Title Page

Protocol Title:		A Double-blind, Randomized, Placebo-controlled Phase 2 Study to Evaluate Efficacy, Safety, and Tolerability of Olpasiran (AMG 890) (a GalNAc-conjugated Small Interfering RNA [siRNA]) in Subjects With Elevated Lipoprotein(a)
Short Protocol Title:		Olpasiran trials of Cardiovascular Events And LipoproteiN(a) reduction – DOSE Finding Study (OCEAN[a]-DOSE)
Protocol Number:		20180109
Investigational Product:		Olpasiran (AMG 890)
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Data Elements Standards Version:		6

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures. **The format and content of this protocol is aligned with Good Clinical Practice: Consolidated Guidance (ICH E6).**

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Investigator's Agreement:

I have read the attached protocol entitled A Double-blind, Randomized, Placebo-controlled Phase 2 study to evaluate Efficacy, Safety, and Tolerability of Olpasiran (AMG 890) (a GalNAc-conjugated Small Interfering RNA [siRNA]) in subjects with elevated lipoprotein(a), dated **02 May 2022**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by: me (including, if applicable, my spouse or legal partner and dependent children) and my subinvestigators (including, if applicable, their spouses or legal partners and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

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1. Protocol Summary

1.1 Synopsis

Protocol Title: A Double-blind, Randomized, Placebo-controlled Phase 2 Study to Evaluate Efficacy, Safety, and Tolerability of Olpasiran (AMG 890) (a GalNAc-conjugated Small Interfering RNA [siRNA]) in Subjects with Elevated Lipoprotein(a)

Short Protocol Title: Olpasiran trials of Cardiovascular Events And LipoproteiN(a) reduction – DOSE Finding Study (OCEAN[a]-DOSE)

Study Phase: 2

Indication: Cardiovascular disease

Rationale

Study 20180109 is a double-blind, randomized, multicenter dose finding study in subjects with atherosclerotic cardiovascular disease and elevated lipoprotein(a) (Lp[a]). The primary objective is to test olpasiran subcutaneous (SC) once every 12 weeks (Q12W) compared with placebo on percent change from baseline in Lp(a) after 36 weeks of treatment. Additionally, an exploratory dose of 225 mg **once** every 24 weeks (Q24W) will be evaluated. Olpasiran is being developed for the treatment of patients with atherosclerotic cardiovascular disease and elevated Lp(a) to reduce the risk of cardiovascular events. Lp(a) reductions of $\geq 80\%$ from baseline are anticipated with olpasiran and it is expected that this level of reduction in Lp(a) may result in clinically meaningful cardiovascular benefit in patients with atherosclerotic cardiovascular disease (Kamstrup et al, 2009, Burgess et al, 2018, Lamina et al, 2019, Madsen et al, 2020). Lp(a) baseline is defined in Section 9.4.2.1.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To evaluate the effect of olpasiran administered subcutaneous (SC) **once** every 12 weeks (Q12W) compared with placebo, on percent change from baseline in **lipoprotein(a) (**Lp**[a]**) after 36 weeks of treatment	• Percent change in Lp(a) from baseline at week 36
Primary Estimand	
The primary estimand consists of: • The target population, which is adults with atherosclerotic cardiovascular disease and elevated Lp(a) • The primary variable, which is percent change from baseline in Lp(a) at week 36 • The intercurrent events which are the discontinuation of investigational product and excluded medication(s) taken during study. For the primary estimand, the treatment effect will be estimated in subjects who are randomized and received at least 1 dose of investigational product regardless of the occurrence of these intercurrent events • The summary measure, which is the difference between olpasiran and placebo in the mean percent change from baseline in Lp(a) at week 36 • The treatments to be compared are each olpasiran group vs. placebo The primary estimand is the difference between each olpasiran group and placebo in the mean percent change from baseline in Lp(a) at week 36 in adults with atherosclerotic cardiovascular disease and with elevated Lp(a) who are randomized and received at least 1 dose of investigational product, regardless of discontinuation of investigational product and excluded medication(s) taken during the study.	

Objectives	Endpoints
Secondary	
• To evaluate the effect of olpasiran administered SC Q12W compared with placebo, on percent change from baseline in: - Lp(a) after 48 weeks of treatment - Low-density lipoprotein cholesterol (LDL-C) after 36 and 48 weeks of treatment - Apolipoprotein(B) (ApoB) after 36 and 48 weeks of treatment	• Percentage change from baseline in: - Lp(a) at week 48 - LDL-C at week 36 and week 48 - ApoB at week 36 and week 48
• To characterize the pharmacokinetic (PK) properties of olpasiran	• PK parameters for olpasiran including, but not limited to, maximum observed concentration (C_{max}), and the area under the concentration time curve (AUC)
Estimands for Secondary Endpoints	
The estimands for the secondary endpoints Lp(a), LDL-C, and ApoB are the differences between each olpasiran group and placebo in the mean percent change from baseline in: • Lp(a) at week 48 • LDL-C at week 36 • LDL-C at week 48 • ApoB at week 36 • ApoB at week 48 For adults with atherosclerotic cardiovascular disease and elevated Lp(a) who are randomized and received at least 1 dose of investigational product, regardless of discontinuation of investigational product and excluded medication(s) taken during the study.	
Safety	
• To evaluate the safety and tolerability of olpasiran SC Q12W compared with placebo in subjects with elevated Lp(a)	• Treatment emergent adverse events • Clinically significant safety laboratory values and vital signs at each scheduled visit

Overall Design

This is a phase 2, double-blind, randomized, placebo-controlled, multicenter, dose finding study to evaluate efficacy, safety, and tolerability of olpasiran on Lp(a) compared to placebo in subjects with atherosclerotic cardiovascular disease and with elevated Lp(a).

Subjects will be randomized in a 1:1:1:1:1 ratio, with 4 arms being treated with olpasiran and 1 arm with placebo (some olpasiran arms will include placebo to maintain blind).

The randomization will be stratified by screening Lp(a) $\leq$ 200 nmol/L vs. $>$ 200 nmol/L and by region (Japan vs. Non-Japan).

The study treatment period is 48 weeks with doses at day 1, week 12, week 24, and week 36. After week 48 there will be an extended safety follow-up without further dosing with investigational product for **a minimum of 24** weeks. Subjects will remain on standard of care (including stable lipid-altering therapy) per their local guidelines during the treatment period and extended safety follow-up period.

Number of Subjects

Approximately 290 subjects will be enrolled in the study, with approximately 58 subjects per treatment arm.

Summary of Subject Eligibility Criteria

A summary of eligible criteria for subjects to be included in the study are:

Male or female adults age 18 to 80 years old, fasting Lp(a) > 150 nmol/L during screening, atherosclerotic cardiovascular disease, and subjects receiving lipid-altering therapy (not required to participate in the study), must remain on stable dose.

For a full list of eligibility criteria, please refer to Section 5.1 to Section 5.2.

Treatments

Subjects will be randomized in a 1:1:1:1:1 ratio to 1 of the following 5 treatment groups:

- Group 1: 10 mg Q12W
- Group 2: 75 mg Q12W
- Group 3: 225 mg Q12W
- Group 4: 225 mg Q24W
- Group 5: Placebo Q12W

Procedures

After providing informed consent, eligible subjects will undergo the following assessments during this study: physical examination, neurological examination, physical measurements (height, weight, waist circumference) vital signs (blood pressure and heart rate),electrocardiogram, laboratory assessments (including serum pregnancy test, if applicable, serum Lp(a), lipids and fasting glucose, very low-density lipoprotein, coagulation, hematology, hemoglobin A1C, chemistry, high sensitivity C-reactive protein **(hs-CRP)**, estimated glomerular filtration rate (eGFR), urinalysis, anti-olpasiran antibody test, biomarker, **pharmacokinetic (**PK**)** assessments, and a PROMIS (patient-reported outcomes measurement information system) general health assessment. Reporting of adverse events, serious adverse events, and cases of pregnancy and lactation exposure will be performed as described in Section 8.2.4.

For a full list of study procedures, including the timing of each procedure, please refer to Section 8.2 and the Schedule of Activities in Table 1-1.

Statistical Considerations

All categorical variables will be summarized using the number and percent of subjects and all continuous variables will be summarized using mean, standard error or standard deviation, median, minimum, maximum, and number of subjects with observations.

An interim analysis will be performed when approximately 240 subjects have had the opportunity to complete the week 24 assessments or have early terminated. At that point, approximately 120 subjects may have had the opportunity to complete the week 36 assessments or have early terminated.

Primary analysis will be performed when all randomized subjects have had the opportunity to complete the week 36 assessments or have early terminated.

End of Treatment Period analysis will be performed when all randomized subjects have had the opportunity to complete week 48 assessments or have early terminated.

Final analysis will be performed when all randomized subjects either complete the extended safety follow-up and ended the study or early terminate from the study.

The primary endpoint (percent change from baseline in Lp(a) at week 36) will be compared between groups using repeated measures linear effects model including terms of treatment group, stratification factor, scheduled visit, and the interaction of treatment with scheduled visit. Hochberg procedure will be used to control the type I

error for multiple comparisons between active and placebo arms for the primary endpoint. The secondary endpoints percent change from baseline in Lp(a) at week 48, in ApoB and LDL-C at week 36 and 48 will be analyzed similarly as the primary endpoint. Safety endpoints will be summarized descriptively.

Baseline Lp(a) is defined as the mean of the two most recent non-missing Lp(a) values measured through central lab prior to or on study day 1. If for any reason only 1 value is available then that value will be used as baseline.

For a full description of statistical analysis methods, please refer to Section 9.

Statistical Hypotheses

The null hypothesis is that there is no difference between olpasiran and placebo in percent change from baseline in Lp(a) at week 36 in subjects with atherosclerotic cardiovascular disease and with elevated Lp(a).

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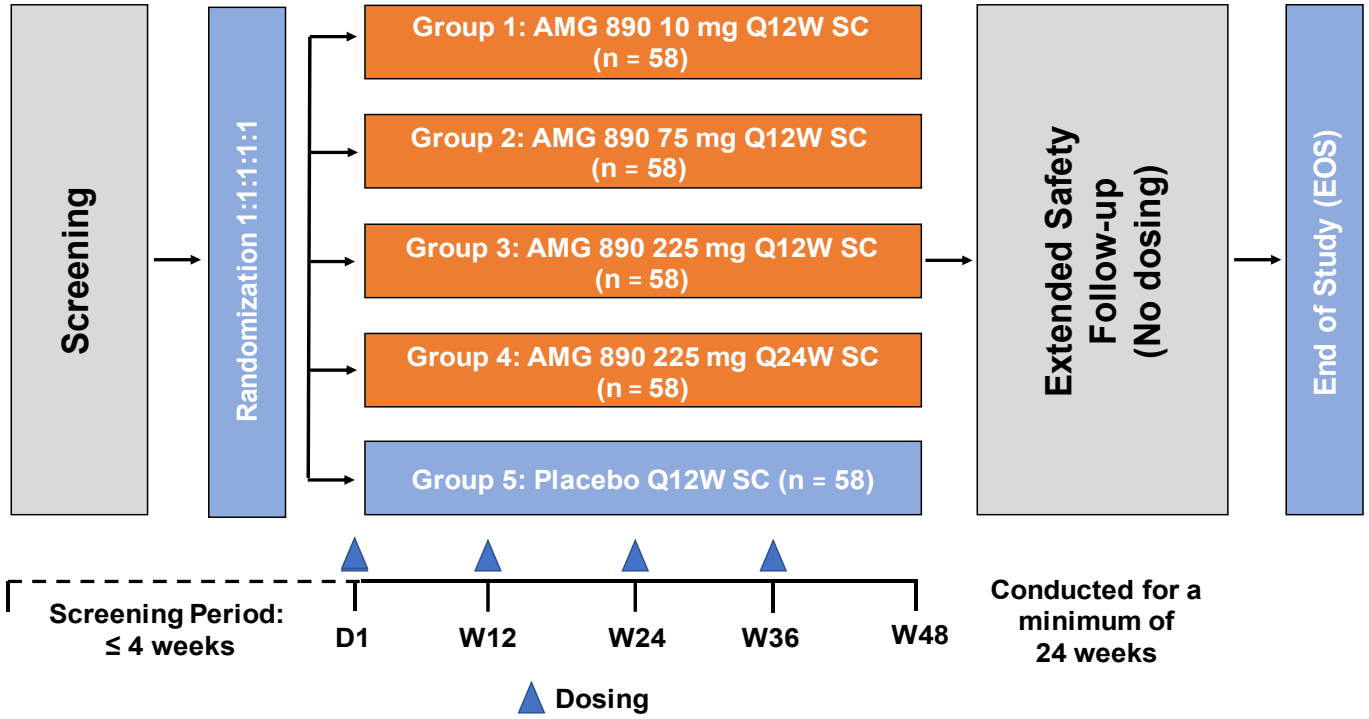
1.2 Study Schema

Figure 1-1. Study Schema



D = day; EOS = End of Study; Q12W = once every 12 weeks; Q24W = once every 24 weeks; SC = subcutaneous; W = week

1.3 Schedule of Activities (SoA)

Table 1-1. Schedule of Activities (Screening Through Week 24)

PROCEDURE	Screening (≤ 28 days before day 1)	Treatment Period: Screening to Week 24 (Duration of 48 weeks)[a]														
		Day 1			D2	W4	W8	W12			W16	W20	W24			W24
		Pre-dose	+1 hr	+3 hr	+ 2 days	± 3 days		Pre-dose	+1 hr	Phone call[b]	± 3 days		Pre-dose	+ 1 hr	+3 hr	Phone call[b]
								± 3 days		+ 1 day			± 3 days			+ 1 day
GENERAL AND SAFETY ASSESSMENTS																
Informed consent	X															
Inclusion and exclusion criteria	X	X														
Demographics	X															
Physical, neurological, and muscular examination	X	X						X					X			
Physical measurements (body weight, height, waist circumference)		X														
Medical history	X	X														
ECG (single)		X						X					X			
Vital signs	X	X						X					X			
Survival status[c]																
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious adverse events[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapies review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization (after eligibility confirmed)		X														
LABORATORY ASSESSMENTS																
Serum pregnancy test (females of childbearing potential only)[e]	X															
FSH	X															
Urine Pregnancy Test (females of childbearing potential only)[e]		X						X					X			
Lipid Panel and Lp(a)[f]	X	X			X	X	X	X			X	X	X			
Fasting glucose	X	X				X		X					X			
Apolipoprotein A1 and Apolipoprotein B[f]	X	X				X		X					X			

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Footnotes and abbreviations defined on last page of this table.

Table 1-1. Schedule of Activities (Screening Through Week 24)

PROCEDURE	Screening (≤ 28 days before day 1)	Treatment Period: Screening to Week 24 (Duration of 48 weeks)[a]														
		Day 1			D2	W4	W8	W12			W16	W20	W24			W24
		Pre-dose	+1 hr	+3 hr	+ 2 days	± 3 days		Pre-dose	+1 hr	Phone call[b]	± 3 days		Pre-dose	+ 1 hr	+3 hr	Phone call[b]
								± 3 days		+ 1 day			± 3 days			+ 1 day
LABORATORY ASSESSMENTS CONTINUED																
Coagulation	X	X				X		X					X			
Hematology	X	X				X		X					X			
Hemoglobin A1C	X	X				X		X					X			
Chemistry including hs-CRP[f]	X	X				X		X					X			
eGFR	X	X				X		X					X			
Urinalysis	X	X				X		X					X			
Anti-olpasiran-antibody		X						X					X			
BIOMARKER ASSESSMENTS																
hs-IL-6[f]		X														
Biomarker Discovery (eg, OxPL/ApoB and Lp(a) isoform)		X														
Biomarker Development (optional)[g]		X														
(OPTIONAL) PHARMACOGENETIC ASSESSMENTS																
Pharmacogenetic Development[h]		X														
PHARMACOKINETIC ASSESSMENTS																
Olpasiran serum PK[i]		X	X	X		X		X	X				X	X	X	
CLINICAL OUTCOME ASSESSMENTS																
PROMIS General Health		X						X					X			
STUDY TREATMENT																
Olpasiran or placebo		X						X					X			

Footnotes and abbreviations defined on last page of this table.

Table 1-1. Schedule of Activities (Week 28 Through End of Study)

	Treatment Period: Week 28 to Week 48 (Duration of 48 weeks)[a]									Extended Safety Follow-up[k]	End of Study
			W36			W36					
	W28	W32	Pre-dose	+1 hr	+3 hr	Phone call[b]	W40	W44	W48	W60	W72[l]
PROCEDURE	± 3 days					+ 1 day	± 3 days			± 7 days	
GENERAL AND SAFETY ASSESSMENTS											
ECG (single)			X						X		X
Physical, neurological, and muscular examination			X						X		X
Physical measurement (weight only)									X		X
Vital signs			X						X		X
Survival status[c]										**X**	**X**
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Serious adverse events[d]	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapies review	X	X	X	X	X	X	X	X	X	X	X
LABORATORY ASSESSMENTS											
Urine Pregnancy Test (females of childbearing potential only)[e]			X						X		X
Lipid Panel and Lp(a)[f]	X	X	X				X	X	X	X	X
Fasting glucose			X						X		X
Apolipoprotein A1 and Apolipoprotein B[f]			X						X		X
Coagulation			X						X		X
Hematology			X						X		X
Hemoglobin A1C			X						X		X
Chemistry including hs-CRP[f]			X						X		X
eGFR			X						X		X
Urinalysis			X						X		X
Anti-olpasiran-antibody			X						X		X
BIOMARKER ASSESSMENTS											
hs-IL-6[f]			X						X		X
Biomarker Discovery (eg, OxPL/ApoB and Lp(a) isoform)			X						X		X
Biomarker Development (optional)[g]			X						X		X

Footnotes and abbreviations defined on last page of this table.

Table 1-1. Schedule of Activities (Week 28 Through End of Study)

	Treatment Period: Week 28 to Week 48 (Duration of 48 weeks)[a]									Extended Safety Follow-up[k]	End of Study
			W36			W36					
	W28	W32	Pre-dose	+1 hr	+3 hr	Phone call[b]	W40	W44	W48	W60	W72[l]
PROCEDURE	± 3 days					+ 1 day	± 3 days			± 7 days	
PHARMACOKINETIC ASSESSMENTS											
Olpasiran serum PK[i]	X		X	X	X		X		X		(X)[j]
CLINICAL OUTCOME ASSESSMENTS											
PROMIS General Health			X						X		(X)[j]
Exit Survey									X		(X)[j]
STUDY TREATMENT											
Olpasiran or placebo			X								

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A1C = glycated hemoglobin; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; hs-CRP = high sensitivity C-reactive protein; hs-IL-6 = high sensitivity interleukin 6; Lp(a) = Lipoprotein(a); OxPL/ApoB = oxidized phospholipids on apolipoprotein B 100; PK = pharmacokinetics; PROMIS = Patient-Reported Outcomes Measurement Information System; **W = week**

[a] Clinical outcome assessments should always be performed first at study visits, with study treatment administration performed last, except for days when post-dose PK samples are collected (day 1, week 12, week 24, and week 36).

[b] Safety Follow-up calls are scheduled at 1 day after weeks 12, 24, and 36 visits.

[c] **Survival status checks should be performed for any subject who withdraws consent, or subjects considered lost to follow-up, or subjects unwilling to continue schedule of assessments, to the extent permitted by local law. Refer to Section 8.2.3.2 for additional details.**

[d] **After end of study, if the investigator becomes aware of serious adverse events suspected to be related to investigational product, then these serious adverse events will be reported to Amgen. Please refer to Section 8.2.4.1.3 for additional details.**

[e] Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations. Urine pregnancy test can be completed by study staff or local laboratory.

[f] Blinded laboratory results: Lp(a), lipid panel, hs-CRP, hs-IL-6, ApoA1, and ApoB laboratory result will be provided to sites at Screening and Day 1, but will be blinded after Day 1.

[g] Biomarker development samples will be obtained from the biomarker discovery blood draw, for subjects who consent.

[h] Optional pharmacogenomic sample will be derived from the biomarker plasma draw.

[i] Additional PK samples will be collected in a subset of subjects (N = approximately 75) who consent to the optional PK sub-study. Refer to Table 1-2 below for additional time points required for these subjects.

[j] Collected at the end of study visit if this visit occurs prior to week 48.

[k] **After week 48 there will be an extended safety follow-up without further dosing with investigational product for a minimum of 24 weeks.**

[l] **Per Protocol Amendment 2, some subjects will have an End of Study visit after week 72.**

Table 1-2. Schedule of Activities-PK Sub-study

PROCEDURE	Screening	Week 1 (Dose 1)		Week 24 (Dose 2 [Q24W], Dose 3 [Q12W])	
		6 to 12 hrs post-dose	24 to 72 hrs post-dose	6 hr to 12 hrs post dose	24 hrs to 72 hrs post dose
GENERAL AND SAFETY ASSESSMENTS					
PK Sub-study Informed Consent	X				
Adverse events		X	X	X	X
Serious adverse events[a]	X	X	X	X	X
Concomitant therapies review		X	X	X	X
PHARMACOKINETIC ASSESSMENTS					
Olpasiran serum PK[b]		X	X	X	X

Hr(s) = hour(s); PK = pharmacokinetics**; Q12W = once every 12 weeks; Q24W = once every 24 weeks**

[a] **After end of study, if the investigator becomes aware of serious adverse events suspected to be related to investigational product, then these serious adverse events will be reported to Amgen. Please refer to Section 8.2.4.1.3 for additional details.**

[b] PK sub-study subjects will also have the required PK samples drawn as part of the main study (refer to Table 1-1 for time points).

2. Introduction

2.1 Study Rationale

Study 20180109 is a double-blind, randomized, multicenter dose finding study in subjects with atherosclerotic cardiovascular disease and elevated lipoprotein(a) (Lp[a]). The primary objective is to test olpasiran administered subcutaneous (SC) **once** every 12 weeks (Q12W) compared with placebo on percent change from baseline in Lp(a) after 36 weeks of treatment. Additionally, an exploratory dose of 225 mg **once** every 24 weeks (Q24W) will be evaluated. The treatment period is 48-weeks, with the last dose of investigational product administered at week 36. **After t**he week 48 treatment period **there will be** an extended safety follow-up **for a minimum** of **24** weeks.

Olpasiran is being developed for the treatment of patients with atherosclerotic cardiovascular disease and elevated lipoprotein(a) (Lp[a]) to reduce the risk of cardiovascular events. Lp(a) reductions of $\geq 80\%$ from baseline are anticipated with olpasiran and it is expected that this level of reduction in Lp(a) may result in clinically meaningful cardiovascular benefit in patients with atherosclerotic cardiovascular disease (Kamstrup et al, 2009, Burgess et al, 2018, Lamina et al, 2019, Madsen et al, 2020).

Available data from the initial cohorts of the first in human (FIH) study has shown the following:

- Olpasiran can effectively lower Lp(a) levels.
- Pharmacodynamic (PD) effects last up to at least 3 months.
- At single doses up to 225 mg (cohort 7), olpasiran was tolerated with no safety concerns identified as of day 225.

The olpasiran target population is patients with atherosclerotic cardiovascular disease and significantly elevated Lp(a). All patients will be receiving optimized standard of care for other cardiovascular risk factors, including elevated low-density lipoprotein cholesterol (LDL-C), but still be at risk for cardiovascular events from high Lp(a) levels.

The Lp(a) cutoff of 150 nmol/L is based on the epidemiological data that is available showing that Lp(a) $>$ 125 nmol/L is considered elevated from the general population data (Averna et al, 2017; Nordestgaard and Langsted, 2016; Ohro-Melander, 2015; Leebmann et al, 2013). In addition, based on the degree of absolute Lp(a) reduction necessary to demonstrate a corresponding effect on cardiovascular events, the enrolled population would need to have high baseline Lp(a). Therefore, an enrollment criterion of

Lp(a) > 150 nmol/L would result in a study population with a median Lp(a) of approximately 200 nmol/L and allows evaluation of the effectiveness and safety of olpasiran in subjects with very high Lp(a).

A recent Mendelian randomization study suggests that in individuals with very high baseline Lp(a) concentrations, reducing Lp(a) by 80% to 90% is expected to translate into a clinically meaningful reduction in the risk of cardiovascular events (Khan et al, 2017; Leebmann et al, 2013; Safarova et al, 2013, Burgess et al, 2018, Lamina et al, 2019, Madsen et al, 2020).

2.2 Background

2.2.1 Disease

Despite significant advances in the identification and control of modifiable risk factors for cardiovascular disease, including smoking, hypertension, diabetes, and dyslipidemias, cardiovascular disease remains the leading cause of death and disability worldwide, accounting for approximately 31% of all deaths according to the World Health Organisation (WHO, 2014). Furthermore, after a cardiovascular event, patients may suffer from both acute and long-term reductions in health-related quality of life, including diminished mobility and functionality, as well as anxiety, depression, fatigue, and sexual dysfunction (Bach et al, 2011; Schweikert et al, 2009; Brink et al, 2005; Simpson and Pilote, 2003; Mendes de Leon et al, 1998).

While lipid-lowering therapy research has historically focused on LDL-C to reduce cardiovascular risk, epidemiologic evidence identifies elevated plasma Lp(a) as a strong independent risk factor for atherosclerotic cardiovascular disease (Kassner et al, 2015; Willeit et al, 2014; Kamstrup et al, 2013; Jacobson, 2013; Dubé et al, 2012; Emerging Risk Factors Collaboration, 2009; Kamstrup et al, 2009; Bennet et al, 2008; Kamstrup et al, 2008; Danik et al, 2006). Elevated plasma Lp(a) levels have also been associated with atherosclerotic disease severity and progression (Kotani et al, 2017; Poller et al, 2015; Stather et al, 2014; Guler et al, 2013; Ronald et al, 2011; Gardener et al, 2009; Habib et al, 2009; Takagi et al, 2009; Schillinger et al, 2002).

The physiological function of Lp(a) is unclear, but Lp(a) has been shown to have a pathogenic role in atherosclerosis and thrombosis formation (Nordestgaard and Langsted, 2016). The connection between Lp(a) levels and coronary artery disease, myocardial infarction, stroke, peripheral vascular disease, and aortic valve stenosis has been described in several genetic and observational studies

(Schmidt et al, 2016). It has been noted that this risk relationship is continuous and becomes proportionally more impactful with higher Lp(a) levels. The association persists after correction for other lipid parameters (Emerging Risk Factors Collaboration, 2009).

Elevated Lp(a) has varying definitions depending upon the population under study and the assay being used. Some studies have estimated that 20% to 30% of the population have Lp(a) > 50 mg/dL (Varvel et al, 2016; Nordestgaard et al, 2010). The American College of Cardiology/American Heart Association (ACC/AHA) Cholesterol guidelines further state that if a decision is made to measure Lp(a), an Lp(a) ≥ 50 mg/dL or ≥ 125 nmol/L, may be considered a risk enhancing factor (Grundy et al, 2019). The National Lipid Association suggest that Lp(a) > 50 mg/dL (> 100 nmol/L) be considered the elevated risk threshold (Wilson et al, 2019); the Canadian Cardiovascular Society states that levels > 30 mg/dL are considered elevated (Anderson et al, 2016); and a study in the Chinese Han observed increasing risk at > 17 mg/dL (Cui et al, 2018). The prevalence of Lp(a) > 50 mg/dL (> 125 nmol/L) varies by country of origin with an estimated 30% in Africa; 25% in South Asia; 20% in Europe, Oceania, and North America; 15% in South America; and 10% in Asia (Tsimikas et al, 2018). The risk for the development of significant coronary artery disease appears to be increased with plasma Lp(a) levels as low as 30 mg/dL in European populations, and the risk of myocardial infarction is elevated by 2- to 3.5-fold in individuals with elevated Lp(a) levels (Norderstgaard and Langstedt, 2016; Kamstrup et al, 2009).

The ESC/EAS dyslipiaemia guidelines state that Lp(a) measurement should be considered at least once in each adult's lifetime (Mach et al, 2020). American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines state that Lp(a) is a modified form of LDL-C that appears to possess atherogenic potential. Indications for its measurement are a family history of premature atherosclerotic cardiovascular disease or personal history of atherosclerotic cardiovascular disease not explained by major risk factors (Grundy et al, 2019). Recommendations for measuring Lp(a) levels in adults have also been added to guidelines or scientific statements from the Canadian Cardiovascular Society, the National Lipid Association, and HEART UK (Anderson et al, 2016; Wilson et al, 2019; Cegla et al, 2019).

High plasma Lp(a) concentration is genetically defined, remains at stable levels, cannot be controlled by habit modifications (diet, exercise, or other environmental factors), and is not effectively controlled by any of the currently available lipid reducing medications. Currently, there are no approved therapies indicated to reduce the risk of cardiovascular events through reductions in Lp(a). Approaches to lower Lp(a) include use of proprotein

convertase subtilisin/kexin type 9 (PCSK9) inhibitors, niacin, or mipomersen (Santos et al, 2015; Yeang et al, 2015; Landray et al, 2014), which decrease Lp(a) moderately. While lipoprotein apheresis is effective in lowering Lp(a), it is currently used only in a few countries with limited access (Julius, 2018). In addition, it is an invasive, very expensive procedure requiring frequent visits, which makes it unfeasible as a long-term treatment for subjects who need lifelong therapy (Khan et al, 2017; Roeseler et al, 2016; Leebmann et al, 2013; Safarova et al, 2013).

Therefore, novel agents that lower high Lp(a) concentrations are being investigated to confer additional protection against cardiovascular disease. Although definitive evidence that the reduction in plasma Lp(a) will provide cardiovascular risk reduction is lacking, Mendelian randomization epidemiologic studies, lipoprotein apheresis cohort results, and experimental data suggest a causal role for elevated Lp(a) (Averna et al, 2017; Nordestgaard and Langsted, 2016; Ohro-Melander, 2015; Leebmann et al, 2013) and provide the rationale for exploring the therapeutic concept.

2.2.2 Amgen Investigational Product Background: Olpasiran

Small interfering (also called short interfering) RNA molecules (siRNA) are synthetic RNA duplexes that disrupt the expression of specific genes with complementary nucleotide sequences by degrading mRNA after transcription, preventing translation (Agrawal et al, 2003). The serum pharmacokinetics in Amgen's nonclinical program support fast clearance from the blood compartment and effective delivery to liver due to GalNAc conjugation via the asialoglycoprotein receptor (ASGPR). Olpasiran is a fully chemically modified siRNA, and is therefore, slowly degraded by endo- and exo-nucleases in the liver (Nair et al, 2017).

Uptake of the siRNA into cells involves endocytosis and release from the endosome to the cytosol, a mechanism that is not currently well understood. Once in the cytosol, the antisense (guiding) strand of the siRNA double strand is loaded into an RNA-induced silencing complex (RISC), while the other one is degraded. The loaded RISC is then directed to an mRNA which has complementary sequence of the guide strand. Argonaute proteins present in RISC cleave the target mRNA, which is then further degraded by exonucleases. Dissociation of the target mRNA strand from RISC after the cleavage allow more mRNA to be silenced, enabling continual degradation of target mRNA and leading to efficient and potent gene silencing (Agrawal et al, 2003). Small interfering RNA molecules can also be targeted for uptake in select tissues via conjugation of the siRNA to high-affinity antibody or antibody fragments, nucleic acids, or receptor ligands to bind to cell surface receptors and to mediate cell-specific uptake.

Targeted uptake has the advantages of being effective at a lower dose and may confer reduced toxicity from uptake and knockdown in unintended tissues. In particular, SC administration of siRNAs conjugated to trivalent N-acetylgalactosamine (GalNAc), which mediates hepatocyte uptake through the hepatocyte-restricted ASGPR in liver-targeted, durable gene knockdown (Wittrup and Lieberman, 2015).

Olpasiran is an siRNA designed to target the mRNA transcribed from the *LPA* gene, which encodes apo(a) protein in liver cells. Thus, olpasiran is able to specifically knock down hepatic Lp(a) production. The siRNA molecule is formed by the hybridization of two partially complementary single-strands of RNA with 21 consecutive complementary base pairs.

Pharmacology

Amgen's nonclinical program showed that olpasiran can achieve a sustained $> 80\%$ reduction in plasma Lp(a). The studies supporting this conclusion included efficacy data collected from transgenic mice and cynomolgus monkeys demonstrating that Lp(a) levels can be specifically targeted with olpasiran to inhibit apo(a) translation.

A detailed description of the chemistry, pharmacology, efficacy, and safety of olpasiran is provided in the Investigator's Brochure.

2.3 Benefit/Risk Assessment

Elevated plasma Lp(a) has been identified as a strong independent risk factor for the development and progression of atherosclerotic disease (Ellis et al, 2017). Lp(a) has been associated with increased risk for myocardial infarction, aortic valve stenosis development, carotid artery stenosis and abdominal aorta aneurism progression. High plasma Lp(a) concentration is genetically defined, cannot be controlled by healthy habit modifications and is not effectively controlled by any of the currently available lipid-reducing medications. Therefore, the development of a novel agent to lower high Lp(a) concentrations is a valid approach to confer additional protection against cardiovascular disease. Although definitive evidence that the reduction in plasma Lp(a) will provide cardiovascular risk reduction is not yet available, mendelian randomization epidemiologic studies, plasma apheresis cohort results, and experimental data suggest a causal role for elevated Lp(a) (Averna et al, 2017; Nordestgaard and Langsted, 2016; Ohro-Melander, 2015) and provide the rationale for exploring the therapeutic concept.

There are no identified risks for olpasiran and potential risks are limited to liver enzyme elevation and hypersensitivity reactions. Other events of interest for olpasiran, that have not been borne out either by the non-clinical or available clinical data, but that are based

on the siRNA/oligotherapeutics platform include: effects on platelets and coagulation, immune inflammatory response, and peripheral neuropathy. Additionally, very low levels of Lp(a) have been associated with increased incidence of type 2 diabetes, but whether pharmacologic lowering of Lp(a) would be associated with an increased risk for development of type 2 diabetes is unknown (Paige et al, 2017; Ye et al, 2014). These risks have not been borne out by either the non-clinical data or clinical data to date for olpasiran.

All study subjects will be closely monitored and frequently assessed for adverse events throughout the study. The laboratory safety monitoring includes evaluation of routine chemistry (including liver function tests and renal function), hematology, HbA1c, and coagulation assessments. Potential anaphylactic reactions will be assessed by the investigator based on Sampson clinical criteria for diagnosing anaphylaxis (Sampson et al, 2006) and reported accordingly on the adverse event electronic case report form (eCRF). If Sampson criteria are positive, the potential anaphylactic reaction will be confirmed by measuring tryptase in blood plasma within 30 minutes of symptoms, if feasible. Bioanalytical testing for anti-olpasiran antibodies will be conducted only if there are unexpected PD findings or a safety signal in this study or future studies that warrants further investigation.

Amgen has been closely monitoring the evolving Coronavirus disease-19 (COVID-19) pandemic around the globe. As part of this effort, Amgen has performed a rigorous assessment, in discussion with study investigators, considering the study design, patient safety, public health risk, risk-benefit ratio, as well as the burden on country healthcare systems. Given the safety concerns around COVID-19 and the associated risk to maintaining normal clinical study operations, Amgen is making decisions on a study-by-study and country-by-country basis to minimize risk to patients and avoid undue burden on healthcare facilities and accordingly, is allowing enrollment to continue in studies where the potential for significant benefit in a serious or life-threatening condition exists and where site resources allow new patients to be safely enrolled and appropriately monitored.

Potential risks associated with study participation, in particular with added challenges due to COVID-19, may be outweighed by anticipated benefits associated with the study treatment.

Patients who display symptoms consistent with COVID-19 infections or who have tested positive for COVID-19 should urgently contact their site medical monitor to ensure appropriate care as well as documentation and management of study activities.

Amgen considers that it is important to continue the proposed development of olpasiran in this study in order to advance potential therapy options for patients as rapidly as possible, while balancing this with appropriate measures to monitor and mitigate the potential impact of COVID-19.

The above benefit risk assessment supports the conduct of this clinical trial. Reference should be made to the Investigator's Brochure for further data on olpasiran.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of olpasiran administered subcutaneous (SC) **once** every 12 weeks (Q12W) compared with placebo, on percent change from baseline in **lipoprotein(a) (**Lp**[**a**]**) after 36 weeks of treatment	• Percent change in Lp(a) from baseline at week 36
Primary Estimand	
The primary estimand consists of: • The target population, which is adults with atherosclerotic cardiovascular disease and elevated Lp(a) • The primary variable, which is percent change from baseline in Lp(a) at week 36 • The intercurrent events which are the discontinuation of investigational product and excluded medication(s) taken during study. For the primary estimand, the treatment effect will be estimated in subjects who are randomized and received at least 1 dose of investigational product regardless of the occurrence of these intercurrent events • The summary measure, which is the difference between olpasiran and placebo in the mean percent change from baseline in Lp(a) at week 36 • The treatments to be compared are each olpasiran group versus placebo The primary estimand is the difference between each olpasiran group and placebo in the mean percent change from baseline in Lp(a) at week 36 in adults with atherosclerotic cardiovascular disease and elevated Lp(a) who are randomized and received at least 1 dose of investigational product, regardless of discontinuation of investigational product and excluded medication(s) taken during the study.	
Objectives	**Endpoints**
Secondary	
• To evaluate the effect of olpasiran administered SC Q12W compared with placebo, on percent change from baseline in: - Lp(a) after 48 weeks of treatment - Low-density lipoprotein cholesterol (LDL-C) after 36 and 48 weeks of treatment - Apolipoprotein(B) (ApoB) after 36 and 48 weeks of treatment	• Percentage change from baseline in: - Lp(a) at week 48 - LDL-C at week 36 and week 48 - ApoB at week 36 and week 48
• To characterize the pharmacokinetic (PK) properties of olpasiran	• PK parameters for olpasiran including, but not limited to, maximum observed concentration (C_{max}), and the area under the concentration time curve (AUC)
Estimands for Secondary Endpoints	

The estimands for the secondary endpoints in Lp(a), LDL-C, and ApoB are the differences between each olpasiran group and placebo in the mean percent change from baseline in: • Lp(a) at week 48 • LDL-C at week 36 • LDL-C at week 48 • ApoB at week 36 • ApoB at week 48 For adults with atherosclerotic cardiovascular disease and elevated Lp(a) who are randomized and received at least 1 dose of investigational product, regardless of discontinuation of investigational product and excluded medication(s) taken during the study.

Exploratory	
• To evaluate the effect of olpasiran administered SC Q12W compared with placebo, on: - percent change from baseline in Lp(a) - percent change from baseline in LDL-C - percent change from baseline in ApoB - achievement of Lp(a) < 125 nmol/L - achievement of Lp(a) < 100 nmol/L - achievement of Lp(a) < 75 nmol/L - achievement of Lp(a) < 50 nmol/L	• Percent change from baseline at each scheduled visit, except weeks 36 and 48, in: - Lp(a) - LDL-C - ApoB • Achievement at each scheduled visit of the following: - Lp(a) < 125 nmol/L - Lp(a) < 100 nmol/L - Lp(a) < 75 nmol/L - Lp(a) < 50 nmol/L
• To evaluate the effect of olpasiran administered SC **once every 24 weeks (**Q24W**)** compared with olpasiran administered SC Q12W and placebo, on: - percent change from baseline in Lp(a) - percent change from baseline in LDL-C - percent change from baseline in ApoB - achievement of Lp(a) < 125 nmol/L - achievement of Lp(a) < 100 nmol/L - achievement of Lp(a) < 75 nmol/L - achievement of Lp(a) < 50 nmol/L	For the olpasiran SC Q24W group: • Percent change from baseline at each scheduled visit, in: - Lp(a) - LDL-C - ApoB • Achievement at each scheduled visit of the following: - Lp(a) < 125 nmol/L - Lp(a) < 100 nmol/L - Lp(a) < 75 nmol/L - Lp(a) < 50 nmol/L

Objectives	**Endpoints**
Exploratory	
• To estimate cardiovascular event rates in subjects treated with olpasiran, including aggregated exploratory analyses across the olpasiran program	• Adjudicated events
• To describe the effect of olpasiran of quality of life (QoL) measures as assessed using the PROMIS Global Health	• Change from baseline in PROMIS Global Health measures at each scheduled visit
• To evaluate the effect of olpasiran administered SC on inflammatory biomarkers	• Change from baseline at week 48 in: - high sensitivity C-reactive protein (hs-CRP) - **high sensitivity** Interleukin 6 (hs-IL-6)

• To assess the anti-olpasiran antibody response	• Anti-olpasiran antibody formation, if tested
Safety	
• To evaluate the safety and tolerability of olpasiran administered SC compared with placebo in subjects with elevated Lp(a)	• Treatment emergent adverse events • Clinically significant safety laboratory values and vital signs at each scheduled visit

4. Study Design

4.1 Overall Design

This is a phase 2, double-blind, randomized, placebo-controlled, multicenter, dose finding study to evaluate efficacy, safety, and tolerability of olpasiran on Lp(a) compared to placebo in subjects with atherosclerotic cardiovascular disease and with elevated Lp(a).

Subjects will be randomized in a 1:1:1:1:1 ratio to 1 of the following 5 treatment groups (some olpasiran arms will include placebo to maintain blind):

- Group 1: 10 mg Q12W
- Group 2: 75 mg Q12W
- Group 3: 225 mg Q12W
- Group 4: 225 mg Q24W
- Group 5: Placebo Q12W

The randomization will be stratified by screening Lp(a) $\leq$ 200 vs. $>$ 200 nmol/L and by region (Japan vs. Non-Japan).

The study treatment period is 48 weeks with doses at day 1, week 12, week 24, and week 36. After week 48 there is an extended safety follow-up without further dosing with investigational product for **a minimum of 24** weeks. Subjects will remain on standard of care (including stable lipid-altering therapy) per their local guidelines during the treatment period and extended safety follow-up period.

An interim analysis will be performed when approximately 240 subjects have had the opportunity to complete the week 24 assessments or have early terminated. At that point, approximately 120 subjects may have had the opportunity to complete the week 36 assessments or have early terminated.

The interim analysis results will be used to support dose selection for a phase 3 registrational study and trigger early planning for the phase 3 program. In addition, the safety and efficacy results may be used in company internal discussions and external

interactions with regulatory agencies. The study continues regardless of the administrative interim results.

The primary analysis will occur when all randomized subjects have had the opportunity to complete the week 36 assessments or have early terminated. The end of treatment period analysis will occur when all subjects have had the opportunity to complete the week 48 assessments or have early terminated. Final analysis will occur after the last subject either completes the extended safety follow-up and has ended the study or has early terminated from the study.

Team members that remain directly involved with the conduct of the study, investigators, and subjects will not receive results of the interim **and primary** analyses and will remain blinded **until formally unblinded.**

The study will be formally unblinded to Amgen or Amgen designees after treatment period is ended, database is locked, and the snapshot is taken for end of treatment analysis. Sites and subjects will not have access to unblinded information until the study is formally ended at EOS (as defined in Section 4.4.1), database is locked, and the snapshot is taken for final analysis.

The overall study design is described by a study schema in Section 1.2. The endpoints are defined in Section 3.

4.2 Number of Subjects

Approximately 290 subjects will be enrolled in the study, with approximately 58 subjects per treatment arm.

Subjects in this clinical investigation shall be referred to as “subjects”. For the sample size justification, see Section 9.2.

4.2.1 Replacement of Subjects

Subjects who are withdrawn or removed from treatment or the study will not be replaced.

4.2.2 Number of Sites

Approximately 36 investigative sites in United States, Canada, Europe, Japan, and Australia will be included in the study. Sites that do not enroll subjects within 3 months of site initiation may be closed.

4.3 Justification for Investigational Product Dose

Investigational product dose ranges were selected based on available data from phase 1 Study 20170544 and the additional following considerations:

- General understanding of safety regarding oligonucleotide-based therapeutics, ie, antisense oligonucleotide and siRNA therapeutics and their mechanism of action.
- Lp(a) reductions of ≥ 80% from baseline are being targeted because this level of reduction is anticipated to be required to observe cardiovascular benefit in patients with atherosclerotic cardiovascular disease.
- Olpasiran PK/PD modelling and simulation results based on data from Study 20170544 indicate that:
  - A low dose of 10 mg administered Q12W will provide target (≥ 80%) Lp(a) suppression in approximately half (42%) of subjects with baseline Lp(a) ≥ 150 nmol/L by month 12. Despite median Lp(a) % reductions from baseline of approximately 77% at months 6 and 12, only 41% and 64% of these subjects will achieve Lp(a) values of ≤ 50 nmol/L by month 12. Therefore, the 10 mg dose will provide additional PK and Lp(a) data within the lower dynamic range of the olpasiran exposure-response relationship and help support selection of the phase 3 dose in the target patient population.
  - An intermediate dose of 75 mg administered Q12W was selected as it is anticipated to provide target (80%) Lp(a) suppression from baseline within 2 to 3 doses in the majority (94%) of subjects by month 12. Furthermore, approximately 90% of subjects are expected to achieve Lp(a) ≤ 50 nmol/L, which may support selection of this dose for phase 3 evaluation.
  - A high dose of 225 mg Q12W is expected to provide a similar degree of Lp(a) suppression (≥ 80%) in the majority of subjects (98%), but with a greater proportion of subjects (96%) achieving reductions of Lp(a) ≤ 50 nmol/L by month 12. Given that the magnitude and durability of Lp(a) suppression appears to increase with dose, the 225 mg dose will also provide greater magnitudes of Lp(a) suppression with multiple dosing.
- A frequency of Q12W dosing was selected for the above doses based on the durability of Lp(a) response over time and to ensure target suppression levels are maintained throughout the entire dosing interval in the majority (≥ 90%) of subjects with elevated Lp(a) levels > 150 nmol/L.
- A dose of 225 mg administered Q24W will also be evaluated in this study to explore opportunities for less frequent (Q24W) dosing in this patient population and to assess Lp(a) lowering impact throughout the 6-month dosing interval in a multiple dose setting. Modeling and simulation data suggest that 225 mg Q24W dosing will result in median Lp(a) reductions from baseline of 88% and with approximately 74% of subjects achieving Lp(a) levels ≤ 50 nmol/L.

4.4 End of Study

4.4.1 End of Study Definition

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s).

The primary completion date is the date when the last subject has completed the assessments for week 36.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

End of Study: The end of study **(EOS)** date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, extended safety follow-up, additional antibody testing), as applicable.

4.4.2 Study Duration for Subjects

The anticipated study duration will be approximately **76** weeks. This includes a 4-week screening window, a treatment period of 48 weeks, followed by an extended safety follow-up of **a minimum of 24** weeks.

4.5 Patient Input on Study Design

The team conducted Facilitated Reviews and Patient Panels with patients with high Lp(a) and with caregivers to obtain the patient voice to incorporate into the protocol and study conduct.

5. Study Population

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening). This log may be completed and updated via an Interactive Response Technology.

Eligibility criteria will be evaluated during screening.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 11.3).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions will not be provided.

5.1 Inclusion Criteria

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

101 Subject has provided informed consent prior to initiation of any study specific activities/procedures.

102 Age 18 to 80 years

103 Fasting Lp(a) $>$ 150 nmol/L during screening by central laboratory (approximately corresponds to $>$ 60 mg/dL: note that molarity determines eligibility)

104 Atherosclerotic cardiovascular disease based on 1 of the following:

- History of coronary revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)
- Diagnosis of coronary artery disease with or without prior myocardial infarction
- Diagnosis of atherosclerotic cerebrovascular disease
- Diagnosis of peripheral arterial disease

105 For subjects receiving lipid-altering therapy (not required to participate in this study), lipid-altering therapy, including statin dose, must remain stable per local guidelines for ≥ 4 weeks prior to and during screening

5.2 Exclusion Criteria

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

Disease Related

201 Severe renal dysfunction, defined as an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 during screening

202 History or clinical evidence of active liver disease or hepatic dysfunction, defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 x upper limit of normal (ULN), or total bilirubin (TBL) > 2 x ULN during screening

203 Inherited or other bleeding disorders

204 Recent major cardiovascular event (myocardial infarction, unstable angina, PCI, CABG, or stroke) within 6 months prior to day 1

205 Planned cardiac surgery, PCI or carotid stenting, or planned major non-cardiac surgery during the study period

Other Medical Conditions

206 Malignancy (except non-melanoma skin cancers, cervical in-situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma) within the last 5 years prior to day 1

207 Moderate to severe heart failure (New York Heart Association (NYHA) Functional Classification III or IV at day 1) or last known left ventricular ejection fraction < 30%

208 Uncontrolled cardiac arrhythmia defined as recurrent and highly symptomatic ventricular tachycardia, atrial fibrillation with rapid ventricular response, or supraventricular tachycardia that are not controlled by medications, in the past 3 months prior to day 1

209 Uncontrolled hypertension at day 1, defined as an average systolic blood pressure of ≥ 160 mmHg or an average diastolic blood pressure of ≥ 100 mmHg at rest

210 Fasting triglycerides ≥ 400 mg/dL (4.5 mmol/L) during screening

211 Type 1 diabetes or poorly controlled (HbA1c ≥ 8.5%) type 2 diabetes mellitus as determined by central laboratory at screening

212 Known active infection or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction, or a chronic disease or infection (eg, HIV) that is not currently stable and appropriately managed in the judgment of the investigator at day 1

Prior/Concomitant Therapy

213 Previously received treatment with antisense oligonucleotides (ASO), siRNA therapies (eg, inclisiran), or any experimental therapy targeting Lp(a)

215 Currently undergoing lipid apheresis or < 3 months since last apheresis treatment at day 1

216 Subject has taken a cholesterol ester transfer protein inhibitor (eg, anacetrapib, dalcetrapib, evacetrapib) or lomitapide in the last 12 months prior to day 1

226 Currently receiving, or < 3 months at day 1 since receiving > 200 mg/day Niacin

Prior/Concurrent Clinical Study Experience

217 Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded.

218 Use of any herbal medicines, vitamins or supplements known to affect lipid metabolism (eg, fish oil > 4000 mg/day, red yeast rice extract), within 30 days prior to day 1

Other Exclusions

219 Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 90 days after the last dose of investigational product.

220 Female subjects of childbearing potential unwilling to use a highly effective method of contraception during treatment and for an additional 90 days after the last dose of investigational product. Refer to Section 11.5 for additional contraceptive information.

221 Female subjects of childbearing potential with a positive serum pregnancy test assessed at Screening or positive urine pregnancy test on day 1.

222 Subject has known sensitivity to any of the products to be administered during dosing.

223 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, Clinical Outcome Assessments) to the best of the subject and investigator's knowledge.

224 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

5.3 Lifestyle Considerations

5.3.1 Activity

Subjects will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests.

5.4 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable (see Section 11.3).

The subject must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (after signing the informed consent) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by IRT. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened. This number will not necessarily be the same as the randomization number assigned for the study.

5.5 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, medical history, prior therapies, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time. Refer to Section 8.1.1.

5.6 Washout Period/Run-in Period/Invasive Procedure(s)

Washout Period, /Run-in period, and Invasive Procedure(s) are not applicable to this study.

6. Treatments

Study treatment is defined as any investigational product(s), non-investigational product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

Note that in several countries, investigational product and non-investigational product are referred to as investigational medicinal product and non-investigational medicinal product, respectively.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment shown in Table 6-1 below.

6.1 Treatment(s) Administered

6.1.1 Investigational Products

Table 6-1. Study Treatments

Study Treatment Name	Amgen Investigational Product:[a,b] olpasiran	Placebo
Dosage Formulation	The final container is a 2R vial size. Type I glass vial and contains 1 mL deliverable volume of olpasiran (1 mL vial target fill volume).	Placebo will be presented in identical containers, and stored/packaged the same as olpasiran
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	• Treatment Group 1: 10 mg Q12W • Treatment Group 2: 75 mg Q12W • Treatment Group 3: 225 mg Q12W • Treatment Group 4: 225 mg Q24W	• Treatment Group 5: Placebo Q12W
Route of Administration	SC injection	
Accountability	The volume, start date, start time, injection site, and box number(s) of investigational product are to be recorded on each subject's CRF.	
Dosing Instructions	Study treatment are to be administered at study visits by authorized investigational site study staff per the investigational product instructional manual (IPIM). Olpasiran administration should be completed after all study visit activities including pre-dose PK blood draws have been performed, but prior to the 1 hour and 3 hour post-dose PK measurements. An observation period of 1-hour will occur after each injection of study treatment.	

CRF = case report form; PK = pharmacokinetic; Q12W = once every 12 weeks; Q24W = once every 24 weeks; SC = subcutaneous
[a] Olpasiran will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.
[b] In order to maintain blinding, placebo will administered to some olpasiran treatment groups, as applicable.

6.1.2 Medical Devices

A diagnostic test will be used to measure Lp(a) to select subjects for treatment based on subject samples collected prospectively during the study. The diagnostic test is intended to measure Lp(a) in serum, as further described in Section 8.2.9.

6.1.3 Other Protocol-required Therapies

Other protocol-required therapies are not applicable for this study.

6.1.4 Other Treatment Procedures

No other treatment procedures are required for this study.

6.1.5 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product, or device after it is released for distribution to market or clinic by either **(1)** Amgen or **(2)** distributors and partners for whom Amgen manufactures the material.

This includes **olpasiran/placebo** provisioned and/or repackaged/modified by Amgen.

Any product complaint(s) associated with an investigational product(s) **(olpasiran/placebo), non-investigational products** supplied by Amgen are to be reported.

6.1.6 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

The following treatments are not permitted during the study:

- Anti-sense Oligonucleotide therapies (ASO)
- Other small interfering Ribonucleic Acid (siRNA) therapies (eg, inclisiran)
- Niacin > 200 mg/day
- Lipid apheresis
- Cholesterol ester transfer protein inhibitor (eg, anacetrapib, dalcetrapib, evacetrapib)
- Lomitapide
- any investigational therapies other than study provided IP
- any lipid-altering therapies not taken at the time of screening and enrollment

If starting a new lipid-altering therapy is medically warranted during the trial, the subject should continue to receive IP; these situations should be discussed with the Amgen medical monitor as soon as possible.

All herbal supplements, vitamins, and nutritional supplements known to affect lipid metabolism (eg, fish oil > 4000 mg/day, red yeast rice extract) should not be taken within 30 days prior to dosing on day 1 and should not be used during the study, unless reviewed and approved by the investigator and Amgen Medical Monitor.
Niacin > 200 mg/day should not be taken within 3 months prior to day 1. Written documentation of this review and Amgen acknowledgement is required for subject participation.

Any changes regarding concomitant medications should be recorded on the subject's source documents and the CRF along with the reason for the change:

6.2 Dose Modification

6.2.1 Dose-cohort Study Escalation/De-escalation and Stopping Rules

There are no dose-cohort study escalation/de-escalation or stopping rules for this study.

6.2.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

6.2.2.1 Amgen Investigational Product: Olpasiran

The reason for withholding dose of olpasiran is to be recorded on each subject's CRF(s).

6.2.3 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 11.7 for details regarding drug-induced liver injury guidelines, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

6.3 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product during the study are provided in the IPIM.

6.4 Measures to Minimize Bias: Randomization and Blinding

6.4.1 Method of Treatment Assignment

Subjects will be randomized in 1:1:1:1:1 allocation ratio, to 4 different doses of olpasiran and placebo, respectively, in a double-blind manner.

The randomization will be performed by IRT, and the randomization number will be provided by the IRT. Subjects are considered randomized once a unique subject randomization number has been assigned.

The randomization will be stratified by:

- Screening Lp(a) ≤ 200 nmol/L vs. > 200 nmol/L, and by
- Region (Japan vs. Non-Japan)

The randomization date is to be documented in the subject's medical record and on the enrollment CRF.

6.4.2 Blinding

This is a double-blind study. Treatment assignment will be blinded to all subjects, site personnel, and Amgen as described below.

6.4.2.1 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment is to only be unblinded by the investigator when knowledge of the treatment is essential for the further management of the subject on this study or may potentially impact the safety of the subject. Unblinding at the study site for any other reason will be considered a protocol deviation. It is encouraged that the Amgen Trial Manager be notified before the blind is broken unless the investigator believes that identification of the study treatment is required for a medical emergency. If this is not possible, the Amgen Trial Manager must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation.

6.4.2.2 Access to Individual Subject Treatment Assignments by Amgen or Designees

The study will be formally unblinded **to Amgen or Amgen designees** after **treatment period is ended, database is locked, and the snapshot is taken for end of treatment analysis**. **Sites and subjects** will not have access to unblinded information until the study is formally ended **at EOS (as defined in Section 4.4.1)**, database is locked, and the snapshot is taken for final analysis. Unblinding and potentially unblinding information is not to be distributed to the study team, investigators or subjects prior to the study being formally unblinded except as specified (eg, Section 6.4.2.1). Staff from Clinical Supply Chain, Biological Sample Management, Clinical Pharmacology Modeling and Simulation (CPMS), Computational Biology, Clinical Immunology, Clinical Biomarkers and Diagnostics, Global Statistical Programming and Global Biostatistical Sciences departments who may be responsible for tracking, assaying, or analyzing biological samples and/or data during the conduct of this study are considered unblinded to the treatment assignments in this study. These individuals will not have access to subject level clinical data apart from the sample types they are assaying and/or

analyzing during the course of the study and they will not be involved in study conduct decisions or communications with the sites or subjects.

An exposure-response analysis will be performed to support dose selection for a phase 3 registrational study. The exposure-response analysis team, including CPMS, Global Statistical Programming, and Global Biostatistical Sciences may be unblinded. The analysis plan for the exposure-response analysis will detail the analyses and describe the timing for unblinding according to Amgen's standard operating procedure.

See Section 8.2.5 for clinical laboratory results that will be blinded from the Amgen study team, site staff, and subjects.

In addition, study team members directly involved with the conduct of the study, investigators, and subjects will remain blinded to the results of the interim analyses unless specified. Amgen staff with access to the interim analysis results will be specified and documented according to Amgen's standard operating procedure. The interim analyses results may be used to support company internal discussions and external interactions with regulatory agencies.

6.5 Treatment Compliance

Study treatment are to be administered at study visits by authorized investigational site study staff. Each injection will be documented.

6.6 Treatment of Overdose

Overdose with this product has not been reported. No specific antidote exists. In the case of an overdose, the subject should be treated symptomatically, and supportive measures implemented as necessary.

6.7 Prior and Concomitant Treatment

6.7.1 Prior Treatment

Prior lipid-altering therapies that were being taken/used from 12 months prior to enrollment through the first dose of investigational product will be collected. Therapy name, dose, unit, frequency, start and stop dates will be collected.

6.7.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.1.6.

Any lipid-altering therapy, including statins, that were being taken by the subject at screening and enrollment must remain stable throughout the study, including the screening, treatment and extended safety follow-up periods. Lipid-altering therapies are not required for study participation. If any changes to lipid-altering therapies are medically warranted after randomization, the Amgen medical monitor or designee should be consulted before making the change, if possible.

Concomitant therapies are to be collected from informed consent through the **EOS**. For lipid-altering therapies and diabetes therapies (if applicable), collect therapy name, dose, unit, frequency, start and stop dates, reason for stop or change. For all other concomitant therapies, collect therapy name, start and stop dates.

7. Discontinuation Criteria

Subjects have the right to withdraw from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 7.1, 7.2.1, and 7.2.2.

7.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Table 1-1) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 11.3.

Reasons for early removal from protocol-required investigational product(s) or procedural assessments may include any of the following:

- Decision by Sponsor
- Lost to follow-up
- Death
- Adverse event
- Subject request
- Pregnancy

7.2 Discontinuation From the Study

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study, and must document the subject's decision to withdraw in the subject's medical records.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Section 11.6 for further details). Refer to the Schedule of Activities (Table 1-1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.2.1 Reasons for Removal From Washout Period, Run-in Period, or Invasive Procedures

Reasons for removal from the washout period, run-in period, invasive procedures are not applicable for this study.

7.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- Decision by sponsor
- Withdrawal of consent from study
- Death
- Lost to follow-up

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.
- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For subjects who are lost to follow-up, the investigator can search publicly available records where permitted to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

8. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Table 1-1).

As protocol waivers or exemptions are not allowed if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

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

8.1 General Study Periods

8.1.1 Screening, Enrollment, and/or Randomization

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the ICF, the site will register the subject in the IRT and screen the subject in order to assess eligibility for participation. The screening window is up to 28 days (4 weeks) and all activities shown in the Schedule of Activities for screening must be completed in this time period.

For a subject to be eligible for study participation, the subject must have a fasting Lp(a) > 150 nmol/L confirmed during screening. This serum sample needs to be collected after informed consent is obtained but prior to treatment start (see Section 8.2.9). Diagnoses of coronary artery disease, atherosclerotic cerebrovascular disease, or peripheral arterial disease are expected to be consistent with locally applicable professional society guidelines.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, (see Section 5.5) as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening 1 time if they failed criteria other than elevated Lp(a).

Rescreen subjects must first be registered as screen failures in IRT and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 28-day (4 week) screening window will begin. Subjects will retain the same subject identification number assigned at the original screening and must complete all screening assessments, except for the retesting of Lp(a). If the rescreening period begins more than 30 days after the original signing of the ICF, all screening procedures, including informed consent, must be repeated.

8.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Table 1-1). On-study visits may be completed within ± 3 day, aside from Day 2 visit which may be completed + 2 day. The date of the first dose of investigational product is defined as day 1 and will occur on day of randomization. All subsequent doses and study visits will be scheduled based on the day 1 date, with the final day of the treatment period defined as week 48. Administration of investigational product is to be administered last during each visit that it is required, except when post-dose PK samples are being collected.

Telemedicine, paper PRO completion, and home healthcare visits may be implemented at randomization/day 1 onward, where circumstances outside the subject's, site's, and sponsor's control (eg, pandemic) result in study visits being unable to be conducted. The sponsor must authorize use of these approaches in advance of each visit, and this approach may only be used where allowable by local health authorities, ethics

committees, and healthcare provider guidelines (eg, hospital policies). The minimum possible number of visits should occur outside the clinic, and visits should return to "in-clinic" at the earliest possible opportunity.

Subjects that withdraw from study treatment should continue with on-study visits (see Section 7.1 for more details). If a subject withdraws from the study early, all efforts should be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. The procedures for the EOS visit should be completed at the time of withdrawal (Section 8.1.4).

8.1.3 Extended Safety Follow-up

Visits will occur per the Schedule of Activities (Table 1-1). Extended Safety Follow-up visits should be completed within ± 7 day**s**. The Extended Safety Follow-up period will be **conducted for a minimum of 24** weeks in duration from week 48.

If a subject withdraws from the study early, all efforts should be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. The procedures for the EOS visit should be completed at the time of withdrawal (Section 8.1.4).

8.1.4 End of Study

The EOS visit will occur after the Extended Safety Follow-up period, or at the time a subject discontinues from the study early.

8.2 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required time points.

8.2.1 General Assessments

8.2.1.1 Informed Consent

All subjects must sign and personally date the IRB/IEC approved informed consent before any study-specific procedures are performed.

8.2.1.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally, demographic data will be used to study the impact on biomarkers variability and pharmacokinetics (PK) of the protocol-required therapies.

8.2.1.3 Medical History

The Investigator or designee will collect a complete medical history that started or was ongoing within 6 months prior to enrollment through day 1. Medical history will include information on the subject's concurrent medical conditions. In addition to the medical history above, the following should be collected back to the date of original diagnosis:

- cardiovascular history, including details of atherosclerotic cardiovascular disease and elevated Lp(a)
- history of cancer and/or malignancy
- history of immunologic or chronic inflammatory disease
- history of hepatobiliary dysfunction (including asymptomatic and/or transient liver function test abnormalities)
- history of renal disorder or abnormal renal findings
- history of non-stroke related neurological findings (eg, peripheral neuropathy)
- history of platelet disorder or coagulopathy
- diabetes mellitus history including, but not limited to, duration and complications (eg, acute metabolic complications, retinopathy, neuropathy)
- familial history of diabetes mellitus
- familial history of cardiac disorder

Record all findings on the medical history CRF. The current severity will be collected for each condition that has not resolved.

8.2.1.4 Physical Examination

Physical examination will be performed as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event).

8.2.1.4.1 Neurological and Muscular Examination

The clinical neurologic musculoskeletal examination will be performed to assess signs of new onset peripheral neuropathy or myopathy. The examination should be reported in the subject records and must include the following assessments:

- muscle mass and tone, presence of tremor, fasciculation or paralysis
- strength in all extremities, including proximal and distal muscular groups
- gait, by observation of a short regular walk, heel and toe walk
- symmetry of sensitivity to pressure (dull tool), temperature and pain (sharp tool)
- proprioception in upper and lower extremities
- symmetry of reflexes assessed on the upper extremities (biceps, triceps and brachioradial) and lower extremities (patellar and achilles)

If there is clinical evidence of treatment-emergent neuropathy or myopathy, dosing will be suspended, the subject will be directed to a specialist for a complete neurologic or musculoskeletal assessment. The identified neurologic or musculoskeletal abnormality is to be reported on the adverse **E**vent**s** CRF.

8.2.1.5 Physical Measurements

Height in centimeters should be measured without shoes. Weight in kilograms should be measured without shoes.

Waist circumference: Subjects should wear minimal clothing to ensure that the measuring tape is correctly positioned. Subjects should stand erect with the abdomen relaxed, arms at the sides, feet together and with their weight equally divided over both legs. To perform the waist measurement, the lowest rib margin is first located and marked. The iliac crest is then palpated in the midaxillary line, and also marked. It is recommended to apply an elastic tape horizontally midway between the lowest rib margin and the iliac crest, and tie firmly so that it stays in position around the abdomen about the level of the umbilicus. The elastic tape thus defines the level of the waist circumference, which can then be measured by positioning the measuring tape over the elastic tape. Subjects are asked to breathe normally, and to breathe out gently at the time of the measurement to prevent them from contracting their muscles or from holding their breath. Measurements should be performed using the same procedure throughout the study. The reading is taken to the nearest centimeter or 1/2 inch and entered in the source document.

8.2.2 Efficacy Assessments

Planned time points for all efficacy assessments are listed in the Schedule of Activities see (Table 1-1). Serum Lp(a), LDL-C, and ApoB will be collected with other clinical laboratory assessments described in Section 8.2.5.

8.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see (Table 1-1).

8.2.3.1 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure and heart rate. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible.

The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. Record all measurements on the vital signs CRF.

8.2.3.2 Survival Status

Survival status should be obtained for all subjects within the limits of local law. This includes subjects who withdraws consent, or subjects considered lost to follow-up, or subjects unwilling to continue schedule of assessments and should include interrogation of medical, national, and public databases, if necessary. If deceased, the date and reported cause of death should be obtained.

8.2.3.3 Electrocardiograms (ECGs)

Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The principal investigator designated site physician will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen. Findings should be recorded on the ECG eCRF.

8.2.4 Adverse Events and Serious Adverse Events

8.2.4.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

8.2.4.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the Amgen Standard Grading Scale and is described in Section 11.4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after enrollment through the **EOS** are reported using the Events CRF.

8.2.4.1.2 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through **EOS** are reported using the Events CRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours of the investigator’s knowledge of the event, as indicated in

Section 11.4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

8.2.4.1.3 Serious Adverse Events After the Protocol-required Reporting Period

After EOS, there is no requirement to **actively** monitor study subjects **with regards to study subjects treated by the investigator**. **However,** if the investigator becomes aware of serious adverse events **suspected to be related to investigational product, then** these serious adverse events **will be** reported to Amgen within 24 hours following the investigator's awareness of the event **using the Serious Adverse Event Contingency Form**.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to investigational product.

If further safety related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study.

8.2.4.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

8.2.4.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 11.4.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event**s** CRF.

8.2.4.4 Regulatory Reporting Requirements for Serious Adverse Events

If subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities. Aggregate analyses may also be unblinded by the Safety Assessment Team, as appropriate. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

8.2.4.5 Safety Monitoring Plan

Subject safety will be routinely monitored as defined in Amgen's safety surveillance and signal management processes.

8.2.4.6 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and pregnancy details for female partners of male subjects will be collected after the start of study treatment and until 90 days after receiving the last dose of study drug.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in

Section 11.5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Section 11.5.

8.2.5 Clinical Laboratory Assessments

Refer to Section 11.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Table 1-1) for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event**s** CRF. The investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

All protocol-required laboratory assessments, as defined in Section 11.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Table 1-1).

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been formally unblinded. In order to protect the blinding of the double-blind treatment period, the following labs will be blinded to the Amgen study team and site staff after day 1 until the study has been formally unblinded, and will not be reported to sites:

- Serum Lp(a)
- Lipid panel (see Appendix 2 Section 11.2 for a list of analytes)
- high sensitivity C-reactive protein (hs-CRP)
- **high sensitivity Interleukin 6 (**hs-IL-6**)**
- anti-olpasiran antibodies
- ApoA1
- ApoB

In addition, investigators and staff involved with this trial and all medical staff involved in the subject's medical care should not perform non-protocol testing of these analytes during a subject's study participation and until the end of the study, to prevent unblinding the patient and site to the treatment assignment, except when it is medically necessary. If a local lipid panel is drawn, all reasonable steps must be undertaken to avoid informing the subject and study personnel of the results.

If triglycerides are > 1000 mg/dL (11.3 mmol/L) at any scheduled assessment, the investigator will be informed, and a fasting triglyceride repeat test will be requested. If the retest confirms triglycerides > 1000 mg/dL (11.3 mmol/L), the Amgen medical monitor and the investigator will be informed so that appropriate medical follow up for the subject can be initiated.

Pregnancy Testing

A highly sensitive (serum) pregnancy test should be completed at screening and a screening urine pregnancy test should be completed the day of initiation of investigational product (prior to dosing) for females of childbearing potential.

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Form, see Figure 11-2). Refer to Section 11.5 for contraceptive requirements.

Additional urine pregnancy testing should be performed prior to each administration of protocol-required therapies and 90 days after the last dose of investigational product. In the case of a positive urine result, a serum pregnancy test should be performed for confirmation.

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

8.2.6 Pharmacokinetic Assessments

All subjects enrolled will have PK samples assessed.

Blood samples will be collected for measurement of serum concentrations of olpasiran as specified in the Schedule of Activities (Table 1-1 and Table 1-2). Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.2.6.1 Pharmacokinetic Sub-study

A PK sub-study will be conducted with a total of approximately 75 subjects (approximately 15 from each treatment cohort). A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Pharmacokinetic samples will be collected as per the PK sub-study schedule of assessments (see Table 1-1 and Table 1-2).

8.2.7 Pharmacogenetic Assessments

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of cardiovascular diseases and/or to identify subjects who may have positive or negative response to olpasiran. No additional samples are collected for this part of the study. For subjects who consent to this/these analysis/analyses, DNA may be extracted from residual cell pellets retained from selected biomarker plasma blood draws.

The final disposition of samples will be described in Section 11.6.

8.2.8 Antibody Testing Procedures

Blood sample(s) for antibody testing are to be collected according to the time points specified in the Schedule of Activities (Table 1-1). Bioanalytical testing for anti-olpasiran antibodies will be conducted on these samples only if there are unexpected PD findings or antibody-related safety concerns in this study. Samples testing positive may be further characterized. Additional blood samples may be obtained to rule out anti-drug antibodies during the study.

Subjects who test positive for binding antibodies at the final antibody-scheduled time point and have clinical sequelae that are considered potentially related to an anti-olpasiran antibody response may also be asked to return for additional follow-up testing.

8.2.9 Biomarkers

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

8.2.9.1 Biomarker Assessment to Determine Eligibility

Blood Samples

For a subject to be eligible for study participation, a subject must have a Lp(a) value of $>$ 150 nmol/L demonstrated during screening. Blood sample(s) need(s) to be collected after informed consent is obtained but prior to randomization. Screening for Lp(a) will be conducted using either an approved or investigational assay, investigational devices will follow regional regulatory requirements. The Lp(a) assay will be developed by Roche and screening will take place at a central laboratory as described in the Schedule of Activities (Table 1-1) and Appendix 2 (Section 11.2).

8.2.9.2 Biomarker Assessment During the Study

Serum samples are to be collected for assessment of hs-CRP and hs-IL-6 at the time points specified in the Schedule of Activities (Table 1-1); however, the results of these biomarkers will not be included in the final clinical study report unless noteworthy.

Biomarker Discovery

Samples will also be collected for biomarker analysis, eg, to evaluate potential biomarkers that may correlate with treatment response.

Blood will be collected for biomarker discovery at the time points specified in the Schedule of Activities (Table 1-1), but results will not be reported in the final clinical study report.

Biomarker samples may include: oxidized phospholipids on apolipoprotein B-100 (OxPL/ApoB) and Lp(a) isoform size.

8.2.9.2.1 Biomarker Development/Future Research

Biomarker Development refers to using samples collected for Biomarker Discovery for future research after the study ends.

Biomarker development can be useful in developing markers to identify disease subtypes, guide therapy, and/or predict disease severity.

If consent is provided by subjects, biomarker development samples collected at the time points specified in the Schedule of Activities (Table 1-1) will be retained for future biomarker development as described in Appendix 6 (Section 11.6).

Amgen or another third-party manufacturer may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to olpasiran to investigate and further understand cardiovascular diseases.

8.2.10 Optional Sub-studies

See Section 8.2.6.1 for the PK sub-study details.

Obtain confirmation that the optional PK sub-study ICF has been signed prior to performing optional PK sub-study procedures.

8.2.11 Other Assessments

8.2.11.1 PROMIS Global Health

The PROMIS Global Health is a 10-item static measure of global ratings of the five primary PROMIS domains (physical function, fatigue, pain, emotional distress, and social health) and general health perceptions that cut across domains. The first seven items do not use a specific recall period, and the last three items have a recall period of "the past seven days". The first nine items of the PROMIS Global Health use a five-point Likert-type scale. Response options for the first six items (Global 01 to 05 and Global 09) range from "Excellent", corresponding to a score of 5 to "Poor", corresponding to a score of 1; response options for item 7 (Global 06) ranged from "Completely", corresponding to a score of 5 to "Not at all", corresponding to a score of 1; response options for item 8 (Global 10) ranged from "Never", corresponding to a score of 5 to "Always", corresponding to a score of 1; and response options for item 9 (Global 08) ranged from "None", corresponding to a score of 5 to "Very severe", corresponding to a score of 1. Item 10 (Global 07) uses an 11-point numeric rating scale with 0 corresponding to "No pain" and 10 corresponding to "Worst pain imaginable". The PROMIS Global Health should be completed first at study visits and takes approximately 3 minutes to complete using the provided ePRO tablet device.

8.2.11.2 Exit Survey

Subjects will be asked to complete an Exit Survey at week 48 to provide feedback on their experience in the study and to help inform future studies. The Exit Survey will take approximately 10 minutes to complete using the provided ePRO tablet device.

9. Statistical Considerations

9.1 Statistical Hypotheses

The null hypothesis is that there is no difference between olpasiran and placebo in percent change from baseline in Lp(a) at week 36 in subjects with atherosclerotic cardiovascular disease and with elevated Lp(a).

9.2 Sample Size Determination

Assuming standard deviation of 30% as observed in phase 1 study, a 5% drop-out rate and with Bonferroni multiplicity adjustment to control family-wise type 1 error rate at 0.05, at least 48 subjects per arm provides at least 90% power to detect a treatment difference of 25% between active and placebo arm in mean percent change of Lp(a) from baseline. It is expected to have 99% power to detect a treatment effect of -80% vs. -3% between active and placebo arms in mean percent change of Lp(a) from baseline. Considering 5% drop-out rate, at least 48 subjects per arm (at least 192 subjects in the 4 active treatment arms) provides a 95% confidence of detecting 1 case of an adverse event at an incidence of 1/60.

Up to a total of approximately 290 subjects may be enrolled to accommodate individual country-specific enrollment requirements.

9.3 Analysis Sets, Subgroups, and Covariates

9.3.1 Analysis Sets

Full Analysis Sets (FAS): FAS includes all randomized subjects who received at least one dose of investigational product and will be used to perform the efficacy analysis based on randomized treatment group.

For safety analysis, FAS will be used based on the actual treatment received.

9.3.2 Covariates

Baseline covariates include, but are not limited to:

- Stratification factors
  - Screening Lp(a) ($\leq$ 200 nmol/L vs. $>$ 200 nmol/L)
  - Region (Japan vs. Non-Japan)
- Age
- Sex
- Race
- Baseline Lp(a)

9.3.3 Subgroups

Subgroups include, but are not limited to the following:

- Stratification factors
  - Screening Lp(a) (≤ 200 nmol/L vs. > 200 nmol/L)
  - Region (Japan vs. Non-Japan)
- Age (< 65 years, ≥ 65 years)
- Sex (male, female)
- Race (black, white, other)
- Baseline Lp(a)
  - Lipid lowering therapy at baseline (high intensity, not high intensity)

9.3.4 Handling of Missing and Incomplete Data

All attempts will be made to capture missing or partial data for this trial prior to the data lock. The frequency and pattern of missing data for efficacy endpoints will be assessed through descriptive summaries of the measurements over time.

Details on the imputation rules for partial dates relating to adverse events, concomitant medications and historical events are provided in the Statistical Analysis Plan (SAP)

9.4 Statistical Analyses

The first version of the SAP will be developed and finalized before the snapshot of the primary analysis. Below is a summary of the timing and methods for the planned statistical analyses. The final analysis will be conducted and reported following the EOS, as defined in Section 4.4.1.

9.4.1 Planned Analyses

9.4.1.1 Administrative Interim Analyses for Efficacy

An interim analysis will be performed when approximately 240 subjects have had the opportunity to complete week 24 assessments or have early terminated. At that point, approximately 120 subjects may have had the opportunity to complete week 36 assessments or have early terminated. The study continues regardless of the administrative interim results.

Interim analysis results will be reviewed by an Interim Analysis Review Steering Committee (IARSC) which consists of internal experts, who are independent of the study team. Further detail regarding the interim analysis process in protecting trial integrity will be provided by an IARSC Charter.

9.4.1.2 Primary Analysis

Primary analysis will be performed when all randomized subjects have had the opportunity to complete the week 36 assessments or have early terminated. At that time, the database related to the primary analyses will be cleaned, processed and a snapshot will be taken.

Only the unblinded team will be unblinded at the primary analysis. Individuals unblinded are prohibited from remaining involved in the conduct of the study.

9.4.1.3 End of Treatment Period Analysis

The end of treatment period analysis will be performed when all randomized subjects have had the opportunity to complete week 48 assessments or have early terminated. At that time, the database related to the end of treatment analyses will be cleaned, processed and a snapshot will be taken.

The study will be formally unblinded to Amgen or Amgen designees after treatment period is ended, database is locked, and the snapshot is taken for end of treatment analysis. Sites and subjects will not have access to unblinded information until the study is formally ended at EOS (as defined in Section 4.4.1), database is locked, and the snapshot is taken for final analysis.

9.4.1.4 Final Analysis

Final analysis will be performed when all randomized subjects either complete the extended safety follow-up and ended the study or early terminate from the study. At that time, the database related to the final analysis will be cleaned, processed and the database will be locked. All efficacy and safety analyses during the extended follow-up period will be performed.

9.4.2 Methods of Analyses

9.4.2.1 General Considerations

Unless specified otherwise, efficacy analyses will be performed on the FAS by randomized treatment group, and safety analyses will be performed on the FAS by actual treatment group.

All categorical variables will be summarized using the number and percent of subjects and all continuous variables will be summarized using mean, standard error or standard deviation, median, minimum, maximum, and number of subjects with observations. Analysis of exploratory endpoints will be specified in SAP.

Definition of Baseline Lp(a):

Baseline Lp(a) is defined as the mean of the two most recent non-missing Lp(a) values measured through central lab prior to or on study day 1. If for any reason only 1 value is available, then that value will be used as baseline.

9.4.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The analysis of percent change from baseline in Lp(a) at week 36 will be performed when all randomized subjects have had the opportunity to complete the week 36 assessments or have early terminated. A repeated measures linear effects model including terms for treatment group, stratification factors, scheduled visit and the interaction of treatment with scheduled visit will be used. The least squares means (LS means) by treatment group and the treatment difference (olpasiran - placebo) based on the model above will be summarized. The Hochberg procedure will be used to control the type I error for multiple comparisons between active and placebo arms. A sensitivity analysis will be performed using multiple imputation to impute missing data. Details of the imputation rules for the sensitivity analysis will be provided in the SAP. Additional analysis of the primary endpoint will be explored using Multiple Comparison Procedure - Modelling (MCP-Mod) methodology (Bretz et al, 2005). Details will be provided in the SAP.
Secondary	Analysis of the secondary endpoints will be performed when all randomized subjects have had opportunity to complete week 48 assessments or have early terminated. Analysis of the secondary endpoints (including percent change from baseline at week 36 in ApoB and LDL-C, and percent change from baseline at week 48 in ApoB, Lp(a) and LDL-C) will be performed similarly to the analysis of the primary endpoint.
Exploratory	Will be described in the statistical analysis plan finalized before database lock

9.4.2.3 Safety Analyses

9.4.2.3.1 Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class, high level term, and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product, and significant treatment emergent adverse events will also be provided.

9.4.2.3.2 Laboratory Test Results

The analyses of safety laboratory endpoints will include summary statistics at each scheduled visit by treatment group. Shifts in grades of select safety laboratory values between baseline and the maximum post-baseline grade will be tabulated by treatment group.

9.4.2.3.3 Vital Signs

The analyses of vital signs will include summary statistics at each scheduled visit by treatment group.

9.4.2.3.4 Electrocardiogram

The ECG measurements from this clinical study are performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential corrected QT (QTc) effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; summaries and statistical analyses of ECG measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other trials.

9.4.2.3.5 Antibody Formation

Identified anti-olpasiran binding antibodies will be summarized descriptively. Subject level listing may be provided instead of summary if there is a small number of subjects that are tested for anti-olpasiran antibodies.

9.4.2.3.6 Exposure to Investigational Product

The exposure to IP will be summarized using descriptive statistics by treatment group.

9.4.2.3.7 Exposure to Concomitant Medication

Number and proportion of subjects receiving therapies of interest will be summarized by preferred term or category for each treatment group as coded by the World Health Organization Drug dictionary.

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11. Appendices

11.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
A1C	glycated hemoglobin
ACC/AHA	American College of Cardiology/American Heart Association
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ApoB	apolipoprotein(B)
ASGPR	asialoglycoprotein receptor
ASO	Antisense oligonucleotides
AST	aspartate aminotransferase
AUC	area under the concentration time curve
Baseline Lp(a)	mean of the two most recent non-missing Lp(a) values measured through central lab prior to or on study day 1. If for any reason only 1 value is available, then that value will be used as baseline.
CABG	coronary artery bypass grafting
CFR	U.S. Code of Federal Regulations
C_{max}	maximum observed concentration
COVID 19	Coronavirus disease-19
CPMS	Clinical Pharmacology Modeling and Simulation
CRF	case report form
DILI	drug induced liver injury
DRT	Data Review Team
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
Enrollment	defined as the day a subject has signed the ICF
EOS	end of study
Exposure-Response Analysis	mechanism-based modeling & simulation and statistical analyses based on individual pharmacokinetic (PK) exposure (eg, population pharmacokinetic modeling) and response, which may include biomarkers, pharmacodynamic (PD) effects, efficacy and safety endpoints.
End of Follow-up	defined as when the last subject completes the last protocol-specified assessment in the study
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject

Abbreviation or Term	Definition/Explanation
End of Study (primary completion)	defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early
End of Study (end of trial)	defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
ESC/EAS	European Society of Cardiology/European Atherosclerosis Society
ESFU	extended safety follow-up
FAS	full analysis set
FDA	Food and Drug Administration
FIH	first in human
FSH	follicle-stimulating hormone
GalNAc	N-Acetylgalactosamine
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HRT	hormone replacement therapy
hs-CRP	high sensitivity C-reactive protein
hs-IL-6	high sensitivity Interleukin 6
IARSC	Interim Analysis Review Steering Committee
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IND	Investigational new drug
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
IRT	interactive response technology that is linked to a central computer in real time as an interface to collect and process information
LDL-C	low-density lipoprotein cholesterol
LS means	least square means
Lp(a)	lipoprotein(a)
NCT	National Clinical Trials

Abbreviation or Term	Definition/Explanation
NYHA	New York Heart Association
OCEAN(a)	Olpasiran trials of Cardiovascular Events And LipoproteiN(a) reduction
OxPL/ApoB	oxidized phospholipids on apolipoprotein B-100
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	pharmacodynamic
PK	pharmacokinetic
PROMIS	Patient-Reported Outcomes Measurement Information System
QoL	quality of life
QTc	Corrected QT
Q12W	**once** every 12 weeks
Q24W	**once** every 24 weeks
Randomization	defined as the day a subject has met all eligibility criteria and is assigned a treatment arm
RISC	RNA-induced silencing complex
SAP	Statistical Analysis Plan
SC	subcutaneous
siRNA	small interfering ribonucleic acid
Study Day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
TBL	total bilirubin
ULN	upper limit of normal

11.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 11-1 will be performed by the central laboratory, except for urine pregnancy for females of childbearing potential which will be done by the study staff or local laboratory.

Local laboratory results are only required in the event that additional tests are needed for monitoring of a possible drug induced liver injury (DILI) event per Section 11.7.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 5.1 to 5.2 of the protocol.

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

Table 11-1. Analyte Listing

Chemistry[a]		Hematology	Urinalysis	
ALT (SGPT)	GGT	Absolute Neutrophil Count	Macro:	Micro:
Albumin	Glucose (fasting)	Agranular Cells	Appearance	Bacteria
ALP	hs-CRP	Hematocrit	Bilirubin	Epithelial cells
Amylase	Lipase	Hemoglobin	Blood	Casts
Anion Gap	Magnesium	Hypersegmented Neutrophil	Glucose	Crystals
AST (SGOT)	Phosphorus	Hyposegmented Neutrophil	Ketones	RBCs
Bicarbonate, Total CO2	Potassium	MCH	Leukocyte Esterase	WBCs
Bilirubin, Direct, Conjugated	Sodium	MCHC	pH	
Bilirubin, Indirect	Total protein	MCV	Protein	
Bilirubin, Total	BUN or Urea Nitrogen	Platelets count	Specific gravity	
Calcium	Uric acid	RBC count	Urine Color	
Chloride	Adjusted calcium	RBC morphology	Urobilinogen	
CK	LDH	RDW		
Creatinine		WBC count		
eGFR		WBC Differential		
FSH		• Bands/stabs		
		• Eosinophils		
		• Basophils		
		• Lymphocytes		
		• Total neutrophils		
		• Monocytes		
		• Segmented neutrophils		

Table 11-1. Analyte Listing

Lipid Panel	Coagulation	Other Labs	Biomarker Assessment	Local Laboratory
Total Cholesterol HDL-C LDL-C Lp(a) Non-HDL-C Total cholesterol/HDL-C ratio Triglycerides VLDL-C	PT/INR APTT Fibrinogen Fibrin split products D-dimer	Apolipoprotein A1 Apolipoprotein B ApoB/ApoA1 ratio Olpasiran Antibodies Hemoglobin A1C Serum Pregnancy Pharmacokinetics	**h**s-CRP hs-IL-6 OxPL/ApoB Lp(a) isoforms	Urine Pregnancy (completed by study staff or local laboratory) Lactate (if applicable)[b] Additional observational labs for DILI criteria (if applicable)

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[a] Fasting is only required when fasting glucose sample is taken. When fasting is required, subject must be fasting (not eating or drinking anything except for water) for at least 9 hours.
[b] To be performed at the discretion of the investigator or designee if anion-gap metabolic acidosis is identified.
ALP = alkaline phosphatase; ALT = alanine aminotransferase; APTT = activated partial thromboplastin time
AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase;
DILI = drug induced liver injury; eGFR = estimated glomerular filtration rate;
FSH = follicle-stimulating hormone; GGT = gamma glutamyl transferase; HDL = high density lipoprotein;
HLA = human leukocyte antigen; hs-CRP = high sensitivity C-reactive protein;
hs-IL-6 = high sensitivity Interleukin-6; INR = international normalized ratio; LDH = lactate dehydrogenase;
LDL = low-density lipoprotein; Lp(a) = lipoprotein(a); MCH = mean corpuscular hemoglobin;
MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume;
OxPL/ApoB = oxidized phospholipids on apolipoprotein B-100; PT = prothrombin time;
RBC = red blood cell count; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; VLDL = very-low-density lipoprotein; WBC = white blood cell count

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded (see Section 8.2.5 for details).

11.3 Appendix 3. Study Governance Considerations

Clinical Events, Interim Analysis Review Steering, and Data Review Team Committee(s)

Clinical Events Committee

Deaths and major cardiovascular events will be adjudicated by an independent external Clinical Events Committee, using standardized definitions. Adjudication will include, but may not be limited, to the following events:

- death by any cause
- cardiovascular death
- myocardial infarction
- hospitalization for unstable angina
- coronary revascularization
- stroke
- transient ischemic attack
- cerebrovascular revascularization

In addition, major adverse limb events (acute limb ischemia, major amputation, or urgent peripheral revascularization for ischemia) may also be adjudicated.

Interim Analysis Review Steering Committee

Amgen will use an Interim Analysis Review Steering Committee (IARSC) to review accumulating efficacy data from the planned administrative interim analyses of Study 20180109 to support dose selection for a phase 3 registrational study and trigger early planning for the phase 3 program, but will not assess for futility. The IARSC will be an internal group within Amgen, but external to the relevant study team for olpasiran. The IARSC will follow guidelines outlined in the IARSC charter. The charter will set forth the governance and responsibilities of the IARSC for olpasiran Study 20180109.

It is important to note that the IARSC is separate from the Data Review Team (DRT), described below. While both are internal Amgen committees, the IARSC will review accumulating efficacy data and the DRT will review accumulating safety data.

Data Review Team

In addition to routine pharmacovigilance monitoring by Amgen, an internal unblinded DRT will be implemented. In order to maintain trial integrity, the unblinded data reviewed by the DRT will be restricted and not accessible by the olpasiran team.

The DRT is a group internal to Amgen, but external to the olpasiran product team with at least 3 members, including at least 2 with clinical expertise (eg, a member from Clinical or Early Development and a member from Global Patient Safety) and a member from Global Biostatistical Science. The DRT will periodically review accumulating data from the ongoing clinical study to enable prompt identification of serious and unexpected suspected adverse reactions to ensure no avoidable increased risk for harm to subjects. The DRT will follow the procedures outlined in a charter that will detail the DRT responsibilities and ensure controls are in place to prevent any unintentional unblinding of the olpasiran team involved in conduct of the study. Serious adverse events, adverse events of interest, and relevant clinical laboratory test results, will be reviewed as well as any other available important safety information, as deemed necessary. The DRT will perform unblinded comparisons of event rates in investigational and control groups to detect serious and unexpected suspected adverse reactions as well as any other safety findings that may prompt further actions such as update to the protocol, Investigators' Brochure or Informed Consent Form (ICF). An ad-hoc DRT may be convened at any time for reasons such as a significant and unanticipated safety finding. In accordance with Food and Drug Administration (FDA) guidance on the safety assessment for Investigational new drug (IND) safety reporting (FDA, 2015), identification of any serious and unexpected suspected adverse reactions will trigger regulatory safety reporting.

Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable ICH laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the Institutional Review Board/Independent Ethics Committee (IRB/IEC). A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen
- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the U.S. Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Informed Consent Process

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the sample informed consent form are to be communicated formally in writing from the Amgen Trial Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential patient population.

The investigator or his/her delegated representative will explain to the subject, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered, and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study site.

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

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study unless it is a local requirement. The investigator shall then inform the primary care physician. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 7.

Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the study.

The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the subject.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)

A subject who is rescreened is not required to sign another informed consent form if the rescreening occurs within 30 days from the previous informed consent form signature date.

The informed consent form (ICF) will contain a separate section that addresses the use of remaining mandatory samples for optional future research. The investigator or authorized designee will explain to each subject the objectives of the future research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate

signature will be required to document a subject's agreement to allow any remaining specimens to be used for future research. Subjects who decline to participate will not provide this separate signature.

Data Protection/Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

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

On the case report form (CRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does

not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states: Authorship credit is to be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All persons designated as authors must qualify for authorship, and all those who qualify are to be listed. Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- A recognized expert in the therapeutic area
- An Investigator who provided significant contributions to either the design or interpretation of the study
- An Investigator contributing a high number of eligible subjects

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

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

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

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

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research and Development Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Retention of study documents will be governed by the Clinical Trial Agreement.

Case report forms (CRF) must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

Source Documents

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

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

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the Interactive Response Technology system (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment).

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

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Subject files containing completed CRFs, informed consent forms, and subject identification list

- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen

- Investigational product-related correspondence including [Proof of Receipts, Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable

Retention of study documents will be governed by the Clinical Trial Agreement.

Study and Site Closure

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

11.4 Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure. • Note: Treatment-emergent adverse events will be defined in the Statistical Analysis Plan (SAP).

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

Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other medically important serious event Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Definition of Adverse Device Effect

The detection and documentation procedures for adverse device effects described in this protocol apply to all Non-Amgen medical devices provided for use in the study (see Section 6.1.2 for the list of Non-Amgen medical devices).

Adverse Device Effect Definition
An adverse device effect is any adverse event related to the use of a combination product or medical device. Adverse device effects include, but are not limited to, adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant adverse event/serious adverse event information in the Event case report form (CRF).
- The investigator must assign the following adverse event attributes:
  - Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Dates of onset and resolution (if resolved);
  - Did the event start prior to first dose of investigational product, other protocol-required therapies;
  - Assessment of seriousness;
  - Severity (or toxicity defined below);
  - Assessment of relatedness to investigational product **(olpasiran/placebo) and/or other protocol-required therapies**;
  - Action taken, and
  - Outcome of event.
- If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Event**s** CRF.
- It is not acceptable for the investigator to send photocopies of the subject's medical records to Amgen in lieu of completion of the Event**s** CRF page.
- If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity

The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on:

The Amgen Standard Grading Scale as show below:

Grade	Definition
MILD	Aware of sign or symptom, but easily tolerated
MODERATE	Discomfort enough to cause interference with usual activity
SEVERE[a]	Incapacitating with inability to work or do usual activity

[a] An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of a serious adverse event, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between investigational product, and/or study-mandated procedure and each occurrence of each adverse event/serious adverse event.
- Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality.
- There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.
- The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed Event**s** CRF.
- The investigator will submit any updated serious adverse event data to Amgen within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool
• The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system. • If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using an electronic Serious Adverse Event Contingency Report Form (also referred to as the electronic Serious Adverse Event (eSAE) Contingency Report Form) (see Figure 11-1) within 24 hours of the investigator's knowledge of the event. • The site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the site can report this information on the paper based Serious Adverse Event Contingency Report Form (see Figure 11-1). • **Once the study has ended, serious adverse event(s) suspected to be related to investigational product will be reported to Amgen if the investigator becomes aware of a serious adverse event. The investigator should use the paper-based Serious Adverse Event Contingency Report Form to report the event**.

Figure 11-1. Sample Electronic Serious Adverse Event Contingency Form

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for clinical trial studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions

The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

Types of Events to be reported on this form

- **Serious Adverse Events (regardless of causal relationship to IP)**

1. **Site Information**

   Site Number* – Enter your assigned site number for this study

   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested

2. **Subject Information**

   Subject ID Number* – Enter the entire number assigned to the subject

   Age at event onset, Sex, and Race – Enter the subject's demographic information

   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the serious adverse event term for the previous report as well as the start date for the initial event.

3. **Serious Adverse Event**

   Provide the date the investigator became aware of this information

   Serious Adverse Event Diagnosis or Syndrome* –
   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

   Date Started* – Enter date the adverse event first started (not the date on which the event met serious criteria)rather than the date of diagnosis or hospitalizion. . **This is a mandatory field.**

   Date Ended – Enter date the adverse event ended and not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

   If event occurred before the first dose of Investigational Product (IP)/drug under study, add a check mark in the corresponding box.

   Is event serious?* – Indicate Yes or No. This is a mandatory field.

   Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:
   - Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

   Relationship to IP – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**

   Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

   Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**
   - Resolved – End date is known
   - Not resolved / Unknown – End date is unknown
   - Fatal – Event led to death

   If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP or concomitant medication – only diagnostic tests or activities mandated by the protocol.

4. **Hospitalization**

   If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

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Completion Instructions - Electronic Adverse Event Contingency Report Form (for use for Studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

5. **IP Administration including Lot # and Serial # when known / available.**
   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label
   Initial Start Date – Enter date the product was first administered, regardless of dose.
   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
   Action Taken with Product – Enter the status of the product administration.
6. **Concomitant Medications**
   Indicate if there are any medications.
   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
   Co-suspect – Indicate if the medication is co-suspect in the event
   Continuing – Indicate if the subject is still taking the medication
   Event Treatment – Indicate if the medication was used to treat the event
7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**
   Indicate if there are any relevant laboratory values.
   For each test type, enter the test name, units, date the test was run and the results.
9. **Other Relevant Tests**
   Indicate if there are any tests, including any diagnostics or procedures.
   For each test type, enter the date, name, results and units (if applicable).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

10. **Case Description**
    Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

AMGEN®
Study # 20180109
AMG 890

Electronic Serious Adverse Event Contingency Report Form

For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site
☐ Is not yet available for this study
☐ Has been closed for this study

<<For completion by COM prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____
and start date: Day _____ Month _____ Year _____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____ Month___ Year_____

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? AMG 890 No / Yes	Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No				
				☐Yes ☐No				
				☐Yes ☐No				

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability /incapacity; 06 Congenital anomaly / birth defect; 08 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event: Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
AMG 890	☐blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

AMGEN® Study # 20180109 AMG 890	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

<<IP Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

Site Number	Subject ID Number

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No✓	 Yes✓	Continuing No✓	 Yes✓	Dose	Route	Freq.	Treatment Med No✓	 Yes✓

7. RELEVANT MEDICAL HISTORY *(include dates, allergies and any relevant prior therapy)*

8. RELEVANT LABORATORY VALUES *(include baseline values)* Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date Day Month Year	Test / Unit											

9. OTHER RELEVANT TESTS *(diagnostics and procedures)* Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date Day Month Year	Additional Tests	Results	Units

AMGEN® Study # 20180109 AMG 890	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee -	Title	Date
_____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*		

11.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for female of childbearing potential are outlined in Section 5.2.

Female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant during treatment and for 90 days after the last dose of protocol-required therapies.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered female of childbearing potential:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy;
  - Documented bilateral salpingectomy; or
  - Documented bilateral oophorectomy.

  Note: Site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.
- Premenarchal female
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Methods for Female Subjects of Childbearing Potential

Highly Effective Contraceptive Methods

Note: Failure rate of < 1% per year when used consistently and correctly.

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)

- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device
- Intrauterine hormonal-releasing system
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)

Unacceptable Methods of Birth Control for Female Subjects

Birth control methods that are considered unacceptable in clinical trials include:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 90 days.
- Information will be recorded on the Pregnancy Notification Form (see Figure 11-2). The form must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 90 days of the study drug. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal

complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.

- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Section 11.4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 7.1 for details).

Male Subjects With Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

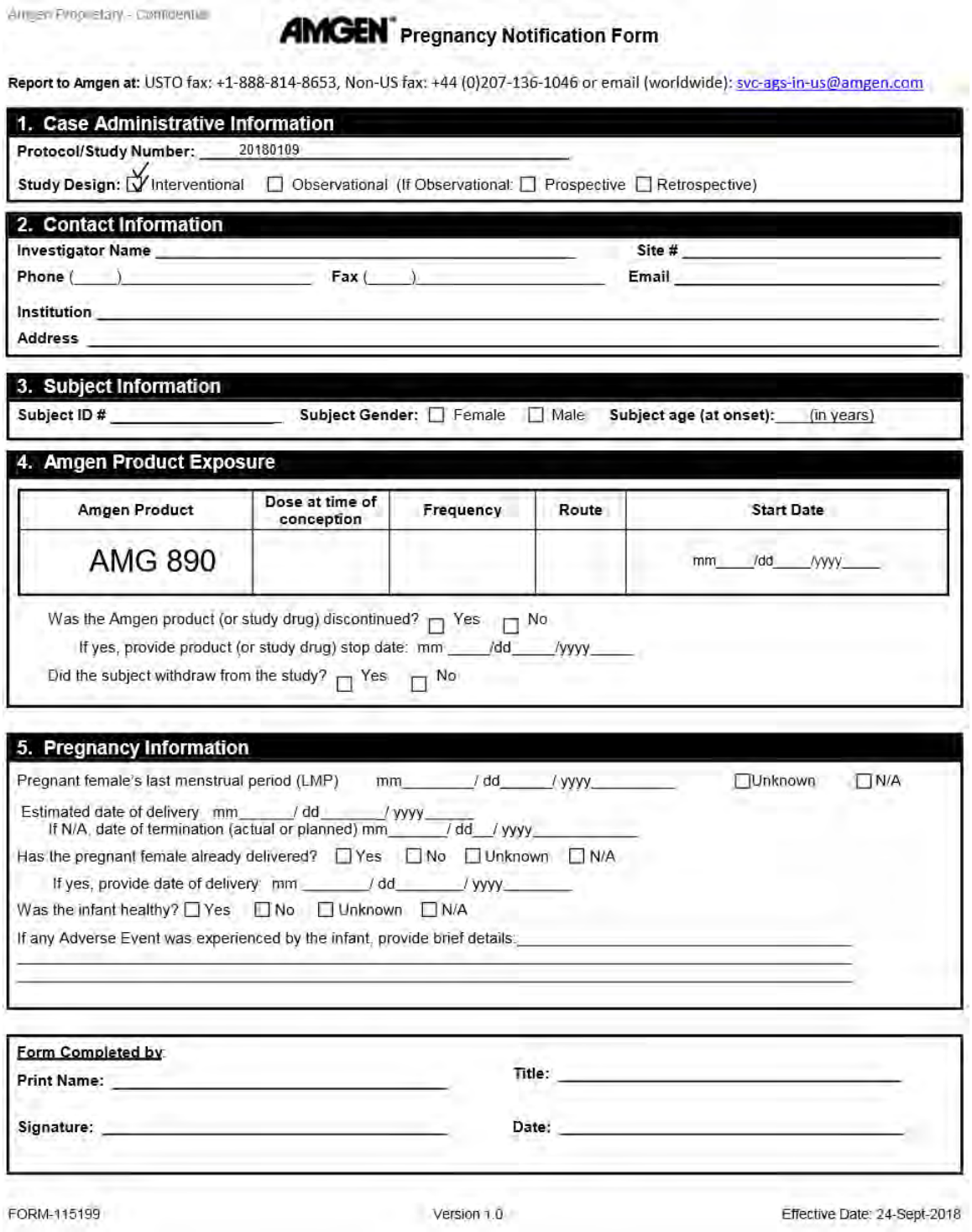
- In the event a male subject fathers a child during treatment, and for an additional 90 days after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Form. The form (see Figure 11-2) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 90 days.
- Information will be recorded on the Lactation Notification Form (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 219.

- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 90 days after discontinuing protocol-required therapies.

Figure 11-2. Pregnancy and Lactation Notification Forms



Amgen Proprietary - Confidential

AMGEN Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20180109

Study Design: ☑ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):** ____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
AMG 890				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐ N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd__/ yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

AMGEN Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20180109

Study Design: ☑ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):** ____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
AMG 890				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

11.6 Appendix 6. Sample Storage and Destruction

Any blood (eg, biomarker, pharmacokinetics [PK]) sample collected according to the Schedule of Activities (Table 1-1 and Table 1-2) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the cardiovascular disease, the dose response and/or prediction of response to olpasiran, characterize antibody response, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic, biomarker development or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the

request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 11.3 for subject confidentiality.

11.7 Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other protocol-required therapies, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR, and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis
- Non-hepatic causes (eg, rhabdomylosis, hemolysis)

If investigational product(s) is/are withheld, the subject is to be followed for possible drug induced liver injury (DILI) according to recommendations in the last section of this appendix.

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

Table 11-2. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3x ULN at any time	> 2x ULN
		OR
INR	--	> 1.5x (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8x ULN at any time > 5x ULN but < 8x ULN for ≥ 2 weeks > 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule > 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values > 3x ULN (when baseline was < ULN)
	OR	
ALP	> 8x ULN at any time	--

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal

Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the subject is to be discussed and agreed upon unanimously by the subject, investigator, and Amgen.

If signs or symptoms recur with rechallenge, then olpasiran is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 11-2) are never to be rechallenged.

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation, according to the criteria specified in the above, require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate Case Report Form (CRF) (eg, Event**s** CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 11.4.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 11-2 or who experience AST or ALT elevations > 3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels. Local laboratory results are required in the event that additional tests are needed for DILI criteria.

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (BIL) (total and direct), and INR within 24 hours
- In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin (Ig)G, anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels
- A more detailed history of:
  - Prior and/or concurrent diseases or illness

  - Exposure to environmental and/or industrial chemical agents
  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - Prior and/or concurrent use of alcohol, recreational drugs and special diets
  - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Viral serologies
- Creatine phosphokinase, haptoglobin, lactate dehydrogenase and peripheral blood smear
- Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in the corresponding CRFs.

Amendment 3

Protocol Title: A Double-blind, Randomized, Placebo-controlled Phase 2 Study to Evaluate Efficacy, Safety, and Tolerability of Olpasiran (AMG 890) (a GalNAc conjugated Small Interfering RNA [siRNA]) in Subjects With Elevated Lipoprotein(a)

Amgen Protocol Number Olpasiran (AMG 890) 20180109

EudraCT number: 2019-003688-23

NCT number: NCT04270760

Amendment Date: 02 May 2022

Rationale:

This protocol amendment has two main reasons. The first one is to reduce the duration of the extended safety follow-up period from ≥ 40 weeks to a minimum of 24-week follow-up and to remove the requirement for the subject's lipoprotein(a) to return to 80% of baseline levels. Based on the non-clinical and first-in-human experience to date, the half-life of olpasiran ranges from 4 to 7 hours. Olpasiran is predominantly eliminated from the systemic circulation within 2 to 3 days of exposure. In addition, there was histopathologic evidence of recovery observed 16 weeks post-treatment in preclinical liver tissue, indicating a low potential for a clinically meaningful effect or adverse event. Thus, a minimum 24-week follow-up after the last administered dose is considered appropriate to ensure olpasiran is eliminated from the systemic circulation and liver. Clinical studies have not observed new, residual, or long-lasting adverse effects post-administration. In the sustained absence of exposure to investigational product, there is no expected difference in patient safety with the reduced monitoring plan.

The second reason is to update access to individual subject treatment assignments for Amgen (or designee) team members after the treatment period has ended, the database is locked, and the snapshot is taken for the end of treatment analysis. Sites and subjects will be formally unblinded after the study is ended, the database is locked, and the snapshot is taken for final

analysis. This is to support planning for the phase 3 study. Additional minor updates were incorporated including important clarifications, administrative changes, grammatical corrections, and formatting. Below is a list of the additional important clarifications incorporated in this amendment:

- Include survival status within General and Safety Assessments in the Schedule of Activities to provide clarification and additional guidelines for collection of information (Table 1-1 and section 8.2.3.2).
- To provide clarification and maintain consistency, the word ‘once’ was added to every instance the dosing schedules were defined, QW12 defined as once every 12 weeks and Q24W defined as once every 24 weeks (sections 1.1, 2.1, 3, Table 1-2, and Appendix 1).
- Incorporate current protocol template language related to recording and reporting of safety events in relevant sections of the protocol (Table 1-1, Table 1-2, sections 6.1.5, 8.2.4.1.3, and 11.4).

Amendment 2

Protocol Title: A Double-blind, Randomized, Placebo-controlled Phase 2 Study to Evaluate Efficacy, Safety, and Tolerability of Olpasiran (AMG 890) (a GalNAc-conjugated Small Interfering RNA [siRNA]) in Subjects With Elevated Lipoprotein(a)

Amgen Protocol Number Olpasiran 20180109

EudraCT number: 2019-003688-23

NCT number: NCT04270760

Amendment Date: 01 April 2021

Rationale:

The following changes were made to the protocol dated 01 April 2021.

- Amended to provide clarification to the wording of the Current Protocol Summary Synopsis, Statistical Consideration (Section 1.1), the Study Design, Overall Design (Section 4.1), and Number of Subjects (Section 4.2) for the 20180109 study.
    - Updated number of subjects from 240 to 290 and subjects per treatment arm from 48 to 58
    - Updated details of the planned Interim Analyses
    - Updated number of subjects per treatment arm in the study schema
- Updated administrative edits.

Amendment 1

Protocol Title: A Double-blind, Randomized, Placebo-controlled Phase 2 Study to Evaluate Efficacy, Safety, and Tolerability of Olpasiran (AMG 890) in Subjects With Elevated Lipoprotein(a)

Amgen Protocol Number (**olpasiran**) 20180109

Amendment Date: 25 November 2020

Rationale:

The following changes were made to the protocol, dated November 25th, 2020, to provide pandemic related guidance, clarify the exclusion criteria regarding the use of niacin and fish oil, and to clarify/correct other items in the protocol.

Pandemic related guidance included:

- Addition of telemedicine, paper PRO completion, and home healthcare visits to Section 8.1.2.

Clarification of exclusion criteria regarding niacin and fish oil included:

- Modified Exclusion Criterion 218 and added Exclusion Criterion 226 to clarify the upper dosage limit for niacin and fish oil.

Other changes include:

- Updated the short protocol title to reflect study name.
- Updated Amgen investigational product name.
- Clarified laboratory testing, including triglycerides in Section 8.2.5.
- Updated statistical consideration to clarify interim analysis for efficacy timeframe.
- Updated the schedule of activities to reflect changes in protocol.
- Corrected fasting lipid panel within Table 11-1 to appropriate analytes and added missing analytes collected.
- Modified Exclusion Criterion 203 to clarify the exclusion of inherited or acquired known bleeding disorders.

- Updated references and study rationale.
- Modified exploratory objectives and endpoints to include achievement of Lp(a) < 125 nmol/L.
- Updated the number of sites from 50 to 60.
- Modified inclusion criterion 103 to clarify fasting Lp(a) threshold during screening.
- Updated study treatment period in section 8.1.2 to clarify the day 2 visit window.
- Updated safety language in alignment with the current protocol template.
- Administration, typographical and formatting changes were made throughout the protocol