Protocol J3L-MC-EZEB Initial Protocol

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

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Title Page

Protocol Title:

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

Protocol Number: J3L-MC-EZEB

Amendment Number: This is the initial protocol.

Compound: LY3819469

Brief Title:

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

Study Phase: 2

Sponsor Name: Eli Lilly and Company

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1. Protocol Summary

1.1. Synopsis

Protocol Title:

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

Brief Title:

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

Regulatory Agency Identifier Number(s):

IND: 154938

EU trial number: 2022-501426-38-00

Rationale:

Elevated lipoprotein(a) (Lp[a]) is recognized as an important risk factor for cardiovascular disease; there are currently no approved pharmaceutical interventions for lowering Lp(a). LY3819469 is a novel Dicer-substrate small interfering ribonucleic acid (siRNA) oligonucleotide designed to reduce the levels of LPA mRNA and apolipoprotein(a) (Apo[a]) expression and thereby to decrease Lp(a). In Phase 1 Study J3L-MC-EZEA, single subcutaneous (SC) doses of LY3819469 significantly and durably decreased Lp(a) and no safety issues were identified. This Phase 2 study aims to investigate the impact of a range of LY3819469 doses on Lp(a) level and on safety in a larger population of participants with elevated Lp(a) to enable Phase 3 development of this compound.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
• To evaluate if LY3819469 is superior to placebo in percent Lp(a) reduction	• Percent change from baseline in time-averaged Lp(a) over Days 60-180
Secondary	
• To evaluate if LY3819469 is superior to placebo in percent Lp(a) reduction over Days 240-360	• Percent change from baseline in time-averaged Lp(a) over Days 240-360
• Compare proportion of participants on LY3819469 versus placebo achieving Lp(a) threshold levels	• Proportion of participants achieving Lp(a) <125 and <75 nmol/L at Days 60, 180, 240, 360, and 540

Objectives	Endpoints
• Compare the effect of LY3819469 to placebo on cardiovascular biomarkers	• Percent change from baseline to Days 60, 180, 240, 360, and 540 for ○ Lp(a) ○ ApoB ○ hsCRP
• Characterize the PK of LY3819469	• Population PK parameters

Abbreviations: ApoB = apolipoprotein B; hsCRP = high-sensitivity C-reactive protein; Lp(a)_= lipoprotein(a); PK = pharmacokinetics.

Estimands

The primary clinical question of interest is: What is the study intervention difference in percent change from baseline in time-averaged Lp(a) over Days 60-180 of study intervention in participants who meet the enrollment criteria regardless of treatment discontinuation for any reason?

A similar estimand as the estimand for the primary objective will be used for the secondary objectives.

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

Overall Design

Study is a parallel, double-blinded, placebo-controlled, dose-finding, Phase 2 study of LY3819469 in participants with elevated Lp(a).

Approximately 254 participants will be randomized in a 1:2:2:2:2 ratio to 1 of the following arms:

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

Brief Summary:

The purpose of this study is to measure difference in percent change from baseline in time-averaged Lp(a) on over Days 60-180 with LY3819469 versus placebo in participants with elevated Lp(a).

Study details include:

- The study duration will be up to 20 months.
- The treatment duration will include doses at the randomization visit and at Day 180.

Study Population:

The study will include adults at least 40 years old. People in the study who are on particular medicines should stay on the same doses for the whole study. People who have had a major illness or surgery in the 3 months prior to the study will not participate. People who have certain abnormal laboratory values will not be included.

Number of Participants:

Approximately 254 participants will be randomly assigned to study intervention.

Intervention Groups and Duration:

All participants will receive a subcutaneous injection at the randomization visit and at Day 180 (Visit 7). LY3819469 is formulated at a concentration of 160 mg/mL.

	Arm A	Arm B	Arm C	Arm D	Arm E
Intervention Name	LY3819469	LY3819469	LY3819469	LY3819469 and Placebo	Placebo[a]
Dosage #1					
LY3819469 Solution (160mg/mL)	16 mg (0.1 mL)	96 mg (0.6 mL)	400 mg (2.5 mL)	400 mg (2.5 mL)	–
Placebo (0.9% sodium chloride solution for injection)	–	–	–	–	Placebo[a]
Dosage #2					
LY3819469 Solution (160mg/mL)	16 mg (0.1 mL)	96 mg (0.6 mL)	400 mg (2.5 mL)	–	–
Placebo (0.9% sodium chloride solution for injection)	–	–	–	Placebo[b]	Placebo[a]
Route of Administration	SC injection	SC injection	SC injection	SC injection	SC injection
Authorized as defined by EU Clinical Trial Regulation	Not authorized in EU	Not authorized in EU	Not authorized in EU	Not authorized in EU	Not authorized in EU

Abbreviations: EU = European Union; SC = subcutaneous.

[a] Participants in Arm E 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.

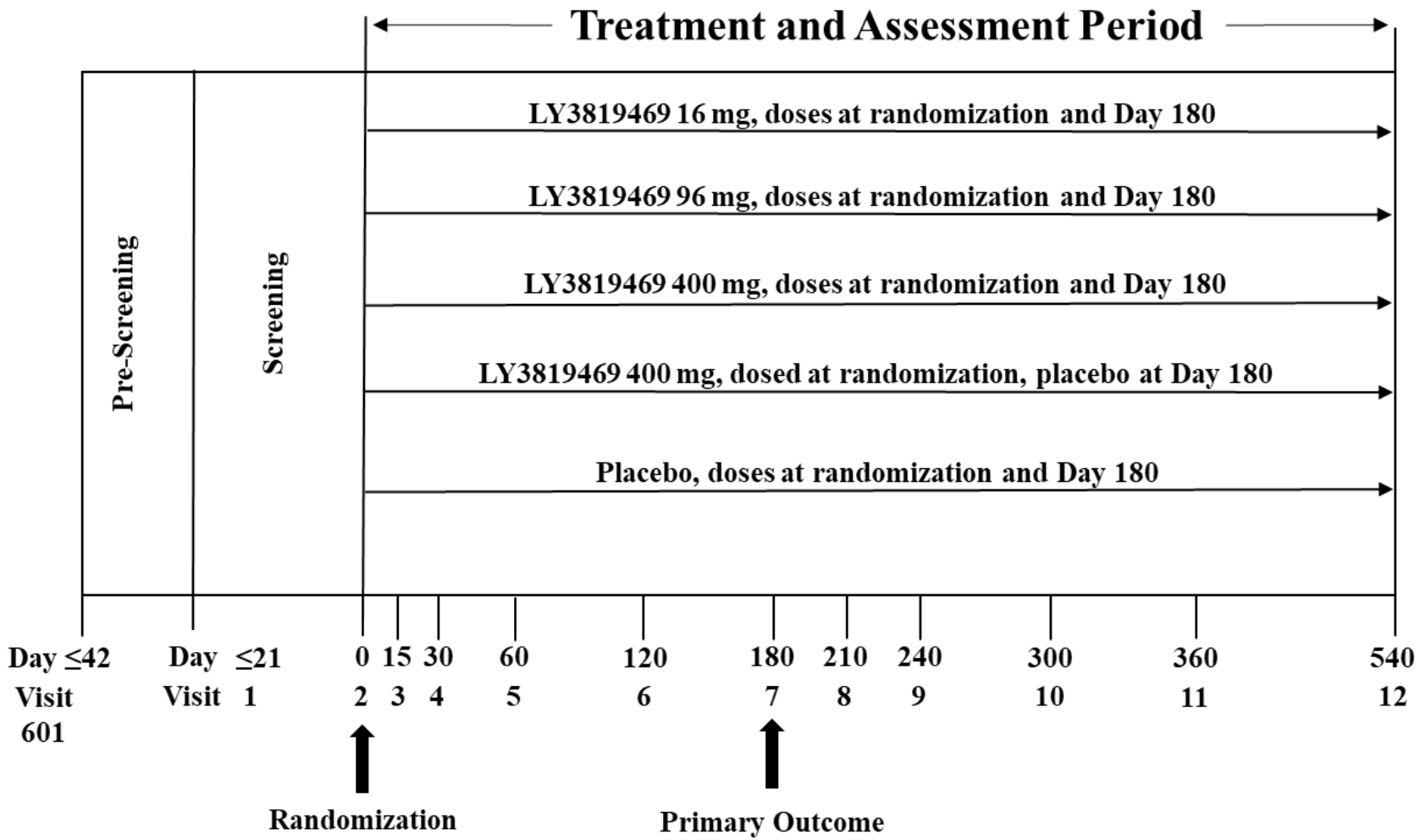
[b] Participants in Arm D will receive a 2.5-ml placebo dose at Day 180 (Visit 7).

Ethical Considerations of Benefit/Risk:

Based on current information, the study medicine treatment is believed to have more benefits than risks.

Data Monitoring Committee: No

1.2. Schema


Treatment and Assessment Period
Pre-Screening
Screening
LY3819469 16 mg, doses at randomization and Day 180
LY3819469 96 mg, doses at randomization and Day 180
LY3819469 400 mg, doses at randomization and Day 180
LY3819469 400 mg, dosed at randomization, placebo at Day 180
Placebo, doses at randomization and Day 180
Day ≤42 Visit 601
Day ≤21 Visit 1
0 15 30 60 120 180 210 240 300 360 540
2 3 4 5 6 7 8 9 10 11 12
Randomization
Primary Outcome

1.3. Schedule of Activities (SoA)

Period I - Optional Prescreening: The study includes an optional prescreening visit (Visit 601) as a simple way for sites to determine whether participants meet Lp(a) criteria, as assessed by a central laboratory assessment, before the full screening activities are initiated at Visit 1. If the participant has not had Lp(a) measured before or is unknown, the prescreening visit should be completed. The prescreening visit can be conducted at the study site, or remotely, for example, at a mobile healthcare or alternate laboratory. The prescreening determination of Lp(a) will be described in an appropriate informed consent form (ICF). Informed consent for the prescreening activities will be obtained, a participant identification number will be assigned, and sample for the Lp(a) prescreening laboratory test will be obtained. The optional prescreening visit can be repeated 1 time (no more) per participant if the investigator believes the participant would meet criteria at a later time, with a minimum of 4 weeks between visits. Repeated sampling in the prescreening visit will not require re-consenting or assignment of a new participant identification number. Note: If the optional prescreening is opted for, central laboratory testing for Lp(a) is still required as part of the screening procedures conducted at Visit 1. Participants with Lp(a) <175 nmol/L at Visit 1 will not be eligible for enrollment, despite their values in prescreening. A prescreening visit occurring longer or shorter than 21 days (3 weeks) from screening will not be considered a protocol deviation.

Period II - Screening: Visit 1 procedures may be conducted over more than 1 day as long as all activities are completed prior to Visit 2.

Period III - Treatment and Assessment Period: All procedures (screening and baseline) need to be completed prior to the first dose of study intervention. For an early discontinuation (ED) from the study intervention that occurs before the last visit in treatment period, see the activities listed for ED in this table.

	Period I - Pre-Screening	Period II - Screening	Period III –- Treatment and Assessment Period												Participants are required to fast before Visits 1-12. See Section 5.3.1. If a participant arrives not fasted, schedule the laboratory draw for another date.
Visit number	601	1	2	3	4	5	6	7	8	9	10	11	12	ED	
Days from randomization	≤42	≤21	—	15	30	60	120	180	210	240	300	360	540		Visit 1 procedures may be conducted over more than 1 day if all activities are completed within the allowable visit tolerance.
Visit interval tolerance (days)	See Section 1.3	—	—	±3	±3	±3	±7	±7	±7	±7	±7	±7	±14	---	
Prescreening informed consent	X														
Informed consent		X													The ICF must be signed before any protocol-specific tests or procedures are performed. See Appendix 10.1.3 for additional details.
Inclusion and exclusion criteria, review and confirm		X	X												Inclusion and exclusion criteria should be confirmed-prior to drug assignment and administration of first dose of study intervention.
Ascertainment of high risk for cardiovascular events		X													High risk for cardiovascular events will be defined as CAD, stroke, or peripheral artery disease, or ASCVD risk equivalents (familial hypercholesterolemia or type 2 diabetes)
Demographics		X													Includes year of birth, sex, ethnicity (where permissible), and race.
Preexisting conditions and medical history, including relevant surgical history		X													All conditions ongoing and relevant past surgical and medical history should be collected.

	Period I - Pre-Screening	**Period II - Screening**	**Period III –- Treatment and Assessment Period**												Participants are required to fast before Visits 1-12. See Section 5.3.1. If a participant arrives not fasted, schedule the laboratory draw for another date.
Visit number	601	1	2	3	4	5	6	7	8	9	10	11	12	ED	
Days from randomization	≤42	≤21	—	15	30	60	120	180	210	240	300	360	540		Visit 1 procedures may be conducted over more than 1 day if all activities are completed within the allowable visit tolerance.
Visit interval tolerance (days)	See Section 1.3	—	—	±3	±3	±3	±7	±7	±7	±7	±7	±7	±14	---	
Prespecified medical history (indication and history of interest)		X													Prespecified medical history includes history of cardiovascular events.
Prior treatments for indication		X													Relevant prior therapies include, but are not limited to, lipid-lowering medications.
Substance use (alcohol, caffeine, and tobacco use)		X						X				X	X		
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	Additional data will be collected for medications of interest.
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 (Appendix 10.3). Additional data are collected for certain AEs.
Physical Evaluation															
Height		X													Participant should remove shoes.
Weight		X	X					X				X	X	X	Participant should remove shoes.

	Period I - Pre-Screening	**Period II - Screening**	**Period III –- Treatment and Assessment Period**												Participants are required to fast before Visits 1-12. See Section 5.3.1. If a participant arrives not fasted, schedule the laboratory draw for another date.
Visit number	601	1	2	3	4	5	6	7	8	9	10	11	12	ED	
Days from randomization	≤42	≤21	—	15	30	60	120	180	210	240	300	360	540		Visit 1 procedures may be conducted over more than 1 day if all activities are completed within the allowable visit tolerance.
Visit interval tolerance (days)	See Section 1.3	—	—	±3	±3	±3	±7	±7	±7	±7	±7	±7	±14	---	
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	Includes pulse rate and blood pressure measured 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	The physical examination is performed (excludes pelvic, rectal, and breast examinations unless clinically indicated).
Symptom-directed physical assessment			X												Symptom-directed physical assessment will be conducted at the discretion of the PI or qualified personnel, per local regulations, as indicated based on participant status and standard of care.
12-Lead ECG (local)		X						X				X	X	X	Collect single, local ECG 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 PI's discretion at any visit. See Section 8.2.1.

	Period I - Pre-Screening	**Period II - Screening**	**Period III –- Treatment and Assessment Period**												Participants are required to fast before Visits 1-12. See Section 5.3.1. If a participant arrives not fasted, schedule the laboratory draw for another date.
Visit number	601	1	2	3	4	5	6	7	8	9	10	11	12	ED	
Days from randomization	≤42	≤21	—	15	30	60	120	180	210	240	300	360	540		Visit 1 procedures may be conducted over more than 1 day if all activities are completed within the allowable visit tolerance.
Visit interval tolerance (days)	See Section 1.3	—	—	±3	±3	±3	±7	±7	±7	±7	±7	±7	±14	---	
Laboratory Tests and Sample Collections															
Hematology		X			X	X		X	X	X		X	X		
Clinical chemistry		X	X	X	X	X		X	X	X		X	X	X	
Lipid panel		X	X			X		X		X		X	X	X	
Urinalysis		X				X		X		X		X	X	X	
UACR		X				X		X		X		X	X	X	
Serum pregnancy		X													Females only.
FSH		X													Optional; performed as needed to confirm postmenopausal status. See Appendix 10.4.
TSH		X													
HbA1c		X						X				X	X	X	
Lp(a)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ApoB		X	X			X	X	X	X	X	X	X	X	X	
hsCRP		X	X			X	X	X	X	X	X	X	X	X	
HIV screening test		X													

	Period I - Pre-Screening	**Period II - Screening**	**Period III –- Treatment and Assessment Period**												Participants are required to fast before Visits 1-12. See Section 5.3.1. If a participant arrives not fasted, schedule the laboratory draw for another date.
Visit number	601	1	2	3	4	5	6	7	8	9	10	11	12	ED	
Days from randomization	≤42	≤21	—	15	30	60	120	180	210	240	300	360	540		Visit 1 procedures may be conducted over more than 1 day if all activities are completed within the allowable visit tolerance.
Visit interval tolerance (days)	See Section 1.3	—	—	±3	±3	±3	±7	±7	±7	±7	±7	±7	±14	---	
HCV screening test		X													If HCV antibody test is positive, it must be followed by an HCV RNA test. See Section 8.2.5.
HBV screening test		X													If HBsAg is negative and HBcAb is positive, further testing with HBV DNA is required. If the screening HBV DNA is negative, the participant is not excluded. See Section 8.2.4.
eGFR		X				X		X		X		X	X	X	Calculated using CKD-EPI method.
Postdose PK sample			X					X							Visit 2: Collect 2 samples. • 0.5 hours postdose • 4-9 hours postdose (minimum 2 hours) Visit 7: Collect 1 sample. 1. 24-36 hours postdose, will require participant to return 1 day after Visit 7.
Immunogenicity (ADA)			P	X	X		X	P		X		X	X	X	Visit 2 and 7 will be collected predose.
PK sample for immunogenicity				X	X		X	P		X		X	X	X	Collect a time-matched PK sample for all scheduled and unscheduled immunogenicity samples. Visit 7 will be collected predose.

	Period I - Pre-Screening	Period II - Screening	Period III –- Treatment and Assessment Period												Participants are required to fast before Visits 1-12. See Section 5.3.1. If a participant arrives not fasted, schedule the laboratory draw for another date.
Visit number	601	1	2	3	4	5	6	7	8	9	10	11	12	ED	
Days from randomization	≤42	≤21	—	15	30	60	120	180	210	240	300	360	540		Visit 1 procedures may be conducted over more than 1 day if all activities are completed within the allowable visit tolerance.
Visit interval tolerance (days)	See Section 1.3	—	—	±3	±3	±3	±7	±7	±7	±7	±7	±7	±14	---	
Stored Samples															**On dosing days, collect samples before dosing**
Optional genetics sample			X												Sample can be obtained at or after the specified visit. See Appendix 10.5.
Exploratory biomarker samples			X			X		X		X		X	X		
Randomization and Dosing															
Register visit with IWRS		X	X	X	X	X	X	X	X	X	X	X	X	X	Unscheduled visits are not required to be registered in IWRS.
Randomization via IWRS			X												
Dispense study intervention via IWRS			X					X							
Administer study intervention			X					X							

Abbreviations: ACC/AHA = American College of Cardiology/American Heart Association; ADA = anti-drug antibody; AE = adverse event; ApoB = apolipoprotein b; ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ED = early discontinuation; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; ICF = informed consent form; IWRS = Interactive Web-Response System; Lp(a) = Lipoprotein(a); P = predose; PI = principal investigator; PK = pharmacokinetic; RNA = ribonucleic acid; TSH = thyroid stimulating hormone; UACR = urine albumin creatinine ratio.

2. Introduction

LY3819469 is a novel Dicer-substrate small interfering ribonucleic acid (siRNA) oligonucleotide designed to reduce the levels of *LPA* mRNA and apolipoprotein(a) (Apo[a]) expression and thereby to decrease lipoprotein(a) (Lp[a]). LY3819469 is being developed to reduce the risk of cardiovascular events in patients with or at high risk of atherosclerotic cardiovascular disease (ASCVD) and high levels of Lp(a)

2.1. Study Rationale

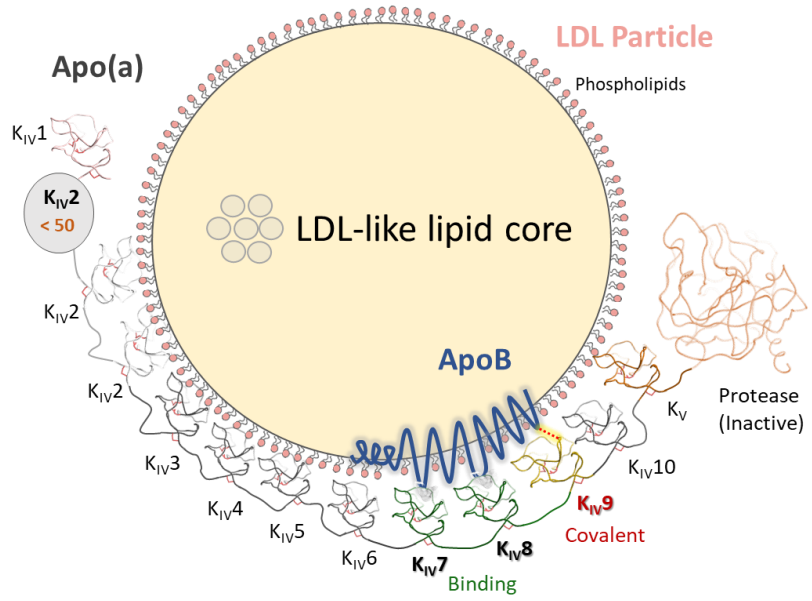
Elevated Lp(a) is recognized as an important risk factor of cardiovascular disease; there are currently no approved pharmaceutical interventions for lowering Lp(a). LY3819469 is an siRNA, that decreases Lp(a) formation and has been shown to reduce Lp(a) in preclinical studies. In Phase 1 Study J3L-MC-EZEA (EZEA) with single doses of LY3819469, Lp(a) was significantly decreased and no safety issues were identified. This Phase 2 study aims to investigate the impact of a range of LY3819469 doses on Lp(a) level and on safety in a larger population of participants with elevated Lp(a) to enable Phase 3 development of this compound.

2.2. Background

2.2.1. Introduction to Lp(a)

Lp(a) is an atherogenic lipoprotein consisting of a low-density lipoprotein particle linked via a disulfide bond to Apo(a) (see Figure 1).

Apo(a) is a protein found in new-world monkeys, great apes, and humans (Utermann 1989). The protein, encoded by the LPA gene, includes 10 unique units of kringle IV repeats; the first and third through tenth are present in single copies while the second is present in variable copy numbers (1 to <50). Additionally, the protein includes a kringle V and a protease-like domain that is not biologically active (Dubé et al. 2012; Kronenberg and Utermann 2013; Tsimikas 2017).



Abbreviations: Apo(a) = apolipoprotein(a); ApoB = apolipoprotein b; LDL = low-density lipoprotein; Lp(a) = lipoprotein(a).

Figure 1. Representation of Lp(a) particle.

Lp(a) contains oxidized phospholipids. Plasma levels of Lp(a) are genetically determined. Single-nucleotide polymorphisms (SNPs) of the LPA gene are associated with higher or lower Lp(a) levels; for example, rs10455872 and rs3798220 are associated with increased Lp(a) (Clarke et al. 2009; Li et al. 2011). Additionally, the number of kringle IV2 repeats determines protein size, which is inversely proportional to plasma concentration and mass of Lp(a); larger Apo(a) size is associated with lower concentrations of Lp(a). Despite this genetically induced variability in Lp(a) concentrations between individuals, intra-patient variability in Lp(a) is low and is not thought to be materially impacted by diet, environmental factors, or exercise (Schmidt et al. 2016). However, Apo(a) is an acute-phase reactant, and Lp(a) increases, for example, after surgery, myocardial infarction, and infection (Maeda et al. 1989; Noma et al. 1994; Min et al. 1997).

2.2.2. Elevated Levels of Lp(a) Are Associated with Increased Risk of Cardiovascular Disease

Lp(a) particles are thought to exert adverse cardiovascular effects through atherogenic, inflammatory, and possibly pro-thrombotic activity (Tsimikas 2017).

In a meta-analysis of 36 studies, Lp(a) was associated with risk for nonfatal myocardial infarction or coronary death (Emerging Risk Factors Collaboration et al. 2009). In studies of LPA gene KIV2 repeats or SNPs, genetic variants conferring higher levels of Lp(a) were found to be related to risk for myocardial infarction and coronary disease in Mendelian randomization and genome-wide association studies (Clarke et al. 2009; Kamstrup et al. 2009). In a study including data from the United Kingdom (UK) Biobank, 7 genome-wide association studies, and LPA sequencing, Lp(a) was associated with risk of coronary heart disease, stroke, chronic kidney disease, aortic valve stenosis, heart failure, and peripheral vascular disease (Emdin et al. 2016).

The American Heart Association and American College of Cardiology Guideline on the management of blood cholesterol defined Lp(a) ≥50 mg/dL or ≥125 nmol/L as risk enhancing in 2018 (Grundy et al. 2019). Elevated Lp(a) >50 mg/dL was present in 24% of samples from a reference laboratory and 29.2% of samples from a tertiary care center (Varvel et al. 2016). The estimated prevalence of Lp(a) >60 mg/dL is 64 million in the United States, 150 million in Europe, and 1.4 billion worldwide (Tsimikas and Stroes 2020).

2.2.3. Available Treatments

Lipid apheresis is approved and used in some geographies for patients with elevated Lp(a) (Jaeger et al. 2009; Nugent et al. 2020). Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, alirocumab, evolocumab, and inclisiran, reduce Lp(a) by approximately 25% (Robinson et al. 2015; Sabatine et al. 2015; Stoekenbroek et al. 2019), and prescription-strength niacin also produces 15% to 25% reductions in Lp(a) (AIM-HIGH Investigators 2011; HPS2-THRIVE Collaborative Group 2014), but are not approved treatments for Lp(a) reduction. Novel treatments to reduce Lp(a) are under investigation, including an antisense oligonucleotide (pelacarsen), and 2 siRNA therapies (olpasiran and SLN360), which have been shown to lower Lp(a) concentrations in clinical trials (Viney et al. 2016; Tsimikas et al 2020; Ference 2022; Koren et al. 2022; Nissen et al. 2022).

2.2.4. Introduction to LY3819469

LY3819469 inhibits the production of Apo(a) by causing degradation of *LPA* mRNA through the siRNA mechanism. LY3819469 reduces steady-state levels of Apo(a) protein in a mouse model transgenic for human Apo(a), and Lp(a) in cynomolgus monkeys that endogenously express Lp(a).

Nonclinical toxicology studies of LY3819469 showed no notable adverse drug effects.

In Phase 1 Study EZEA of participants treated with single LY3819469 doses up to 608 mg, Lp(a) was lowered and no notable adverse drug effects were observed.

Efficacy will be determined by measuring circulating levels of Lp(a) in this Phase 2 study to enable dose selection for Phase 3 study.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of LY3819469 may be found in the Investigator's Brochure (IB) or Development Safety Update Report.

2.3.1. Risk Assessment

Study Intervention

The pharmacodynamic (PD) effect of LY3819469 is anticipated to be lowering of Lp(a). Lp(a) serves no known positive functions and is not present in most species. Additionally, people homozygous for null mutations of the LPA gene have not been identified to have any related health issues. Furthermore, toxicology studies of LY3819469 have shown no notable adverse effects. Finally, human Phase 1 Study EZEA showed that single LY3819469 doses up to 608 mg were safe and generally well tolerated by healthy male and female participants.

Study Procedures

The study will include blood draws and safety monitoring, and these procedures are not anticipated to be associated with significant participant risk.

2.3.2. Benefit Assessment

Lp(a) is a lipoprotein particle with atherogenic, inflammatory, and possibly pro-thrombotic activity. In preclinical studies and a previous Phase 1 study, LY3819469 decreased Lp(a). Lowering of Lp(a) is anticipated to have beneficial effects on cardiovascular disease; however, the duration of lowering of Lp(a) in this study may not be sufficient to confer any benefits. Nevertheless, 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

Treatment with study intervention is anticipated to have an acceptable benefit to risk profile.

3. Objectives, Endpoints, and Estimands

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

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

Primary estimand

The primary clinical question of interest is: What is the intervention difference in percent change from baseline in time-averaged Lp(a) over Days 60-180 of study intervention in participants who meet the inclusion criteria regardless of treatment discontinuation for any reason?

The primary estimand characterizes the treatment effect regardless of intercurrent events and is named the "treatment-regimen estimand."

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

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

Endpoint: percent change from baseline in time-averaged Lp(a) over Days 60-180 which will be calculated by area under the curve (AUC) between Day 60 to Day 180 divided by 120.

Treatment condition: the randomized treatment with allowance for safety. Further details on study interventions, and concomitant interventions can be found in Section 6.

There are no intercurrent events. Since each patient can only take one dose for the first 6 months, there is no intercurrent events of treatment discontinuation. The concomitant medication use is not considered intercurrent events as it is considered as a part of patient management.

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

Treatment contrast of interest: difference in mean percent changes in Lp(a) between LY3819469 and placebo.

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

Estimand(s) for secondary objective

A similar estimand for the primary objective will be used for the secondary clinical response before the second injection at Day 180. For the objectives after Day 180, the treatment discontinuation will be handled by treatment policy strategy.

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

4. Study Design

4.1. Overall Design

Study EZEB is a parallel, double-blinded, placebo-controlled, dose-finding, Phase 2 study of LY3819469 in participants with elevated Lp(a).

Approximately 254 participants will be randomized in a 1:2:2:2:2 ratio to 1 of the following arms:

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

Treatment periods and assessments are described in the Schedule of Activities (SoA) (Section 1.3)

The study schema is shown in Section 1.2.

The study population is described in Section 5.

The efficacy and safety assessments are described in Sections 8.1 and 8.2, respectively.

4.2. Scientific Rationale for Study Design

Interim data from Phase 1 Study EZEA showed a decrease in Lp(a) in healthy participants with Lp(a) levels ≥75 nmol/L or ≥30 mg/dL given single doses of LY3819469. The current study is intended to be Phase 3 enabling, as it will provide the following information:

- Efficacy and safety data with subcutaneous (SC) administration of doses of study drug at randomization and Day 180 in participants with higher levels of Lp(a). This design is anticipated to provide information regarding the maximal level and durability of lowering of Lp(a) with LY3819469 and information regarding an appropriate dose and dosing frequency of study drug for Phase 3. The primary endpoint is over Days 60-180 to assess the lowering of Lp(a) across time.
- Participants for this study will have Lp(a) ≥175 nmol/L at baseline. This study will thus provide relevant efficacy and safety for participants with Lp(a) sufficiently high to participate in a Phase 3 cardiovascular outcomes trial.

The study includes an optional prescreening Visit 601 where potential participants can be prescreened with an assessment of Lp(a).

Participants qualifying based on the optional prescreening assessment and those known to have a significantly elevated Lp(a) can be screened for inclusion in the trial at Visit 1.

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.

In this study, collection of demographic information includes race and ethnicity. 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.

4.2.1. Participant Input into Design

Throughout this protocol, the term "participant" is used to indicate an individual who participates in a clinical trial, either as a recipient of an investigational intervention or as a control. This usage reflects preferences indicated by patient advocates to more accurately reflect the role of people who take part in clinical trials.

4.3. Justification for Dose

LY3819469 doses of 16 mg, 96 mg, and 400 mg, administered subcutaneously, were selected based on the following:

- Safety and tolerability of LY3819469 doses up to 608 mg in healthy participants in the Phase 1 Study EZEA
- The selected dose levels and dose range support a robust dose-exposure–response analysis of multiple safety and efficacy measures to support selection of dose(s) of LY3819469 with optimal benefit/risk ratio for further clinical development

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the trial globally.

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit or the last scheduled procedure shown in the SoA.

5. Study Population

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

Presence or absence of high risk for cardiovascular events will be a factor for stratification of the randomization. High risk for cardiovascular events will be defined as coronary artery disease (CAD), stroke, or peripheral artery disease, or ASCVD risk equivalents (familial hypercholesterolemia or type 2 diabetes).

5.1. Inclusion Criteria

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

Age

1. Participants must be at least 40 years old at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants with Lp(a) ≥175 nmol/L at Visit 1, measured at the central laboratory.
3. Participants on the following medications according to local practice must be on a stable regimen for at least 4 weeks prior to Visit 1 and expected to remain on a stable regimen through the end of the Treatment and Assessment Period:
    a. lipid-lowering drugs (such as statins, ezetimibe, PCSK9 inhibitors, prescription-dose niacin, fibrates, fish oil, or other products containing omega-3 fatty acids, including over-the-counter [OTC] preparations)
    b. testosterone, estrogens, anti-estrogens, progestins, selective estrogen receptor modulators, or growth hormone

Weight

4. Have a body mass index within the range 18.5 to 40 kg/m^2, inclusive.

Sex and Contraceptive/Barrier Requirements

5. Male and/or female
    a. Males who agree to use highly effective/effective methods of contraception may participate in this trial.
    b. Women of childbearing potential (WOCBP) are excluded from the trial.
    c. Women not of childbearing potential (WNOCBP) may participate in this trial.

    Please refer to Appendix 10.4 for definitions and additional guidance related to contraception.

    Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For the contraception requirements of this protocol, see Appendix 10.4.

Informed Consent

6. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1), which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Other Inclusions

7. Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures, in the opinion of the investigator.

5.2. Exclusion Criteria

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

Medical Conditions

8. Have a history or presence of an underlying disease, or surgical, physical, medical, or psychiatric condition that, in the opinion of the investigator, would potentially affect participant safety within the study or interfere with participating in or completing the study or with the interpretation of data.
9. Any of the following, or other events indicating unstable medical condition in the opinion of the investigator, within 3 months of Visit 1:
    a. major surgery
    b. coronary, carotid, or peripheral arterial revascularization
    c. stroke or transient ischemic attack
    d. myocardial infarction or unstable angina
    e. acute limb ischemia.
10. Have, in the 6 months prior to Visit 1, uncontrolled Type 1 or Type 2 diabetes, defined as an episode of ketoacidosis or hyperosmolar state requiring hospitalization, or have a hemoglobin A1c (HbA1c) ≥8% at Visit 1.
11. Have uncontrolled hypertension with a resting blood pressure ≥160 mm Hg systolic and/or ≥100 mm Hg diastolic at Visit 1; a repeat measure is allowed.
12. New York Health Association Class III or IV heart failure or last known left ventricular ejection fraction <30%.
13. Active or acute infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Visit 2.
14. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated.
15. Recent history of, or current drug or alcohol abuse in the opinion of the investigator.
16. Have 2 or more clinically significant or severe drug allergies, or severe post-treatment hypersensitivity reactions, including, but not limited to
    f. erythema multiforme major
    g. linear immunoglobulin A dermatosis
    h. toxic epidermal necrolysis
    i. exfoliative dermatitis.
17. Hypersensitivity to the active substance or to any of the excipients.

18. Have a current infection with hepatitis B virus (HBV), that is, positive for hepatitis B surface antigen (HBsAg) and/or polymerase chain reaction (PCR) positive for HBV deoxyribonucleic acid (DNA) (Section 8.2.4).
19. Have a current infection with hepatitis C virus (HCV), that is, positive for HCV ribonucleic acid (RNA) (Section 8.2.5).
20. Have human immunodeficiency virus (HIV) infection.

Prior/Concomitant Therapy

21. Lipoprotein apheresis within 3 months of Visit 1, or planned during the study.
22. Treatment with another investigational drug, biological agent, or device within 1 month of Visit 1, or 5 half-lives of investigational agent, whichever is longer.
23. Treatment with any oligonucleotide or siRNA within 9 months of Visit 1.

Prior/Concurrent Clinical Study Experience

24. Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

Diagnostic Assessments

25. Clinically significant abnormalities in screening laboratory values that would render a participant unsuitable for inclusion in the opinion of the investigator.
26. Any of the following abnormalities:
    a. estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2
    b. alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3.0x upper limit of normal (ULN)
    c. bilirubin > 1.5x ULN, except for participants diagnosed with Gilbert's syndrome

Other Exclusions

27. Are Eli Lilly and Company (Lilly) employees, or are employees of any third party involved in a study that requires exclusion of their employees.
28. 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.
29. Are pregnant, or intend to become pregnant or to breastfeed during the study.
30. Are, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Participants are required to fast for at least 10 hours before Visits 1-12. Routine blood chemistry and urine samples should be taken after fasting for at least 10 hours. Fasting is not required for postdose pharmacokinetic (PK) samples. During preparation for fasting samples, the participant can drink water and they should ensure that they consume sufficient water in order to not become

dehydrated. It is not necessary to fast for Visit 601, PK blood draws, or for any confirmatory test, or test taken for safety reasons; these may be taken without regard to fasting status.

5.3.2. Blood Donation

Participants must not donate blood for the duration of 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 serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once if the investigator believes the participant would meet criteria at a later time. Rescreened participants should be assigned a new participant number for every screening or rescreening event.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention of a Participant

Not applicable.

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/used by a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

	Arm A	Arm B	Arm C	Arm D	Arm E
Intervention Name	LY3819469	LY3819469	LY3819469	LY3819469 and Placebo	Placebo[a]
Dosage #1					
LY3819469 Solution (160 mg/mL)	16 mg (0.1 mL)	96 mg (0.6 mL)	400 mg (2.5 mL)	400 mg (2.5 mL)	–
Placebo (0.9% sodium chloride solution for injection)	–	–	–	–	Placebo[a]
Dosage #2					
LY3819469 Solution (160 mg/mL)	16 mg (0.1 mL)	96 mg (0.6 mL)	400 mg (2.5 mL)	–	–
Placebo (0.9% sodium chloride solution for injection)	–	–	–	Placebo[b]	Placebo[a]
Route of Administration	SC injection	SC injection	SC injection	SC injection	SC injection
Authorized as defined by EU Clinical Trial Regulation	Not authorized in EU	Not authorized in EU	Not authorized in EU	Not authorized in EU	Not authorized in EU

Abbreviations: EU = European Union; SC = subcutaneous.

[a] Participants in Arm E 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.

[b] Participants in Arm D will receive a 2.5-ml placebo dose at Day 180 (Visit 7).

The table below describes the injection volume for the different intervention dose groups.

Intervention Group	Injection volume
16 mg or matched placebo participants	0.1 mL
96 mg or matched placebo participants	0.6 mL
400 mg or matched placebo participants	2.5 mL

Packaging and labeling

Study interventions will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice. Study interventions will be labeled as appropriate for country requirements.

6.2. Preparation, Handling, Storage, and Accountability

1. 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.
2. Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer 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.
3. The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions will be provided separately.

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to randomized study intervention using an Interactive Web-Response System (IWRS). Participants will be stratified by high risk for cardiovascular events (yes/no) and baseline Lp(a) (<275 nmol/L, ≥275 nmol/L). 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. Before the study is initiated, the log in information and directions for the IWRS will be provided to each site.

Study intervention will be dispensed and administered at the study visits summarized in SoA.

This is a double-blind study in which participants are blinded to study intervention. 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 participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. 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.

If an investigator, site personnel performing assessments, or participant is unblinded, the participant may be continued in the study.

Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. To maintain this blind, an otherwise uninvolved third party will be responsible for the preparation and dispensation of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense following randomization.

This third party will instruct the participant to avoid discussing the volume of injection, dosing frequency, or packaging of the study intervention with the investigator.

In the event of a quality assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

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 case report form (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

LY3819469 will not be made available to participants after completion of the study.

6.7. Treatment of Overdose

For this study, any dose of LY3819469 greater than the planned dose will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention no longer has a clinical effect or can no longer be detected systemically (at least 2 days).

6.8. Concomitant Therapy

Any medication or vaccine, including OTC or prescription medicines, vitamins, and/or herbal supplements, that the participant is receiving at the time of enrollment or receives during the study must be recorded along with

- reason for use
- dates of administration including start and end dates, and
- dosage information including dose and frequency for concomitant therapy of special interest.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants on the following medications according to local practice must be on a stable regimen for at least 4 weeks prior to screening and expected to remain on a stable regimen through the end of the Treatment and Assessment Period, unless changes need to be made because of AEs:

- lipid-lowering drugs (such as statins, ezetimibe, PCSK9 inhibitors, prescription-dose niacin, fibrates, fish oil, or other products containing omega-3 fatty acids, including OTC preparations), and
- testosterone, estrogens, progesterone, growth hormone, or progestins.

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 Appendix 1 (Section 10.1).

7.1. Discontinuation of Study Intervention

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will remain in the study and follow procedures for remaining study visits, as shown in the SoA.

A participant should be permanently discontinued from study intervention if

- the participant becomes pregnant during the study
- 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 may consult the sponsor
- the participant has an AE or an SAE or a clinically significant change in a laboratory value that, in the opinion of the investigator, merits discontinuation of study intervention and appropriate measures being taken
- if the participant experiences a hepatic event or liver test abnormality as specified in the liver chemistry stopping criteria (see Section 7.1.1), and
- HBV or HCV: The participant tests positive for HBV DNA (see Section 8.2.4) or tests positive for HCV RNA (Section 8.2.5).

  Note: The HBV DNA result is to be confirmed if initial positive test result is positive but below the level of quantification. Prior to discontinuation of any immunomodulatory and/or immunosuppressive therapy, including study intervention, the participant is to be referred to, evaluated, and managed by a specialist physician with expertise in evaluation and management of viral hepatitis. The timing of discontinuation from study intervention relative to the initiation of any antiviral treatment for hepatitis is to be based on the recommendation of the consulting specialist physician, in conjunction with the investigator, and aligned with medical guidelines and standard of care.

7.1.1. Liver Chemistry Stopping Criteria

Interrupting study drug based on liver test elevations in participants with normal or near-normal baseline liver tests

In study participants with normal or near-normal baseline liver tests (ALT, AST, alkaline phosphatase [ALP] <1.5x ULN), the study drug should be **interrupted** or discontinued and close hepatic monitoring initiated (see Appendix 10.6) if one 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	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption 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	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption 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%)	
Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines, with minor modifications	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; FDA = Food and Drug Administration; INR = international normalized ratio; TBL = total bilirubin; ULN= upper limit of normal.

Interrupting study drug based on elevated liver tests in participants with abnormal baseline liver tests

In study participants with abnormal baseline liver tests (ALT, AST, ALP ≥1.5x ULN), the study drug should be **interrupted** or discontinued if one or more of these conditions occur:

Elevation	Exception
ALT or AST >4x baseline	
ALT or AST >3x baseline for more than 2 weeks	
ALT or AST >2x baseline and either TBL >2x ULN or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2x ULN.
ALT or AST >2x baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >2.5x baseline, when the source of increased ALP is the liver	
ALP >2x baseline and TBL >2x ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2x ULN.
ALP >2x baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines, with minor modifications	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; FDA = Food and Drug Administration; INR = international normalized ratio; TBL = total bilirubin; ULN= upper limit of normal.

Resuming study drug after elevated liver tests

Resumption of the study drug 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 nondrug etiology is identified. Otherwise, the study drug should be discontinued.

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 (QTcF) 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 electrocardiogram (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

Discontinuation is expected to be uncommon.

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 enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation (ED) visit, as shown in the SoA. If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

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.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined to be deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

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

See Section 9.3 for definitions of the efficacy endpoints.

8.1.1. Primary Efficacy Assessment

Elevated Lp(a) is recognized as an important risk factor for cardiovascular disease. Lp(a) will be collected for each participant at the times shown in the SoA (Section 1.3).

8.1.2. Secondary Efficacy Assessments

The 2018 AHA/ACC Guideline on the management of blood cholesterol identified Lp(a) ≥50 mg/dL (≥125 nmol/L) as risk enhancing. As a responder analysis, the proportions of participants achieving Lp(a) <125 and <75 nmol/L will be assessed.

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

- ApoB
- high-sensitivity C-reactive protein (hsCRP)

8.2. Safety Assessments

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

8.2.1. Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures pulse rate, QRS, QT, and QTc intervals. Refer to Section 7.1.2 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

8.2.2. Clinical Safety Laboratory Tests

- See Appendix 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 and deemed to be related to LY3819469, in the opinion of the investigator, or within 6 months after the last dose of study intervention 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 Appendix 2 (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.

8.2.3. Hepatic Safety

Close hepatic monitoring

Laboratory tests (Appendix 10.6), including ALT, AST, ALP, total bilirubin (TBL), direct bilirubin (D. Bil), gamma-glutamyl transferase (GGT), and creatine kinase (CK), should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

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 patients 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 patients with Gilbert's syndrome)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN= upper limit of normal.

If the abnormality 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 OTC), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and lab results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if one or more of these conditions 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 patients 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 patients with Gilbert's syndrome)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN= upper limit of normal.

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

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time, international normalized ratio (PT-INR); tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or computerized tomography [CT] 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 (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), 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 (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, or a liver biopsy.

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

Additional hepatic safety data collection in hepatic safety CRF should be performed in study participants who meet 1 or more of the following 5 conditions:

1. Elevation of serum ALT to ≥5x ULN on 2 or more consecutive blood tests (if baseline ALT <1.5x ULN)
   - In participants with baseline ALT ≥1.5x ULN, the threshold is ALT ≥3x baseline on 2 or more consecutive tests
2. Elevated TBL to ≥ 2x ULN (if baseline TBL <1.5x ULN) (except for cases of known Gilbert's syndrome)
   - In participants with baseline TBL ≥1.5x ULN, the threshold should be TBL ≥2x baseline
3. Elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests (if baseline ALP <1.5x ULN)
   - In participants with baseline ALP ≥1.5x ULN, the threshold is ALP ≥2x baseline on 2 or more consecutive blood tests
4. Hepatic event considered to be an SAE
5. Discontinuation of study drug due to a hepatic event

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

8.2.4. Hepatitis B Testing and Monitoring

As specified in the SoA (Section 1.3), initial testing for HBV infection includes HbsAg and hepatitis B core antibody (HbcAb).

- If HbsAg is positive, the participant is excluded.
- If HbsAg is negative and HbcAb is negative, the participant is not excluded.
- If HbsAg is negative and HbcAb is positive, further testing for HBV DNA is required.
  - If the screening HBV DNA is positive, the participant is excluded.
  - If the screening HBV DNA is negative, the participant is not excluded. Repeat testing for HBV DNA is required at least every 3 months during the study.

Management of enrolled participants with detectable HBV DNA during the study

If HBV DNA is detected, study intervention will be temporarily withheld or permanently discontinued, as described in Section 7.1, and the participant should receive appropriate follow-up medical care.

8.2.5. Hepatitis C Testing

As specified in the SoA (Section 1.3), initial testing for HCV infection includes testing for anti-HCV.

- If anti-HCV is positive, a test for circulating HCV RNA is required.
- If HCV RNA test is negative, the participant is not excluded.
- If HCV RNA test is positive, the participant is excluded.

Participants who have had HCV infection and have been successfully treated, defined as a sustained virologic response (HCV RNA by PCR negative for at least 24 weeks following treatment completion), are not excluded on the basis of HCV as long as HCV RNA test is negative at screening.

If HCV RNA is detected during the study, the study intervention will be discontinued (Section 7.1), and the participant should receive appropriate follow-up medical care.

8.2.6. Injection Site Reactions

Symptoms and signs of a local injection site reaction (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).

8.2.7. 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 Appendix 10.2.1. Laboratory results are provided to the sponsor via the central laboratory.

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

The definitions of the following events can be found in Appendix 3:

- AEs
- SAEs
- Product complaints (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 study (see Section 7).

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 Appendix 10.3.

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 ICF	Participation in study has ended	As soon as possible upon site awareness	AE CRF	N/A
AE – related to prescreening study procedure	Signing of the prescreening ICF	Signing of the ICF	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 to 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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
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
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	Participation in study has ended	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form
Product Complaints					
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	

Abbreviations: AE = adverse event; CRF = case report form; ICF = informed consent form; N/A = not applicable; PC = product complaint; SAE = serious adverse event.

[a] SAEs 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 study intervention.
- 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 poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in protocol 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 discontinue study intervention. 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. Major Adverse Cardiovascular Events

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

8.4. Pharmacokinetics

- At the visits and times specified in the SoA (Section 1.3), blood samples will be collected to determine the LY3819469 plasma concentrations.
- Participants may need to return to the clinical site for PK-specific visits to provide postdose PK samples dependent on the time window of PK sampling.
- Instructions for the collection and handling of blood samples will be provided by the sponsor. Sampling times for PK evaluation are provided as a guidance and should be adhered to as closely as possible. The actual date and time (24-hour clock time) of each sample collection will be recorded.
- Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel.
- A validated assay will be used to determine plasma LY3819469 concentrations from the blood samples collected. The blood samples will be analyzed at a laboratory approved by the sponsor. The samples will be retained for a maximum of 1 year following last study visit for the study. During this time, any samples remaining after the bioanalysis is complete may be used for exploratory analyses, such as metabolism, protein binding, or bioanalytical method development or validation work.

8.5. Pharmacodynamics

Samples to evaluate the PD properties of LY3819469 are included in the efficacy measures and not applicable here.

8.6. Genetics

An optional blood sample for DNA isolation will be collected from participants.

See Appendix 10.5 for information regarding genetic research and Appendix 10.1.12 for details about sample retention and custody.

8.7. Biomarkers

Serum and plasma samples will be collected and 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 LY3819469, pathways associated with lipid metabolism, mechanism of action of LY3819469, and/or research method, or for validating diagnostic tools or assay(s) related to lipid metabolism or other relevant disease states.

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

At the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected (if local regulations and ethical review boards allow) and stored for potential future analysis to determine antibody production against LY3819469. Antibodies may be further characterized for their ability to neutralize the activity of LY3819469. To interpret the results of immunogenicity, a venous blood sample will be collected at the same time points to determine the plasma concentrations of LY3819469. Samples for immunogenicity should be taken predose when applicable and possible.

In the event of drug hypersensitivity reactions (immediate or nonimmediate), additional samples will be collected as described in Section 10.2.1.

Samples will be retained for a maximum of 15 years after the last participant visit per Section 10.1.12, or for a shorter period if local regulations and ethical review boards allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to the LY3819469. Any samples remaining after 15 years will be destroyed.

8.9. Health Economics

Health economics or medical resource utilization and health economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

The study hypothesis for the primary objective is that SC injection of LY3819469 16 mg, 96 mg, or 400 mg is superior to placebo in percent change from baseline in time-averaged Lp(a) over Days 60-180 in participants with elevated Lp(a).

9.1.1. Multiplicity Adjustment

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

9.2. Analyses Sets

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

Population	Description
Screened	All participants who sign the ICF.
Randomized	All participants who are randomly assigned to a treatment arm.
Full Analysis Set (FAS)	All data for patients who are randomized, take at least one dose of study medication, and are not discontinued due to inadvertent enrollment. Participants will be analyzed according to the treatment they were assigned.

Abbreviation: ICF = informed consent form.

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 statistical analysis plan (SAP) or the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

Unless otherwise noted, all tests will be conducted at a 2-sided alpha level of 0.05, and confidence intervals will be calculated at 95%, 2-sided.

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.

Handling of missing, unused, and spurious data are addressed prospectively in the overall statistical methods described in the protocol and in the SAP, where appropriate. Adjustments to the planned analyses are described in the final CSR.

9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

The primary efficacy assessment, guided by the “treatment-regimen” estimand, which represents the efficacy regardless of treatment discontinuation, will be conducted using the Full Analysis

Set (FAS). The missing values for Lp(a) measurements at each time point (up to 6 months) will be handled by multiple imputation under the assumption of missing at random (MAR). Then, the time-averaged Lp(a) for each patient will be calculated based on the observed and imputed data. Specifically, the AUC for log-transformed Lp(a) over Day 60 to Day 180 will be calculated using the trapezoidal rule according to the scheduled time, and the time-averaged log[Lp(a)] is the AUC for log[Lp(a)] divided by 120 (days). The time-averaged Lp(a) is calculated as the exponentiation of the time-averaged log[Lp(a)].

The change in the time-averaged log[Lp(a)] from baseline will be analyzed using an analysis of covariance (ANCOVA) model including treatment, high risk of cardiovascular event (yes/no), and baseline log[Lp(a)] as a covariate. For the primary analysis up to Day 180, the two LY3819469 treatment groups assigned to 400 mg will be pooled into one treatment group, because participants are receiving the same study intervention in the first 180 days. The percent change for the time-averaged Lp(a) will be calculated and reported by exponentiating the estimates for the change in the time-averaged log[Lp(a)] in the above model and the corresponding standard error will be calculated using the delta-method.

Additional covariates may be added, and this analysis will be detailed in the SAP.

9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis

Secondary endpoints are listed in Section 3.

The efficacy analyses for the secondary endpoints will use the FAS described in Section 9.3.1.and may also pool the two LY3819469 400-mg treatment groups, where appropriate.

Analyses for percent change from baseline in time-averaged Lp(a) over Days 240-360 will be conducted in a manner similar to the primary efficacy analysis discussed in Section 9.3.2.

The continuous clinical measures, including Lp(a), ApoB, and hsCRP, may be log transformed before statistical analyses, if deemed necessary. Analyses for change from baseline in each log-transformed parameter at Days 60, 180, 240, 360, and 540 will be conducted using mixed model for repeated measures (MMRM). The percent change from baseline will be calculated and reported by exponentiating the estimates for the change from baseline in above model.

Analyses for percentages of participants reaching Lp(a) <125 nmol/L and <75 nmol/L at Day 60, 180, 240, 360, and 540 will be conducted using logistic regression modeling.

In these models, additional covariates may be added, if deemed necessary. The details will be provided in the SAP.

9.3.4. Exploratory Endpoint(s) Analysis

Details of analyses 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 LY3819469 doses with placebo irrespective of adherence to intervention. Thus, safety analyses will be conducted using the FAS. Safety assessments may also pool the 2 LY3819469 400-mg treatment groups, where appropriate.

AEs 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

- treatment-emergent adverse events (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, Vital Signs, and Electrocardiograms

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. Laboratory measures may also pool the 2 LY3819469 400-mg treatment groups, where appropriate. 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 parameters, 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

LY3819469 concentration data will be summarized and analyzed using a population PK approach via nonlinear mixed-effects modeling.

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

9.3.7. Immunogenicity Assessments

If data from validated immunogenicity assays are available, treatment-emergent anti-drug antibodies (TE-ADAs) may be assessed.

TE-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 LY3819469 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 LY3819469 may also be assessed. Additional details may be provided in the SAP.

9.3.8. Subgroup Analyses

Subgroup analyses of important factors, such as baseline Lp(a) level, 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

There may be up to 3 interim analyses.

A planned interim analysis may be conducted when at least 10% of the participants complete Day 180 at Visit 7 or discontinue the study. The interim will be for the purpose of internal planning and decision-making and may assess safety, PK, and/or efficacy measures. Additional details related to statistical methods will be described in the SAP. If this happens, an assessment committee (AC) will be formed to review the interim analyses in an unblinded manner. The details regarding the number of participants and type of analysis will be provided in the AC charter and in the unblinding plan. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team members before the study has been unblinded. Study sites will receive information about interim results only if deemed necessary for the safety of the participants. The study will not be stopped based on the efficacy of LY3819469 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 EZEB may occur when all participants have completed Day 180 (Visit 7). After primary analysis, additional efficacy and safety assessment may occur when all participants have completed 240 days (Visit 9) and 10% of participants have completed 360 days (Visit 11) 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.

The addition of an interim analysis can be determined at any time during the study and will not result in a protocol amendment. The SAP will describe the interim analyses in greater detail.

9.5. Sample Size Determination

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

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

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 Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (for example, advertisements) must be submitted to an Institutional Review Board/Independent Ethics Committee (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
    - Reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity
- Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

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

10.1.5.1. External Clinical Endpoints Committee

An independent clinical endpoint committee, external to Lilly, will be formed to adjudicate major adverse cardiac events (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.

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete data set would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

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 to 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, and blank or annotated case report forms, 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

- 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.

- Quality tolerance limits (QTLs) 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 transcribed into the CRF by authorized site 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 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 Clinical Trial Agreement (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.

An electronic data capture system (EDC) 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 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 product complaint 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.

The first act of recruitment is the first participant to enter screening.

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:

For study termination:

- Discontinuation of further study intervention development

For 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
- 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 LY3819469 or after LY3819469 become(s) commercially available.

Sample Type	Custodian	Retention Period After Last Participant Visit[a]
Exploratory Biomarker Samples	Sponsor or Designee	7 years
PK	Sponsor or Designee	1 years
Genetics	Sponsor or Designee	7 years
Immunogenicity	Sponsor or Designee	15 years

Abbreviation: PK = pharmacokinetic.

[a] Retention periods may differ locally.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in the table below will be performed as noted in the table below.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing (in the table below), 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)	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Absolute neutrophil count (calculation)	
Leukocytes (WBCs)	
Differential	
Percent and/or absolutes count of:	
Neutrophils, segmented	
Bands	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBCs and WBCs)	

Clinical Laboratory Tests	Comments
Clinical Chemistry	Assayed by Lilly-designated laboratory.
Sodium	
Potassium	
Chloride	
Bicarbonate	
Total bilirubin	
Direct bilirubin	
ALP	
ALT	
AST	
GGT	
BUN	
Creatinine	
CK	
Uric acid	
Total protein	
Albumin	
Calcium	
Phosphorus	
Glucose	
Lipid Panel	Assayed by Lilly-designated laboratory.
HDL-C	
LDL-C	Generated by Lilly-designated laboratory. If triglycerides are >400; direct LDL will be measured.
VLDL-C	Generated by Lilly-designated laboratory.
Cholesterol	
Triglycerides	
Urinalysis	Assayed by Lilly-designated laboratory.
Specific gravity	
pH	
Protein	
Glucose	
Ketones	
Bilirubin	
Urobilinogen	
Blood	
Nitrite	
Urine leukocyte esterase	
Microscopic examination of sediment	

Clinical Laboratory Tests	Comments
Hormones (female)	
Serum pregnancy	Assayed by Lilly-designated laboratory.
FSH	Assayed by Lilly-designated laboratory.
Calculations	Generated by Lilly-designated laboratory.
eGFR (CKD-EPI)	
UACR	
TB, HIV, and Hepatitis Serology	Assayed by Lilly-designated laboratory.
HIV testing	
HCV testing:	
HCV antibody	
HCV RNA	
HBV testing:	
HBV DNA	Performed only for participants who test positive for HbcAb.
HbcAb	
HbsAg	
HbsAb	
Pharmacokinetic Samples	Assayed by Lilly-designated laboratory.
LY3819469 concentration	Results will not be provided to the investigative sites.
Immunogenicity (ADA) samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Anti-LY3819469 antibodies	
Additional Testing	Assayed by Lilly-designated laboratory.
Lp(a)	Results will be provided to the investigative sites during prescreening or screening. Results will not be provided to the investigative sites after randomization.
ApoB	Results will not be provided to the investigative sites.
hsCRP	Results will be provided to the investigative sites.
TSH	
HbA1c	
Genetics Sample	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.

Clinical Laboratory Tests	Comments
Whole blood (EDTA)	
Exploratory Biomarker Storage Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Serum	
Plasma (EDTA)	

Abbreviations: ADA = anti-drug antibodies; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ApoB = apolipoprotein b; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; CKD-EPI = chronic kidney disease epidemiology collaboration; DNA = deoxyribonucleic acid; EDTA = ethylenediamine tetraacetic acid; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transferase; HbA1c = hemoglobin A1c; HbcAb = hepatitis B core antibody; HbsAb = hepatitis B surface antibody; HbsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HDL-C = high-density lipoprotein-cholesterol; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein-cholesterol; Lp(a) = Lipoprotein(a); RBC = red blood cell; RNA = ribonucleic acid; TSH = thyroid stimulating hormone; UACR = urine albumin creatinine ratio; VLDL-C = very low-density lipoprotein; WBC = white blood cell.

10.2.1. Laboratory Samples to be 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 test 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	Preferred Sample Type[a]	Laboratory Test[b]
Collect from 30 minutes to 4 hours after the start of the event. ● Note: The optimal collection time is from 1 to 2 hours after the start of event.	Serum	total tryptase
	Serum	complements (C3, C3a, and C5a)
	Serum	cytokine panel (IL-6, IL-1β, IL-10 or any cytokine panel that includes these 3 cytokines)
Collect only if not already collected on the same day as the event. ● Note: If collecting, collect up to 12 hours after the start of the event.	Serum	LY3819469 ADA
	Serum/plasma	LY3819469 concentration

Abbreviations: ADA = anti-drug antibodies; IL = interleukin.

[a] Sample type may be different depending on local requirements.

[b] 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, 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. • Medication error, misuse, or abuse of investigational medicinal product, including signs, symptoms, or clinical 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 <u>NOT</u> 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, 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, 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 product complaint 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 product complaints:
  - Deficiencies in labeling information, and
  - Use errors for device or drug-device combination products due to ergonomic design elements of the product.
- Product complaints 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 product complaint or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint 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/product complaint 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/product complaint 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 product complaint information is reported on the Product Complaint Form.

Note: An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint 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 product complaints.
- 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 health care professionals.

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 medical monitor/SAE coordinator by telephone.
- Contacts for SAE reporting can be found in the SAE paper form.

SAE Reporting via Paper Form

- Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the medical monitor or the SAE coordinator.
- 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 the SAE paper form.

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, IRB/IEC, 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

Word/Phrase	Definition
Women of childbearing potential (WOCBP)	Adult females are considered WOCBP unless they are WNOCBP.
Women not of childbearing potential (WNOCBP)	Females are considered WNOCBP if they • have a congenital anomaly such as Müllerian agenesis • are infertile due to surgical sterilization, or • are postmenopausal. Examples of surgical sterilization include total hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Postmenopausal state	The postmenopausal state is defined as a woman: • at any age at least 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or • aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[a], 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 • 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or • aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy.

Abbreviation: SERM = selective estrogen receptor modulator.

[a] 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

10.4.2.1. Female Participants

Female participants of childbearing potential are excluded from the trial.

10.4.2.2. Male Participants

The table below describes contraception guidance for men.

Topic	Guidance
For all men	should refrain from sperm donation for the duration of the study
Contraception for men with partners of childbearing potential	• either remain abstinent (if this is their preferred and usual lifestyle), or • must use condoms during intercourse for the duration of the study
Contraception for men in exclusively same sex relationships, as their preferred and usual lifestyle	Are not required to use contraception

Examples of highly effective, effective, and unacceptable methods of contraception can be found below.

Methods	Examples
Highly effective contraception	• combination oral contraceptive pill and 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 (i.e., condom with spermicide, diaphragm with spermicide, female condom with spermicide) to be considered effective.
Ineffective forms of contraception	• spermicide alone • immunocontraceptives • periodic abstinence • fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, symptothermal) • withdrawal, • post coital douche • lactational amenorrhea

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, an optional blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to study intervention or cardiovascular disease and related diseases. They may also be used to develop tests or assays including diagnostic tests related to study intervention and cardiovascular disease. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study intervention 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 study intervention continues but no longer than 7 years or other period as per local requirements.

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

Hepatic Evaluation Testing

See Section 8.2.4 for guidance on appropriate test selection.

The Lilly-designated central laboratory should complete the analysis of all selected testing except for testing listed in the investigator-designated local laboratory table. The central laboratory will report results if a validated test or calculation is available.

Local testing may be performed *in addition to central testing* when necessary for immediate participant management.

The local laboratory must be qualified in accordance with applicable local regulations.

Tests assayed by Lilly-designated central laboratory	
Hepatic Hematology Panel	**Hepatitis A virus (HAV) testing:**
Hemoglobin	HAV total antibody
Hematocrit	HAV IgM antibody
Erythrocytes (RBCs – red blood cells)	**Hepatis B virus (HBV) testing:**
Leukocytes (WBCs – white blood cells)	Hepatitis B surface antigen (HbsAg)
Differential:	Hepatitis B surface antibody (anti-HBs)
Neutrophils, segmented	Hepatitis B core total antibody (anti-HBc)
Lymphocytes	Hepatitis B core IgM antibody
Monocytes	HBV DNA [b]
Basophils	**Hepatis C virus (HCV) testing:**
Eosinophils	HCV antibody
Platelets	HCV RNA[b]
Cell morphology (RBC and WBC)	**Hepatitis D virus (HDV) testing:**
Hepatic Clinical Chemistry Panel	HDV antibody
Total bilirubin	**Hepatitis E virus (HEV) testing:**
Direct bilirubin	HEV IgG antibody
Alkaline phosphatase (ALP)	HEV IgM antibody
Alanine aminotransferase (ALT)	HEV RNA [b]
Aspartate aminotransferase (AST)	**Anti-nuclear antibody (ANA)**
Gamma-glutamyl transferase (GGT)	**Anti-smooth muscle antibody (ASMA)** [a]
Creatine kinase (CK)	**Anti-actin antibody** [c]
Hepatic Coagulation Panel	**Immunoglobulin IgA (quantitative)**
Prothrombin time, INR (PT-INR)	**Immunoglobulin IgG (quantitative)**
Urine Chemistry	**Immunoglobulin IgM (quantitative)**
Drug screen	**Epstein-Barr virus (EBV) testing:**
Haptoglobin	EBV antibody
Tests assayed ONLY by investigator-designated local laboratory	
Acetaminophen	**Cytomegalovirus (CMV) testing:**
Acetaminophen protein adducts	CMV antibody
Alkaline phosphatase isoenzymes	CMV DNA [b]
Ceruloplasmin	**Herpes simplex virus (HSV) testing:**
Copper	HSV (Type 1 and 2) antibody
Ethyl alcohol (EtOH)	HSV (Type 1 and 2) DNA [b]
Phosphatidylethanol (Peth)	Liver kidney microsomal type 1 (LKM-1) antibody
Urine Chemistry	**Microbiology**

Tests assayed ONLY by investigator-designated local laboratory	
Ethyl glucuronide (EtG)	Culture:
Epstein-Barr virus (EBV) testing:	Blood
EBV DNA[b]	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.

10.7. Appendix 7: 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), 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, Lp(a), ApoB, hsCRP, and the lipid panel.

Study intervention and ancillary supplies (including participant diaries)

When a participant is unable to go to the site to receive study supplies 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 such as an infusion center.

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 supplies.
- When delivering supplies 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 supplies.

If study intervention will be administered to the participant during a mobile healthcare visit or at an alternate location, these additional requirements must be met:

- Only authorized study personnel may supply, prepare, or administer study intervention.
- Follow all other requirements that are consistent with the main protocol.

Screening period guidance

To ensure safety of study participants, laboratory values, and other eligibility assessments taken at prescreening and screening visits 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 the screening visit.

  - 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 visits 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, visits type, and conducted activities were affected by exceptional circumstances. Dispensing or 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.

10.8. Appendix 8: Abbreviations and Definitions

Term	Definition
AC	assessment committee
ACC	American College of Cardiology
ADA	anti-drug antibodies
AE	adverse event
AHA	American Heart Association
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
Apo(a)	apolipoprotein(a)
ApoB	apolipoprotein B
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
AUC	area under the curve
blinding/masking	A double-blind study is one in which neither the participant nor any of the investigators or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
CAD	coronary artery disease
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMV	cytomegalovirus
Companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product.
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.

CONSORT	Consolidated Standards of Reporting Trials
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.
CSR	clinical study report
CT	computerized tomography
CTA	Clinical Trial Agreement
D. Bil	direct bilirubin
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
ECG	electrocardiogram
ED	early discontinuation
EDC	electronic data capture system
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.
ERCP	endoscopic retrograde cholangiopancreatography
EU	European Union
FAS	Full Analysis Set
GCP	good clinical practice
GGT	gamma-glutamyltransferase
HbA1c	hemoglobin A1c
HBV	hepatitis B virus
HbcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDV	hepatitis D virus
HIV	human immunodeficiency virus

hsCRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committees
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.
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 or locked.
INR	international normalized ratio
investigational product	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	Institutional Review Board
ISR	injection site reaction
IWRS	interactive web-response system
Lp(a)	lipoprotein(a)
MACE	major adverse cardiac events
MedDRA	Medical Dictionary for Regulatory Activities

medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication errors generally involve a failure to uphold one or more of the five "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core five rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
Misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
MMRM	mixed model for repeated measures
MRCP	magnetic resonance cholangiopancreatography
OTC	over the counter
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
PCR	polymerase chain reaction
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	pharmacodynamics
PK	pharmacokinetics
PT-INR	prothrombin time-INR
QTc	corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
QTL	quality tolerance limit
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan

SC	subcutaneous
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.
siRNA	small interfering ribonucleic acid
SNP	single-nucleotide polymorphism
SoA	Schedule of Activities
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.
ULN	upper limit of normal
WNOCBP	women not of childbearing potential
WOCBP	women of childbearing potential

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