Protocol J2O-MC-EKBA(c)
A Safety, Tolerability, and Pharmacokinetic Study of Single- and Multiple-Ascending Doses of LY3473329 in Healthy Subjects

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Confidential Information

LY3473329

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Table of Contents

Section **Page**

List of Tables

Table **Page**

List of Figures

Figure **Page**

List of Appendices

Appendix **Page**

1. Protocol Synopsis

Title of Study:
A safety, tolerability, and pharmacokinetic study of single- and multiple-ascending doses of LY3473329 in healthy subjects

Rationale:
Lipoprotein (a) (Lp[a]) is a lipoprotein subclass consisting of a low-density lipoprotein (LDL) particle bound with one molecule each of apolipoprotein (B) (ApoB) and Apo(a). Elevated levels of Lp(a) are associated with increased risk of cardiovascular disease. Apheresis is the only approved treatment (in some countries) for patients with elevated Lp(a) and advanced cardiovascular disease.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors reduce Lp(a) by approximately 25% and niacin produces modest reductions in Lp(a), but neither are approved for Lp(a) reduction. Novel treatments to reduce Lp(a) are under investigation. One approach has used an antisense oligonucleotide (IONIS-APO(a)-L_{Rx}), which has been shown to lower Lp(a) concentrations and was safe and tolerable in a randomized controlled clinical trial.

LY3473329 is a small molecule designed to disrupt binding of Apo(a) to ApoB on the LDL molecule, which decreases the formation of the Lp(a) moiety with a concomitant decline in steady-state levels of Lp(a). The efficacy of LY3473329 in reducing plasma Lp(a) has been demonstrated in preclinical models.

The current Phase 1 study will evaluate the safety, tolerability, and pharmacokinetics (PK) of LY3473329 after oral administration in healthy subjects (single-ascending dose [SAD]; Part A) and in otherwise healthy subjects with elevated Lp(a) (≥75 nM or 30 mg/dL; multiple-ascending dose [MAD]; Part B).

Objectives/Endpoints:

Objectives	Endpoints
Primary (Part A – SAD)	
To evaluate safety and tolerability of LY3473329 in healthy subjects following a single oral dose	• AEs • SAEs
Primary (Part B – MAD)	
To evaluate safety and tolerability of LY3473329 in otherwise healthy subjects with elevated Lp(a) (≥75 nM or 30 mg/dL) following multiple once-daily oral doses	• AEs • SAEs
Secondary (Part A – SAD)	
To evaluate the pharmacokinetics of LY3473329 in healthy subjects following a single oral dose	• AUC • C_{max} • t_{max}
Secondary (Part B – MAD)	
To evaluate the pharmacokinetics of LY3473329 in otherwise healthy subjects with elevated Lp(a) (≥75 nM or 30 mg/dL) following multiple once-daily oral doses	• AUC • C_{max} • t_{max}

Abbreviations: AE = adverse event; AUC = area under the concentration versus time curve; C_{max} = maximum observed drug concentration; Lp(a) = lipoprotein (a); MAD = multiple-ascending dose; SAD = single-ascending dose; SAE = serious adverse event; t_{max} = time of C_{max}.

Summary of Study Design:

Study J2O-MC-EKBA is a Phase 1, randomized, double-blind, placebo-controlled study of LY3473329 in healthy subjects (SAD; Part A) and in otherwise healthy subjects with elevated Lp(a) (≥75 nmol/L or 30 mg/dL; MAD; Part B).

All doses will be administered orally in a fasting state. Safety data will be reviewed prior to dose escalation in both parts. Additionally, PK and pharmacodynamic (PD) data will be reviewed if required prior to dose escalation. In both parts, the proposed dose levels may be adjusted after review of available safety, PK, and PD data.

Part A

Single-ascending doses of LY3473329 will be administered in up to 7 cohorts of 8 subjects (6 LY3473329, 2 placebo) each. For the first cohort, 2 subjects will receive a sentinel dose (1 each with LY3473329 and placebo). Dosing of the remaining subjects in the cohort will occur after review of the safety data through 24 hours postdose. Dose escalation may proceed after review of all safety data through Day 3 from the prior cohort.

Part B

Multiple-ascending doses of LY3473329 will be administered in healthy subjects with elevated Lp(a) (≥75 nmol/L or 30 mg/dL) in up to 10 evaluable subjects (8 LY3473329, 2 placebo) for each of the first 4 cohorts, and 17 evaluable subjects (15 LY3473329, 2 placebo) for the last cohort. Subjects will receive either LY3473329 or placebo once daily (QD) for 14 days. Dose escalation may proceed after review of all safety data, and available PK data, from at least 8 individuals from the first 14 days from the prior cohort. Safety, PK, and other assessments will be performed at prescribed time points during the stay at the clinical research unit (CRU) and at subsequent study visits in both parts of the study.

Treatment Arms and Planned Duration for an Individual Subject:
Part A: Within each cohort, subjects will be randomly assigned to receive either LY3473329 or placebo in a 6:2 ratio. A single dose of either LY3473329 or placebo will be orally administered to each subject on Day 1 starting at 1 mg with a maximum planned dose of 800 mg.

Part B: In the first 4 cohorts, subjects will be randomly assigned to receive either LY3473329 or placebo in a 8:2 ratio. In the last cohort, subjects will be randomly assigned to receive either LY3473329 or placebo in a 15:2 ratio. The planned dose levels may range between 30 and 700 mg QD.

Following a screening period of up to 28 days (Part A) and 60 days (Part B), eligible subjects will be confined to the CRU a day prior to Day 1 until assessments are complete on Day 4 (Part A) or Day 15 (Part B). All subjects will be followed up for approximately 106 days following administration of the study drug in Part A and for approximately 123 days following administration of the last dose of study drug (Part B). The follow-up period may be altered based on review of available data, such as PK, plasminogen activity, and Lp(a) concentration such that follow-up may cease for an individual once any AEs are resolved and plasminogen activity and Lp(a) levels return to at least 90% of baseline.

Number of Subjects:
Part A: 56 subjects will be enrolled and randomized for an estimated 8 evaluable subjects in each of the 7 cohorts.

Part B: Up to 60 subjects will be randomized for an estimated 10 evaluable subjects in each of the first 4 cohorts and 17 evaluable subjects in the last cohort.

Statistical Analysis:

Safety: The primary safety endpoints are the number of serious and nonserious adverse events. Summary statistics will be provided by dose level and for all placebo-treated subjects combined.

Pharmacokinetics: Plasma LY3473329 PK parameters will be calculated using noncompartmental methods after single- and multiple-dose administration. Additional PK parameters may be calculated if deemed appropriate. Pharmacokinetic parameters will be summarized by dose level using descriptive statistics. Mean and individual LY3473329 plasma concentration versus time curves will be represented graphically.

2. Schedule of Activities

Study Schedule Protocol J2O-MC-EKBA Single-Ascending Dose (SAD) – Part A

	S	Treatment and Follow Up												ED[a]
Study Day	**-28**	**-1**	**1**	**2**	**3**	**4**	**8**	**15**	**22**	**43**	**64**	**85**	**106**	**-**
Visit Window	**-**		**-**	**-**	**-**	**-**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**
Visit	**1[b]**	**2[c]**					**3**	**4**	**5**	**6**	**7**	**8**	**9**	**-**
CRU admission		X												
CRU discharge						X[d]								
Informed consent	X													
Medical history	X													
Height	X													
Weight	X	X					X	X						X
Physical examination (complete [C] or directed [D])	C	D	D	D	D	D	D	C	D	D	D	D	D	C
Urine drug screen and ethanol test	X	X					X	X						X
Vital signs including temperature	X		P	X	X	X	X	X	X	X	X	X	X	X
Hematology and clinical chemistry	X[j]	X				X	X	X						X
Urinalysis[e]	X	X							X	X	X	X	X	
ECG[f]	X		X	X	X			X						X
β-hCG pregnancy test	X	X				X							X	X
HIV, HCV, HBsAg	X													
Eligibility review	X	X												
Randomization			X											
Study drug administration[g]			X											
Adverse event		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK blood sampling[h]			X	X	X	X	X	X	X	X	X	X	X	X
hs-CRP	X			X	X									
Lipoprotein panel blood sample[i]	X		P	X	X	X	X	X						X
Plasminogen concentration			P	X	X		X	X	X	X	X	X	X	X
Plasminogen activity			P	X	X		X	X	X	X	X	X	X	X
PAI			P	X	X		X	X						X
tPA			P	X	X		X	X						X
α_2-antiplasmin			P	X	X		X	X						X

Abbreviations: β-hCG = beta subunit of human chorionic gonadotropin; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HDL-C = high-density lipoprotein-cholesterol; HIV = human immunodeficiency virus; hs-

CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein-cholesterol; Lp(a) = lipoprotein (a); P = pre-dose; PAI = plasminogen activator inhibitor; PK = pharmacokinetics; S = screening; SOP = standard operating procedure; t_{max} = time to reach the maximum observed drug concentration; tPA = tissue plasminogen activator.

[a] Subjects who discontinue prior to study completion will complete the ED visit procedures.

[b] Screening will be performed within 28 days prior to the study drug administration (Day 1).

[c] All subjects will be confined to the CRU a day prior to Day 1 until assessments are complete on Day 4.

[d] Subjects will be discharged after completing all activities on Day 4.

[e] A standard urine dipstick may be used.

[f] 12-Lead ECGs will be recorded in the supine position after 5 minutes rest. A single ECG will be recorded at screening and triplicate ECGs will be recorded at all other indicated time points. Triplicate ECGs will be recorded prior to blood draws when the time points coincide with blood draws; ECG recording will not exceed 5 minutes (for all 3 ECGs). On Day 1, ECG will be recorded pre-dose and at approximately 2, 4, and 6 hours after dosing.

[g] Study drug will be administered in a fasting state. Fasting is considered as approximately 8 hours prior to the dose and 4 hours after the morning dose. The exact time of study drug administration will be recorded.

[h] PK samples will be collected according to the PK Sampling Schedule (Appendix 6). Timing of PK sample collection may be adjusted based on clinical needs. The exact sample collection dates and times must be recorded.

[i] Lipoprotein panel blood sample will include Lp(a), HDL-C, LDL-C, triglycerides, total cholesterol, and ApoB.

[j] Screening laboratory tests should be done under fasting conditions.

* All local requirements with regard to COVID-19 will be followed according to local/site SOP.

Study Schedule Protocol J2O-MC-EKBA Multiple-Ascending Dose (MAD) – Part B

	S1	S2	Treatment Period																FU								ED [a]
Study Day	**-60**	**-28**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**18**	**22**	**29**	**43**	**64**	**85**	**106**	**137**	
Visit Window																			**±1**	**±1**	**±1**	**±4**	**±3**	**±3**	**±3**	**±3**	
Visit	**1[b]**	**2[b]**	**3**																**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
CRU admission			X																								
CRU discharge																		X									
Informed consent	X																										
Medical history		X																									
Height		X																									
Weight		X	X															X									
Physical examination (complete [C] or direct [D])		C		D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	C	D	D	D	D	C
Urine drug screen and ethanol test		X	X															X	X	X		X					X
Vital signs including temperature		X	X	P	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology and clinical chemistry[d]		X	X		X						X						X		X	X		X					X
Urinalysis[c]		X	X																X	X	X	X	X	X	X	X	X
ECG[d]		X		X	X						X						X	X				X					X
β-hCG pregnancy test		X	X															X								X	X
HIV, HCV, HBsAg		X																									
Eligibility review		X	X																								
Randomization				X																							
Study drug administration[e]				X	X	X	X	X	X	X	X	X	X	X	X	X	X										
Adverse event			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK blood sampling[f]				X	X			X			X			X			X	X	X	X	X	X	X	X	X	X	X
hs-CRP		X									X						X										
Lipoprotein panel blood sample	X			P	P			P		P	P			P			P	X	X	X	X	X	X	X	X	X	X

	S1	S2	Treatment Period																FU								ED [a]
Study Day	**-60**	**-28**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**18**	**22**	**29**	**43**	**64**	**85**	**106**	**137**	
Visit Window																			**±1**	**±1**	**±1**	**±4**	**±3**	**±3**	**±3**	**±3**	
Visit	**1[b]**	**2[b]**	**3**																**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Plasminogen concentration [g]	X			P	P	P	P			P							P	X	X	X	X	X	X	X	X	X
Plasminogen activity[g,h]	X			P	P	P	P			P							P	X	X	X	X	X	X	X	X	X
PAI[g]				P	P					P							P				X					X
tPA[g]				P	P					P							P				X					X
α_2-antiplasmin[g]				P	P					P							P				X					X
Storage sample[i]				P			X			P							P				X					

Abbreviations: AE = adverse event; β-hCG = beta subunit of human chorionic gonadotropin;; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; FU = safety follow-up; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hs-CRP = high-sensitivity C-reactive protein; Lp(a) = lipoprotein (a); P = pre-dose; PAI = plasminogen activator inhibitor; PK = pharmacokinetics; S1 = screening visit 1; S2 = screening visit 2; SOP = standard operating procedure; tPA = tissue plasminogen activator.

[a] Subjects who discontinue the study prior to study completion will complete the ED visit procedures. The follow-up period may be altered based on review of available data such as PK, Lp(a) concentration, and plasminogen such that follow-up may cease for an individual once any AEs are resolved and Lp(a) levels and plasminogen activity return to at least 90% of baseline.

[b] Each subject will undergo 2 screening visits. Screening Visit 1 (S1) will be performed within 60 days before the first dose of study drug and screening Visit 2 (S2) will be performed within 28 days before the first dose of study drug. S1 must be completed at least 3 days before the first dose of study drug.

[c] A standard urine dipstick may be used.

[d] 12-Lead ECGs will be obtained in the supine position after 5 minutes rest. A single ECG will be recorded at screening and triplicate ECGs will be recorded at all other indicated time points. Triplicate ECGs will be recorded prior to blood draws when the time points coincide with blood draws; ECG recording will not exceed 5 minutes (for all 3 ECGs). On Day 1, ECGs will be collected at pre-dose and at 2, 4, and 6 hours after the dosing.

[e] Study drug will be administered in a fasting state, preferably at the same time every day at the CRU. Fasting is considered as approximately 8 hours prior to the dose and 4 hours after the dose. The exact time of study drug administration will be recorded.

[f] PK samples will be collected according to the PK Sampling Schedule (Appendix 6). If applicable, a PK sample will be obtained at the ED visit. Timing of PK sample collection may be adjusted based on clinical needs. The exact collection dates and times must be recorded.

[g] Biomarker samples will be collected prior to the morning dose.

[h] Investigator may order additional plasminogen activity samples if needed. This sampling schedule designed based on expectation of timing of the potential effect of LY3473329 on plasminogen activity

i Storage sample to be collected according to Section 9.8.

j Screening laboratory tests should be done under fasting conditions.

* All local requirements with regard to COVID-19 will be followed according to local/site SOP.

3. Introduction

3.1. Study Rationale

Lipoprotein (a) (Lp[a]) is a lipoprotein subclass consisting of a low-density lipoprotein (LDL) particle bound with 1 molecule each of apolipoprotein (B) (ApoB) and Apo(a). Elevated levels of Lp(a) are associated with increased risk of cardiovascular disease. Apheresis is the only approved treatment for patients with elevated Lp(a) and advanced cardiovascular disease. The procedure is similar to dialysis, requiring patients to spend 2 to 4 hours in a specialized center. Lp(a) levels are reduced by approximately 60%, but the procedure must be repeated at every 2 to 3 weeks and is costly. Retrospective and observational data support the lowering of Lp(a) with this technique, with fewer cardiovascular events in treated individuals (Vogt 2017).

PCSK9 inhibitors reduce Lp(a) by approximately 25% and niacin produces modest reductions in Lp(a), but neither are approved for Lp(a) reduction. Novel treatments to reduce Lp(a) are under investigation. One approach has used parenteral delivery of an antisense oligonucleotide (IONIS-APO(a)-L_{Rx}), which has been shown to lower Lp(a) concentrations and was safe and tolerable in a randomized controlled clinical trial (Viney et al. 2016).

The current Phase 1 study will evaluate the safety, tolerability, and pharmacokinetic (PK) properties of LY3473329 after oral administration in healthy subjects (single-ascending dose [SAD]; Part A) and in otherwise healthy subjects with elevated Lp(a) (≥75 nmol/L or 30 mg/dL; multiple-ascending dose [MAD]; Part B).

3.2. Background

LY3473329 is a small orally administered molecule that disrupts binding of Apo(a) to ApoB on the LDL molecule, which decreases the formation of Lp(a) moiety with a concomitant reduction in the plasma steady-state levels of Lp(a).

3.3. Benefit/Risk Assessment

Based on the nonclinical data, LY3473329 is not considered to be a high-risk compound, because based on the mode of action, the nature of the target, and the relevance of the nonclinical species, serious adverse events (SAEs) are not expected in humans. The study will be conducted in accordance with principles outlined in the "Guideline on Strategies to Identify and Mitigate Risks for First-in-Human and Early Clinical Trials with Investigational Medicinal Products" (EMEA/CHMP/SWP/28367/07 Rev.1). Risks for this study are deemed monitorable and manageable at the planned doses, based on preclinical data observed to date. Specifically, repeat-dose good laboratory practice (GLP) 2-week rat (Study 8415-459) and 26-day monkey (Study 8415-460) studies were conducted at daily doses of up to 1000 mg/kg. No adverse effects were noted, hence the no-observed-adverse-effect level (NOAEL) was the limit dose of 1000 mg/kg in both species. The only LY3473329-related effect noted was a decrease in plasma plasminogen activity, which occurred in rats and monkeys. This effect was not considered adverse because there was no observable impact on the health of the animals. Based on these observations in rat and monkey, plasminogen concentration and activity will be monitored in this study. Additional information on the plasminogen activity changes in animals can be found in

Section 4 of the Investigator's Brochure (IB). As shown in Table 5.1, the proposed maximum human dose is less than the animal NOAEL doses on a mg/m^2 basis, but projected human exposure could exceed the NOAEL exposures at the "limit dose" of 1000 mg/kg. Further details about dose justification can be found in Section 5.5 of the IB. Animal exposures increased in a less-than-dose-proportional manner and this exposure limitation may occur with human exposure. Dose escalation in human subjects will be based on review of human safety and exposure data.

It is expected that LY3473329 will produce a reduction in Lp(a) over the duration of the treatment course. Because atherosclerotic vascular disease generally progresses over decades, it is not anticipated that transient reduction in Lp(a) will provide a therapeutic benefit in this study. In epidemiological studies, elevated Lp(a) levels are associated with increased risk of cardiovascular events, and no interventional data are available to inform whether a reduction in Lp(a) would be expected to result in reduced cardiovascular risk. It is unclear if short-term reduction of Lp(a) expected in this study would impact cardiovascular risk or positively affect vascular health through other pleiotropic means. Subjects' health will be monitored for clinical benefits, including reduction in Lp(a) levels.

More information about the known and expected benefits, risks, SAEs, and reasonably anticipated adverse events (AEs) of LY3473329 is to be found in Section 6 of the IB.

4. Objectives and Endpoints

Objectives	Endpoints
Primary (Part A – SAD)	
To evaluate safety and tolerability of LY3473329 in healthy subjects following a single oral dose	• AEs • SAEs
Primary (Part B – MAD)	
To evaluate safety and tolerability of LY3473329 in otherwise healthy subjects with elevated Lp(a) (≥75 nmol/L or 30 mg/dL) following multiple once-daily oral doses	• AEs • SAEs
Secondary (Part A – SAD)	
To evaluate the pharmacokinetics of LY3473329 in healthy subjects following a single oral dose	• AUC • C_{max} • t_{max}
Secondary (Part B – MAD)	
To evaluate the pharmacokinetics of LY3473329 in otherwise healthy subjects with elevated Lp(a) (≥75 nmol/L or 30 mg/dL) following multiple once-daily oral doses	• AUC • C_{max} • t_{max}
Exploratory (Part A – SAD)	
To explore the mechanism of action of LY3473329 based on safety and efficacy biomarkers following a single oral dose	• Lp(a) concentration • Plasminogen activity • Plasminogen concentration • hs-CRP • tPA • PAI • α_2-antiplasmin
Exploratory (Part B – MAD)	
To explore the mechanism of action of LY3473329 based on safety and efficacy biomarkers following multiple once-daily oral doses	• Lp(a) concentration • Plasminogen activity • Plasminogen concentration • hs-CRP • tPA • PAI • α_2-antiplasmin

Abbreviations: AE = adverse event; AUC = area under the concentration versus time curve; C_{max} = maximum observed drug concentration; hs-CRP = high-sensitivity C-reactive protein; Lp(a) = lipoprotein (a); MAD = multiple-ascending dose; PAI = plasminogen activator inhibitor; SAD = single-ascending dose; SAE = serious adverse event; t_{max} = time of C_{max}; tPA = tissue plasminogen activator.

5. Study Design

5.1. Overall Design

Study J2O-MC-EKBA is a Phase 1, randomized, investigator- and subject-blinded, placebo-controlled study of LY3473329 in healthy subjects (SAD; Part A) and in otherwise healthy subjects with elevated Lp(a) (≥75 nmol/L or 30 mg/dL; MAD; Part B).

Figure 5.1 illustrates the study design.

Part A

Single-ascending doses of LY3473329 will be administered in up to 7 cohorts of 8 subjects each. Subjects will be randomly assigned to receive either LY3473329 or placebo in a 6:2 ratio. For the first cohort, 2 subjects will receive a sentinel dose (1 each with LY3473329 and placebo) with subsequent dosing of the remaining cohort after review of the safety data through 24 hours postdose. The guideline for dose escalation is detailed in Section 7.4.

Following a screening period of up to 28 days, eligible subjects will be confined to the clinical research unit (CRU) a day prior to Day 1 until all assessments are complete on Day 4. All subjects will be followed up for approximately 106 days following administration of the study drug (Section 2). The follow-up period may be altered based on review of available data, such as PK, Lp(a) concentration, and plasminogen such that follow-up may cease for an individual once any AEs are resolved and plasminogen activity and Lp(a) levels return to at least 90% of baseline.

Part B

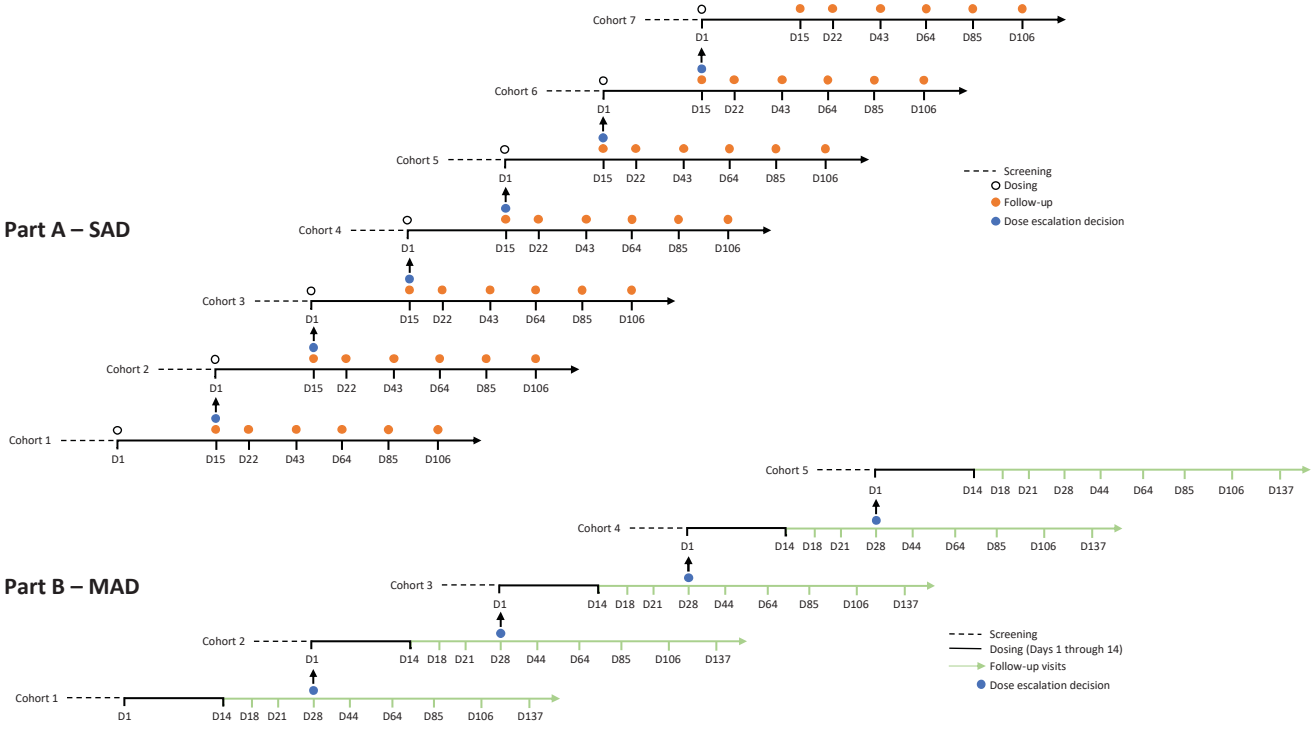
The following data from Part A will be reviewed prior to the initiation of Part B:

- safety data (AE, clinical chemistry, hematology, vital signs/electrocardiogram [ECG]) through Cohort 4, Day 4
- available PK data through Cohort 3, Day 8
- any additional available data (i.e., exploratory biomarkers) from Cohorts 1 through 3

Multiple-ascending doses of LY3473329 will be administered in up to 5 cohorts in otherwise healthy subjects with elevated Lp(a) (≥75 nmol/L or 30 mg/dL), in up to 10 evaluable subjects in the first 4 cohorts and 17 evaluable subjects in the last cohort. Subjects will be randomly assigned to receive either LY3473329 or placebo in an 8:2 ratio in all but the last cohort and in a 15:2 ratio in the last cohort. Subjects will receive either LY3473329 or placebo once daily (QD) for 14 days. The guidelines for dose escalation are detailed in Section 7.4. All subjects will be confined to the CRU a day prior to Day 1 and until all assessments are complete on Day 15. All subjects will be followed up for approximately 123 days following administration of the last dose of study drug (Section 2). The follow-up period may be altered based on review of available data such as PK and Lp(a) concentration and plasminogen such that follow-up may cease for an individual once any AE is resolved and plasminogen activity and Lp(a) levels return to at least 90% of baseline.

In both parts, the proposed doses may be adjusted after a review of available safety, PK, and additional data such as exploratory biomarkers that may include but are not limited to Lp(a) and plasminogen.

Study governance considerations are described in detail in Appendix 3.



Abbreviations: D = Day; MAD = multiple-ascending dose; SAD = single-ascending dose.
Overall timelines may be adjusted by 1 to 3 days to accommodate logistics across countries.

Figure 5.1. Illustration of study design for Protocol J2O-MC-EKBA.

5.2. Number of Participants

Part A: 56 subjects will be randomized for an estimated 8 evaluable subjects in each of the 7 cohorts.

Part B: Up to 60 subjects will be randomized for an estimated 10 evaluable subjects in each of the first 4 cohorts and 17 evaluable subjects in the last cohort.

Subjects who withdraw from the study before completion of all study activities may be replaced at the discretion of the sponsor.

5.2.1. Definition of Evaluable Patients

Part A: Subjects will be considered evaluable if they have received at least 1 dose of study drug and have sufficient PK data to adequately characterize their PK profile.

Part B: Subjects will be considered evaluable if they have received at least 1 dose of study drug and an Lp(a) measurement at baseline and postbaseline on Day 8 or later.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last subject.

5.4. Scientific Rationale for Study Design

This is a first-in-human study of LY3473329 and will include both single- (Part A) and multiple-dose escalations (Part B). Both parts are investigator and subjected blind and placebo-controlled to avoid bias in the collection and evaluation of data. Placebo has been chosen as the control treatment to assess whether any observed effects are treatment related or reflective of the study conditions.

A sentinel dosing strategy for the first dose level will be used, as the study drug has not previously been administered to subjects. In the SAD portion of the study, subjects will reside in the CRU until all Day 4 procedures have been completed for monitoring of vital signs, symptoms, and clinical laboratory test results. The only LY3473329-related effect noted was a decrease in plasma plasminogen activity, which occurred in rats and monkeys. This effect was not considered adverse because there was no observable impact on the health of the animals.

In Part B, subjects will receive the study drug for 14 days, to evaluate safety, tolerability, PK, and exploratory biomarkers after multiple-dose administration. Safety follow-up visits are planned for up to 123 days after the last dose in Part B; this will allow safety monitoring for a reasonable amount of time based on a predicted terminal $t_{1/2}$ of approximately 21 days.

5.5. Justification for Dose

The dose ranges proposed for investigation are single doses of 1 to 800 mg orally for the SAD, and 30 to 700 mg QD orally for the MAD. These doses may be increased or decreased based on evaluation of available safety and PK data during the dose escalation.

The initial SAD projections were based on pharmacodynamic (PD) responses of Lp(a) reductions observed in a monkey efficacy model. The efficacious dose range was originally predicted to be 10 to 15 mg QD; however, the observed LY3473329 exposures in humans were lower than the predictions based on allometry. Also, the 30-mg QD dose achieved a mean reduction in Lp(a) of approximately 26%. Based on the observed safety and tolerability at single doses from 1 mg to 200 mg and multiple daily doses of 30 mg, the planned dose range has been extended to 800 mg as a single dose and 700 mg for multiple daily doses in order to evaluate the potentially pharmacologically active dose range. The planned range of doses to be studied is supported by 1-month GLP toxicology studies in rats and monkeys. Daily oral doses of up to 1000 mg/kg produced no adverse effects in rats or monkeys. Serum plasminogen level decreased, but no effects in animals were attributed to this factor. Importantly, in humans LY3473329 has not appeared to have a clinically relevant effect on plasminogen concentration and activity. Preliminary safety evaluations have occurred on blinded data for the SAD and MAD conducted to date. There are no AEs reported to be severe or meet SAE criteria, and the majority have been mild in severity. Vital signs, ECGs and clinical labs have resulted in no clinically meaningful observations.

Human PK for LY3473329 was predicted based on allometric scaling from a 2-compartment monkey PK model. Projected human PK parameters include systemic clearance (CL) of 0.053 L/h, bioavailability (F) of 8% (apparent oral clearance [CL/F] ~ 0.663 L/h), and volume of distribution at steady state (V_{ss}) of 22 L (Vss/F ~275 L), and a terminal $t_{1/2}$ of 21 days. In contrast, in the 30-mg daily dose cohort of the MAD the observed CL/F was approximately 65 L/h, terminal volume of distribution (V_z/F) was 2775 L, and $t_{1/2}$ was 30 hours A dose of 15 mg QD was expected to achieve average plasma concentrations that approximate the observed half-maximal effective concentration (EC50) in monkey of 900 ng/mL; however, the observed human exposures were lower than predicted. For example, the average steady-state concentration (AUC_{tau}/24h) for a 30-mg daily dose was 19 ng/mL. In nonclinical species, F decreased with increasing dose. Although this nonlinearity in F is expected to be observed in humans, the scaling factor is unknown; therefore, dose determination for each cohort will be based not only on safety/tolerability but also on the observed human PK.

The starting dose of 1 mg was selected to provide an exposure multiple of at least 39-fold compared to the highest dose and exposure tested in monkeys (NOAEL = 1000 mg/kg) and was also approximately one-tenth of the original predicted efficacious dose. No adverse effects were noted in rats or monkeys administered daily doses of up to 1000 mg/kg. Decreases in plasminogen, a known property of LY3473329 for rat and monkey plasminogen specifically, were noted, but no impact on the health of the toxicology study animals was observed. The doses and dose- and exposure-based multiples based on the observed human exposures are provided in Table 5.1, and more detail about the toxicology studies is provided in the IB.

The original top dose of 300 mg was selected to be 20- to 30-fold above the predicted efficacious dose to ensure adequate interrogation of the mechanism, assuming safety and tolerability are maintained. The amended top dose of 800 mg was chosen given the lower-than-expected exposures and the observed human safety and tolerability to date. Furthermore, taking into

consideration the observed human exposure at 200 mg and assuming a dose proportional increase in exposure up to 800 mg, the predicted area under the concentration versus time curve from time zero to infinity ($AUC_{0-\infty}$) at the top dose of 800 mg (3.7 µg*h/mL) is now expected to be 16x lower than the monkey NOAEL. In addition to a maximum unit dose, a maximum single dose ($AUC_{0-\infty}$) of approximately 250 µg*h/mL (geometric mean, approximately 10-fold above the predicted efficacious exposure and the rat NOAEL which would give a margin of safety of approximately 1) is planned, given the uncertainty in the prediction of human PK, PD, and the translation of nonclinical toxicology to humans.

The proposed doses were selected to safely address the study objectives in the context of careful dose escalation while monitoring laboratory parameters such as plasminogen activity and mass. A transient reduction of 70% from baseline plasminogen activity is expected to be safe based on clinical evidence in patients with congenital plasminogen deficiency and in patients taking tranexamic acid, which is intended to reduce plasminogen activity (Shapiro et al. 2018; Thorne et al. 2018).

Table 5.1. Margin of Safety for Oral Administration of LY3473329 Based on Administered Dose and Total Exposure

	Reference Human Dose (mg)	Dose (mg/kg)	Dose (mg/m^2)	Dose Multiple[a]	AUC (µg•h/mL)	C_{max} (µg/mL)	Exposure Multiple (AUC)[a]	Exposure Multiple (C_{max})
Human[b]								
Starting	1	0.017	0.63		0.028	0.0019		
Highest	800	13.3	500		3.74	0.21		
Rat NOAEL[c]	1 800	1000	6000	>9500x 12x	254	14	9100x 68x	7400x 67x
Monkey NOAEL[d]	1 800	1000	12000	>19,000x 24x	58.9	7.2	2100x 16x	3800x 34x

Abbreviations: AUC = area under the concentration versus time curve; AUC0-∞ = AUC from time zero to infinity; AUC0-τ = AUC during 1 dosing interval; C_{max} = maximum observed plasma concentration; NOAEL = no-observed-adverse-effect level; PK = pharmacokinetics.

[a] Dose multiple is the dose in animals/dose in humans based on mg/m^2. Exposure multiple is the calculated $AUC_{0-\tau}$ after repeated dosing in animals/$AUC_{0-\infty}$ in humans using observed human PK and assuming dose proportional increase in exposure from 200 mg to 800 mg.

[b] Plasma PK shown are based on the observations in Study EKBA over a single dose range of 1 mg to 200 mg.

[c] NOAEL was determined in a 2-week repeat-dose toxicity study (Study 8415-459). Exposures are for Day 14 for the combined sex results.

[d] NOAEL was determined in a 26-day repeat-dose toxicity study (Study 8415-460). Exposures are for Day 26 for the combined sex results.

6. Study Population

Eligibility of subjects for the study will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, and ECG.

Screening may occur up to 60 days prior to enrollment.

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

6.1. Inclusion Criteria

Subjects are eligible for inclusion in the study only if they meet all of the following criteria at screening. The time frame included in the following criteria are relative to screening unless otherwise noted in the respective criterion.

1. Healthy male subjects, as determined through medical history and physical examination, must agree to use a reliable method of birth control:
    a. A nonvasectomized, male subject must agree to use a condom or abstain from sexual intercourse from start of dosing until 105 days beyond the last dose of study drug.
    b. No restrictions are required for a vasectomized male provided his vasectomy has been performed at least 4 months or prior to screening. A male who has been vasectomized less than 4 months prior to screening must follow the same restrictions as a nonvasectomized male.
    c. Must agree not to donate sperm from start of dosing until 105 days beyond the last dose of study drug.
2. Healthy female subjects of child-bearing potential who have a fertile male sexual partner must be willing and able to practice effective contraception from admission to 105 days beyond the last dose of study drug. Sexually active subjects must use a combination of 2 of the following methods of contraception, including at least 1 so-called 'barrier' method:
    a. Hormonal contraceptives (oral, transdermal patches, vaginal, or injectable)
    b. intrauterine device with or without hormones
    c. condom, diaphragm, or cervical cap ('barrier' method)
    d. sexual abstinence

    Contraceptive requirements do not apply for subjects who are exclusively in a same-sex relationship.
3. Aged 18 to <70 years, exclusive, at screening.
4. Have given written informed consent, approved by the sponsor and the Independent Ethics Committee governing the site, prior to beginning any study-specific procedures.
5. Are reliable and willing to make themselves available for the duration of the study and are willing to follow CRU-specific study procedures.
6. Parts A and B

Have clinical laboratory test results within normal reference ranges for the population or the CRU, or have abnormal results that are deemed not clinically significant per the investigator

7. Part B, in addition to criterion 6,
    a. Lp(a) ≥75 nmol/L or 30 mg/dL at screening.
    b. Plasminogen concentration and activity are both within the normal range at screening.
8. BMI ≤30 kg/m^2

6.2. Exclusion Criteria

Subjects will be excluded from study enrollment if they meet any of the following criteria at screening. The time frame included in the following criteria are relative to screening unless otherwise noted in respective criterion.

1. Are currently enrolled in, or discontinued within the past 30 days from, a clinical trial involving an investigational drug that has not received regulatory approval for any indication, except for any trial involving antisense Lp(a), for which 6 months must have passed from the subject's last study drug dose.
2. Have previously completed or withdrawn from this study or any other study investigating LY3473329.
3. Are pregnant or breast feeding.
4. Glomerular filtration rate (GFR) is lower than estimated GFR 60 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease Study equation.
5. Have a history or presence of medical illness including, but not limited to, any cardiovascular, thromboembolism or bleeding disorder, hepatic, respiratory, hematological, endocrine, immune, psychiatric or neurological disease, convulsions, or any clinically significant laboratory abnormality that, in the judgment of the investigator, indicate a medical problem that would preclude study participation.
6. Have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study. In addition, subjects with the following findings will be excluded:
    a. Confirmed Fridericia's corrected QT interval >450 msec for men and >470 msec for women. One additional ECG may be performed if required.
7. Have an elevated high-sensitivity C-reactive protein (>3 mg/L) or have a prothrombin time/international normalized ratio (PT/INR) or activated partial thromboplastin time (aPTT) >1.25x upper limit of normal (ULN)
8. Are an investigator or site personnel directly affiliated or immediate families. Immediate family is defined as a spouse, parent, child or sibling, whether biological or legally adopted.
9. Are Lilly employees or contractors or an immediate family member of such.
10. Show evidence of human immunodeficiency virus (HIV) and/or positive human HIV antibodies, hepatitis C and/or positive hepatitis C antibody, or hepatitis B and/or positive hepatitis B surface antigen.
11. Have donated more than 500 mL blood within the past month.

12. Are unwilling to stop alcohol consumption while resident in the CRU.
13. Have an average weekly alcohol intake that exceeds 21 units per week (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits).
14. Have an abnormal blood pressure (supine) defined as diastolic blood pressure >95 or <45 mmHg and/or systolic blood pressure >160 or <90 mmHg. Re-testing may occur once during the screening visit within 2 hours of the initial abnormal blood pressure measurement at the discretion of the investigator at screening.
15. Have positive findings for known drugs of abuse on urinary drug screening.
16. Positive SARS-CoV-2 virus nasopharyngeal PCR test before admission.
17. Contact with SARS-CoV-2- positive or COVID-19 patient within the last 14 days prior to admission to the clinical unit
18. In the opinion of the investigator or the sponsor, are unsuitable for inclusion in the study.
19. Fever >38°C.

6.3. Lifestyle and/or Dietary Requirements

Throughout the study, subjects may undergo medical assessments and review of compliance with requirements before continuing in the study.

6.3.1. Meals and Dietary Restrictions

Study drug will be administered orally in a fasting state with approximately 240 mL of water, as a single dose in Part A and a single daily dose for 14 days in Part B. In Part B, fasting before dosing is required only on Days 1 and 14. Fasting is considered as approximately 8 hours prior to the dose and 4 hours after the dose. Water is permitted ad libitum during the fasting period.

Standard meals will be provided during the stay at the CRU. Otherwise, subjects will maintain their own dietary habits throughout the duration of the study.

6.3.2. Caffeine, Alcohol, and Tobacco

No alcohol will be allowed for 24 hours prior to and during the stay at CRU or other study visits.

Tobacco use is prohibited during the stay at CRU.

6.3.3. Activity

Subjects must refrain from strenuous exercise during the in-house period of the study.

6.4. Screen Failures

Subjects who do not meet the criteria for participation in this study (screen failure) may be re-screened once at the discretion of the investigator. Subjects may be re-tested at the discretion of the investigator (e.g. abnormal laboratory result).

If the time between screening and randomization is prolonged to greater than 28 days, the extent of re-screening will be discussed by the investigator and the sponsor. In these instances, not all tests may need to be repeated based upon the time between screening and dosing.

7. Treatment

7.1. Treatment Administered

LY3473329 or matching placebo will be administered orally in the fasting state with approximately 240 mL of water, as a single dose in Part A and a single daily dose for 14 days in Part B. In Part B, fasting before dosing is required only on Days 1 and 14. Fasting is considered as approximately 8 hours prior to the dose and 4 hours after the dose. Water is permitted ad libitum during the fasting period.

LY3473329 doses are planned to range between 1 mg to 800 mg. The planned dose levels for Part A were 1 mg, 3 mg, 10 mg, 30 mg, 100 mg, and up to 300 mg. The actual dose levels studied based on the review of safety, PK, and PD data were 1 mg, 10 mg, 30 mg, 100 mg, 200 mg, and 400 mg. A seventh single-dose cohort is now planned for a dose of 800 mg, contingent on review of the safety, PK, and PD data at the 400-mg dose level. The planned dose levels for Part B will be dependent on Part A as outlined in Section 5.1. The originally planned dose levels were 1 mg, 5 mg, 20 mg, 50 mg, and up to 100 mg QD. Based on the single-dose data, the first dose level in Part B was 30 mg. The second dose level in Part B was 100 mg, and subsequent dose levels are planned to be 300 mg, 500 mg, and 700 mg QD.

Section 7.4 details dose escalations.

LY3473329 drug product is supplied as capsules prepared extemporaneously by the addition of an adequate amount of LY3473329 drug substance into an empty hydroxypropyl methylcellulose (HPMC) capsule shell and where the dose strength is verified gravimetrically to the nearest decimal place and within ±5% from the target strength (e.g., from 9.5 to 10.5 mg for a 10-mg strength capsule). LY3473329 and placebo capsules should be stored at 15°C to 30°C.

The placebo capsules will be identical in appearance to LY3473329. The LY3473329 and matching placebo capsules are supplied in high-density polyethylene bottles.

The investigator or designee is responsible for

- explaining the correct use of the study drug to the subject
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection, and
- returning all unused medications to Lilly or its designee at the end of the study.

Note: In some cases, sites may destroy the material if, during the investigative site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical materials.

7.1.1. Packaging and Labeling

LY3473329 drug products are manufactured, tested, packaged, and labeled in accordance with all applicable current good manufacturing practice requirements, guidelines, and regulations and will be labeled according to the country's regulatory requirements. A certificate of analysis with lot numbers and expiry dates confirming that the materials are released for human use in clinical

trials will be supplied. LY3473329 drug products are for investigational use only and are to be used only within the context of this study.

7.2. Method of Treatment Assignment

Subjects who meet all criteria for enrollment will be randomly assigned to receive either LY3473329 or placebo. A randomization table will be created using a computer software program. The randomization list will be provided to the designated unblinded CRU staff for subject randomization and dispensing purposes and kept in a secure location, accessible to the designated unblinded CRU staff only.

7.2.1. Selection and Timing of Doses

In Part A, the single dose of the study drug will be administered at the CRU in the morning.

In Part B, study drug will be administered as single daily doses at the CRU in the morning. The doses will be administered at approximately the same times on each day. The actual time of all dose administrations will be recorded in the electronic data capture (EDC).

7.3. Blinding

This is a double-blind study. Subjects, investigators, and the CRU staff performing trial-related activities or with the ability to influence study outcomes will be blinded with regard to LY3473329 and placebo treatment. To preserve the blinding of the study, only a minimum number of Lilly personnel may have access to the randomization treatment assignments before all subjects in a cohort have completed treatment. The CRU staff who are responsible for drug preparation will not be blinded; laboratory personnel and an unblinded CRU team will also not be blinded. Drug products and placebo will have identical appearance.

One set of sealed envelopes containing the randomization code will be made available to the investigator at the start of the trial. A code envelope, which reveals the treatment for a specific study subject, may be opened during the study only if the subject's well-being requires knowledge of the subject's treatment assignment.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted for medical management of the event. The subject's safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

If a subject's study treatment assignment is unblinded, the subject must be discontinued from the study, unless the investigator obtains specific approval from the sponsor's medical monitor for the subject to continue in the study. During the study, emergency unblinding should occur only by accessing the study subject's emergency code.

At the end of the study, unopened envelopes will be returned to Lilly or its designee, or destroyed according to CRU procedures.

7.4. Dose Modification

All safety and available PD and PK data from prior cohorts will be used to support dose escalation. Dosing in the SAD (Part A) is not anticipated to exceed a mean $AUC_{0-\infty}$ of approximately 250 µg·h/mL, which is exposure at the rat NOAEL and is approximately 10-fold above the predicted efficacious exposure. Dosing in the MAD (Part B) is not anticipated to exceed a mean steady-state concentration($C_{ss,avg}$) of 500ng/mL, which is predicted to be achieved by a dose of 700 mg QD; planned dose levels are provided in Section 7.1.

Increases or decreases in dose levels may be warranted, as determined by the sponsor in consultation with the investigator, based on a review of all safety data and available PK and PD data from prior dose levels.

Up to 3 additional cohorts of up to 8 subjects (Part A) or 10 subjects (Part B) may be enrolled after review of all safety and available PD and PK data from all preceding dose levels. The goal of this study is to ensure that as much safety, PK, and PD information is obtained as possible.

7.4.1. Dose Escalation

7.4.1.1. Part A

Dose escalation will occur after review of all safety data, laboratory parameters including Lp(a) and plasminogen, and available PK data, through Day 3 in the prior cohort. At least 4 subjects with evaluable PK data are required for a dose escalation decision.

7.4.1.2. Part B

- Part B will be initiated as described in Section 5.1.
- Dose escalation for Cohorts 1, 2, and 3 in Part B will occur after review of all available safety and PK (LY3473329 plasma concentration) data from at least 8 individuals from the first 14 days in the prior cohorts and available data from Part A. Additionally, any available PD data may be reviewed as needed, including but not limited to Lp(a) and plasminogen.
- Dose confirmation for Cohort 4 in Part B will occur after review of all available safety data from at least the first 14 days in the prior cohorts and PK data through Day 8 of Part B Cohort 2 and also the available data from Cohort 7 in Part A. Additionally, any available PD data may be reviewed as needed, including but not limited to Lp(a) and plasminogen activity.
- Dose confirmation for Cohort 5 in Part B will occur after review of all available safety data from at least the first 14 days in the prior cohorts and PK data through Day 13 of Cohort 3. Additionally, any available PD data may be reviewed as needed, including but not limited to Lp(a) and plasminogen activity.

7.4.2. Stopping Rules

If any of the following scenarios occur, dosing at the current level and further dose escalation will be discontinued:

1. a subject experiences an SAE or clinically significant event that is related to LY3473329 administration, or

2. 3 or more subjects experience AEs within 14 days of dosing that are considered to be possibly related to LY3473329 and graded as at least moderate, clinically significant, and not responsive to supportive care.
3. 2 or more subjects experience a reduction in plasminogen activity relative to baseline ≥70% for ≥48 hours

The study may resume with subsequent cohorts dosed at a lower dose level, following discussion and agreement between the investigator and the sponsor.

7.5. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained, as communicated by the sponsor, during transit for all study drug products received and any discrepancies are reported and resolved before use of the study drug.

Only subjects enrolled in the study may receive study drug, and only authorized CRU staff may supply or administer study drug. All study drug products should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized CRU staff.

The investigator, CRU, or the head of the CRU (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

LY3473329 or matching placebo should be stored at 15° to 30°C.

7.6. Treatment Compliance

All study drugs will be administered at the CRU and documentation of treatment administration will occur at the site.

7.7. Concomitant Therapy

In general, concomitant medication should be avoided; however, over-the-counter medications may be administered at the discretion of the investigator (e.g., acetaminophen for the treatment of headache). If the need for concomitant medication (other than over-the-counter medications) arises, inclusion or continuation of the subject may be at the discretion of the investigator after consultation with the sponsor. Any medication used during the course of the study must be documented.

7.8. Treatment after the End of the Study

Not applicable.

8. Discontinuation Criteria

Subjects discontinuing from the treatment or study prematurely for any reason should complete AE and other follow-up procedures per Section 2 of this protocol.

8.1. Discontinuation from Study Treatment

Discontinuation of the study drug for abnormal liver test results **should be considered** by the investigator when a subject meets 1 of the following conditions after consultation with the Lilly-designated medical monitor:

- Occurrence of 1 case of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5X ULN in the absence of alternate explanation
- ALT or AST >3X ULN, sustained for more than 2 weeks
- ALT or AST >3X ULN and total bilirubin level (TBL) >2X ULN or prolonged prothrombin time or INR >1.5
- ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- alkaline phosphatase (ALP) >3X ULN
- ALP >2.5X ULN and TBL >2X ULN
- ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

Subjects may also be discontinued for a positive SARS-CoV-2 virus PCR test or evidence for COVID-19 during the study. All local requirements with respect to COVID-19 will be followed according to local/ site SOP.

8.1.1. Discontinuation of Inadvertently Enrolled Subjects

If the sponsor or investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the sponsor and the investigator to determine if the subject may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor to allow the inadvertently enrolled subject to continue in the study with or without continued treatment with study drug.

8.2. Discontinuation from the Study

Subjects will be discontinued under the following circumstances:

- Enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- **Investigator Decision**: the investigator decides that the subject should be discontinued from the study for the following reasons:

- If continuation in the study would be detrimental to the subject's well-being, in particular in case of an AE
- Lost to follow-up after 3 attempts to contact the subject through phone, text message, or e-mail

If the investigator withdraws a subject for a study drug-related reason (according to investigator's judgment), he/she is considered a dropout. Dropouts may be replaced, where the sponsor deems this necessary.

- **Subject Decision:** the subject requests to be discontinued from the study.
- **Sponsor's Decision:** Lilly stops the study or stops the subject's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).
- Requirement of prohibited medication.
- Subject's failure to comply with protocol requirements or study-related procedures.
- Termination of the study by the sponsor or regulatory authorities.

8.3. Patients/Subjects Lost to Follow-up

Every effort must be made to contact subject who do not return for a planned visit and the reason for withdrawal should be documented in the EDC. The subject can only be declared as 'lost to follow-up' if the investigator has had no success in contacting the subject. Subjects who withdraw from the study before completion of all study activities may be replaced at the discretion of the sponsor.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, detailing the study procedures and their timing (including tolerance limits for timing).

Appendix 2 lists the laboratory tests that will be performed for this study.

Appendix 5 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

Unless otherwise stated in the following subsections, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

Not applicable.

9.2. Adverse Events

A clinical trial AE is any untoward medical event associated with the use of a drug or drug delivery system in humans, whether or not it is considered related to that drug or drug delivery system.

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the study drug or the study-related procedure, or that caused the subject to discontinue the study drug before completing the study. The subject should be followed up until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

After the informed consent form (ICF) is signed, the CRU staff will record, via EDC, the occurrence and nature of each subject's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Additionally, CRU staff personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment or a study procedure, taking into account the disease, concomitant treatment, or pathologies.

A "reasonable possibility" means that there is a potential cause and effect relationship between the investigational product, study device and/or study procedure, and the AE.

Planned surgeries should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a subject's study drug is discontinued as a result of an AE, CRU staff must report this to Lilly or its designee via EDC.

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in 1 of the following:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent 1 of the other outcomes listed in the definition above.

The CRU staff must alert the sponsor's medical monitor, or its designee, of any SAE as soon as practically possible.

Additionally, study CRU staff must alert Lilly Global Patient Safety, or its designee, of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed up with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Although all AEs are recorded in the EDC after signing informed consent, SAE reporting to the sponsor begins after the subject has signed informed consent and has received the study drug. However, if an SAE occurs after signing informed consent, but prior to receiving the study drug, AND is considered reasonably possibly related to a study procedure then it MUST be reported.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued from and/or completed the study. Serious adverse events will be collected for 30 days after the last dose of study drug. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

Pregnancy (maternal or paternal exposure to the study drug) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

The designated medical monitor of the sponsor will monitor safety data throughout the course of the study. The sponsor and/or its designee will review SAEs within appropriate time frames to meet reporting obligations imposed by regulatory authorities. All serious and unexpected AEs

for this study will be reported to regulatory authorities in accordance with local laws, directives, and regulations.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator reports as related to investigational product or procedure. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance.

9.2.2. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical trials to ensure the safety of subjects, monitor quality, and to facilitate process and product improvements.

Subjects should be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

9.3. Treatment of Overdose

An overdose is not expected, as the study drug will be administered by a trained staff member at the CRU.

There is no known antidote to LY3473329 overdose; use symptomatic measures to treat the overdose.

9.4. Safety

9.4.1. Laboratory Tests

For each subject, laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2).

With the exception of safety laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests.

9.4.2. Vital Signs

For each subject, vital sign measurements should be conducted according to the Schedule of Activities (Section 2).

Subject must be supine for approximately 5 minutes before blood pressure and pulse rate collection and remain supine but awake during measurement. Systolic and diastolic blood pressure and pulse rate should be measured after the ECG (if the ECG is recorded at the same time point) and before other procedures according to the Schedule of Activities (Section 2).

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured during each study period if warranted.

9.4.3. Electrocardiograms

For each subject, ECGs should be collected according to the Schedule of Activities (Section 2).

Subject must be supine for approximately 5 minutes before ECG collection and remain supine but awake during ECG recording. Except screening visit, consecutive triplicate ECGs will be obtained and all 3 recordings should be completed within 5 minutes. Electrocardiograms may be obtained at additional times, when deemed clinically necessary.

Electrocardiograms should be recorded prior to the vital signs and any other scheduled study procedure (Section 2). All ECGs recorded should be stored at the investigational site.

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the subject receives the first dose of the study drug should be reported to Lilly, or its designee, as an AE.

9.4.4. Physical Examination

For each subject, a complete or directed physical examination will be performed according to the Schedule of Activities (Section 2).

9.4.5. Safety Monitoring

The sponsor will monitor safety data throughout the course of the study.

9.4.5.1. Hepatic Safety

If a subject experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatinine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on consultation with the sponsor's medical monitor. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

Additional safety data should be collected if 1 or more of the following conditions occur:

- elevation of serum ALT to ≥5X ULN on 2 or more consecutive blood tests
- elevation of serum TBL to ≥2X ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2X ULN on 2 or more consecutive blood tests
- subject discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be an SAE.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2) and Pharmacokinetic Sampling Schedule (Appendix 6), blood samples of approximately 3 mL each 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 on Day 1 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.

The sampling schedule may be modified following review of PK data from the initial cohorts, to optimize collection times.

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 early termination visit, if applicable.

9.5.1. Bioanalysis

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Plasma concentrations of LY3473329 will be assayed using validated liquid chromatography methods. Analyses of samples collected from placebo-treated subjects are not planned. Samples may also be subjected to metabolite profiling.

Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 2 years following the last subject visit for the study.

9.6. Pharmacodynamics

9.6.1. Lipoprotein(a)

At the visits and times specified in the Schedule of Activities (Section 2), blood samples will be collected to obtain serum for a lipoprotein panel to include levels of Lp(a), high-density lipoprotein-cholesterol, LDL-C, triglycerides, total cholesterol, and ApoB.

9.6.2. Other Pharmacodynamic Markers

At the visits and times specified in the Schedule of Activities (Section 2), blood samples will be collected to measure high-sensitivity C-reactive protein (hs-CRP), plasminogen concentration, plasminogen activity, plasminogen activator inhibitor, tissue plasminogen activator, and α_2-antiplasmin.

9.7. Genetics

Not applicable.

9.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of subject response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of

these questions through measurement of biomolecules including DNA, RNA, proteins, lipids, and other cellular elements.

Blood samples for exploratory biomarker research will be collected at the times specified in the Schedule of Activities (Section 2), and per the list provided in Appendix 2, where local regulations allow.

Samples will be used for research on the drug target, disease process, variable response to study drug, pathways associated with disease, mechanism of action of study drug, and/or research method, or for validating diagnostic tools or assay(s) related to disease. All samples will be coded with the subject number. These samples and any data generated can be linked back to the subject only by the investigative CRU staff.

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or ethical review board (ERB) impose shorter time limits, at a facility selected by Lilly. This retention period 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 study drug or after study drug is commercially available.

A storage sample will be collected for research purposes. A portion of the sample will be used to assess Lp(a) levels by the Randox Assay at a qualified vendor. The remainder of the sample will be stored for assays that cannot be specifically listed at time of collection, or to be tested in assays not yet available to research the drug target, disease process, response to study drug, pathways associated with disease, and/or mechanism of action of study drug. Subjects will be properly consented to allow for such testing in the study informed consent document. The stored samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or ERB impose shorter time limits, at a facility selected by Lilly.

9.9. Health Economics

Not applicable.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Part A: The sample size for each cohort is customary for the first-in-human study in which formal power analyses are not necessary to address the objectives associated with safety, tolerability, PK, and/or other assessments.

Part B: The sample size for each cohort, except the final cohort, is customary for a first multiple-dose study. The sample size for the final cohort of Part B has been shown, through simulations, to be optimal for detecting a clinically meaningful decrease in Lp(a) with confidence appropriate for this Phase 1 study.

10.2. Populations for Analyses

Pharmacokinetic and PD analyses will be conducted using data from all subjects who receive at least 1 dose of the investigational product and have evaluable PK or PD data.

Safety analyses will be conducted for all enrolled subjects, whether or not they completed all protocol requirements.

Analyses will be reported separately for Parts A and B. Placebo-treated subjects from each cohort will pooled into a single treatment group within each study part.

10.2.1. Study Participant Disposition

All subjects who discontinue from the study will be identified, and the extent of their participation in the study will be summarized by treatment. If known, a reason for their discontinuation will be given.

10.2.2. Study Participant Characteristics

Subject demographics (age, gender, race, ethnicity, height, weight, and body mass index) will be summarized by treatment.

10.3. Statistical Analyses

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

10.3.1. Safety Analyses

Safety analyses will be conducted using all subjects who received at least one dose of study drug. No statistical comparisons of treatment groups will be completed for safety endpoints.

All treatment and protocol procedure AEs will be listed. If the frequency of events allows, treatment-emergent AEs, events that emerge or worsen after the first dose of study drug, will be summarized using descriptive methodology. Summary statistics for AE and SAE will be provided by dose level and for all placebo-treated subjects combined.

Safety assessments include laboratory tests, vital signs, ECG, and physical examination. The parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed as required.

10.3.2. Pharmacokinetic Analyses

Pharmacokinetic parameter estimates for LY3473329 will be calculated using standard noncompartmental methods.

The primary PK endpoints will be maximum observed drug concentration (C_{max}), area under the concentration versus time curve (AUC), and time to C_{max} (t_{max}) of LY3473329. Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution may be reported.

Pharmacokinetic parameters will be summarized by dose level using descriptive statistics.

Mean and individual LY3473329 plasma concentration versus time curves will be graphically presented. Other analyses such as population PK modeling may be performed as needed.

10.3.2.1. Pharmacokinetic Statistical Inference

Dose proportionality for exposure parameters (AUC, C_{max}) may be assessed using the power model approach (Smith et al. 2000).

10.3.3. Pharmacodynamic Analyses

Summary statistics for each exploratory biomarker endpoint, including Lp(a) and hs-CRP, will be provided by dose level and for all placebo-treated subjects combined.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Statistical analyses will be detailed in the statistical analysis plan.

10.3.4. Pharmacokinetic/Pharmacodynamic Analyses

The relationship between LY3473329 PK, exploratory biomarkers, and/or safety measures may be evaluated. Other analyses such as population PK/PD modeling or exposure-QT analyses may be performed as needed.

10.3.5. Data Review during the Study

Data will be reviewed following each cohort prior to dose escalation as described in Section 7.4.

10.3.6. Interim Analyses

No interim analyses are planned for this study.

11. References

Shapiro AD, Nakar C, Parker JM, et al. Plasminogen replacement therapy for the treatment of children and adults with congenital plasminogen deficiency. *Blood*. 2018;131(12):1301-1310.

Smith BP, Vandenhende F, DeSante KA, et al. Confidence interval criteria for assessment of dose proportionality. *Pharm Res*. 2000;17(10):1278-1283.

Thorne JG, James PD, Reid RL. Heavy menstrual bleeding: is tranexamic acid a safe adjunct to combined hormonal contraception? *Contraception*. 2018;98(1):1-3.

Viney NJ, van Capelleveen JC, Geary RS, et al. Antisense oligonucleotides targeting apolipoprotein(a) in people with raise lipoprotein(a): two randomized, double-blind, placebo-controlled, dose-ranging trials. *Lancet*. 2016;388(10057):2239-2253.

Vogt A. Lipoprotein(a)-apheresis in the light of new drug developments. *Atherosclerosis Suppl*. 2017;30:38-43.

12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Apo	apolipoprotein
assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and potential risks involved in participating in a study (required by some institutional review boards [IRBs]/ethical review boards [ERBs]).
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
$AUC_{0-\infty}$	area under the concentration versus time curve from time zero to infinity
blinding	A procedure in which 1 or more parties to the study are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A double-blind study is one in which neither the subject nor any of the investigator or the sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received
clinical research physician	Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
C_{max}	maximum observed drug concentration
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 the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be re-tested at some defined time point, depending on the steps required to obtain confirmed results.
CRU	clinical research unit
ECG	electrocardiogram

EDC	electronic data capture
enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.
enter	Subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
F	bioavailability
GCP	good clinical practice
GFR	glomerular filtration rate
GLP	good laboratory practice
HIV	human immunodeficiency virus
hs-CRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
informed consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
INR	international normalized ratio
investigational product (IP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, 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.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
LDL	low-density lipoprotein
legal representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.
Lp(a)	lipoprotein (a)
MAD	multiple-ascending dose

MTD	maximum tolerated dose
NOAEL	no-observed-adverse-effect level
noninvestigational product (non-IP)	A product that is not being tested or used as a reference in the clinical study, but is provided to subjects and used in accordance with the protocol, such as concomitant or rescue/escape medication for preventative, diagnostic, or therapeutic reasons, medication to ensure adequate medical care, and/or products used to induce a physiological response.
PK/PD	pharmacokinetics/pharmacodynamics
QD	once daily
randomize	The process of assigning subjects/patients to an experimental group on a random basis.
SAD	single-ascending dose
SAE	serious adverse event
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.
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life associated with the terminal rate constant in noncompartmental analysis
TBL	total bilirubin level
ULN	upper limit of normal

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

Hematology
- Hematocrit
- Hemoglobin
- Erythrocyte count (RBC)
- Mean cell volume
- Mean cell hemoglobin
- Mean cell hemoglobin concentration
- Leukocytes (WBC)
- Platelets
- PT/INR, (aPTT)
- Differential WBC (absolute counts and/or %) of:
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils

Urinalysis (Dipstick)
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Blood
- Nitrite
- RBC and WBC counts

Clinical Chemistry
- Sodium
- Potassium
- Glucose (fasting)
- Blood urea nitrogen (BUN)
- Total cholesterol
- Total protein
- Albumin
- Total bilirubin
- Alkaline phosphatase (ALP)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Creatinine
- Gamma-glutamyl transferase (GGT)

Alcohol urine test (ethanol testing)[a,b]

Urine drug screen[a,b]
- Amphetamine (including XTC)
- Barbiturates
- Benzodiazepine
- Cannabinoids
- Cocaine
- Methadone
- Opiates

- Hepatitis B surface antigen
- Hepatitis C antibody
- HIV

Abbreviations: HIV = human immunodeficiency virus; RBC = red blood cell; WBC = white blood cell.

[a] Performed at screening and Day -1.

[b] Urine drug screen and sample for ethanol level may be repeated prior to admission to the clinical research unit and at other times indicated in the Schedule of Activities.

Exploratory Biomarkers

Lp(a) (ethylenediaminetetraacetic acid serum)
Plasminogen activator inhibitor (PAI)
High-sensitivity C-reactive protein (hs-CRP)
Tissue plasminogen activator (tPA)
α_2-antiplasmin

Plasminogen activity (citrate plasma)
Plasminogen concentration mass (citrate plasma)

Appendix 3. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

The investigator is responsible for

- ensuring that the subject understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each subject or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's willingness to continue his or her participation in the study.
- providing a copy of the ICF to the participant or the participant's legal representative and retaining a copy on file.

Recruitment

Lilly or its designee is responsible for the central recruitment strategy for subjects. Individual investigators may have additional local requirements or processes. Study-specific recruitment material should be approved by Lilly.

Ethical Review

The investigator must give assurance that the ERB was properly constituted and convened as required by International Council for Harmonization (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the CRU. Lilly or its representatives must approve the ICF before it is used at the CRU. All ICFs must be compliant with the ICH guideline on GCP.

The study site's ERB(s) should be provided with the following:

- study protocol and any amendments during the course of the study
- the current IB and updates during the course of the study
- ICF
- relevant curricula vitae

Regulatory Considerations

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

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
2) applicable ICH GCP Guidelines
3) applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third-party organization.

Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Final Report Signature

The sponsor's responsible medical officer and statistician will sign/approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional materials to the study sites, as appropriate.
- provide training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site.
- be available for consultation and stay in contact with the study site personnel through mail, telephone, and/or fax.
- review and evaluate CRF data and/or use standard computer edits to detect errors in data collection.
- conduct a quality review of the database.

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

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to the original source documents.

Data Collection Tools/Source Data

An EDC system will be used in this study. The site must define and retain all source records and must maintain a record of any data where source data are directly entered into the data capture system.

Data Protection

Data systems used for the study will have controls and requirements in accordance with local data protection law.

The purpose and use of subject personal information collected will be provided in a written document to the subject by the sponsor.

Study and Site Closure

Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with subjects in consultation with Lilly or its designee clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin time
WBC	Prothrombin time, INR
Neutrophils	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Conjugated bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear Antibody[a]**
AST	**Alkaline Phosphatase Isoenzymes[a]**
GGT	**Anti-smooth Muscle Antibody (or Anti-actin**
CPK	**Antibody)[a]**

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cell; WBC = white blood cell.

[a] Assayed by Lilly-designated or local laboratory.

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

Appendix 5. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study.

Protocol J2O-MC-EKBA Sampling Summary Part A

Part A	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests	16	1	16
Clinical laboratory tests	6.5	5	32.5
aPTT/INR	4.5	5	22.5
Pharmacokinetics	3	18	54
Biomarkers tPa	4.5	6	27
Biomarkers plasminogen concentration	4.5	11	49.5
Biomarkers plasminogen activity, PAI, α2-antiplasmin	4.5	6	27
Biomarkers hs-CRP and lipoprotein panel blood sample	3.5	4	14
Total for all cohorts			242.5

Additional samples may be drawn if needed for safety purposes.
Volumes may differ slightly between sites based on local laboratory requirements.

Protocol J2O-MC-EKBA Sampling Summary Part B

Part B	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests	16	1	20.5
Clinical laboratory tests	6.5	8	52
aPPT/INR	4.5	8	36
Pharmacokinetics	3	28	84
Biomarkers tPa	4.5	6	27
Biomarkers plasminogen concentration	4.5	16	72
Biomarkers plasminogen activity. PAI, α2-antiplasmin	4.5	8	36
Biomarkers hs-CRP and lipoprotein panel blood sample	3.5	11	38.5
Storage sample	5	5	25
Total for all cohorts			391

Additional samples may be drawn if needed for safety purposes.
Volumes may differ slightly between sites based on local laboratory requirements.

Appendix 6. Pharmacokinetic Sampling Summary

	Sample Collection Times	
Day	**Part A SAD**	**Part B MAD**
1	Pre-dose	Pre-dose
	Postdose: 1 hour 2 hours 4 hours 6 hours 8 hours 12 hours	Postdose: 1 hour 2 hours 4 hours 6 hours 8 hours 12 hours
2	24 hours postdose	Pre-dose
3	48 hours postdose[a]	
4	72 hours postdose[a]	
5		Pre-dose
8	X[a]	Pre-dose
11		Pre-dose
14		Pre-dose
		Postdose: 1 hour 2 hours 4 hours 6 hours 8 hours 12 hours
15	X[a]	24 hours postdose, prior to discharge
18		X[a]
22	X[a]	X[a]
29		X[a]
43	X[a]	X[a]
64	X[a]	X[a]
85	X[a]	X[a]
106	X[a]	X[a]
137		X[a]
ED[b]	X[a]	X[a]

Abbreviations: ED = early discontinuation; MAD = multiple-ascending dose; PK = pharmacokinetics; SAD = single-ascending dose.

[a] Samples identified with an X may be obtained at any time within the scheduled days; the exact date and time of sample collection must be recorded.

[b] If applicable.

Timing of PK sample collection may be adjusted based on clinical needs. The exact sample collection date and times must be recorded.

Appendix 7. Protocol Amendment J2O-MC-EKBA(c) Summary
A Safety, Tolerability, and Pharmacokinetic Study of Single- and Multiple-Ascending Doses of LY3473329 in Healthy Subjects

Overview

Protocol J2O-MC-EKBA, A Safety, Tolerability, and Pharmacokinetic Study of Single- and Multiple-Ascending Doses of LY3473329 in Healthy Subjects, has been amended. The new protocol is indicated by Amendment (c) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are described in the following table:

Amendment Summary for Protocol J2O-MC-EKBA Amendment (c)

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis, Summary of Study Design	Added additional cohort to Part A.	To extend the dose range
Protocol Synopsis, Treatment Arms and Planned Duration for an Individual Subject	Updated the maximum planned dose to 800 mg in Part A and to 700 mg in Part B.	To extend the dose range
Study Schedule	Added the collection of additional plasminogen samples on S1 and Study Days 3 and 4 for concentration and activity.	To be consistent with inclusion criteria and evaluate the 48-hour window
Section 5.1 Overall Design	Added additional cohort to Part A. Updated the study design to include Cohort 7.	To extend the dose range
Section 5.2 Number of Participants	Increased the number of subjects randomized.	To ensure there are 8 evaluable subjects in the added Cohort 7
Section 5.5 Justification for Dose	Updated the maximum dose to 800 mg in Part A and updated the dose range for Part B from 30 mg up to 700 mg. Provided justification for modifying the doses.	To extend the dose range
Section 6.1 Inclusion Criteria	Clarified that plasminogen activity and concentration should be within normal range. Added plasminogen collection for concentration and activity at S1.	To clarify which plasminogen values are relevant for inclusion
Section 7.1 Treatment Administered	• Clarified the updates to the doses in Part A and Part B. • Updated the weight from ±10% to ±5%.	• To be consistent with the extended dose range • Weight was updated to match the IMPD

Amendment Summary for Protocol J2O-MC-EKBA Amendment (c)

Section 7.4 Dose Modification	Updated the predicted mean steady-state concentration in Part B to 500 ng/mL, which is predicted to be achieved with the updated 700 mg dose.	To replace predictions of human exposure that were based on scaling from nonclinical species to those based on observations in humans
Section 7.4.1.2 Dose Escalation Part B	Clarified that data from Cohort 7, in Part A, will be reviewed and data from Lp(a) and plasminogen activity will be reviewed before dose confirmation for Cohort 4 in Part B occurs. Data from Lp(a) and plasminogen activity will be reviewed before dose confirmation for Cohort 5 in Part B occurs.	To specify the data that will be used to select the dose used in Part B, Cohorts 4 and 5
Section 9.8 Biomarkers	Clarified that a portion of the stored sample will be used for the Randox Assay to asses Lp(a) levels.	To formalize the plan for a portion of the stored samples
Appendix 5 Blood Sampling Summary	Updated the volumes collected to account for the extra plasminogen sample collections.	To account for the additional samples

Abbreviations: IMPD = investigational medicinal product dossier; Lp(a) = lipoprotein (a).

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

1. Protocol Synopsis

Summary of Study Design:

Part A

Single-ascending doses of LY3473329 will be administered in up to ~~6~~ 7 cohorts of 8 subjects (6 LY3473329, 2 placebo) each. For the first cohort, 2 subjects will receive a sentinel dose (1 each with LY3473329 and placebo). Dosing of the remaining subjects in the cohort will occur after review of the safety data through 24 hours postdose. Dose escalation may proceed after review of all safety data through Day 3 from the prior cohort.

Treatment Arms and Planned Duration for an Individual Subject:
Part A: Within each cohort, subjects will be randomly assigned to receive either LY3473329 or placebo in a 6:2 ratio. A single dose of either LY3473329 or placebo will be orally administered to each subject on Day 1 starting at 1 mg with a maximum planned dose of ~~300~~800 mg.

Part B: In the first 4 cohorts, subjects will be randomly assigned to receive either LY3473329 or placebo in a 8:2 ratio. In the last cohort, subjects will be randomly assigned to receive either LY3473329 or placebo in a 15:2 ratio. The planned dose levels may range between ~~1~~30 and ~~100~~700 mg QD.

Number of Subjects:
Part A: ~~48~~56 subjects will be enrolled and randomized for an estimated 8 evaluable subjects in each of the ~~6~~ 7 cohorts.

Study Schedule Protocol J2O-MC-EKBA Multiple-Ascending Dose (MAD) – Part B

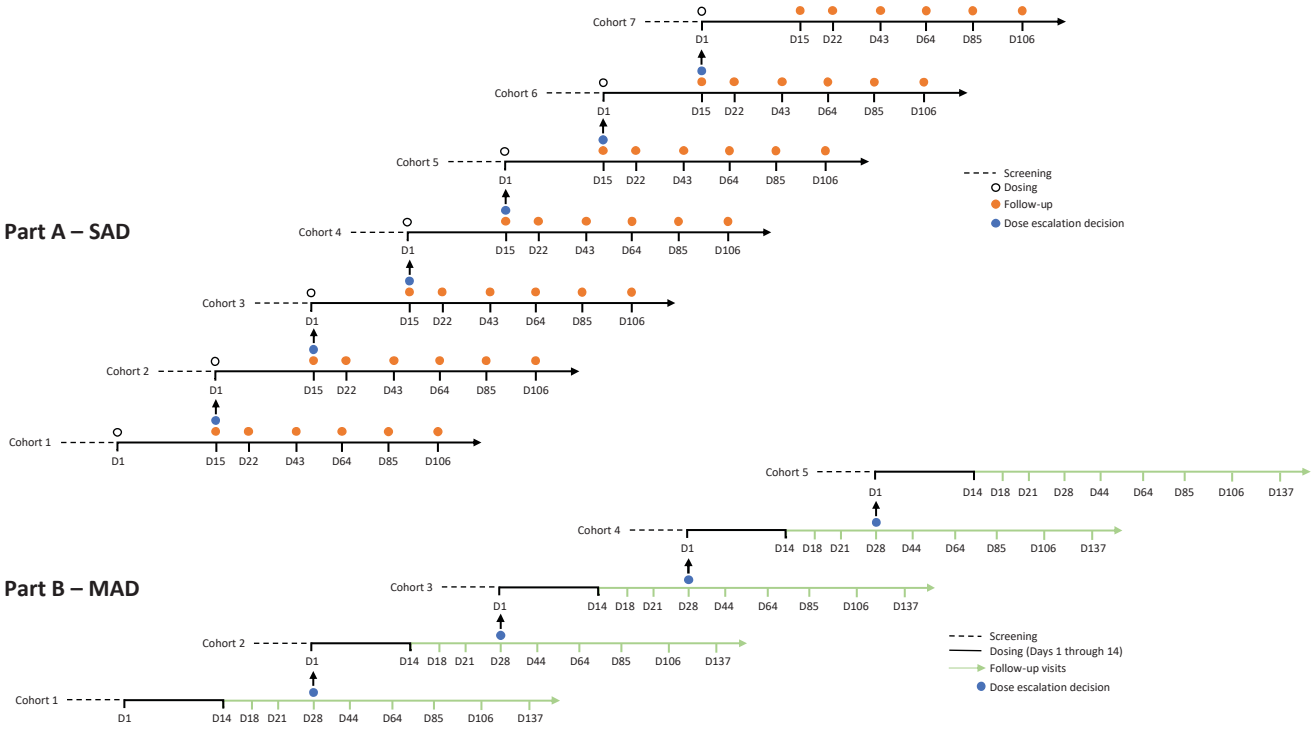
	S1	S2	Treatment Period																FU								ED [a]
Study Day	**-60**	**-28**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**18**	**22**	**29**	**43**	**64**	**85**	**106**	**137**	
Visit Window																			**±1**	**±1**	**±1**	**±4**	**±3**	**±3**	**±3**	**±3**	
Visit	**1[b]**	**2[b]**	**3**																**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Plasminogen concentration [g]	X			P	P	P	P			P							P	X	X	X	X	X	X	X	X	X	X
Plasminogen activity[g,h]	X			P	P	P	P			P							P	X	X	X	X	X	X	X	X	X	X

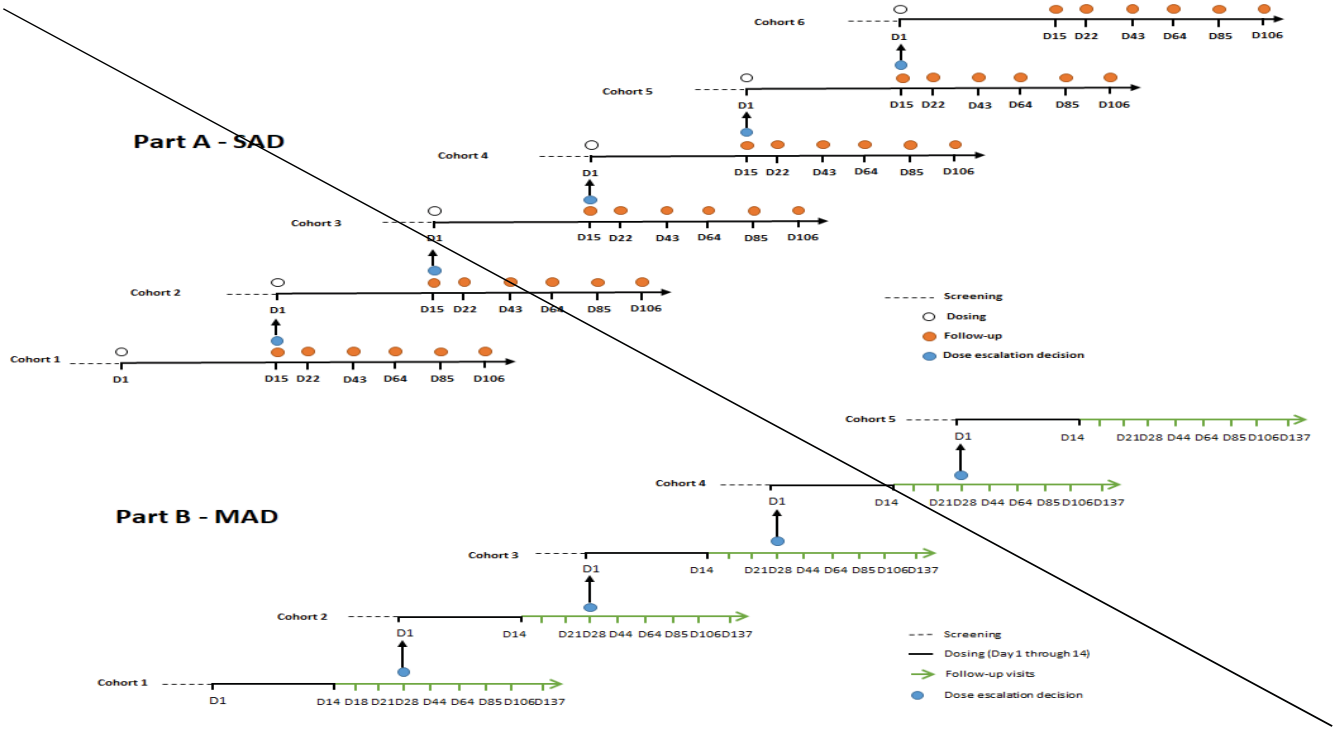
5. Study Design

5.1. Overall Design

Part A

Single-ascending doses of LY3473329 will be administered in up to ~~6~~ 7 cohorts of 8 subjects each. Subjects will be randomly assigned to receive either LY3473329 or placebo in a 6:2 ratio. For the first cohort, 2 subjects will receive a sentinel dose (1 each with LY3473329 and placebo) with subsequent dosing of the remaining cohort after review of the safety data through 24 hours postdose. The guideline for dose escalation is detailed in Section 7.4.


Part A – SAD
Cohort 7
Cohort 6
Cohort 5
Cohort 4
Cohort 3
Cohort 2
Cohort 1
D1
D15
D22
D43
D64
D85
D106
Screening
Dosing
Follow-up
Dose escalation decision
Part B – MAD
Cohort 5
Cohort 4
Cohort 3
Cohort 2
Cohort 1
D1
D14
D18
D21
D28
D44
D64
D85
D106
D137
Screening
Dosing (Days 1 through 14)
Follow-up visits
Dose escalation decision


Part A - SAD
Cohort 6
Cohort 5
Cohort 4
Cohort 3
Cohort 2
Cohort 1
D1
D15 D22 D43 D64 D85 D106
Screening
Dosing
Follow-up
Dose escalation decision
Part B - MAD
D14
D21D28 D44 D64 D85 D106D137
D14 D18 D21D28 D44 D64 D85 D106D137
Dosing (Day 1 through 14)
Follow-up visits

5.2. Number of Participants

Part A: ~~48~~56 subjects will be randomized for an estimated 8 evaluable subjects in each of the ~~6~~ 7 cohorts.

5.5. Justification for Dose

The dose ranges proposed for investigation are single doses of 1 to ~~300~~800 mg orally for the SAD, and ~~1~~30 to ~~100~~700 mg QD orally for the MAD. These doses may be increased or decreased based on evaluation of available safety and PK data during the dose escalation.

The initial SAD projections ~~are~~were based on pharmacodynamic (PD) responses of Lp(a) reductions observed in a monkey efficacy model. The ~~proposed~~ efficacious dose range ~~is~~was originally predicted to be 10 to 15 mg QD; however, the observed LY3473329 exposures in humans were lower than the predictions based on allometry. Also, the 30-mg QD dose achieved a mean reduction in Lp(a) of approximately 26%. Based on the observed safety and tolerability at single doses from 1 mg to 200 mg and multiple daily doses of 30 mg, the planned dose range has been extended to 800 mg as a single dose and 700 mg for multiple daily doses in order to evaluate the potentially pharmacologically active dose range. The planned range of doses to be studied is supported by 1-month GLP toxicology studies in rats and monkeys. Daily oral doses of up to 1000 mg/kg produced no adverse effects in rats or monkeys. Serum plasminogen level decreased, but no effects in animals were attributed to this factor. Importantly, in humans LY3473329 has not appeared to have a clinically relevant effect on plasminogen concentration and activity. Preliminary safety evaluations have occurred on blinded data for the SAD and MAD conducted to date. There are no AEs reported to be severe or meet SAE criteria, and the majority have been mild in severity. Vital signs, ECGs and clinical labs have resulted in no clinically meaningful observations.

Human PK for LY3473329 was predicted based on allometric scaling from a 2-compartment monkey PK model. Projected human PK parameters include systemic clearance (CL) of 0.053 L/h, bioavailability (F) of 8% (apparent oral clearance [CL/F] ~ 0.663 L/h), and volume of distribution at steady state (V_{ss}) of 22 L (Vss/F ~275 L), and a terminal $t_{1/2}$ of 21 days. In contrast, in the 30-mg daily dose cohort of the MAD the ~~observed apparent oral clearance (~~CL/F~~)~~ was approximately ~~47 to~~ 65 L/h, terminal volume of distribution (V_z/F) was 2775 L, and $t_{1/2}$ was ~~19 to~~ 30 hours ~~The predicted efficacious~~ A dose of 15 mg QD ~~is~~was expected to achieve average plasma concentrations that approximate the observed half-maximal effective concentration (EC50) in monkey of 900 ng/mL; however, the observed human exposures were lower than predicted. For example, the average steady-state concentration (AUC_{tau}/24h) for a 30-mg daily dose was 19 ng/mL. In nonclinical species, F decreased with increasing dose. Although this nonlinearity in F is expected to be observed in humans, the scaling factor is unknown; therefore, dose determination for each cohort will be based not only on safety/tolerability but also on the observed human PK.

The starting dose of 1 mg was selected to provide an exposure multiple of at least 39-fold compared to the highest dose and exposure tested in monkeys (NOAEL = 1000 mg/kg) and ~~is~~was also approximately one-tenth of the original predicted efficacious dose. No adverse effects

were noted in rats or monkeys administered daily doses of up to 1000 mg/kg. Decreases in plasminogen, a known property of LY3473329 for rat and monkey plasminogen specifically, were noted, but no impact on the health of the toxicology study animals was observed. The doses and dose- and exposure-based multiples based on the observed human exposures are provided in Table 5.1, and more detail about the toxicology studies is provided in the IB.

The original top dose of 300 mg was selected to be 20- to 30-fold above the predicted efficacious dose to ensure adequate interrogation of the mechanism, assuming safety and tolerability are maintained. The amended top dose of 800 mg was chosen given the lower-than-expected exposures and the observed human safety and tolerability to date. Furthermore, taking into consideration the observed human exposure at 200 mg and assuming a dose proportional increase in exposure up to 800 mg, the predicted area under the concentration versus time curve from time zero to infinity ($AUC_{0-\infty}$) at the top dose of 800 mg (3.7 µg*h/mL) is now expected to be 16x lower than the monkey NOAEL. In addition to a maximum unit dose, a maximum single dose ~~area under the concentration versus time curve from time zero to infinity (~~$AUC_{0-\infty}$~~)~~ of approximately 250 µg*h/mL (geometric mean, approximately 10-fold above the predicted efficacious exposure and the rat NOAEL which would give a margin of safety of approximately 1) is planned, given the uncertainty in the prediction of human PK, PD, and the translation of nonclinical toxicology to humans.

Table 5.1. Margin of Safety for Oral Administration of LY3473329 Based on Administered Dose and Total Exposure

	Reference Human Dose (mg)	Dose (mg/kg)	Dose (mg/m^2)	Dose Multiple[a]	AUC (µg•h/mL)	C_{max} (µg/mL)	Exposure Multiple (AUC)[a]	Exposure Multiple (C_{max})
Human[b]				–			–	
Starting	1	0.017	0.63		0.028	0.0019		
Highest	800	13.3	500		3.74	0.21		
Rat	1	1000	6000	>9500x	254	14	9100x	7400x
NOAEL[c]	800			12x			68x	67x
Monkey	1	1000	12000	>19,000x	58.9	7.2	2100x	3800x
NOAEL[d]	800			24x			16x	34x

Abbreviations: AUC = area under the concentration versus time curve; $AUC_{0-\infty}$ = AUC from time zero to infinity; AUC0-τ = AUC during 1 dosing interval; C_{max} = maximum observed plasma concentration; NOAEL = no-observed-adverse-effect level; PK = pharmacokinetics.

a Dose multiple is the dose in animals/dose in humans based on mg/m^2. Exposure multiple is the calculated $AUC_{0-\tau}$ after repeated dosing in animals/$AUC_{0-\infty}$ in humans~~,~~ using observed human PK and assuming dose proportional increase in exposure from 200 mg to 800 mg.

b Plasma PK shown ~~was estimated based on allometric scaling of the monkey PK~~ are based on the observations in Study EKBA over a single dose range of 1 mg to 200 mg.

c NOAEL was determined in a 2-week repeat-dose toxicity study (Study 8415-459). Exposures are for Day 14 for the combined sex results.

d NOAEL was determined in a 26-day repeat-dose toxicity study (Study 8425-460). Exposures are for Day 26 for the combined sex results.

~~Table 5.1. Margin of Safety for Oral Administration of LY3473329 Based on Administered Dose and Predicted Exposure~~

	~~Reference Human Dose (mg)~~	~~Dose (mg/kg)~~	~~Dose (mg/m^2)~~	~~Dose Multiple[a]~~	~~AUC (µg•h/mL)~~	~~C_{max} (µg/mL)~~	~~Exposure Multiple (AUC)[a]~~	~~Exposure Multiple (C_{max})~~
~~Human[b]~~				–			–	
~~Starting~~	~~1~~	~~0.017~~	~~0.63~~		~~1.5~~	~~0.019~~		
~~Highest~~	~~300~~	~~5~~	~~185~~		~~453~~	~~5.8~~		
~~Rat NOAEL[c]~~	~~1~~ ~~300~~	~~1000~~	~~6000~~	~~>9500x~~ ~~32x~~	~~254~~	~~14~~	~~170x~~ ~~0.56x~~	~~740x~~ ~~2.4x~~
~~Monkey NOAEL[d]~~	~~1~~ ~~300~~	~~1000~~	~~12000~~	~~>19,000x~~ ~~65x~~	~~58.9~~	~~7.2~~	~~39x~~ ~~0.13x~~	~~380x~~ ~~1.2x~~

6. Study Population

6.1. Inclusion Criteria

7. Part B, in addition to criterion 6,
    a. Lp(a) ≥75 nmol/L or 30 mg/dL at screening.
    b. Plasminogen concentration and activity are both ~~is~~ within the normal range at screening.

6.2. Exclusion Criteria

16. Positive SARS-CoV-2 virus nasopharyngeal PCR test ~~at Day -1~~before admission.

7. Treatment

7.1. Treatment Administration

LY3473329 doses are planned to range between 1 mg to ~~300~~800 mg~~daily~~. The planned dose levels for Part A ~~are~~were 1 mg, 3 mg, 10 mg, 30 mg, 100 mg, and up to 300 mg. The actual dose levels studied based on the review of safety, PK, and PD data were 1 mg, 10 mg, 30 mg,100 mg, 200 mg, and 400 mg. A seventh single-dose cohort is now planned for a dose of 800 mg, contingent on review of the safety, PK, and PD data at the 400-mg dose level. The planned dose levels for Part B will be dependent on Part A as outlined in Section 5.1. ~~Potential~~The originally planned dose levels ~~are~~were 1 mg, 5 mg, 20 mg, 50 mg, and up to 100 mg QD. Based on the single-dose data, the first dose level in Part B was 30 mg. The second dose level in Part B was 100 mg, and subsequent dose levels are planned to be 300 mg, 500 mg, and 700 mg QD.

LY3473329 drug product is supplied as capsules prepared extemporaneously by the addition of an adequate amount of LY3473329 drug substance into an empty hydroxypropyl methylcellulose (HPMC) capsule shell and where the dose strength is verified gravimetrically to the nearest decimal place and within ±~~10~~5% from the target strength (e.g., from 9.~~0~~5 to 1~~1~~0.~~0~~5 mg for a 10-mg strength capsule). LY3473329 and placebo capsules should be stored at 15°C to 30°C.

7.4. Dose Modification

All safety and available PD and PK data from prior cohorts will be used to support dose escalation. Dosing in the SAD (Part A) is not anticipated to exceed a mean $AUC_{0-\infty}$ of approximately 250 µg·h/mL, which is exposure at the rat NOAEL and is approximately 10-fold above the predicted efficacious exposure. Dosing in the MAD (Part B) is not anticipated to exceed a mean steady-state concentration($C_{ss,avg}$) of ~~6300~~500 ng/mL, which is predicted to be achieved by a dose of ~~100~~700 mg QD; planned dose levels are provided in Section 7.1.

7.4.1. Dose Escalation

7.4.1.2. Part B

- Dose confirmation for Cohort 4 in Part B will occur after review of all available safety data from at least the first 14 days in the prior cohorts and PK data through Day 8 of Part B Cohort 2 and also the available data from Cohort 7 in Part A. Additionally, any available PD data may be reviewed as needed, including but not limited to Lp(a) and plasminogen activity.
- Dose confirmation for Cohort 5 in Part B will occur after review of all available safety data from at least the first 14 days in the prior cohorts and PK data through Day 13 of Cohort 3. Additionally, any available PD data may be reviewed as needed, including but not limited to Lp(a) and plasminogen activity.

9. Study Assessments and Procedures

9.8 Biomarkers

A storage sample will be collected for research purposes. A portion of the sample will be used to assess Lp(a) levels by the Randox Assay at a qualified vendor. The remainder of the sample will be stored for assays that cannot be specifically listed at time of collection, or to be tested in assays not yet available to research the drug target, disease process, response to study drug, pathways associated with disease, and/or mechanism of action of study drug. Subjects will be properly consented to allow for such testing in the study informed consent document. The stored samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or ERB impose shorter time limits, at a facility selected by Lilly.

Appendix 5. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study.

Protocol J2O-MC-EKBA Sampling Summary Part B

Part B	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests	16	1	~~16~~20.5
Clinical laboratory tests	6.5	8	52
aPPT/INR	4.5	8	36
Pharmacokinetics	3	28	84
Biomarkers tPa	4.5	6	27
Biomarkers plasminogen concentration	4.5	~~14~~16	~~63~~72
Biomarkers plasminogen activity. PAI, α2-antiplasmin	4.5	~~6~~8	~~27~~36
Biomarkers hs-CRP and lipoprotein panel blood sample	3.5	11	38.5
Storage sample	5	5	25
Total for all cohorts			~~368~~391

Additional samples may be drawn if needed for safety purposes.
Volumes may differ slightly between sites based on local laboratory requirements.

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Approver: PPD

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Signature meaning: Approved

Approver: Robert PPD

Approval Date & Time: 19-Jan-2021 17:06:40 GMT

Signature meaning: Approved