Protocol J2O-MC-EKBC (Initial Version)

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

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Approval Date: 28-Jul-2022

Title Page

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Protocol Number: J2O-MC-EKBC

Amendment Number: This is the initial protocol.

Compound: LY3473329

Brief Title:

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

Study Phase: 2

Acronym: KRAKEN

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s):

IND: 155551

EU trial number: 2022-501466-21-00

Document ID: VV-CLIN-070060

Approval Date: Protocol Electronically Signed and Approved by Lilly on date provided below.

Medical Monitor Name and Contact Information will be provided separately.

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1. Protocol Summary

1.1. Synopsis

Protocol Title:

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

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

Regulatory Agency Identifier Number(s):

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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). LY3473329 is an orally administered disrupter of Lp(a) formation and has been shown to reduce Lp(a) in preclinical studies. In Phase 1 Study J2O-MC-EKBA (EKBA) with oral dosing of LY3473329 once-daily for 14 days, Lp(a) was significantly decreased and no safety issues were identified. This Phase 2 study aims to investigate the impact of a range of LY3473329 doses for 3 months on Lp(a) level and on safety in a larger population of participants with elevated Lp(a) and high risk for cardiovascular events to enable Phase 3 development of this compound.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
• To evaluate if LY3473329 is superior to placebo in percent Lp(a) reduction	• Percent change in Lp(a) from baseline to Week 12
Secondary	
• Compare proportion of participants on LY3473329 versus placebo achieving Lp(a) threshold levels	• Proportion of participants achieving Lp(a) <125 nmol/L at Week 12
• Compare the effect of LY3473329 to placebo on cardiovascular biomarkers	• Percent change from baseline to Week 12 for o ApoB o hsCRP

Objectives	Endpoints
• Characterize the PK of LY3473329	• 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 intervention difference in percent change from baseline in Lp(a) after 12 weeks of study intervention in participants who meet the enrollment criteria and would have completed the treatment period?

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

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of LY3473329 doses with placebo irrespective of adherence to study intervention, including data collected during the treatment period and safety follow-up.

Overall Design

Study J2O-MC-EKBC (EKBC) is a parallel, double-blinded, placebo-controlled, dose-finding, Phase 2 study of LY3473329 in participants with elevated Lp(a) and at high risk for cardiovascular events.

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

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

Brief Summary:

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

Study details include:

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

Number of Participants:

Approximately 233 participants will be randomly assigned to study intervention.

Intervention Groups and Duration:

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

	Arm A	Arm B	Arm C	Arm D
Intervention Name	LY3473329 and placebo	LY3473329 and placebo	LY3473329	Placebo
Dose Formulation	Tablet	Tablet	Tablet	Tablet
Dosage Levels				
LY3473329	10 mg (1 tablet, 10 mg)	60 mg (1 tablet, 60 mg)	240 mg (4 tablets, 60 mg)	0 tablets
Placebo	3 tablets	3 tablets	0 tablets	4 tablets
Frequency	QD	QD	QD	QD
Route of Administration	PO	PO	PO	PO
Authorized as defined by EU Clinical Trial Regulation	Not authorized in EU	Not authorized in EU	Not authorized in EU	Not authorized in EU

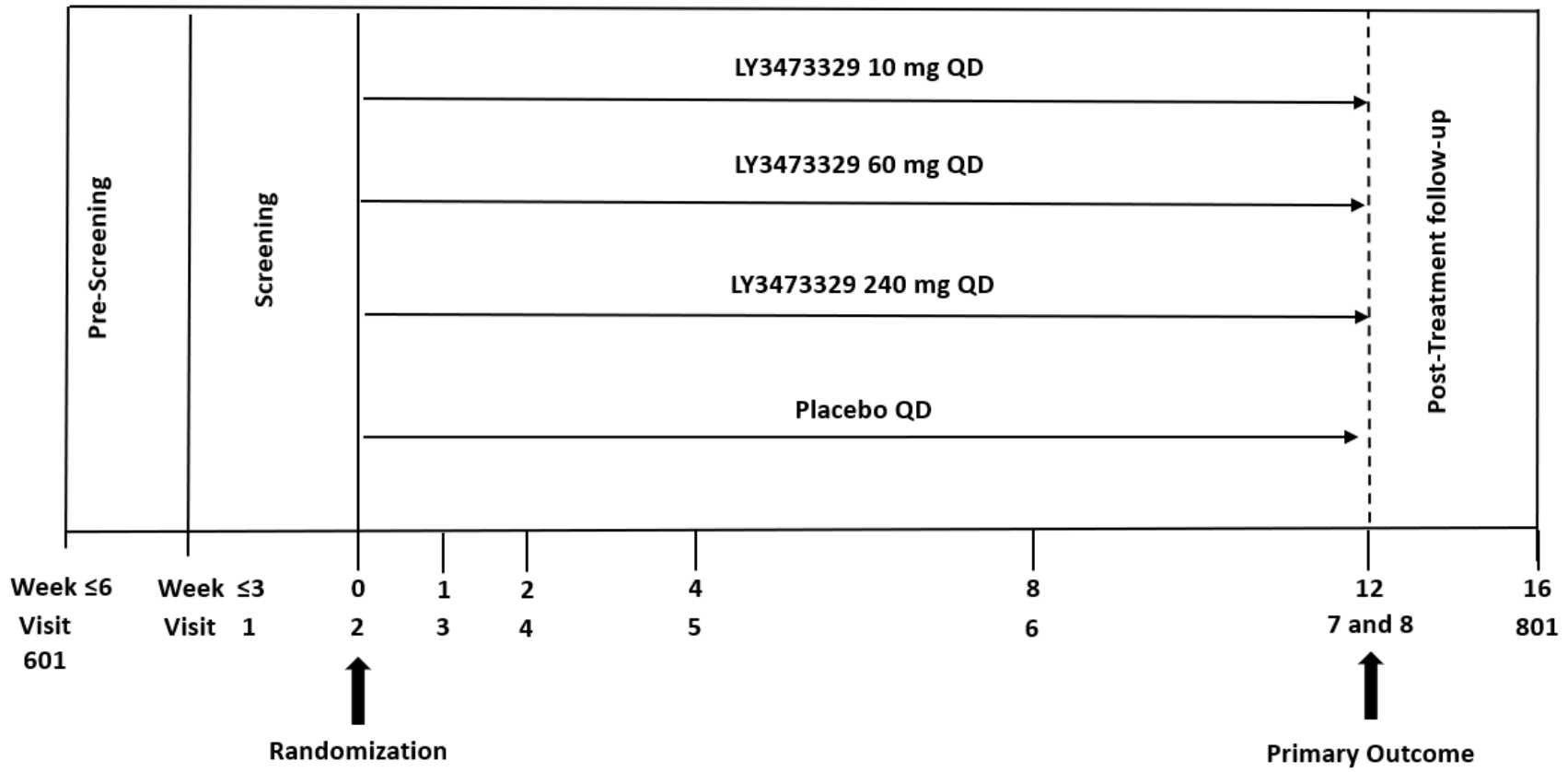
Abbreviations: EU = European Union; PO = by mouth; QD = once daily

Ethical Considerations of Benefit/Risk:

Scientists believe that Lp(a) is a harmful kind of cholesterol. The study drug is likely to lower Lp(a) while it is being taken, and this effect will go away after the study drug is stopped. Studies of the study drug performed so far in animals and in people do not show harmful effects.

Data Monitoring Committee: No

1.2. Schema



Abbreviation: QD = once daily.

NOTE: Optional Pre-Screening for participants to evaluate Lp(a) requirements for inclusion.

1.3. Schedule of Activities (SoA)

Period I - Optional Pre-screening: 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 insufficiently high Lp(a) at Visit 1 will not be eligible for enrollment, despite their values in prescreening. A pre-screening visit occurring longer or shorter than 3 weeks (21 days) 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 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 IV - Post Treatment Follow-Up: After completing Visits 7 and 8, there will be a follow-up Visit 801 approximately 4 weeks after discontinuing study intervention. This 4-week duration is greater than 5 times the effective half-life of the drug and thus will support adequate drug washout.

Additionally, laboratory assessments at Visit 801 will provide information about the pharmacodynamic (PD) offset of study intervention on Lp(a).

	Period I - Pre-Screening	Period II - Screening	Period III - Treatment Period								Period IV - Post-Treatment Follow-Up	
Visit number	601	1	2	3	4	5	6	7	8	ED	801	
Weeks from randomization	≤6	≤3	—	1	2	4	8	12	12*	—	4 weeks from last dose	*Visit 8 occurs 1-3 days after final dose
Visit interval tolerance (days)	See Section 1.3	—	—	±2	±3	±3	±4	±4	—	—	±5	
Fasting Visit		X	X	X	X	X	X	X				If a participant arrives not fasted, schedule the laboratory draw for another date. See Section 5.3.1.
Pre-Screening 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.
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.
Prespecified medical history (indication and history of interest)		X										Prespecified medical history includes indication and 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										
Concomitant medications		X	X	X	X	X	X	X		X	X	Additional data will be collected for medications of interest.

	Period I - Pre-Screening	Period II - Screening	Period III - Treatment Period								Period IV - Post-Treatment Follow-Up	
Visit number	601	1	2	3	4	5	6	7	8	ED	801	
Weeks from randomization	≤6	≤3	—	1	2	4	8	12	12*	—	4 weeks from last dose	*Visit 8 occurs 1-3 days after final dose
Visit interval tolerance (days)	See Section 1.3	—	—	±2	±3	±3	±4	±4	—	—	±5	
Fasting Visit		X	X	X	X	X	X	X				If a participant arrives not fasted, schedule the laboratory draw for another date. See Section 5.3.1.
AEs	X	X	X	X	X	X	X	X		X	X	Any events that occur after signing the informed consent are considered AEs as defined (Section 10.3). Additional data are collected for certain AEs.
Physical Evaluation												
Height		X										Participant should remove shoes.
Weight		X	X					X		X		Participant should remove shoes.
Vital signs		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										The physical examination is performed (excludes pelvic, rectal, and breast examinations unless clinically indicated).
Symptom-directed physical assessment			X (refer to comment)									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.

	Period I - Pre-Screening	Period II - Screening	Period III - Treatment Period								Period IV - Post-Treatment Follow-Up	
Visit number	601	1	2	3	4	5	6	7	8	ED	801	
Weeks from randomization	≤6	≤3	—	1	2	4	8	12	12*	—	4 weeks from last dose	*Visit 8 occurs 1-3 days after final dose
Visit interval tolerance (days)	See Section 1.3	—	—	±2	±3	±3	±4	±4	—	—	±5	
Fasting Visit		X	X	X	X	X	X	X				If a participant arrives not fasted, schedule the laboratory draw for another date. See Section 5.3.1.
12-Lead ECG (local)		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.
Participant Diary (paper)												
Study drug administration log dispensed			X	X	X	X	X					
Study drug administration log return (by participant)				X	X	X	X	X		X		
Study drug administration log review				X	X	X	X	X		X		
PROs (Paper) *Complete prior to any clinical administered assessments*												
SF-36 v2 acute			X					X		X		
Participant Education												
Study drug administration log education and completion			X									Additional education can be provided as appropriate based on participants needs. Participants should be trained to get one pill from each bottle and should do this themselves at Visit 2 under supervision.

	Period I - Pre-Screening	Period II - Screening	Period III - Treatment Period								Period IV - Post-Treatment Follow-Up	
Visit number	601	1	2	3	4	5	6	7	8	ED	801	
Weeks from randomization	≤6	≤3	—	1	2	4	8	12	12*	—	4 weeks from last dose	*Visit 8 occurs 1-3 days after final dose
Visit interval tolerance (days)	See Section 1.3	—	—	±2	±3	±3	±4	±4	—	—	±5	
Fasting Visit		X	X	X	X	X	X	X				If a participant arrives not fasted, schedule the laboratory draw for another date. See Section 5.3.1.
Laboratory Tests and Sample Collections												
Hematology		X	X	X	X	X	X	X		X	X	
Clinical chemistry		X	X	X	X	X	X	X		X	X	
Lipid panel		X	X			X	X	X		X	X	
Urinalysis		X				X		X		X		
UACR		X						X		X		
Serum pregnancy		X						X		X	X	Only for WOCBP. See Appendix 10.4.
Urine pregnancy (local)			X			X	X					Collect for WOCBP only. Done locally and prior to administering study intervention. OR Additional pregnancy tests (beyond those required per the SoA) should be performed at any time during the trial if a menstrual period is missed or there is clinical suspicion of pregnancy. See Appendix 10.4. If required per local regulations and/or institutional guidelines, pregnancy testing can occur at other times during the study treatment period.
FSH		X										Optional; performed as needed to confirm postmenopausal status. See Appendix 10.4.
TSH		X										
HbA1c		X										

	Period I - Pre-Screening	Period II - Screening	Period III - Treatment Period								Period IV - Post-Treatment Follow-Up	
Visit number	601	1	2	3	4	5	6	7	8	ED	801	
Weeks from randomization	≤6	≤3	—	1	2	4	8	12	12*	—	4 weeks from last dose	*Visit 8 occurs 1-3 days after final dose
Visit interval tolerance (days)	See Section 1.3	—	—	±2	±3	±3	±4	±4	—	—	±5	
Fasting Visit		X	X	X	X	X	X	X				If a participant arrives not fasted, schedule the laboratory draw for another date. See Section 5.3.1.
Lp(a)	X	X	X	X	X	X	X	X		X	X	
ApoB		X	X			X	X	X		X	X	
Plasminogen activity		X	X	X	X	X	X	X		X	X	
hsCRP		X	X	X	X	X	X	X		X	X	
HIV screening test		X										
HCV screening test		X										If HCV antibody test is positive, it must be followed by a HCV RNA test. See Section 8.2.6.
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 8.2.5.
eGFR		X						X		X		Calculated using CKD-EPI method.
PK sample (predose)			X	X	X		X	X				See Section 6.1 for dosing instructions and Section 8.4.
PK sample (postdose)			X			X			X			Post-dose PK sample at the following times: • Visit 2: 1 to 2 hours after dose • Visit 5: 4 to 6 hours after dose • Visit 8: 1-3 days after final dose Fasting not required for Visit 5 post-dose PK sample.
PK sample (random)										X	X	See Section 8.4.

	Period I - Pre-Screening	Period II - Screening	Period III - Treatment Period								Period IV - Post-Treatment Follow-Up	
Visit number	601	1	2	3	4	5	6	7	8	ED	801	
Weeks from randomization	≤6	≤3	—	1	2	4	8	12	12*	—	4 weeks from last dose	*Visit 8 occurs 1-3 days after final dose
Visit interval tolerance (days)	See Section 1.3	—	—	±2	±3	±3	±4	±4	—	—	±5	
Fasting Visit		X	X	X	X	X	X	X				If a participant arrives not fasted, schedule the laboratory draw for another date. See Section 5.3.1.
Stored Samples												
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	
Randomization and Dosing												
Register visit with IWRS		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	X					
Participant take study intervention at site			X									First dose of study intervention must be taken at site. For other visits, participants may take study invention at site provided they meet PK sample timepoints.
Dispense study intervention to participant			X			X	X					At Visits 3 and 4, study intervention will be assessed for compliance and returned to the participant.
Participant returns study intervention				X	X	X	X	X		X		
Assess study intervention compliance				X	X	X	X	X		X		

Abbreviations: AE = adverse event; ApoB = apolipoprotein b; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; 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); PI = principle investigator; PK = pharmacokinetic; PRO = Patient-Reported Outcomes; RNA = ribonucleic acid; SoA = Schedule of Activities; TSH = thyroid stimulating hormone; UACR = urine albumin creatinine ratio; WOCBP = women of childbearing potential.

2. Introduction

LY3473329 is a small molecule that disrupts the binding of apolipoprotein(a) (apo[a]) to apolipoprotein B (ApoB) of low-density lipoprotein (LDL) particles, decreasing the formation and plasma steady-state levels of lipoprotein(a) (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). LY3473329 is an orally administered disrupter of Lp(a) formation and has been shown to reduce Lp(a) in preclinical studies. In Phase 1 Study J2O-MC-EKBA (EKBA) with oral dosing of LY3473329 once-daily for 14 days, Lp(a) was significantly decreased and no safety issues were identified. This Phase 2 study aims to investigate the impact of a range of LY3473329 doses for 3 months on Lp(a) level and on safety in a larger population of participants with elevated Lp(a) and high risk for cardiovascular events 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 an LDL-like particle linked via a disulfide bond to apo(a).

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).

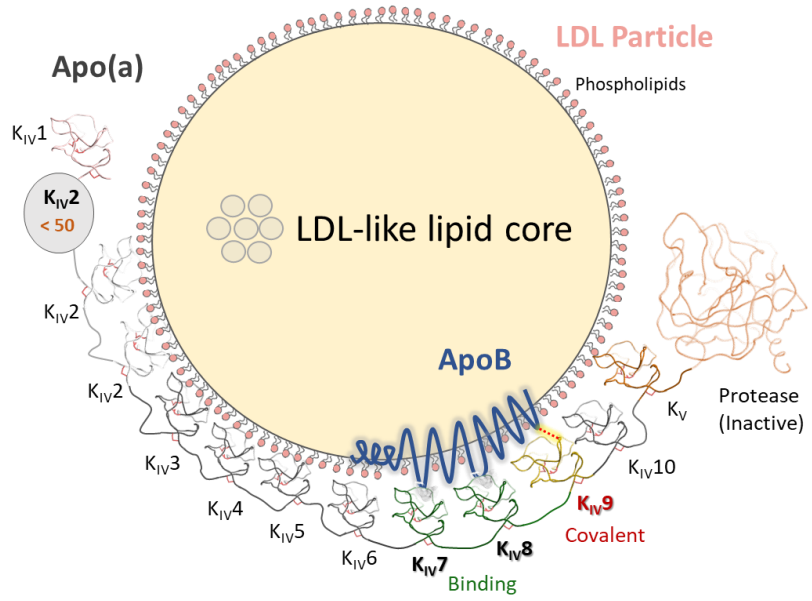


Figure 1. Representation of Lp(a) particle.

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

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; Min et al. 1997; Noma et al. 1994).

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 Cardiologists 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 et al. 2014), but are not approved treatments for Lp(a) reduction. Novel treatments to reduce Lp(a) are under investigation, including an antisense oligonucleotide (IONIS-APO(a)-LRx), and 2 siRNA therapies (olpasiran and SLN360), which have been shown to lower Lp(a) concentrations in clinical trials (Viney et al. 2016; Ference 2022; Koren et al. 2022).

2.2.4. Introduction to LY3473329

LY3473329 binds Apo(a) KIV7/8 domains causing disruption of Lp(a) particle formation in vivo. LY3473329 reduces steady-state levels of Lp(a) in both a mouse model transgenic for human apo(a) and ApoB, and in cynomolgus monkeys that endogenously express Lp(a).

LY3473329 was assessed in nonclinical toxicology studies. In summary, up to a daily oral dose of 1000 mg/kg, no adverse effects were observed in rats or monkeys.

In Phase 1 Study EKBA of participants treated with LY3473329 doses up to 800 mg/day for 14 days, Lp(a) was lowered while there were no clinically relevant changes in plasminogen activity.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of LY3473329 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 LY3473329 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 LY3473329 show no notable adverse drug effects. Finally, human phase 1 Study EKBA showed that single and multiple LY3473329 doses up to 800 mg/day were safe and generally well tolerated by healthy male and female participants. A preclinical finding of LY3473329 showed lowering of plasminogen without any associated

toxicological sequelae, but there were no clinically relevant changes in plasminogen activity in humans.

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, LY3473329 decreased Lp(a). Chronic lowering of Lp(a) is anticipated to have beneficial effects on cardiovascular disease; however, the relatively short-term lowering of Lp(a) in this study may be insufficient to confer any benefits. 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 LY3473329 is superior to placebo in percent Lp(a) reduction	• Percent change in Lp(a) from baseline to Week 12
Secondary	
• Compare proportion of participants on LY3473329 versus placebo achieving Lp(a) threshold levels	• Proportion of participants achieving Lp(a) <125 nmol/L at Week 12
• Compare the effect of LY3473329 to placebo on cardiovascular biomarkers	• Percent change from baseline to Week 12 for o ApoB o hsCRP
• Characterize the PK of LY3473329	• Population PK parameters
Exploratory	
• Compare proportion of participants on LY3473329 versus placebo achieving absolute lowering of Lp(a) threshold	• Proportion of participants achieving Lp(a) lowering of at least 150 nmol/L at Week 12
• To compare the effect of LY3473329 versus placebo on plasminogen	• Change in plasminogen activity
• Compare the lipid profile in response to LY3473329 versus placebo	• Lipid profile o LDL o total cholesterol o HDL o triglycerides
• Health-related quality of life	• SF-36v2 acute form domain scores

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

Primary estimand

The primary clinical question of interest is: What is the intervention difference in percent change from baseline in Lp(a) after 12 weeks of study intervention in participants who meet the inclusion criteria and would have completed the treatment period?

The efficacy 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 to Week 12 in Lp(a).

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

The intercurrent event "intervention discontinuation for any reason" is addressed by the hypothetical strategy, and the potential outcome of interest is the response in the efficacy measurement if participants had adhered to the randomized treatment. There are no remaining intercurrent events.

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

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

Rationale for estimand: This Phase 2 study aims to study the efficacy of LY3473329 under the ideal condition that all participants adhere to the randomized treatment.

A similar 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 LY3473329 doses with placebo irrespective of adherence to study intervention, including data collected during the treatment period and safety follow-up.

Secondary estimand

The primary clinical question of interest is: What is the intervention difference in percent change from baseline in Lp(a) after 12 weeks of study intervention in participants who meet the inclusion criteria regardless of treatment discontinuation for any reason?

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 to Week 12 in Lp(a).

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

The intercurrent event "intervention discontinuation for any reason" is addressed by the treatment-regimen strategy, and the potential outcome of interest is the response in the efficacy measurement regardless of whether participants had adhered to the randomized treatment. There are no remaining intercurrent events.

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

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

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

4. Study Design

4.1. Overall Design

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

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

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

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 maximum number of participants entered based on familial hypercholesterolemia or type 2 diabetes is approximately 93 (40%).

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

4.2. Scientific Rationale for Study Design

Previously completed Phase 1 Study EKBA showed a decrease in Lp(a) in healthy participants with Lp(a) levels ≥75 nmol/L or ≥30 mg/dL given LY3473329 for 14 days. The current study is intended to be Phase 3 enabling as it will provide the following information:

- Efficacy and safety data with daily oral administration of study drug for 12 weeks. This duration is anticipated to provide information regarding the maximal lowering of Lp(a) with LY3473329 and information regarding an appropriate dose of study drug for Phase 3. The primary endpoint is at 12 weeks, a time anticipated to achieve nadir levels of Lp(a) lowering.
- Participants for this study will have Lp(a) ≥175 nmol/L at baseline and have high risk for cardiovascular events. This study will thus provide relevant efficacy and safety for participants appropriate for a Phase 3 cardiovascular outcomes trial.

The study includes an optional pre-screening Visit 601 where potential participants can be pre-screened with an assessment of Lp(a).

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

The follow-up visit after the last dose of study drug is to capture any additional safety signals and to quantitate the return to baseline for Lp(a).

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 to assess variable response in safety and/or efficacy based on these variables.

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

LY3473329 doses of 10 mg, 60 mg, and 240 mg, administered orally QD, were selected based on the following:

- Safety and tolerability of LY3473329 doses up to 800 mg in healthy participants in the Phase 1 Study EKBA
- 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 LY3473329 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.

The maximum number of participants entered based on familial hypercholesterolemia or type 2 diabetes is approximately 93 (40%).

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. High risk for cardiovascular events defined as documented coronary artery disease (CAD), stroke, or peripheral artery disease or atherosclerotic cardiovascular disease (ASCVD) risk equivalents (familial hypercholesterolemia or type 2 diabetes).
   - CAD documentation should include at least 1 of the following:
     a. angiographic evidence of ≥50% stenosis of 1 or more major epicardial coronary arteries
     b. Coronary Artery Calcification Agatston score on computerized tomography (CT) scan of ≥300
     c. history of myocardial infarction documented by positive enzymes, and either symptoms of myocardial ischemia, or electrocardiogram (ECG) changes (Thygesen et al. 2012)
     d. history of coronary revascularization
     e. evidence of cardiac ischemia on exercise testing or imaging study.
   - Stroke (an acute episode of focal cerebral, spinal, or visual dysfunction caused by infarction of central nervous system tissue) documentation should include CT scan, magnetic resonance imaging, or other visualization method. Transient ischemic attack or embolic stroke (not of atherosclerotic origin) are not qualifying events.
   - Peripheral artery disease documentation should include intermittent claudication with an ankle-brachial index ≤0.90 and/or limb amputation or revascularization due to lower limb ischemia. Thromboangiitis obliterans is not a qualifying event.
4. 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 post-treatment follow-up period:

a. lipid-lowering drugs (e.g., 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

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

Sex and Contraceptive/Barrier Requirements

6. Male and/or female
   a. Males who agree to use highly effective or effective methods of contraception may participate in this trial. Please refer to Appendix 10.4 for definitions and additional guidance related to contraception.
   b. Women of childbearing potential (WOCBP) who agree to use highly effective or effective methods of contraception and women not of childbearing potential (WNOCBP) may participate in this trial. See Appendix 10.4 for definitions and additional requirements 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

7. Capable of giving signed informed consent as described in Appendix 10.1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Other Inclusions

8. Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures, including willing and able to take four 12-mm round concave tablets of study drug every day for 12 weeks, 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

9. 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.

10. 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.
11. 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.
12. 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.
13. New York Health Association Class III or IV heart failure or last known left ventricular ejection fraction <30%.
14. Active or acute infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Visit 2.
15. 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.
16. Recent history of, or current drug or alcohol abuse in the opinion of the investigator.
17. Have 2 or more clinically significant or severe drug allergies, or severe post-treatment hypersensitivity reactions, including, but not limited to
    a. erythema multiforme major
    b. linear immunoglobulin A dermatosis
    c. toxic epidermal necrolysis
    d. exfoliative dermatitis.
18. Hypersensitivity to the active substance or to any of the excipients.
19. Have a current infection with hepatitis B virus (HBV), that is, positive for hepatitis B surface antigen (HBsAg) and/or PCR positive for HBV deoxyribonucleic acid (DNA) (Section 8.2.5).
20. Have a current infection with hepatitis C virus (HCV), that is, positive for HCV ribonucleic acid (RNA) (Section 8.2.6).
21. Have human immunodeficiency virus (HIV) infection.

Prior/Concomitant therapy

22. Lipoprotein apheresis within 3 months of Visit 1, or planned during the study.
23. 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.
24. Treatment with any investigational oligonucleotide or siRNA within 9 months of Visit 1.

Prior/Concurrent Clinical Study Experience

25. 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

26. Clinically significant abnormalities in screening laboratory values that would render a participant unsuitable for inclusion in the opinion of the investigator.
27. 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

28. Are Lilly employees, or are employees of any third party involved in a study that requires exclusion of their employees.
29. 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.
30. Are pregnant, or intend to become pregnant or to breastfeed during the study.
31. 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 the Visits 1-7. Routine blood chemistry and urine samples should be taken after fasting for at least 10 hours. Fasting is not required for the Visit 5 post-dose PK sample. During preparation for fasting samples, the participant can drink water and they should ensure that they consume sufficient water so they do not become dehydrated. It is not necessary to fast for Visits 601, Visit 8, 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

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

	Arm A	Arm B	Arm C	Arm D
Intervention Name	LY3473329 and placebo	LY3473329 and placebo	LY3473329	Placebo
Dose Formulation	Tablet	Tablet	Tablet	Tablet
Dosage Levels				
LY3473329	10 mg (1 tablet, 10 mg)	60 mg (1 tablet, 60 mg)	240 mg (4 tablets, 60 mg)	0 tablets
Placebo	3 tablets	3 tablets	0 tablets	4 tablets
Frequency	QD	QD	QD	QD
Route of Administration	PO	PO	PO	PO
Authorized as defined by EU Clinical Trial Regulation	Not authorized in EU	Not authorized in EU	Not authorized in EU	Not authorized in EU

Abbreviations: EU = European Union; PO = by mouth; QD = once daily.

LY3473329 and placebo tablets will be taken orally with approximately 240 mL of water at approximately the same time, preferably in the morning, each dosing day. On specific visit days, participants will be required to not take the drug at home and follow directions provided by the site on when to take the drug after they arrive at the clinical site.

Participants should be trained to get one pill from each bottle and should do this themselves at Visit 2 under supervision.

6.2. Preparation, Handling, Storage, and Accountability

- The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- 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.
- The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.

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 country and baseline Lp(a) (<275 nmol/L, ≥275 nmol/L). 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 at the study visits summarized in SoA.

Returned study intervention should not be re-dispensed to the participants.

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.

6.4. Study Intervention Compliance

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning and counting returned tablets and documented in the source documents and case report form (CRF).

A record of the number of study intervention tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays, will also be recorded in the CRF.

6.5. Dose Modification

This protocol does not allow dose adjustments.

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

LY3473329 will not be made available to participants after completion of the study.

6.7. Treatment of Overdose

For this study, any dose of LY3473329 greater than the planned dose will be considered an overdose.

The 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, and
- 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 14 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 post-treatment follow-up period, unless changes need to be made because of AEs:

- lipid-lowering drugs (e.g., 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 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 to complete procedures for an ED visit and post-treatment follow-up, if applicable, 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 8.2.5) or tests positive for HCV RNA (Section 8.2.6).

  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

The study drug should be interrupted or discontinued if 1 or more of these conditions occur:

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

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; INR = international normalized ratio; TBL = total bilirubin; ULN= upper limit of normal.

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, non-drug etiology is identified.

7.1.2. QTc Stopping Criteria

If a clinically significant finding is identified, including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula (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 ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.3. Temporary Discontinuation

If for some reason, study intervention is temporarily stopped for reasons other than safety, participant should resume intervention as soon as possible.

7.1.4. Rechallenge

If study intervention is temporarily stopped for safety, participants may be rechallenged with study intervention once if appropriate in the opinion of the investigator.

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 ED visit and post-treatment follow-up, if applicable, 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

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 nmol/L at Week 12 will be assessed.

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

- ApoB
- hsCRP

See Section 9.3 for definitions of the efficacy endpoints.

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 PR, 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 or within 4 weeks 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 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, TBL, direct bilirubin (D. Bil), gamma-glutamyltransferase (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 1 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 participants with Gilbert's syndrome
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥1.5x baseline, except for participants with Gilbert's syndrome

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 over the counter), 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 laboratory 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 1 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 participants with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline with hepatic signs/symptoms[a], or ALT or AST ≥3x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥2x baseline (except for participants with Gilbert's syndrome)

[a] Hepatic signs or 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 (PT)-INR; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study, for example, ultrasound or CT scan.

Based on the participant'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, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.

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

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. 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.

8.2.5. 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.

8.2.6. 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.

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

The definitions of the following events can be found in Appendix 10.3:

- AEs
- SAEs, and
- 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 or 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
SAE[a] – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	At least 65 days after the last dose of study intervention	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 post-study 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 or be withdrawn from the study. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.3.3. 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,
- cerebrovascular events, including cerebrovascular accident (stroke) and transient ischemic attack,
- cardiogenic shock,
- resuscitated sudden death,
- peripheral revascularization procedure, and
- peripheral arterial event.

8.4. Pharmacokinetics

- At the visits and times specified in the SoA (Section 1.3), blood samples will be collected to determine the LY3473329 plasma concentrations.
- 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.
- The pre-dose sample at Visit 2 can be taken between waking up and dosing. On subsequent dosing days, pre-dose samples should be obtained no more than 1 hour prior to dosing.
- A maximum of 3 additional PK samples may be drawn at other time points during the study, if warranted and agreed upon by both the investigator and the sponsor. A PK sample should be obtained at the ED visit, if applicable and the follow-up visit.
- Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.
- A validated assay will be used to determine plasma LY3473329 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 Pharmacodynamic properties of LY3473329 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 LY3473329, pathways associated with lipid metabolism, mechanism of action of LY3473329, 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

Immunogenicity is not evaluated in this study.

8.9. Health Economics

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

9. Statistical Considerations

The statistical analysis plan (SAP) will be finalized prior to first participant first visit, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and secondary endpoints.

9.1. Statistical Hypotheses

The study hypothesis for the primary objective is that oral QD administration of LY3473329 10 mg, 60 mg, or 240 mg is superior to placebo in percent change from baseline for Lp(a) at Week 12 in participants with elevated Lp(a) and at high risk for cardiovascular events at baseline.

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.
Efficacy Analysis Set (EAS)	Data obtained during treatment period from all randomly assigned participants who are exposed to at least 1 dose of double-blind study treatment. Excludes data after discontinuation of study drug and for participants inadvertently enrolled. Participants will be included in the treatment group to which they were randomly assigned.
Full Analysis Set (FAS)	Data obtained during the treatment period from all randomly assigned participants who are exposed to at least 1 dose of intervention, regardless of adherence to intervention. Excludes data for participants inadvertently enrolled. Participants will be included in the treatment group to which they were randomly assigned.
Safety Analysis Set (SS)	Data obtained during the treatment period plus safety follow-up from all randomly assigned participants who are exposed to at least 1 dose of intervention, regardless of adherence to intervention. Participants will be included in the treatment group to which they were randomly assigned.

9.3. Statistical Analyses

9.3.1. General Considerations

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

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP or the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

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

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

Primary estimand of interest and efficacy assessment

The primary estimand is a precise definition of the treatment effect to be estimated. The primary estimand of interest is comparing efficacy of LY3473329 doses to placebo and is named the "efficacy estimand" (Section 3). The efficacy estimand represents the efficacy prior to discontinuation of intervention. The primary efficacy assessment guided by the efficacy estimand will be conducted using the EAS (Section 9.2).

Secondary estimand of interest

The secondary estimand of interest is comparing efficacy of LY3473329 doses to placebo and is named the "treatment-regimen estimand" (Section 3). The treatment-regimen estimand represents the efficacy regardless of discontinuation of intervention. The secondary efficacy assessment guided by the treatment-regimen estimand will be conducted using the FAS (Section 9.2).

Safety assessments

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of LY3473329 doses with placebo irrespective of adherence to intervention. Thus, safety analyses will be conducted using the SS (Section 9.2).

Exploratory analyses

Additional exploratory analyses may be performed as deemed appropriate. Details will be provided in the SAP.

Continuous data

Continuous data will be summarized using the sample size, mean, SD, median, minimum, and maximum. The analysis model to make comparisons among treatment groups relative to continuous measurements assessed over time, in addition to the baseline and end-of-treatment measurements, will be a mixed model for repeated measures (MMRM).

The model terms are

- treatment
- visit
- treatment-by-visit interaction
- baseline-by-visit interaction
- baseline measurement
- baseline Lp(a) stratum (<275 nmol/L, ≥275 nmol/L), and
- country or region.

Analysis of covariance (ANCOVA) may be used to make comparisons among treatment groups for continuous measurements with only 1 post-baseline assessment. In this case, ANCOVA will be conducted with available data and missing values will not be imputed in the analysis.

Categorical data

Categorical data will be summarized by sample size, frequency, and percentage. Fisher's exact test will be used to examine the treatment difference in categorical outcomes. Logistic regression may be used to examine the treatment difference in binary efficacy outcomes. The negative binomial regression model may be used for the treatment comparison of discrete count measures if deemed appropriate. Participant-specific random effects may be added to the logistic and the negative binomial regression models if longitudinal measurements are available. Model terms in the longitudinal logistic or negative binomial regression models are the same as in the MMRM.

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

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/Estimand Analysis

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

For the efficacy estimand, the hypothetical strategy is used to handle the intercurrent events of permanent discontinuation of intervention. The "treatment-regimen" estimand, which represents the efficacy regardless of treatment discontinuation, may also be used to compare the primary efficacy of LY3473329 doses with placebo. The analysis guided by the "treatment-regimen" estimand will use the FAS.

The primary efficacy comparison will be based on the contrast between each treatment group of LY3473329 and placebo for the mean percent change of Lp(a) from randomization at Visit 2 to Week 12 at Visit 7.

The primary analyses model will be MMRM as described in Section 9.3.1. The Lp(a) will be log transformed before statistical analyses, and then back-transformed to present percentage change from baseline. Treatment comparisons will be performed at the full significance level of 0.05. Additional covariates may be added, and this analysis will be detailed in the SAP.

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

Secondary endpoints are listed in Section 3.

The efficacy analyses for the secondary endpoints will use the EAS described in Section 9.3.1.

The continuous clinical measures, including change in ApoB and hsCRP, may be log transformed before statistical analyses, if deemed necessary. Analyses will be conducted in a manner similar to the primary efficacy analyses discussed in Section 9.3.2.

Analyses for percentages of participants reaching Lp(a) <125 nmol/L at Week 12 will be conducted using a longitudinal logistic regression model described in Section 9.3.1. Missing Lp(a) data at Week 12 may be imputed first before conducting the analyses.

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

Exploratory endpoints are listed in Section 3.

The continuous clinical measures, including change in lipid profile and change in plasminogen activity, will be analyzed using an MMRM. Baseline measures will be used for adjustment. The change in SF-36v2 acute form domain scores will be analyzed using an ANCOVA model. Baseline domain scores will be used for adjustment. Analyses for proportion of participants achieving Lp(a) lowering of at least 150 nmol/L at Week 12 will be conducted using a longitudinal logistic regression model described in Section 9.3.1.

Details of other analyses used for the exploratory objectives will be provided in the SAP.

9.3.5. Safety Analyses

Safety assessments will be guided by an estimand comparing safety of LY3473329 doses with placebo irrespective of adherence to intervention. Thus, safety analyses will be conducted using the SS.

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

- 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. 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

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

9.3.7. Subgroup Analyses

Subgroup analyses of important factors, such as baseline SF-36v2 acute form domain scores , 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

A planned interim analysis may be conducted when at least 50% of the participants complete Week 12 at Visit 7 or discontinue the study. The 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. Study team members who have potential contact with the sites will remain blinded throughout the study. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team members before the study has been unblinded. Study sites will receive information about interim results only if deemed necessary for the safety of the participants. The study will not be stopped based on the efficacy of LY3473329 versus placebo. Therefore, there will be no inflation of the type 1 error rate, and no need to employ an alpha spending function or multiplicity adjustment.

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

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

9.5. Sample Size Determination

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

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

Assuming a standard deviation of 20%, and a 2-sided alpha level of 0.05, the completers for each treatment arm will provide >99% power to detect a treatment difference of 60% reduction for the primary endpoint of LY3473329 verses placebo. The sample size was determined appropriate to provide a sufficient amount of safety data.

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 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 (IRB)/Independent Ethics Committees (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 (CTA).

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant and is kept on file.

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

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets, or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The sponsor has processes in place to ensure data protection, information security, and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.5. Committees Structure

10.1.5.1. External Clinical Endpoints Committee

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

10.1.6. Dissemination of Clinical Study Data

Reports

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

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 dataset 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 pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined 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 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.

Additionally, clinical outcome assessment data (participant-focused outcome instrument) and other data and study drug administration log will be collected by the participant via a paper source document, and the information required from this document for completing the CRF will

be transcribed by the authorized study personnel into the EDC system and will serve as the source documentation.

Data collected via the sponsor-provided data capture system(s) 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 LY3473329 or after LY3473329 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

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	
LDL-C	Generated by Lilly-designated laboratory. If triglycerides are >400; 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.
Urine pregnancy	Assayed and evaluated locally.
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.
LY3473329 concentration	Results will not be provided to the investigative sites.
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.
Plasminogen activity	Results will 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.
Whole blood (EDTA)	

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

Abbreviations: 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; 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 = high-density lipoprotein; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein; Lp(a) = Lipoprotein(a); RBC = red blood cell; 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 pre-dose samples at the next regularly scheduled laboratory sample collection, ideally prior to the next dose after the event, to assess post-event return-to-baseline values.

Timing	Sample Type	Laboratory Test[a]
Collect from 30 minutes to 4 hours after the start of the event. ● Note: The optimal collection time is from 1 to 2 hours after the start of event.	Serum	Total tryptase
	Serum	Complements (C3)
	Plasma	Complements (C3a and C5a)
	Serum	Cytokine panel (IL-6, IL-1β, IL-10, or any cytokine panel that includes these 3 cytokines)

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

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

What information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

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

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

10.3.1. Definition of AE

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, and vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator, that is, not related to progression of underlying disease. • Exacerbation of a chronic or intermittent pre-existing 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 pre-existing 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 1 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 pre-existing 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 PCs:
  - 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 PC and as an AE/SAE.

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

AE, SAE, and Product Complaint Recording

- When an AE/SAE/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 PCs.
- There may be instances when copies of medical records for certain cases are requested by Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with a 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 and/or Product Information, for marketed products, 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 a 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 a 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 a 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 a 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 or state other documents 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 post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative or medical 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. [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

Contraception methods should be aligned with local regulations for both male and female participants.

WOCBP who are completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship as their preferred and usual lifestyle:

Must…	Must not…

agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males	• use periodic abstinence methods
	  ○ calendar
	  ○ ovulation
	  ○ symptothermal, or
	  ○ post-ovulation
	• declare abstinence just for the duration of a trial, or

	• use the withdrawal method

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or NOT in a same-sex relationship as their preferred and usual lifestyle, must do the following:

Topic	Condition
Pregnancy testing	Have a negative serum test result at screening followed by a negative urine result within 24 hours prior to treatment exposure. See the protocol SoA for subsequent pregnancy testing requirements.
Contraception	Agree to use 2 forms of effective contraception, where at least 1 form must be highly effective. These forms of contraception must be used during the study and after the study for at least 95 days after the last dose of the study intervention.

Examples of different forms of contraception:

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• female sterilization • combination oral contraceptive pill • progestin-only contraceptive pill (mini-pill) • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices

Effective contraception	• male or female condoms with spermicide
	• diaphragms with spermicide or cervical sponges
	• barrier method with use of a spermicide
	  o condom with spermicide
	  o diaphragm with spermicide, or
	  o female condom with spermicide
	
	Note: The barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, or female condom with spermicide) to be considered effective.

Ineffective forms of contraception whether used alone or in any combination	• spermicide alone • periodic abstinence • fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) • withdrawal • postcoital douche, or • lactational amenorrhea

The tables below describes contraception guidance for men.

Topic	Guidance
For all men	Should refrain from sperm donation for the duration of the study and for the predicted time until estimated plasma levels of partner would be below the level of toxicologic concern, plus 90 days
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, and • for the predicted time until estimated plasma levels of partner would be below the level of toxicologic concern, plus 90 days
Contraception for men in exclusively same-sex relationships, as their preferred and usual lifestyle	Are not required to use contraception

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, 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 8.2.3 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]

Tests assayed ONLY by investigator-designated local laboratory	
Phosphatidylethanol (PEth)	Liver kidney microsomal type 1 (LKM-1) antibody
Urine Chemistry	**Microbiology**
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, plasminogen activity, 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, and
- arranging delivery of study supplies.

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.

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 types, 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
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
blinding/masking	A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
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
EAS	Efficacy Analysis Set
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
FSH	follicle-stimulating hormone
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
IWRS	interactive web-response system
LDL	low-density lipoprotein
Lp(a)	lipoprotein(a)
MACE	major adverse cardiac events
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MRCP	magnetic resonance cholangiopancreatography
NONMEM	Nonlinear Mixed-Effects Modeling
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
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	pharmacodynamics

PI	principle investigator
PK	pharmacokinetics
PO	by mouth
PT-INR	prothrombin time-INR
QD	once daily
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
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.
SCORE2	Systematic COronary Risk Evaluation 2
SNP	single-nucleotide polymorphism
SoA	Schedule of Activities
SS	Safety Analysis Set
TBL	total bilirubin
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.
TSH	thyroid stimulating hormone
UACR	urinary albumin creatine ratio
ULN	upper limit of normal
US	United States
WNOCBP	women not of childbearing potential
WOCBP	women of childbearing potential

11. References

AIM-HIGH Investigators. The role of niacin in raising high-density lipoprotein cholesterol to reduce cardiovascular events in patients with atherosclerotic cardiovascular disease and optimally treated low-density lipoprotein cholesterol Rationale and study design. The Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: Impact on Global Health outcomes (AIM-HIGH). *Am Heart J*. 2011;161(3):471-477.e2. doi: 10.1016/j.ahj.2010.11.017. Epub 2011 Feb 2. PMID: 21392600; PMCID: PMC3120226.

Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath SC, Parish S, Barlera S, Franzosi MG, Rust S, Bennett D, Silveira A, Malarstig A, Green FR, Lathrop M, Gigante B, Leander K, de Faire U, Seedorf U, Hamsten A, Collins R, Watkins H, Farrall M; PROCARDIS Consortium. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med*. 2009;361(26):2518-28. doi: 10.1056/NEJMoa0902604. PMID: 20032323.

Dubé JB, Boffa MB, Hegele RA, Koschinsky ML. Lipoprotein(a): more interesting than ever after 50 years. *Curr Opin Lipidol*. 2012;23(2):133-40. doi: 10.1097/MOL.0b013e32835111d8. PMID: 22327610.

Emdin CA, Khera AV, Natarajan P, Klarin D, Won HH, Peloso GM, Stitziel NO, Nomura A, Zekavat SM, Bick AG, Gupta N, Asselta R, Duga S, Merlini PA, Correa A, Kessler T, Wilson JG, Bown MJ, Hall AS, Braund PS, Samani NJ, Schunkert H, Marrugat J, Elosua R, McPherson R, Farrall M, Watkins H, Willer C, Abecasis GR, Felix JF, Vasan RS, Lander E, Rader DJ, Danesh J, Ardissino D, Gabriel S, Saleheen D, Kathiresan S; CHARGE–Heart Failure Consortium; CARDIoGRAM Exome Consortium. Phenotypic Characterization of Genetically Lowered Human Lipoprotein(a) Levels. *J Am Coll Cardiol*. 2016;68(25):2761-2772. doi: 10.1016/j.jacc.2016.10.033. PMID: 28007139; PMCID: PMC5328146.

Emerging Risk Factors Collaboration, Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, White IR, Marcovina SM, Collins R, Thompson SG, Danesh J. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA*. 2009;302(4):412-23. doi: 10.1001/jama.2009.1063. PMID: 19622820; PMCID: PMC3272390.

Ference BA. The Potential Clinical Benefit of Lowering Lipoprotein(a) [published online ahead of print, 2022 Apr 3]. *JAMA*. 2022;10.1001/jama.2022.5333. doi:10.1001/jama.2022.5333

Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC Jr, Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139(25):e1082-e1143. doi: 10.1161/CIR.0000000000000625. Epub 2018 Nov 10. Erratum in: Circulation. 2019 Jun 18;139(25):e1182-e1186. PMID: 30586774; PMCID: PMC7403606.

HPS2-THRIVE Collaborative Group. Effects of extended-release niacin with laropiprant in high-risk patients. NEJM. 2014;371:203-212.

Jaeger BR, Richter Y, Nagel D, Heigl F, Vogt A, Roeseler E, Parhofer K, Ramlow W, Koch M, Utermann G, Labarrere CA, Seidel D; Group of Clinical Investigators. Longitudinal cohort study

on the effectiveness of lipid apheresis treatment to reduce high lipoprotein(a) levels and prevent major adverse coronary events. *Nat Clin Pract Cardiovasc Med*. 2009;6(3):229-39. doi: 10.1038/ncpcardio1456. PMID: 19234501.

Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA*. 2009;301(22):2331-9. doi: 10.1001/jama.2009.801. PMID: 19509380.

Koren MJ, Moriarty PM, Baum SJ, et al. Preclinical development and phase 1 trial of a novel siRNA targeting lipoprotein(a). *Nat Med*. 2022;28(1):96-103. doi:10.1038/s41591-021-01634-w

Kronenberg F, Utermann G. Lipoprotein(a): resurrected by genetics. *J Intern Med*. 2013;273(1):6-30. doi: 10.1111/j.1365-2796.2012.02592.x. Epub 2012 Nov 12. PMID: 22998429.

Li Y, Luke MM, Shiffman D, Devlin JJ. Genetic variants in the apolipoprotein(a) gene and coronary heart disease. *Circ Cardiovasc Genet*. 2011;4(5):565-573. doi:10.1161/CIRCGENETICS.111.959601

Maeda S, Abe A, Seishima M, Makino K, Noma A, Kawade M. Transient changes of serum lipoprotein(a) as an acute phase protein. *Atherosclerosis*. 1989;78(2-3):145-150. doi:10.1016/0021-9150(89)90218-9

Min WK, Lee JO, Huh JW. Relation between lipoprotein(a) concentrations in patients with acute-phase response and risk analysis for coronary heart disease. *Clin Chem*. 1997;43(10):1891-1895.

Noma A, Abe A, Maeda S, et al. Lp(a): an acute-phase reactant?. *Chem Phys Lipids*. 1994;67-68:411-417. doi:10.1016/0009-3084(94)90164-3

Nugent AK, Gray JV, Gorby LK, Moriarty PM. Lipoprotein Apheresis: First FDA Indicated Treatment for Elevated Lipoprotein(a). *J Clin Cardiol*. 2020; 1:16-21

Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, Stroes ES, Langslet G, Raal FJ, El Shahawy M, Koren MJ, Lepor NE, Lorenzato C, Pordy R, Chaudhari U, Kastelein JJ; ODYSSEY LONG TERM Investigators. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372(16):1489-99. doi: 10.1056/NEJMoa1501031. Epub 2015 Mar 15. PMID: 25773378.

Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, Ballantyne CM, Somaratne R, Legg J, Wasserman SM, Scott R, Koren MJ, Stein EA; Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372(16):1500-9. doi: 10.1056/NEJMoa1500858. Epub 2015 Mar 15. PMID: 25773607.

Schmidt K, Noureen A, Kronenberg F, Utermann G. Structure, function, and genetics of lipoprotein (a). *J Lipid Res*. 2016;57(8):1339-59. doi: 10.1194/jlr.R067314.

Stoekenbroek R, Ray K, Landmesser U, et al. 4945 Inclisiran-mediated reductions in Lp(a) in the ORION-1 trial. *European Heart Journal*. 2019;40(Supplement_1) https://doi.org/10.1093/eurheartj/ehz746.0015

Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *J Am Coll Cardiol*. 2012;60(16):1581-1598. doi:10.1016/j.jacc.2012.08.001

Tsimikas S. A Test in Context: Lipoprotein(a): Diagnosis, Prognosis, Controversies, and Emerging Therapies. *J Am Coll Cardiol*. 2017;69(6):692-711. doi: 10.1016/j.jacc.2016.11.042. PMID: 28183512.

Tsimikas S, Stroes ESG. The dedicated "Lp(a) clinic": A concept whose time has arrived? *Atherosclerosis*. 2020;300:1-9. doi: 10.1016/j.atherosclerosis.2020.03.003. Epub 2020 Mar 13. PMID: 32234580.

Utermann G. The mysteries of lipoprotein(a). *Science*. 1989;246(4932):904-10. doi: 10.1126/science.2530631. PMID: 2530631.

Varvel S, McConnell JP, Tsimikas S. Prevalence of Elevated Lp(a) Mass Levels and Patient Thresholds in 532 359 Patients in the United States. *Arterioscler Thromb Vasc Biol*. 2016;36(11):2239-2245. doi: 10.1161/ATVBAHA.116.308011. Epub 2016 Sep 22. PMID: 27659098.

Viney NJ, van Capelleveen JC, Geary RS, Xia S, Tami JA, Yu RZ, Marcovina SM, Hughes SG, Graham MJ, Crooke RM, Crooke ST, Witztum JL, Stroes ES, Tsimikas S. Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials. *Lancet*. 2016;388(10057):2239-2253. doi: 10.1016/S0140-6736(16)31009-1. Epub 2016 Sep 21. PMID: 27665230.

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