on 2 or more consecutive blood tests	

Note: The interval between the 2 consecutive blood tests should be at least 2 days.

8.2.7. Pregnancy Testing

Pregnancy testing will occur throughout the duration of the study as outlined in the SoA.

8.3. Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of these events can be found in Section 10.3.

- AEs
- SAEs, and
- PCs.

These events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet these definitions and remain responsible for following up events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or the study.

Care will be taken not to introduce bias when detecting events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about event occurrences.

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). For PCs, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Section 10.3.4.

8.3.1. Timing and Mechanism for Collecting Events

This table describes the timing, deadlines, and mechanism for collecting events.

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	Signing of the informed consent form (ICF)	Participation in study has ended	As soon as possible upon site awareness	AE CRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related with study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE CRF	SAE paper form
SAE and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hours of awareness	SAE CRF	SAE paper form
SAE[a] – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	4 days after the last dose of intervention	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form
Product Complaints (PCs)					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	PC form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	PC form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed PC form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	PC form	

[a]Serious adverse events should not be reported unless the investigator deems them to be possibly related to study treatment or study participation.

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive LY3561774.

After learning of a pregnancy in the female partner of a study participant, the investigator will obtain a consent to release information from the pregnant female partner directly, and within 24 hours after obtaining this consent will record pregnancy information on the appropriate form and submit it to the sponsor.

The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will be withdrawn from the study. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.3.3. Hypersensitivity Reactions

Many drugs, including oral agents and biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data should be provided to the sponsor in the designated CRFs.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving study intervention. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per national and international guidelines.

In the case of a suspected systemic hypersensitivity event, additional blood samples should be collected as described in Section 10.2.1. Laboratory results are provided to the sponsor via the central laboratory.

8.3.4. Injection-Site Reactions

Symptoms and signs of a local ISR may include erythema, induration, pain, pruritus, and edema.

If an ISR is reported by a participant or site staff, the ISR CRF will be used to capture additional information about this reaction, for example, injection-site pain, degree and area of erythema, induration, pruritis, and edema.

At the time of ISR occurrence, collect an immunogenicity and PK sample.

8.3.5. Major Adverse Cardiovascular Events (MACE)

Nonfatal cardiovascular AEs will be adjudicated by a committee of physicians external to Lilly with cardiology expertise. This committee will be blinded to treatment assignment.

The nonfatal cardiovascular AEs 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.

8.4. Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of LY3561774 as specified in the SoA.

Participants may need to return to the clinical site for PK-specific visits to provide post-dose PK samples dependent on the time window of PK sampling.

Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample and the most recent LY3561774 dose prior to PK blood draw must be recorded.

Samples will be used to evaluate the PK of LY3561774. Only samples from participants assigned to treatment with LY3561774 will be analyzed for drug concentration. Samples collected for analyses may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Intervention concentration information that may unblind the study will not be reported to investigative sites or blinded personnel.

8.4.1. Bioanalytical

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Concentrations of LY3561774 will be assayed using a validated bioanalytical method. Analyses of samples collected from placebo-treated participants are not planned.

Sample retention is described in Section 10.1.12. Remaining samples used for PK may be pooled and used for exploratory metabolism or bioanalytical method experiments as deemed appropriate.

8.5. Pharmacodynamics

Pharmacodynamic parameters are described in Section 8.1.

8.6. Genetics

A whole-blood sample will be collected for pharmacogenetic analysis where local regulations allow. See Clinical Laboratory Tests, and the SoA for sample collection information.

See Section 10.5 for genetic research, custody, and Section 10.1.12 for sample retention information.

8.7. Biomarkers

Serum and plasma samples will be used for exploratory biomarker research, where local regulations allow. See Clinical Laboratory Tests, and the SoA for sample collection information.

Samples will be used for research on the drug target, disease process, variable response to LY3561774, pathways associated with lipid metabolism, mechanism of action of LY3561774, and/or research method, or for validating diagnostic tools or assay(s) related to lipid metabolism.

Samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to the intervention target, disease state, pathways associated with disease, and/or the mechanism of action of the study intervention.

Sample retention is described in Section 10.1.12.

8.8. Immunogenicity Assessments

Visits and times

At the visits and times specified in the SoA, venous blood samples will be collected to determine antibody production against LY3561774. The actual date and time (24-hour clock time) of each sample collection will be recorded.

Sample collection, handling, and use

Instructions for the collection and handling of blood samples will be provided by the sponsor.

Immunogenicity may be assessed by a validated assay designed to detect ADAs in the presence of LY3561774 at a laboratory approved by the sponsor. Antibodies may be further characterized for their ability to neutralize the activity of LY3561774.

Samples used for immunogenicity may be used for exploratory analyses as deemed appropriate.

Sample retention

Sample retention is described in Appendix 1, Section 10.1.12.

8.9. Health Economics

Health economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

The study hypothesis for the primary objective is if 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.

9.2. Analyses 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.
Efficacy Analysis Set (EAS)	Data obtained during the treatment period from all randomly assigned participants who are exposed to at least 1 dose of intervention. Excludes data after permanent discontinuation of intervention. Participants will be included in the treatment group to which they were randomly assigned.
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. Participants will be included in the treatment group to which they were randomly assigned.
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. Participants will be included in the treatment group to which they were randomly assigned.

9.3. Statistical Analyses

9.3.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the CSR. Additional exploratory analyses of the data will 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 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.

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

Primary estimand of interest and efficacy assessment

The primary estimand is a precise definition of the treatment effect to be estimated. The primary estimand of interest is comparing efficacy of LY3561774 doses to placebo and is named the "efficacy estimand" (Section 3). The efficacy estimand represents the efficacy prior to discontinuation of intervention.

The primary efficacy assessment guided by the efficacy estimand will be conducted using the EAS (Section 9.2).

Safety assessments

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of LY3561774 doses with placebo irrespective of adherence to intervention. Thus, safety analyses will be conducted using the SS (Section 9.2).

Exploratory analyses

Additional exploratory analyses of the data will be conducted as deemed appropriate.

Continuous data

Continuous data will be summarized by the sample size, mean, SD, median, minimum, and maximum.

Categorical data

Categorical data will be summarized by sample size, frequency, and percentage.

Analysis models for the comparison among treatment groups

The analysis model for comparisons among treatment groups relative to continuous measurements assessed over time, in addition to the baseline and end of treatment measurements, will be an MMRM. The model terms are

- treatment
- visit
- treatment-by-visit interaction
- baseline measurement, and
- Visit 1 TG stratum (<250mg/dL, ≥250 mg/dL).

Additional covariates may be added and will be detailed in SAP.

Logistic regression will be used to examine the treatment difference in binary efficacy outcomes. Fisher's exact test or Pearson's chi-square test will be used to examine the treatment difference in categorical outcomes. The negative binomial regression model will be used for the treatment comparison of discrete count measures if deemed appropriate.

Other statistical methods may be used, as appropriate, and details will be documented in the SAP.

9.3.2. Primary Endpoint/Estimand Analysis

The primary efficacy assessment, guided by the efficacy estimand, will be conducted using the EAS for the primary endpoint.

For the efficacy estimand, the hypothetical strategy is used to handle the intercurrent events of permanent discontinuation of intervention.

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 from randomization at Visit 2 to Day 180 at Visit 9.

The primary analyses model will be MMRM as described in Section 9.3.1. Treatment comparisons will be performed at the full significance level of 0.05. Additional covariates may be added, and this analysis will be detailed in the SAP.

9.3.3. Secondary Endpoint(s) Analysis

Secondary endpoints are listed in Section 3.

The efficacy analyses for the secondary endpoints will use the EAS and MMRM analysis described in Section 9.3.1. The clinical measures for secondary endpoints may be log transformed before statistical analyses, if deemed necessary. This analysis will be detailed in SAP.

9.3.4. Tertiary/Exploratory Analysis

Exploratory endpoints are listed in Section 3.

The average of AUC (Day 120-180) and AUC (Day 210-270) of the ApoB reduction will be calculated for participants with complete ApoB measurements during the specified period.

The calculated AUCs will be analyzed using an ANCOVA model. Baseline ApoB measurements will be used for adjustment. A Bayesian approach will be used as the dose-response model for time averaged AUC measures. The placebo group will be modeled with LY3561774 doses.

Details of the prior distribution specifications along with other analyses used for the exploratory objectives will be provided in the SAP.

9.3.5. Safety Analyses

Safety assessments will be guided by an estimand comparing safety of LY3561774 doses with placebo irrespective of adherence to intervention. Thus, safety analyses will be conducted using the SS.

Adverse events will be coded from the actual term using the Medical Dictionary for Regulatory Activities (MedDRA) and reported with preferred terms and system organ class. Selected notable AEs of interest may be reported using high-level terms or Standardized MedDRA Queries.

Summary statistics will be provided for incidence of

- TEAEs
- SAEs
- study discontinuation due to AEs
- intervention discontinuation due to AEs
- deaths, and
- other cardiovascular endpoints.

Counts and proportions of participants experiencing AEs will be reported for each treatment group, and Fisher's exact test will be used to compare the treatment groups.

9.3.5.1. Laboratory Measures and Vital Signs

Laboratory measures and vital signs will be summarized for each scheduled visit by

- actual measures at baseline and postbaseline
- change from baseline to postbaseline, or
- percent change from baseline to postbaseline.

The laboratory measures may be log transformed before statistical analyses, if deemed necessary. Continuous variables, as well as the change from baseline for these variables or other appropriate transformed variables, will be analyzed by MMRM models as described in Section 9.3.1.

The percentages of participants with treatment-emergent abnormal, high, or low measures, including laboratory and vital signs, will be summarized and compared between treatment groups using Fisher's exact test.

The analysis details will be provided in the SAP.

9.3.6. Pharmacokinetic and Pharmacodynamic Analyses

A population PK approach using nonlinear mixed-effects modeling will be used to summarize and analyze LY3561774 concentration data.

The relationships between LY3561774 dose and concentration and selected efficacy and safety endpoints may be characterized. 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 titers are detected from immunogenicity testing, then the impact of immunogenicity titers on LY3561774 PK or any relevant efficacy parameters may also be examined. Additional analyses may be conducted if they are deemed appropriate.

9.3.7. Immunogenicity Assessments

If data from validated immunogenicity assays are available, TE-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 TE-ADA positive (TE-ADA+) to LY3561774 will be tabulated.

The distribution of titers and frequency of neutralizing antibodies (if assessed) for the TE-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. Additional details may be provided in the SAP.

9.3.8. Subgroup Analyses

Subgroup analyses of important factors, such as age, sex, ethnicity, baseline TG, and other factors to be specified in the SAP, are planned for the key outcomes.

The models used for these analyses will vary depending on the subgroups and the outcome. Other exploratory subgroup analyses may be performed as deemed appropriate.

Details of the modeling will be provided in the SAP.

9.4. Interim Analysis

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. The SAP will describe the interim analysis in greater detail.

If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the 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 (Section 10.1.5). Details on the timing of the interim analyses, operational support, and unblinding will be specified in the IAC charter and in the study unblinding plan.

Information that may unblind the study during the analyses will not be reported to study sites or blinded study team members before the study has been unblinded until final database lock. 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 superiority of LY3561774 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 primary database lock and primary data analysis for study EZCB will occur when all participants have completed 180 days (Visit 9) of treatment. Another efficacy and safety assessment will occur when all participants have completed 270 days (Visit 12) of the treatment. The final database lock and final data analysis will occur when all randomized participants have completed the study. Participants and investigators will remain blinded until the completion of the study.

9.5. 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 20% dropout rate, this results in approximately 20 completers for 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 arms will provide >99% power to detect a treatment difference of -30% for the primary endpoint.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Investigator sites are compensated for participation in the study as detailed in the CTA.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant and is kept on file.

Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that their medical records may be examined by clinical quality assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The sponsor has processes in place to ensure data protection, information security and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.5. Committees Structure

Internal assessment committee (IAC)

If there are unplanned interim analyses, an IAC will review the interim efficacy and safety data in an unblinded fashion.

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.

Participant safety will be continuously monitored by the sponsor's blinded internal safety review team, which includes safety signal detection at any time during the study.

All safety data collected will be summarized and reviewed by the sponsor's internal safety review committee for agreement of next steps.

Evaluation of unblinded safety data by the IAC will occur if any of these events are observed following review by the blinded safety review team

- three or more participants experience hematologic TEAE graded as severe by the investigator and are judged as related to blinded study treatment by the investigator
- three or more participants experience MACE, or
- a malignancy SAE occurs during the study.

Enrollment and dosing may be paused during the review by the IAC.

Case unblinding may be performed for above reviews if necessary.

External clinical endpoint committee

An independent clinical endpoint committee, external to Lilly, will be formed to adjudicate MACE and deaths. This committee will be blinded to treatment assignment.

10.1.6. Dissemination of Clinical Study Data

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

Data

The sponsor provides access to all individual participant data collected during the trial, after anonymization, with the exception of PK or genetic data. Data are available for request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, SAP, CSR, blank or annotated CRFs, will be provided in a secure data sharing environment for up to 2 years per proposal.

For details on submitting a request, see the instructions provided at www.vivli.org.

10.1.7. Data Quality Assurance

Investigator responsibilities

All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (for example, laboratory data).

The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Data monitoring and management

Quality tolerance limits will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important excursions from the QTLs and remedial actions taken will be summarized in the CSR.

Monitoring details describing strategy, for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring, methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (for example, contract research organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized study personnel are accurate, complete, and verifiable from source documents, that the safety and rights of participants are being protected, and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records retention and audits

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the CTA unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

In addition, sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data capture system

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

Electronic data capture system

An EDC system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Data storage and access

Data collected via the sponsor-provided data capture systems will be stored at third parties.

The investigator will have continuous access to the data during the study and until decommissioning of the data capture systems. Prior to decommissioning, the investigator will receive or access an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

Data from complaint forms submitted to the sponsor will be encoded and stored in the global PC management system.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on or entered in the CRF and are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in Section 10.1.7.

10.1.9. Study and Site Start and Closure

First act of recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

Study or site termination

The sponsor or sponsor's designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to

- study termination
  - discontinuation of further study intervention development
- site termination

- failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- inadequate recruitment (evaluated after a reasonable amount of time) of participants by the investigator, or
- total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

In accordance with the sponsor's publication policy, the results of this study will be submitted for publication by a peer-reviewed journal.

10.1.11. Investigator Information

Researchers with appropriate education, training, and experience, as determined by the sponsor, will participate as investigators in this clinical trial.

10.1.12. Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3561774 or after LY3561774 become(s) commercially available.

Sample Type	Custodian	Retention Period After Last Patient Visit[a]
Exploratory Biomarkers	Sponsor or Designee	7 years
PK	Sponsor or Designee	1 year
Genetics	Sponsor or Designee	7 years
Immunogenicity	Sponsor or Designee	7 years

[a]Retention periods may differ locally.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by the Lilly-designated laboratory or by the local laboratory as specified in the table below.

In circumstances where the sponsor approves local laboratory testing in lieu of Lilly-designated laboratory testing, the local laboratory must be qualified in accordance with applicable local regulations.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Investigators must document their review of the laboratory safety results.

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel.

Clinical Laboratory Tests	Comments
Hematology	Assayed by Lilly-designated laboratory.
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs - red blood cells)	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (WBCs - white blood cells)	
Differential	
Percent and Absolute Count of:	
Neutrophils, segmented	
Bands	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBC and WBC)	
Clinical Chemistry	Assayed by Lilly-designated laboratory.
Sodium	
Potassium	
Chloride	
Bicarbonate	
Total bilirubin	
Direct bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	
Blood urea nitrogen (BUN)	
Creatinine	
Creatine kinase (CK)	
Uric acid	
Total protein	
Albumin	
Calcium	
Phosphorus	
Glucose	
Amylase	
Lipase	
LDH	
Lipid Panel	Assayed by Lilly-designated laboratory.

Clinical Laboratory Tests	Comments
	After randomization, results will not be provided to investigative sites.
High-density lipoprotein cholesterol (HDL-C)	
Non-HDL-C	
Low-density lipoprotein cholesterol (LDL-C) direct	
Very-low-density lipoprotein cholesterol (VLDL-C)	
Cholesterol	
Triglycerides	
Coagulation Panel	Assayed by Lilly-designated laboratory.
PT-INR	
aPTT	
Urinalysis	Assayed by Lilly-designated laboratory.
Specific gravity	
pH	
Protein	
Glucose	
Ketones	
Bilirubin	
Urobilinogen	
Blood	
Nitrite	
Urine leukocyte esterase	
Microscopic examination of sediment	
Hormones (female)	
Follicle-stimulating hormone (FSH)	Assayed by Lilly-designated laboratory.
Urine pregnancy	Local laboratory.
Serum pregnancy	Assayed by Lilly-designated laboratory.
Urine Chemistry	Assayed by Lilly-designated laboratory.
Albumin	
Creatinine	
Calculations	Generated by Lilly-designated laboratory.
eGFR (CKD-EPI)	
Urinary albumin/creatinine ratio (UACR)	
HIV and Hepatitis Serology	Assayed by Lilly-designated laboratory.
HIV testing	
Hepatitis C virus (HCV) testing:	
HCV antibody	
Hepatitis B virus (HBV) testing:	
Hepatitis B surface antigen (HBsAg)	
Pharmacokinetic Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.

Clinical Laboratory Tests	Comments
LY3561774 concentration	
Additional Testing	Assayed by Lilly-designated laboratory.
HbA1c	
C-reactive protein, high-sensitivity (hsCRP)	Results will not be provided to investigative sites.
ANGPTL3 and ANGPTL3/8	Results will not be provided to investigative sites.
ApoB	After randomization, only Day 270 results will be provided to investigative site.
ApoA-I,	Results will not be provided to investigative sites.
ApoC-III	Results will not be provided to investigative sites.
TSH	
Insulin	
Genetics Sample	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Exploratory Biomarker Storage Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Serum	
Plasma (EDTA)	
Immunogenicity Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Anti-LY3561774 antibodies	

10.2.1. Laboratory Samples Obtained at the Time of a Systemic Hypersensitivity Event

Purpose of collecting samples after a systemic hypersensitivity event

The samples listed in this appendix are not collected for acute study participant management. The sponsor will use the laboratory tests results from these samples to characterize hypersensitivity events across the clinical development program.

When to collect samples after a systemic hypersensitivity event occurs

Collect the samples listed below if a systemic hypersensitivity event is suspected. The timing should be as designated in the table, assuming the participant has been stabilized.

Obtain follow-up predose samples at the next regularly scheduled laboratory sample collection, ideally prior to the next dose after the event, to assess post-event return to baseline values.

Timing	Sample Type	Laboratory Test[a]
Collect from 30 minutes to 4 hours after the start of the event. ● Note: The optimal collection time is 1 to 2 hours after the start of event.	Serum	total tryptase
	Serum	complements C3
	Plasma	compliments C3a and C5a
	Serum	cytokine panel (IL-6, IL-1β, IL-10 or any cytokine panel that includes these 3 cytokines)
Collect samples on the same day as the event. If samples were already collected per the SoA on the same day as the event, then duplicate samples are not collected. ● Note: the optimal collection time is up to 12 hours after the start of the event.	Serum	LY3561774 anti-drug antibodies (ADA)
	Plasma	LY3561774 concentration

Abbreviation: IL = interleukin.

[a]All samples for hypersensitivity testing will be assayed by Lilly-designated laboratory. Results will not be provided to the study site. If samples are not collected or are collected outside the specified time period, this will not be considered a protocol deviation.

What information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

The investigator may perform additional tests locally, if clinically indicated, for acute study participant management.

10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, and vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (for example, endoscopy and appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life-threatening

The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Product Complaints

Product Complaint

- A PC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also PCs:
  - Deficiencies in labeling information, and
  - Use errors for device or drug-device combination products due to ergonomic design elements of the product.
- PCs related to study interventions used in clinical trials are collected in order to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.
- Investigators will instruct participants to contact the site as soon as possible if he or she has a PC or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

10.3.4. Recording and Follow-up of AE and/or SAE and Product Complaints

AE, SAE, and Product Complaint Recording

- When an AE/SAE/PC occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/PC information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page and PC information is reported on the Product Complaint Form.

  Note: An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for PCs.
- There may be instances when copies of medical records for certain cases are requested by sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the IB in their assessment. • For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor or designee. • The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide sponsor or designee with a copy of any post-mortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the SAE paper form (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on an SAE paper form (see next section) or to the sponsor by telephone.
- Contacts for SAE reporting can be found in site training documents.

SAE Reporting via Paper Form

- Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the sponsor.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in site training documents.

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Women of childbearing potential

Adult females are considered WOCBP unless they are WNOCBP.

Females less than 18 years of age are considered WOCBP if they have

- they have had at least 1 cycle of menses, or
- they have Tanner 4 breast development.

Any amount of spotting should be considered menarche.

Women not of childbearing potential

Females are considered WNOCBP if

- they have a congenital anomaly such as Mullerian agenesis,
- they are infertile due to surgical sterilization, or
- they are postmenopausal.

Examples of surgical sterilization include hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.

Postmenopausal

The postmenopausal state should be defined as:

- A woman at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note
  OR
- A woman at least 40 years of age and up to 55 years old with an intact uterus, not on hormone therapy*, who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND
  With a follicle-stimulating hormone >40 mIU/mL
  OR
- A woman 55 years of age or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea
  OR
- A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

*Women should not be taking medications during amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, SERMs, or chemotherapy that could induce transient amenorrhea.

10.4.2. Contraception Guidance

Guidance for women of childbearing potential

This outlines the rules for WOCBP to ensure they do not become pregnant during the study.

If, as part of their preferred and usual lifestyle, WOCBP…	**Then…**
are in a same sex relationship	• they must stay in same sex relationships without sexual relationships with males, and • take pregnancy tests.
are completely abstinent	• they must agree to remain completely abstinent
are not completely abstinent	• they must agree to o use 2 forms of contraception, with at least 1 form of highly effective contraception, and o take pregnancy tests.
Note on forms of contraception: At least 1 form of contraception must be highly effective, meaning that it has a less than 1% failure rate.	

Methods of contraception for male participants and their female partners and for women of childbearing potential

Methods	**Examples**
Highly effective contraception (less than 1% failure rate)	• female sterilization • combination oral contraceptive pill • progestin-only contraceptive pill (mini-pill) • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices
Effective contraception	• male or female condoms with spermicide • diaphragms with spermicide or cervical sponges • barrier method with use of a spermicide o condom with spermicide o diaphragm with spermicide, or o female condom with spermicide

	Note: The barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, or female condom with spermicide) to be considered effective.
Ineffective forms of contraception whether used alone or in any combination	• spermicide alone • periodic abstinence • fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) • withdrawal • postcoital douche, or • lactational amenorrhea

Guidance for all men

All men should refrain from sperm donation for the duration of the study and for the predicted time until estimated plasma levels of partner would be below the level of toxicologic concern, plus 94 days.

Men with partners of childbearing potential must

- either remain abstinent if this is their preferred and usual lifestyle,
  OR
- use highly effective/effective methods of contraception during intercourse for the duration of the study, and
  for the predicted time until estimated plasma levels of partner would be below the level of toxicologic concern, plus 94 days.

Men in exclusively same sex relationship, as their preferred and usual lifestyle are not required to use contraception.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to LY3561774 or mixed dyslipidemia and related diseases. They may also be used to develop tests/assays including diagnostic tests related to LY3561774 or mixed dyslipidemia and related diseases. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome, as appropriate.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to LY3561774 or study interventions of this class to understand study disease or related conditions.

The results of genetic analyses may be reported in the CSR or in a separate study summary.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on LY3561774 or study interventions of this class or indication continues but no longer than 15 years or other period as per local requirements.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Hepatic Evaluation Testing

The Lilly-designated laboratory must complete the analysis of all selected testing except for microbiology testing.

Local testing may be performed in addition to Lilly-designated testing when necessary for immediate participant management.

Results will be reported if a validated test or calculation is available.

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol (EtOH) (quantitative)
Prothrombin time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin A (IgA) (quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin G (IgG) (quantitative)
HAV total antibody	Immunoglobulin M (IgM) (quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA) [a]
HBV DNA [b]	Anti-actin antibody [c]

Hematology	**Clinical Chemistry**
Hepatis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA [b]	EBV DNA [b]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA [b]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA [b]	HSV (Type 1 and 2) DNA [b]
Microbiology [d]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

[a] Not required if anti-actin antibody is tested.

[b] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

[c] Not required if anti-smooth muscle antibody (ASMA) is tested.

[d] Assayed ONLY by investigator-designated local laboratory; no Lilly-designated testing available.

10.7. Appendix 7: Concomitant Medication Information

10.7.1. ACC/AHA Statin Therapy List

This table describes different types of statin therapy by intensity according to the American College of Cardiology and the American Heart Association (ACC/AHA) rating system (Stone et al. 2014).

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy
Daily dose lowers LDL-C by approximately ≥50%	Daily dose lowers LDL-C by approximately 30% to <50%
Atorvastatin 40 mg, 80 mg Rosuvastatin 20 mg, 40 mg	Atorvastatin 10 mg, 20 mg Rosuvastatin 5 mg, 10 mg Simvastatin 20 mg, 40 mg Pravastatin 40 mg, 80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 2 mg, 4 mg

Simvastatin 80 mg is not allowed in this study.

10.7.2. Permitted Concomitant Medications

This section describes concomitant medications and vaccinations allowed in this study.

Other medications may be allowed if they are approved by the sponsor or its designee.

Permitted Concomitant Medications for Study EZCB	
Drug Class	**Comments**
Over-the-counter	
Vitamin and mineral supplements	
Low-dose aspirin	
Occasional acetaminophen or ibuprofen	
Corticosteroids	
Local, topical, intra-articular, inhalation or nasal	
Lipid-regulating medication	
Statins	
PCSK9 inhibitors	
Bempedoic acid	
Ezetimibe	
Other concomitant treatments	
Medications to regulate hypertension	Participant must be on a stable dose 30 days prior to screening
Vaccinations	• mRNA • Use of live or live attenuated vaccines is permitted up to 4 weeks before screening. • A non-live or inactivated vaccine is allowed if it is received at least 2 weeks before randomization in the study or after the last visit.

Permitted Concomitant Medications for Study EZCB	
Drug Class	**Comments**
	• Inactivated influenza ("Flu"), pneumococcal, and SARS-CoV-2 vaccines are allowed during the study. **Note:** It is recommended that study intervention not be administered on the same day as a SARS-CoV-2 vaccination.

10.7.3. Prohibited Concomitant Medications and Procedures

This section describes medications prohibited in the study. If a prohibited treatment listed here is required, the study intervention should be permanently discontinued.

Prohibited Concomitant Medications and Procedures for Study EZCB	
Drug Class/Procedure	**Comments**
Lipid lowering therapy including, but not limited to: • Triglyceride lowering medication o Example: Vascepa	Prohibited within 4 weeks prior to screening and during the study.
• Simvastatin 80 mg/day • Fibrates • Bile acid sequestrants	Prohibited within 6 weeks prior to screening and during the study.
• Over-the-counter and health food preparations o 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/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	
Factor Xa inhibitors	
Heparins or heparinoids	
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 the stable dose during the study.	Prohibited

10.8. Appendix 8: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

Exceptional circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing changes under exceptional circumstances

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

After approval by local Ethical Review Boards, regulatory bodies and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required (for example, upon implementation and suspension of changes). All approvals and notifications must be retained in the study records.

If the sponsor grants written approval for changes in study conduct, the sponsor will also provide additional written guidance, if needed.

Considerations for making a change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with GCP, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed consent

Additional consent from the participant will be obtained, if required, for:

- participation in remote visits, as defined in Section "Remote Visits"
- dispensation of additional study intervention during an extended treatment period
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

Changes in study conduct during exceptional circumstances

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations.

Remote visits

Types of remote visits

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to

- AE review
- Concomitant medication review
- Substance use (alcohol)
- Verification of negative urine pregnancy test, and
- PCs (if applicable).

Mobile healthcare: Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor. Procedures performed at such visits include, but are not limited to, concomitant medications, collection of blood samples, physical assessments, and health information.

Other alternative locations: A local laboratory may be used for laboratory draws.

Assessments that may need to be delayed until the next on-site visit or missed, depending on the length of time that sites or participants are impacted and depending on when on-site visits are due, include

- Vital signs
- Weight
- Symptom-directed physical examination, and
- Laboratory tests if a local laboratory cannot be used.

Data capture

In source documents and the CRF, the study site should capture the visit method, with a specific explanation for any data missing because of missed in-person site visits.

Safety reporting

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and PCs remain unchanged.

Return to on-site visits

Every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

Local laboratory testing option

Local laboratory testing may be conducted in lieu of Lilly-designated laboratory testing. The local laboratory must be qualified in accordance with applicable local regulations.

Lilly-designated laboratory testing must be retained for PK, immunogenicity, ANGPTL3 and ANGPTL3/8, ApoB, ApoA-I, ApoC-III, and the lipid panel.

Study intervention

When a participant is unable to go to the site to receive study intervention during normal on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include:

- asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit,
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf,
- arranging delivery of study supplies, and
- working with the sponsor to determine how study intervention that is typically administered on site will be administered to the participant; for example, during a mobile healthcare visit or at an alternate location.

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study intervention.
- When delivering study intervention to a location other than the study site (for example, participant's home), the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study intervention.

Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at screening visit are valid for a maximum of 60 days. The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to exceptional circumstances:

- If screening is paused for less than 60 days from signing the ICF to randomization visit, the participant will proceed to the next study visit per the usual SoA, provided that randomization visit must be conducted within 45 days from first screening.
    - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay.
    - Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.
- If screening is paused for more than 60 days from screening to randomization visit: The participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. This rescreen is in

addition to the one allowed by the main protocol. The screening procedures per the usual SoA should be followed, starting at screening visit to ensure participant eligibility by randomization visit.

Adjustments to visit windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual SoA. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.

Documentation

Changes to study conduct will be documented

Sites will identify and document the details of how participants, visit types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

Source documents at alternate locations

Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

10.9. Appendix 9: Abbreviations and Definitions

Term	Definition
ADA	anti-drug antibodies
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANGPTL	angiopoietin-like
Apo	apolipoprotein
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
blinding	A single-blind study is one in which the investigator and/or the investigator's staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/the investigator's staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.
Clinical Research Physician	Individual responsible for the medical conduct of the study. Responsibilities may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CSR	clinical study report

CTA	clinical trial agreement
EAS	efficacy analysis set
ECG	electrocardiogram
EDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
eGFR	estimated glomerular filtration rate
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
Enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
FAS	full analysis set
GCP	good clinical practice
GGT	gamma-glutamyl transferase
HbA1c	hemoglobin A1c
HDL-C	high-density lipoprotein-cholesterol
IAC	internal assessment committee
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IMP	investigational medicinal product
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
PT-INR	Prothrombin Time – International Normalized Ratio
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
intervention	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.

IRB/IEC	Institutional Review Board/Independent Ethics Committee
ISR	injection-site reaction
IWRS	interactive web-response system
LDH	lactate dehydrogenase
LDL-C	low-density lipoprotein-cholesterol
MACE	major cardiovascular events
MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
NOAEL	no-observed-adverse-effect
participant	Equivalent to CDISC term “subject”: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control.
PC	product complaint
PK/PD	pharmacokinetics/pharmacodynamics
QTc	corrected QT interval
QTLs	quality tolerance limits
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SERMs	selective estrogen receptor modulators
SS	safety analysis set
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
TBL	total bilirubin
TE-ADA	treatment-emergent anti-drug antibodies
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TG	triglyceride
tmax	time of maximum concentration

TSH	thyroid stimulating hormone
$t_{½}$	terminal half-life
ULN	upper limit of normal
WOCBP	women of childbearing potential
WNOCBP	women not of childbearing potential

10.10. Appendix 10: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment [d]

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The rationale for the amendment is to clarify how to maintain the blind during IMP administration.

Section # and Name	Description of Change	Brief Rationale
5.1. Inclusion Criteria	Corrected second WOBCP acronym to be consistent with Section 10.4.1	Accuracy
6.3. Measures to Minimize Bias: Randomization and Blinding	One sentence changed to clarify what third party will be responsible for to maintain the blind. Additional sentences added to clarify lower risk of unblinding and administering IMP.	Clarification

Amendment [c]

This amendment is considered to be substantial because it is likely to have a significant impact on the reliability and robustness of the data generated in the clinical study.

Overall Rationale for the Amendment:

This amendment includes protocol revisions in response to FDA feedback and request for changes for Sections 7.1, 9.4, and 10.4.1. Additional changes to the protocol and the corresponding rationale for the changes are detailed in the table below.

Section # and Name	Description of Change	Brief Rationale
7.1. Discontinuation of Study Intervention	Changed text to state that participants will remain in the study and follow procedures for the remaining study visits.	FDA feedback and request.
8.3.5. Major Adverse Cardiovascular Events (MACE)	Added cardiogenic shock due to myocardial infarction and resuscitated sudden death to the list of adjudicated events.	To match the Adjudicated Report & Charter.
9.4. Interim Analysis	• Added information about planned interim analyses. • Moved text that states that the SAP will describe the interim analysis in greater detail up near the new text about the planned interim analyses. • Added text for unplanned interim analysis. • Removed text that was no longer relevant.	• FDA feedback and request • Better readability, and • Updates per Lilly policy.

Section # and Name	Description of Change	Brief Rationale
10.2.1. Laboratory Samples Obtained at the Time of a Systemic Hypersensitivity Event	• Corrected the sample type for compliments C3a and C5a from serum to plasma.	• Correction of sample type.
10.4.1. Definitions	Corrected the abbreviation for women not of childbearing potential.	Editorial update.

Amendment [b]

This amendment is considered to be substantial because it is likely to have a significant impact on the reliability and robustness of the data generated in the clinical study.

Overall Rationale for the Amendment:

Recently published data suggest that AngPTL3 inhibition is most likely to be efficacious in patients with a relatively more severe risk for cardiovascular disease (Bergmark et al. 2022). As such, this amendment includes protocol revisions designed to better target the intervention to those who will benefit from it, as well as to streamline the protocol by eliminating one medium-level dosage and by designating a new, more relevant primary outcome variable. Additional changes to the protocol and the corresponding rationale for the changes are detailed in the table below.

Section # and Name	Description of Change	Brief Rationale
Title Page	Acronym added	Accuracy
1.1 Synopsis	• Moved ApoB to primary endpoint, replaced Non-HDL-C. Changed all Non-HDL-C to ApoB when referring to primary endpoint throughout document. • Changed > 80% to ≥ 80% for ApoB. • Moved non-HDL-C to Secondary Endpoint. • Changed Number of Participants from 225 to 175. • Removed 600 mg arm of study. • Schema changed from non- HDL-C to ApoB; 600 mg arm also removed; >80% changed to ≥80%.	• Study Design Change • For Accuracy • Study Design Change • Study Design Change • Study Design Change • Study Design Change
1.2 Schema	• Wording for safety follow up changed to ApoB • Level changed to ≥ 80% from >80%.	• Alignment • Study Design Change
1.3 Schedule of Activities	• Changed non-HDL-C to ApoB for primary endpoint. • United States removed from demographics.	• For alignment

Section # and Name	Description of Change	Brief Rationale
	• Added urine pregnancy test for Visit 6 and Visit 9. Comment adjusted accordingly.	• Ethnicity data collection criteria updated from US only to where permissible in alignment with current data collection rules • FDA Feedback
3 Objectives, Endpoints, and Estimands	• Changed non-HDL-C to ApoB for Primary endpoint. • Moved non-HDL-C to Secondary Endpoint. • Changed all corresponding Non-HDL-C to ApoB when referring to Primary Endpoint	• Study Design Change • Study Design Change • Study Design Change
4.1 Overall Design	• 600 mg arm removed. • Non-HDL-C changed to ApoB.	• Study Design Change • Study Design Change
4.2 Scientific Rationale for Study Design	• Primary Endpoint paragraph wording adjusted for using ApoB as Primary Endpoint • Non-HDL-C changed to ApoB. • United States removed.	• Study Design Change • Study Design Change • Ethnicity data collection criteria updated from US only to where permissible in alignment with current data collection rules
4.3 Justification for Dose	• 600 mg arm removed. • Non-HDL-C changed to ApoB.	• Study Design Change • Study Design Change
5.1 Inclusion Criteria	• Non-HDL-C ≥100 mg/dL (2.59 mmol/L). removed and triglycerides levels changed to 200-499 mg/dL for IC#2. • Fasting LDL-C changed from >40 mg/dL to ≥100 mg/dL and corresponding mmol/L number for IC #3. • MRI image quality IC #13 added.	• Study Design Change • Study Design Change • Study Design Change
5.4 Screen Failures	Sentence added to in regard to MRI imaging not requiring another identification number.	Clarification
6.1 Study Intervention(s) Administered	Removed 600 mg arm wording in both tables.	Study Design Change
6.3 Measures to Minimize Bias: Randomization and Blinding	• Removed 600 mg arm. Ratio adjusted. • Changed triglyceride level <225 mg/dL to <250 mg/dL. • Changed triglyceride level ≥225 mg/dL to ≥ 250 mg/dL.	• Study Design Change • Study Design Change • Study Design Change

Section # and Name	Description of Change	Brief Rationale
8.1.1 Primary Efficacy Assessment	Non-HDL-C changed to ApoB.	Study Design Change
8.1.2 Secondary Efficacy Assessments	Non-HDL-C changed to ApoB.	Study Design Change
8.2.7 Pregnancy Testing	Wording added in regard to duration of testing	Clarification
9.1 Statistical Hypotheses	• Removed 600 mg arm. • Non-HDL-C changed to ApoB.	• Study Design Change • Study Design Change
9.3.1 General Considerations	• Changed triglyceride level <225 mg/dL to <250 mg/dL. • Changed triglyceride level ≥225 mg/dL to ≥ 250 mg/dL.	• Study Design Change • Study Design Change
9.3.2 Primary Endpoint/Estimand Analysis	• Non-HDL-C changed to ApoB. • Sentence on non-HDL-C regarding log transformed was removed.	• Study Design Change • Change in primary endpoint
9.3.4 Tertiary/Exploratory Analysis	• Non-HDL-C removed. • Sentence on non-HDL-C regarding log transformed was removed.	• Study Design Change • Change in primary endpoint
9.3.5.1 Laboratory Measures and Vital Signs	• Title changed (Electrocardiogram word removed. • Selected ECG parameters wording removed.	• For Accuracy • Clarification
9.3.8 Subgroup Analyses	• Important factors age, ethnicity added, gender wording changed to sex. • Non-HDL-C changed to TG.	• Alignment • Study Design Change
9.4 Interim Analysis	• Planned interim analysis, Additional interim analyses sub-title wording removed. • Sentence removed regarding interim analyses and data being reviewed. • Added wording to clarify IAC's data analysis. • Sentence added to reference interim analysis will be described in SAP.	• Formatting • Clarification • Alignment • Clarification
9.5 Sample Size Determination	• Non-HDL-C changed to ApoB. • Changed Number of Participants from 225 to 175. • Removed 600 mg arm. • Standard deviation changed from 20% to 15%.	• Study Design Change • Study Design Change • Study Design Change • Accuracy

Section # and Name	Description of Change	Brief Rationale
10.1.12 Sample Retention	Biomarkers, Genetics, and Immunogenicity samples retention period changed from 15 years to 7 years; PK sample retention changed from 2 years to 1 year.	New Regulations
10.1.5 Committees Structure	Sentence added in regard to unplanned interim analyses for IAC	Clarification
10.2 Appendix 2: Clinical Laboratory Tests	• For Lipid Panel, 270-day wording removed. • For Coagulation Panel, Assay wording added. • For ApoB, only Day 270 results will be provided to investigative site. • ApoA-I and ApoC-III placed in their own cells	• For Accuracy • For Accuracy • For Accuracy • For Accuracy
10.4 Contraceptive and Barrier Guidance	Contraceptive language updated.	New Guidelines
10.4.2 Contraception Guidance	Contraceptive language updated.	New Guidelines
11 References	New References added.	For Accuracy
Throughout the protocol	Minor formatting, grammar and editorial changes.	Minor, therefore, not detailed

Amendment [a]: 08-Dec-2021

Overall Rationale for the Amendment:

The main rationale for the amendment was to add an immunogenicity (ADA) and related PK sample at Visit 2 to the Schedule of Activities. These samples are needed prior to first dose for treatment-emergent ADA analysis.

Additional changes to the protocol and the corresponding rationale for the changes are detailed in the table below.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	In the Brief Summary, added the number of visits after randomization that will occur about 15 days apart.	Clarification.
1.1 Synopsis	Changed the response for Data Monitoring Committee to No.	No formal DMC will occur for this study.
1.3 Schedule of Activities	Changed Symptom-directed physical examination to Symptom-directed physical assessment.	To better reflect the intent of this procedure and qualified personnel.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Added an immunogenicity (ADA) and PK sample for immunogenicity sample at Visit 2.	A sample is needed prior to first dose for treatment-emergent ADA analysis.
6.1 Study Intervention(s) Administered	Removed the injection volumes for the different intervention groups.	This information will be provided in the pharmacy manual.
6.3 Measures to Minimize Bias: Randomization and Blinding	Updated text explaining participant stratification and changed “baseline” to “Visit 1” for triglycerides.	Clarification.
8.2.1 Physical Examinations	Changed symptom-directed physical examinations to symptom-directed physical assessments.	To better reflect the intent of this procedure and qualified personnel, and for consistency across the document.
9.3.1. General Considerations for statistical analyses	Updated text explaining the model terms and changed “baseline” to “Visit 1” for triglycerides.	For consistency with Section 6.3 change.

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