Protocol

An Open-label, Single-dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of Olpasiran in Chinese Subjects With Elevated Serum Lipoprotein(a)

Protocol Status: Final

Protocol Date: 28 July 2021
Protocol Version: 3.0

Investigational Product: Olpasiran (AMG 890)

Amgen Protocol Reference Number: 20190095
Labcorp Study Number: 8424665

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NCT Number: NCT04987320
This NCT number has been applied to the document
for purposes of posting on Clinicaltrials.gov

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INVESTIGATOR AGREEMENT

I have read the protocol entitled "An Open-label, Single-dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of Olpasiran in Chinese Subjects with Elevated Serum Lipoprotein(a)" and agree to conduct the study as described herein.

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.

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Date (DD Month 2021)

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SYNOPSIS

Title of study: An Open-label, Single-dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of Olpasiran in Chinese Subjects with Elevated Serum Lipoprotein(a)
Objectives: The primary objective of the study is: • to evaluate the pharmacokinetics (PK) of a single dose of Olpasiran in Chinese subjects with elevated serum lipoprotein(a) (Lp[a]). The secondary objectives of the study are: • to evaluate the safety and tolerability of a single dose of Olpasiran in Chinese subjects with elevated serum Lp(a) • to evaluate the pharmacodynamics (PD) of a single dose of Olpasiran in Chinese subjects with elevated serum Lp(a).
Study design: This will be an open-label, randomized, single-dose parallel group study in Chinese subjects with elevated serum Lp(a). Potential subjects will be screened within 40 days prior to the dose. Subjects will be admitted into the phase I Clinical Research Unit (CRU) on Day -1 and will be confined to the CRU until discharge on Day 4. Subjects will return to the CRU for out-patient visits on Days 7, 15, 29, 57, 85, 113, 155, and 183, and at the End of Study (EOS) visit on Day 225. A telephone visit will be scheduled for treatment emergent adverse event (TEAE) assessments on Day 211. Subjects will be randomized in a 1:1 ratio to receive a single subcutaneous (SC) dose of Olpasiran at [redacted] mg (Group A) or [redacted] mg (Group B).
Number of subjects: Approximately 24 subjects (12 per group) will be enrolled in the study.
Diagnosis and main criteria for inclusion: Male or female subjects living in mainland China, Hong Kong, or Taiwan, and of Chinese ancestry, 18 to 60 years of age (inclusive), body mass index of 18 to 32 kg/m^2 (inclusive), and serum Lp(a) $\geq$ 70 nmol/L (or approximately $\geq$ 27 mg/dL).
Investigational products, dose, and mode of administration: Investigational Medicinal Product: [redacted] mg/mL Olpasiran. Group A = [redacted] mg administered as a [redacted] ([redacted] mg/mL) SC injection Group B = [redacted] mg administered as [redacted] ([redacted] mg/mL) SC injections
Duration of subject participation in the study: Planned Screening duration: approximately 6 weeks. Planned study duration (Screening to EOS): approximately 38 weeks.

Endpoints:

Primary:

The primary endpoints for this study are Olpasiran PK parameters:

- maximum observed concentration (C_{max})
- area under the concentration-time curve (AUC)

Additional PK parameters may include, but are not limited to: time to maximum observed concentration (t_{max}), half-life ($t_{1/2}$), apparent volume of distribution during the terminal elimination phase (V_z/F), and apparent total body clearance (CL/F).

Secondary:

Secondary endpoints for this study are: TEAEs, clinical laboratory tests, 12-lead electrocardiograms (ECGs), vital signs, lipids and serum Lp(a).

Statistical methods:

Data will be analyzed for all subjects who are randomized and receive Olpasiran. Descriptive statistics by treatment group will be provided for selected demographics, safety, PK and Lp(a) data. Descriptive statistics on continuous measurements will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. PK, Lp(a), lipids, vital signs, electrocardiogram, and clinical laboratory data will be summarized at each scheduled visit per Schedule of Assessment.

The final safety analysis for the study will be performed at the end of the study. Each TEAE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). No imputation will be done for safety assessments and endpoints for clinical laboratory tests, 12-lead ECGs, and vital signs will be summarized using descriptive statistics.

Additional details will be included in the Statistical Analysis Plan.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
Apo B	apolipoprotein B
ApoA1	apolipoprotein A1
APTT	activated partial thromboplastin time
ASCVD	atherosclerotic cardiovascular disease
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
BP	blood pressure
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CRU	Clinical Research Unit
CVD	cardiovascular disease
DILI	drug-induced liver injury
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOS	end of study
FIH	first in human
FSH	follicle-stimulating hormone
GalNac	N-acetylgalactosamine
HDL-C	high-density lipoprotein cholesterol
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonisation
IMP	investigational medicinal product
LDL-C	low-density lipoprotein cholesterol
Lp(a)	lipoprotein(a)
MDRD	Modification of Diet in Renal Disease

Abbreviation	Definition
MI	myocardial infarction
NOAEL	no observed adverse effect level
PK	pharmacokinetic(s)
PD	pharmacodynamics(s)
PT	prothrombin time
QTcF	QT interval corrected for heart rate based on the Fridericia correction
SAP	Statistical Analysis Plan
SC	subcutaneous
siRNA	small interfering ribonucleic acid
$t_{1/2}$	half-life
TBL	total bilirubin
TEAE	treatment-emergent adverse event
Tg	transgenic
t_{max}	time to maximum observed concentration
ULN	upper limit of normal
VLDL-C	very low-density lipoprotein cholesterol
V_z/F	apparent volume of distribution during the terminal elimination phase

1. INTRODUCTION

1.1 Background

According to the World Health Organization (WHO), cardiovascular disease (CVD) is the leading cause of death globally. An estimated 17.9 million people died from CVDs in 2016, representing 31% of all deaths worldwide[1]. Of the deaths related to CVD, approximately 85% are from myocardial infarction (MI) and stroke[1].

The morbidity associated with MI and stroke continues to be serious and multifaceted, and reducing this morbidity is an important treatment goal. After a cardiovascular event, patients may struggle to regain their independence and suffer from both acute and long-term reductions in health-related quality of life, including diminished mobility and functionality, as well as increased anxiety, depression, fatigue, and sexual dysfunction[2, 3, 4, 5, 6, 7].

While lipid-lowering therapy research has historically focused on lowering low-density lipoprotein cholesterol (LDL-C) to reduce cardiovascular risk, elevated serum levels of lipoprotein(a) (Lp[a]) have recently been identified as a potential risk factor for atherosclerotic cardiovascular disease (ASCVD) [8, 9, 10, 11, 12.]

An Lp(a) molecule is composed of a LDL-like particle and an apo(a) that is bound to apolipoprotein B-100 by a disulfide bridge[13]. Lp(a) molecules are heterogeneous in size, depending upon the number of kringle IV type 2 repeats in the apo(a) gene[14]. Lp(a) levels are largely genetically determined, stable over time, and not significantly influenced by diet, exercise, or other environmental factors[15]. Lp(a) has been shown to have a pathogenic role in atherosclerosis and thrombosis formation[16]. The potential association between Lp(a) levels and coronary artery disease, MI, stroke, peripheral vascular disease, and aortic valve stenosis has been described in several genetic and observational studies[13].

Olpasiran (AMG 890) is a synthetic small interfering ribonucleic acid (siRNA) that targets the liver by conjugation to a tri-*N*-acetylgalactosamine moiety and inhibits the translation of apo(a) and Lp(a) production (the latter being a protein-lipid complex, of which apo[a] is a component). Olpasiran is being developed to reduce Lp(a) for the treatment of adults with ASCVD to reduce the risk of cardiovascular events.

Amgen's nonclinical program demonstrated that Olpasiran can achieve a sustained $> 80\%$ reduction in serum Lp(a) and is suitable for monthly subcutaneous (SC) administration. The studies supporting this conclusion included efficacy data collected from transgenic (Tg) mice and cynomolgus monkeys demonstrating that Lp(a) levels can be specifically targeted with

Olpasiran to inhibit apo(a) translation. Based on available data, Olpasiran is a potentially promising molecule to reduce Lp(a) for the treatment of adults with ASCVD to reduce the risk of cardiovascular events. Additional information related to the physical, chemical, and pharmaceutical properties and formulation(s), pharmacology and pharmacokinetic(s) (PK) of the Olpasiran is provided in the Investigator Brochure (IB)[17].

Currently, Olpasiran is being studied in two phase 1 studies in healthy subjects (first-in-human [FIH] Study 20170544 and Study 20180222). The FIH Study 20170544 is an ongoing double-blind placebo-controlled study in healthy subjects with elevated plasma Lp(a), which is designed to evaluate safety and tolerability as primary endpoints, and to address PK and pharmacodynamics (PD) effects as secondary endpoints. Study 20180222 is a completed open-label study in Japanese and non-Japanese subjects to characterize Olpasiran PK as the primary endpoint and assess safety and tolerability as the secondary endpoints. Olpasiran was evaluated at dose ranges of [redacted] mg to [redacted] mg in both phase 1 studies.

1.2 Nonclinical Summary

A detailed description of the chemistry, pharmacology, and PK of Olpasiran is provided in the IB[17].

1.2.1 Pharmacology

The Olpasiran nonclinical pharmacology program to date has consisted of in vivo PD studies in Tg mice and cynomolgus monkeys and exploratory in vitro cytokine release and complement and platelet activation assays in human systems. In Tg mice, Olpasiran achieved $>$ 80% reduction in serum Lp(a) for 36 days after administration of a single SC dose of 1 mg/kg. In cynomolgus monkeys, a single 2 mg/kg dose of Olpasiran significantly reduced serum Lp(a) and apo(a) levels by $>$ 80% for up to 6 weeks. In a dose response study in cynomolgus monkeys, Olpasiran demonstrated $>$ 80% reductions in serum Lp(a) in the 3 and 10 mg/kg dose groups.

1.2.2 Pharmacokinetic

Olpasiran was administered subcutaneously (SC) to cynomolgus monkeys at a single dose of 0.1, 1, 3, or 10 mg/kg. Olpasiran PK was linear over the dose range of 0.1 to 10 mg/kg SC. Mean terminal half-life ($t_{1/2}$) values after SC administration ranged from 3.13 hours to 5.09 hours.

In repeat-dose toxicology studies in the cynomolgus monkey (see Section 1.2.3 below), Olpasiran exposure increased approximately in proportion to Olpasiran dose between 10 and

30 mg/kg and greater than dose proportionally between 30 and 150 mg/kg. No accumulation of Olpasiran was observed following multiple-dose administration.

The in vitro metabolism of Olpasiran was evaluated in Sprague Dawley rats, cynomolgus monkeys, and human whole liver cell lysate preparations by high performance liquid chromatography-mass spectrometry (HPLC-MS). Metabolite profiles were qualitatively similar across species with no disproportionate human metabolites. Overall, the nonclinical PK and metabolism data support the clinical testing of Olpasiran in human subjects.

1.2.3 Toxicology

The Sprague Dawley rat and cynomolgus monkey were selected as the species for nonclinical safety assessment. The SC route of administration was chosen based on the intended clinical route of administration. The monkey is a pharmacologic relevant animal model, in contrast to the rat, which does not produce apo(a). In monkey safety pharmacology assessments, there were no Olpasiran-related qualitative or quantitative electrocardiogram (ECG) changes or changes in blood pressure (BP), heart rate, body temperature, respiratory rate or neurological function at doses up to 150 mg/kg, the highest dose level tested. In the in vitro secondary PD studies, Olpasiran did not cause complement activation in human serum or cytokine stimulation or platelet activation in human whole blood.

Olpasiran was well tolerated in the Investigational New Drug (IND)-enabling (57-day rat and monkey) and registrational (6-month rat, 9-month monkey) GLP toxicology studies. All dose levels in the monkey toxicology studies reduced serum Lp(a) by $\geq$ 90%. In the IND-enabling GLP 57-day rat and monkey toxicology studies and in the registrational GLP 6-month rat and 9-month monkey studies, Olpasiran was administered at 10, 30, and 150 mg/kg once monthly. In rats at 10 mg/kg, the only Olpasiran related change was minimal to mild accumulation of basophilic granular material in the proximal convoluted tubular epithelium of the renal cortex in the 6-month study. In monkeys at 10 mg/kg, the only Olpasiran-related changes were Kupffer cell hypertrophy/hyperplasia (with cytoplasmic vacuolization and basophilia) in the liver and vacuolation of macrophages in the subcutis at the injection site and in the lymph nodes; the vacuolation of macrophages in the subcutis at the injection site was not observed in the 9-month monkey toxicology study. Olpasiran-related changes in the liver, kidneys, lymph nodes, and injection site were consistent with investigational product uptake, a known N-acetylgalactosamine (GalNAc) conjugated siRNA-related platform effect and not specific to Olpasiran[18, 19, 20].

There were other Olpasiran-related changes that occurred either at higher dose levels or a more frequent dosing regimen (e.g., weekly in the exploratory studies) included transient, minimal to mild increases in cholesterol (rats only), serum alanine aminotransferase (ALT), and minimal to mild increases in serum alkaline phosphatase (ALP), and bilirubin. Additional Olpasiran-related changes occurring at higher dose levels or with increased frequency of dosing included basophilic granules in the proximal tubular epithelial cells of the kidney. Olpasiran-related liver changes at higher dose levels or increased frequency of dosing consisted of hepatocellular vacuolation, increased single cell necrosis and mitoses of hepatocytes, and basophilic granular material in Kupffer cells in the liver in rats and hepatocellular hypertrophy with cytoplasmic rarefaction in monkeys. The only Olpasiran-related finding considered secondary to silencing of *LPA* gene expression was a reduction in serum Lp(a) in monkeys. None of the Olpasiran-related changes were considered adverse due to their low severity and absence of light microscopic evidence of tissue injury. All the Olpasiran-related changes in rats were partially reversed at the end of the recovery phase in the 57-day study. All the Olpasiran-related changes in monkeys were fully reversed at the end of the recovery phase in the 57-day study except for GalNAc conjugated siRNA platform related effects in Kupffer cells of the liver and mesenteric lymph node macrophages. All the Olpasiran related changes in the 6-month rat toxicology study were partially or fully reversed at the end of a 4-month recovery period; the recovery period of the 9-month monkey toxicology study is ongoing. In both the rat and monkey, the no observed adverse effect level (NOAEL) for the GLP toxicology studies was determined to be 150 mg/kg, the highest dose evaluated.

In an exploratory embryo fetal development toxicology study in the rat, there were no Olpasiran-related mortalities, clinical signs, maternal ovarian or uterine abnormalities, or fetal external or visceral abnormalities when pregnant rats received up to 200 mg/kg Olpasiran SC daily on gestation Day (GD) 7 through GD 17. In a GLP fertility and early embryonic development study in the rat, there were no Olpasiran-related clinical signs or macroscopic findings or effects on mating and fertility parameters, male reproductive organ weights, sperm parameters (vas deferens sperm motility, caudal epididymal sperm density, or sperm morphology) in males, and no Olpasiran-related clinical signs or macroscopic findings or effects on any ovarian or uterine parameter (corpora lutea, implantation sites, live and dead embryos), or on estrous cycling or mating and fertility in females. Additionally, there were no Olpasiran-related microscopic effects observed in reproductive organs in the rat (up to 6-month duration) or monkey (up to 9-month duration) toxicology studies.

In conclusion, Olpasiran-associated changes were primarily associated with uptake of the siRNA molecule and were non-adverse. Based on the rat and monkey NOAEL from the GLP toxicology studies, there are sufficient safety margins for the doses studied in humans.

1.3 Clinical Summary

Olpasiran is being studied in two phase 1 studies in healthy subjects, specifically a FIH Study 20170544 and a Japanese PK Study 20180222.

Study 20170544 (FIH)

As of the 19 March 2020 data snapshot date, Olpasiran or placebo had been administered to 64 subjects (48 Olpasiran and 16 placebo). Of these 30 subjects with screening plasma Lp(a) between ≥ 70 to ≤ 199 nmol/L received 5 different single doses (cohorts 1 to 5: [redacted] mg) and 18 subjects with screening plasma Lp(a) ≥ 200 nmol/L received 2 different single doses (high Lp[a] cohorts 6 and 7: [redacted] mg). Two additional cohorts were added to Study 20170544 and are ongoing (cohort 8 [redacted] mg] and cohort 9 [redacted] mg] included subjects with screening plasma Lp(a) ≥ 200 nmol/L). As of 19 March 2020, no data are available for reporting from cohorts 8 and 9. All 64 subjects enrolled in cohorts 1 to 7 of Study 20170544 have completed the treatment phase of the study (cohorts 1 and 2: Day 113 and cohorts 3 to 7: Day 225). There have been no life-threatening or fatal adverse events (AEs) reported, and no serious AEs reported in subjects treated with Olpasiran. No clinically relevant changes in liver function tests, platelets or coagulation parameters, or renal function (creatinine) have been detected. Overall, no notable trends in AEs, vital signs, or laboratory results have been observed to date.

After single doses of [redacted] mg, preliminary PK data in cohorts 1 to 7 indicated that Olpasiran was rapidly absorbed with maximum observed concentration (C_{max}) occurring approximately 3 to 8 hours after dosing. The half-life ($t_{1/2}$) ranged from 3 to 8 hours and Olpasiran was predominantly cleared from systemic circulation within 2 to 3 days. In general, serum exposures increased in an approximately dose-proportional manner at doses between [redacted] mg. Mean Olpasiran exposures in subjects with screening Lp(a) ≥ 200 nmol/L (cohorts 6 and 7) were 53% to 55% and 18% to 33% lower compared to those in subjects with screening Lp(a) ≥ 70 to ≤ 199 nmol/L (cohorts 1 to 5) for C_{max} and area under the concentration-time curve (AUC), respectively.

Study 20180222 (Japanese PK)

Phase 1 Study 20180222 was conducted to evaluate the PK, safety, and tolerability of Olpasiran in Japanese and non-Japanese subjects; pre-study Lp(a) level was not an eligibility criterion. The study was an open-label, single SC dose study evaluating Olpasiran at 4 dose levels [redacted] mg; n = 4 to 6 subjects per group). This study was designed to support integration of Japanese subjects (in Japan) into the global clinical phase 2 study. Eligible subjects received a single dose of Olpasiran by SC administration on Day 1 and PK samples were collected from predose through Day 29. Subjects were assessed for safety endpoints and for serum Lp(a) levels from screening through Day 225.

Olpasiran was administered to a total of 27 subjects: 21 subjects in 4 different single doses ([redacted] mg) in Japanese subjects and to 6 subjects in 1 single dose ([redacted] mg) in non-Japanese subjects. Olpasiran was shown to be safe and well tolerated. No patterns indicative of clinically important adverse events, laboratory abnormalities, or vital sign abnormalities were observed. No serious or fatal adverse events were reported from this study.

[redacted]

A detailed description of the efficacy and safety of Olpasiran is provided in the IB[17].

1.4 Study Rationale

This study will be conducted to confirm and evaluate the PK, PD, safety, and tolerability of a single dose of Olpasiran at two dose levels ([redacted] mg and [redacted] mg) in Chinese subjects with elevated serum Lp(a) to support the conduct of further clinical studies of Olpasiran in mainland China, Hong Kong, or Taiwan.

1.5 Benefit-risk Assessment

Despite the scientific advances of the last 50 years leading to an armamentarium of evidence-based guidelines and risk reducing drugs, ASCVD still represents a major cause of death and morbidity, and an enormous financial burden[21]. Recently, elevated serum Lp(a) has been identified as a strong independent risk factor for the development and progression of atherosclerotic disease[15]. Lp(a) has been associated with increased risk for MI, aortic valve stenosis development, carotid artery stenosis, and abdominal aorta aneurism progression. High serum Lp(a) concentration is genetically defined; it cannot be controlled by habit modifications and it 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 CVD. Although definitive evidence that the reduction in serum Lp(a) will provide cardiovascular (CV) risk reduction is not yet available, Mendelian randomization epidemiologic studies, plasma lipid apheresis cohort results, and experimental data suggest a causal role for elevated Lp(a)[22, 23, 24].

The current nonclinical package supports conduct of a study in humans[25]. In nonclinical toxicology studies, Olpasiran was able to reduce Lp(a) levels, with no significant safety concerns identified. Olpasiran-related changes were limited to generally minimal to mild. Non adverse changes that were consistent with those expected for the modality. To date, based on nonclinical data, and safety data from Studies 20170544 and 20180222, there are no expected adverse drug reactions with Olpasiran and potential risks include hypersensitivity reactions and liver enzyme elevations.

The benefit-risk assessment supports the conduct of this clinical study. Refer to the IB[17] for more information.

1.5.1 Key Benefits

Subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study.

1.5.2 Risks

There are no identified adverse drug reactions for Olpasiran and important potential risks are limited to liver enzyme elevations and hypersensitivity reactions. Olpasiran is an oligonucleotide-based therapy, and events of interest associated with other antisense oligonucleotide (ASO)-based therapies include: effects on platelets and coagulation, immune-inflammatory response, development of anti-drug antibodies, 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 [26, 27]. These risks have not been borne out by either the nonclinical data or clinical data to date for Olpasiran. Safety monitoring measures for these concerns have been implemented in the protocol.

As stated in Section 1.3, no notable trends in safety and tolerability have been observed to date for Olpasiran in two clinical studies in human.

Oligonucleotide-based therapies include ASOs and siRNAs. Key safety concerns associated with these products are further discussed below. Refer to the Olpasiran IB, Section 6.4, for additional information regarding safety concerns with related molecules.

Hypersensitivity Reactions

Administration of any drug may trigger hypersensitivity reactions. Immune-mediated hypersensitivity has been reported with biologics, including systemic and locally restricted reactions (including injection site reactions). ASO based therapies, including siRNAs, do not share molecular similarities with traditional amino acid-based biologics. Nevertheless, double stranded siRNA may be recognized by the innate immune system, triggering innate immune responses[28]. No hypersensitivity attributed to Olpasiran has been observed to date in clinical trials.

Liver Enzymes Elevation

ASOs, such as mipomersen, have been associated with liver enzyme elevations and hepatic steatosis. Olpasiran-related changes in the liver in the exploratory rat toxicology studies included hepatocellular vacuolation at all dose levels and, at higher dose levels, minimal to mild increased single cell necrosis of hepatocytes sometimes associated with increased mitoses. Hepatocellular mitoses are considered a regenerative response to the single cell necrosis. These liver changes were accompanied by transient, minimal increases in serum alanine aminotransferase (ALT). Minimal to mild increases in serum ALP and bilirubin were also observed. Olpasiran-related changes in the liver were considered to be siRNA platform -related

changes that were not adverse because of their low severity and ultrastructural characteristics. At the doses planned for administration in this study, organ toxicity related to intracellular accumulation is not expected. No safety concern for liver enzyme elevation and Olpasiran has been observed to date in clinical trials.

During the study, safety monitoring based on organ target toxicity and other antisense toxicity[29, 30] will be conducted. Safety assessments throughout the study include TEAE and serious TEAE collection; physical examination, including assessment for peripheral neuropathy; monitoring for hypersensitivity reactions; ECGs; laboratory tests, including liver function tests; renal function tests; coagulation and hematologic parameters; metabolic acidosis, if needed; and glucose. Potential anaphylactic reactions will be assessed by Sampson criteria[31]. 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.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

The primary objective of the study is:

- to evaluate the PK of a single dose of Olpasiran in Chinese subjects with elevated serum Lp(a).

The secondary objectives of the study are:

- to evaluate the safety and tolerability of a single dose of Olpasiran in Chinese subjects with elevated serum Lp(a).
- to evaluate the PD of a single dose of Olpasiran in Chinese subjects with elevated serum Lp(a).

2.2 Endpoints

2.2.1 Primary Endpoints

The primary endpoints of the study are Olpasiran PK parameters:

- C_{max}
- AUC

Additional PK parameters may include, but are not limited to: time to maximum observed concentration (t_{max}), half-life ($t_{1/2}$), apparent volume of distribution during the terminal elimination phase (V_z/F), and apparent total body clearance (CL/F).

2.2.2 Secondary Endpoints

The secondary endpoints of the study are:

- treatment-emergent adverse events (TEAEs)
- clinical laboratory tests
- 12-lead ECGs
- vital signs
- lipids
- serum Lp(a).

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This study is an open-label, randomized, single-dose, parallel-group study in Chinese subjects with elevated serum Lp(a) to assess the PK, safety and tolerability, and PD of Olpasiran. Subjects will be randomized in a 1:1 ratio to receive a single SC dose of Olpasiran at [redacted] mg (Group A) or [redacted] mg (Group B). A total of approximately 24 subjects (12 per group) will be enrolled in this study.

Subjects must be living in mainland China, Hong Kong, or Taiwan, and be of Chinese ancestry with an age of 18 to 60 years old (inclusive) and have body mass index of 18 to 32 kg/m^2 (inclusive) and serum Lp(a) ≥ 70 nmol/L (or approximately ≥ 27 mg/dL).

Subjects will be assigned to 1 of 2 treatment groups shown in Table 1.

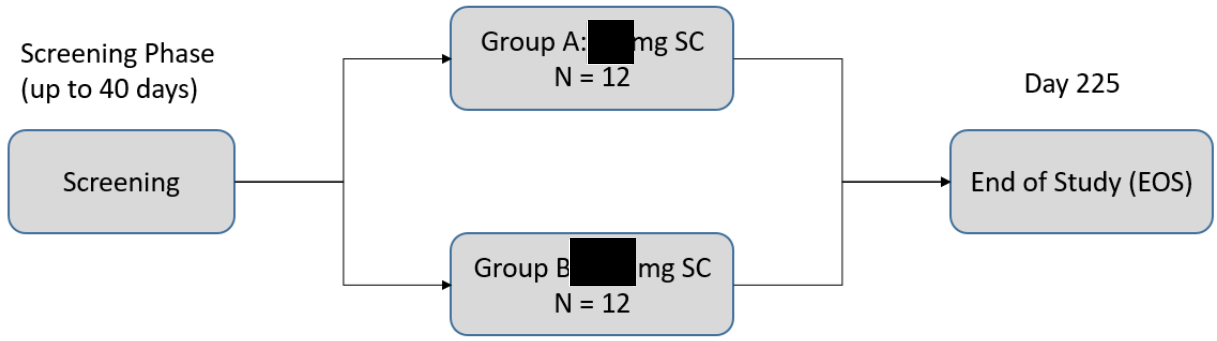
Table 1. Treatment Groups

Group	Number of subjects	Dose
A	12	[redacted] mg SC
B	12	[redacted] mg SC

Abbreviations: SC = subcutaneous.

An overview of the study design is shown in Figure 1. The endpoints are defined in Section 2.2.

Figure 1. Study Schematic



AMG 890 Chinese PK Study (N = 24)

Abbreviations: SC = subcutaneous.

Potential subjects will be screened to assess their eligibility to enter the study within 40 days prior to dose administration. Subjects will be admitted into the phase I Clinical Research Unit

(CRU) on Day -1 and be confined to the CRU until discharge on Day 4. Subjects will return to the CRU for outpatient visits on Days 7, 15, 29, 57, 85, 113, 155, and 183, and at the end of study (EOS) visit on Day 225. A telephone visit will be scheduled for TEAE assessments on Day 211. The total duration of study participation for each subject (from Screening through EOS visit) is anticipated to be approximately 265 days (about 38 weeks).

The start of the study is defined as the date the first subject signs an Informed Consent Form (ICF). The point of enrollment occurs at the time of subject randomization number allocation. The enrollment date is the same as the randomization date. The EOS for overall study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

A Schedule of Assessments is presented in Appendix 9.

3.2 Discussion of Study Design

This study will be open-label.

Conducting the study in subjects with elevated serum Lp(a) in Chinese subjects is necessary to support a comparison of Olpasiran PK parameters with those observed in the FIH study (20170544) and therefore to assess the ethnic difference, as baseline Lp(a) levels may impact Olpasiran exposure and the interpretation of these analyses.

3.3 Selection of Doses in the Study

The selection of the doses for this study are supported by the dose margins determined from the NOAEL in rat and cynomolgus monkey (150 mg/kg). [redacted]. These calculated dose margins are conservative as only a single dose will be given in this study, and the NOAEL was determined based on data from every 4-week dosing (x3) in rat and cynomolgus monkey repeat-dose toxicology studies.

The preliminary data from the FIH study (20170544) and the Japanese phase 1 PK study (20180222) indicated that Olpasiran is rapidly absorbed and eliminated with low, but detectable serum exposures, as expected for a siRNA oligonucleotide. Given the hepatic site target and rapid elimination of Olpasiran from systemic circulation, the dose-response relationship related to reductions in Lp(a) were used to support dose selection in this study and for future studies. The preliminary PD data demonstrated effective lowering of Lp(a) levels across the evaluated dose range of [redacted] mg and [redacted] mg, and with no identified safety concerns.

In this study, the [redacted] and [redacted] mg SC doses are selected to evaluate the PK, PD, safety, and tolerability of Olpasiran in Chinese subjects with elevated serum Lp(a) levels. [redacted]

[redacted].

Evaluation of these 2 dose levels in the current study will allow a direct comparison of Olpasiran PK and Lp(a) reductions with those observed in FIH Study (20170544) in subjects with same screening Lp(a) levels ≥ 70 nmol/L. [redacted]

[redacted]

[redacted]

Therefore, the dose margins, the FIH study results, and the PK study in Japanese subjects support the selection of the dose levels to be evaluated in this study to assess the PK, PD, safety, and tolerability of Olpasiran, and to evaluate the magnitude and durability of Lp(a) reduction in Chinese subjects with elevated serum Lp(a).

3.4 End of Study

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 endpoints (see Section 2.2.1), whether the study concluded as planned in the protocol or was terminated early.

The primary completion date is the date when the last subject has completed the assessments on Day 225 of the study.

If the study concludes prior to the primary completion date originally planned in the protocol (i.e., 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 (i.e., last subject last visit).

End of Study: The 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 (i.e., last subject last visit), after any additional parts in the study (e.g., long-term follow-up), as applicable.

4. SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

Inclusion eligibility criteria will be evaluated in 2 parts during the screening period:

- **Part 1**: After written informed consent is obtained, subjects will provide a blood sample for a preliminary Lp(a) assessment to determine eligibility for Part 2 screening. Subjects with Lp(a) ≥ 70 nmol/L (or approximately ≥ 27 mg/dL) will be eligible to return to the CRU for Part 2 screening. Subjects not eligible to return for Part 2 screening will be screen failed.
- **Part 2**: Eligible subjects will complete all remaining screening procedures and tests that establish eligibility within 40 days prior to the Day 1 visit.

To be eligible for the study, subjects must provide written informed consent to participate and must fulfill the following criteria:

Inclusion Criteria (Part 1)

1. Subject has provided informed consent before initiation of any study-specific activities/procedures.
2. Must be a resident in mainland China, Hong Kong, or Taiwan, and of Chinese ancestry.
3. Male or female subjects, between 18 and 60 years of age (inclusive) at the time of Screening.
4. Screening serum Lp(a) ≥ 70 nmol/L (or approximately ≥ 27 mg/dL).

Inclusion Criteria (Part 2)

1. In good health, determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital sign measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [e.g., suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) as assessed by the Investigator (or designee).
2. Body mass index between 18 and 32 kg/m^2 (inclusive) at the time of Screening.
3. Subjects who are on statin must be on a stable dose of the same statin for at least 6 weeks prior to enrollment, and plan to remain on a stable dose (i.e., no change in medication or dosage) for the duration of the study
4. Females must be of non-reproductive potential:
    a. Postmenopausal defined as:
        i. Age of ≥ 55 years with no menses for at least 12 months; OR
        ii. Age of < 55 years with no menses for at least 12 months AND with a follicle stimulating hormone (FSH) level > 40 IU/L or according to the definition of "postmenopausal range" for the laboratory involved; OR
    b. History of hysterectomy; OR
    c. History of bilateral oophorectomy

4.2 Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria prior to enrollment unless otherwise stated:

1. History or clinical evidence of peripheral neuropathy.
2. Currently receiving apheresis as lipid reducing therapy.
3. History or clinical evidence of bleeding diathesis or any coagulation disorder, including prothrombin time (PT), activated partial thromboplastin time (APTT), or platelet count outside of the laboratory's normal reference range at screening. Subjects with PT and/or APTT values that are outside of the laboratory's normal reference range at screening may still be eligible to proceed to enrollment if the results are judged by the investigator in consultation with the study medical monitor to not be clinically significant.
4. History or clinical evidence of diabetes mellitus, including a fasting glucose $\geq$ 125 mg/dL (6.9 mmol/L) at Screening.
5. History or evidence, at Screening or Check-in, of clinically significant disorder, condition, or disease not otherwise excluded that, in the opinion of the Investigator (or designee), would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.

   Exceptions include:

   a. Subjects with controlled and stable arterial hypertension. Controlled and stable hypertension with a systolic blood pressure [BP] $<$ 150 mmHg or diastolic BP $<$ 90 mmHg at Screening and Day -1, with no change in medication and dosage for at least 8 weeks prior to enrollment and expected to remain on this dose and medication for the entire duration of the study. If the initial BP is elevated, the reading may be repeated again at least 15 minutes later and the lower of the 2 readings may be used.
   b. Subjects with diagnosis of hyperlipidemia on treatment with a stable dose of the same statin (with or without concomitant ezetimibe) for at least 6 weeks prior to enrollment and expected to remain on this dose and medication for the entire duration of the study.
6. A QT interval corrected for HR based on the Fridericia correction (QTcF) interval $>$ 450 msec in male subjects or $>$ 470 msec in female subjects or history/evidence of long QT syndrome, at Screening.
7. Subject has known sensitivity to any of the products or components to be administered during dosing.
8. Estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2 as calculated by the Modification of Diet in Renal Disease (MDRD) equation, at Screening.
9. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $>$ 1.1 x upper limit of normal (ULN), at Screening or Check-in. For subjects on a stable dose of statin, ALT or AST $>$ 1.5 x ULN of the laboratory's reference at Screening or Check-in.

10. Positive hepatitis B or hepatitis C panel and/or positive human immunodeficiency virus antibodies test at Screening. Subjects whose results are compatible with prior immunity (vaccination or prior recovered infection) may be included.
11. Use of any over-the-counter or prescription medications within 14 days or 5 half-lives (whichever is longer) before dosing on Day 1 and during the study is not permitted, unless to treat a TEAE. Continued use, if applicable, will be reviewed by the Principal Investigator (or designee) and in consultation with the Sponsor. Written documentation of this review and Sponsor acknowledgement is required for subject participation. Exceptions are:
    a. Acetaminophen (paracetamol) up to 2 g per day for analgesia
    b. Hormone replacement therapy (e.g., estrogen, thyroid) provided the subject is stable on replacement therapy
    c. Medication for the management of arterial hypertension, including, but not limited to, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers, or low dose thiazides, provided it is stable (i.e., no change in drug or dose) for at least 8 weeks prior to enrollment
    d. Use of anti-platelet therapy (low-dose acetylsalicylic acid [up to 162.5 mg daily], clopidogrel, or ticagrelor) is allowed, provided subjects have been on a stable dose for at least 6 weeks prior to enrollment and plan to be on the same dose for the duration of the study
    e. If subjects are on a statin, subjects must be on a stable dose of the same statin for at least 6 weeks prior to enrollment, and plan to remain on the same dose (i.e., no change in medication or dosage) for the duration of the study
    f. Use of ezetimibe is allowed, provided subjects have been on a stable dose for at least 6 weeks prior to enrollment and plan to be on the same dose for the duration of the study
    g. Medication used to manage chronic conditions not excluded by other exclusion criteria, provided subjects have been on a stable dose for at least 6 weeks prior to enrollment and plan to be on the same dose for the duration of the study. Medication must be reviewed and approved by the Investigator (or designee) and acknowledged by the Sponsor. Written documentation of this review and Sponsor acknowledgement is required for subject participation.
12. Subjects are on niacin, or have received niacin $>$ 200 mg/day within 3 months prior to dosing on Day 1.
13. Use of any herbal medicines, vitamins or dietary supplements known to affect lipid metabolism (e.g., fish oils $>$ 1000 mg/day, red yeast rice extract), within 30 days prior to dosing on Day 1 and for the duration of the study.
14. All herbal medicines (e.g., St. John’s wort) and dietary supplements (with the exception of those known to affect lipid metabolism, which are excluded above) consumed by the subject within the 30 days prior to Check-in, unless deemed acceptable by the Investigator (or designee) and in consultation with the Sponsor.
15. Triglycerides $\geq$ 5.65 mmol/L (i.e., 500 mg/dL) at Screening
16. History of drug/chemical abuse within 1 year prior to Check-in.
17. Alcohol consumption within 48 hours prior to Check-in and during in-house residency period.

18. Alcohol consumption of > 14 units per week for males and > 7 units per week for females. One unit of alcohol equals 12 oz (360 mL) beer, 1½ oz (45 mL) liquor, or 5 oz (150 mL) wine.
19. Positive test for illicit drugs and/or alcohol use at Screening or Check-in.
20. Female subjects with a positive pregnancy test at Screening or Check-in.
21. Female subjects lactating/breastfeeding or who plans to breastfeed during the study through 90 days after Olpasiran dosing.
22. Unwilling to abstain from sperm donation through 90 days after Olpasiran dosing (see Appendix 4).
23. Male subjects with a female partner of childbearing potential and not willing to inform his partner of his participation in this clinical study.
24. Male subjects with a pregnant partner or partner planning to become pregnant while the subject is on study through 90 days after Olpasiran dosing.
25. Subject has received a dose of an investigational drug within the past 30 days or 5 half-lives, whichever is longer, prior to Check-in. Other investigational procedures while participating in this study are excluded.
26. Have previously completed or withdrawn from this study or any other study investigating Olpasiran or have previously received the investigational product.
27. Donation of blood from 60 days prior to Check-in, plasma from 2 weeks prior to Check-in, or platelets from 6 weeks prior to Check-in.
28. Performed strenuous exercise within 72 hours prior to Screening or Check-in.
29. Unwilling to abide with study restrictions.
30. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.

4.3 Screen Failures and Rescreening

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled (i.e., randomized) into 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 TEAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Refer to Section 7.1.1.

4.4 Subject Number and Identification

Subjects will have a unique identification number used at screening. Subjects will be assigned a unique subject number at randomization. Assignment of subject numbers will be in ascending order and no numbers will be omitted (e.g., Subjects 0101, 0102, 0103). Replaced subjects will

be assigned a subject number corresponding to the number of the subject he/she is replacing plus 1000 (e.g., Subject 1101 replaces Subject 0101).

Subjects will be identified by subject number only on all study documentation. A 1-digit site identification number will be added to the subject number when entering the subject into the database (example: site 1, Subject 0101 will be entered as 10101 into the database). A list identifying the subjects by subject number will be kept in the Site Master File.

4.5 Subject Withdrawal and Replacement

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn if any of the following criteria are met:

- change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the Investigator (or designee)
- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator (or designee)
- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal.

If a subject is withdrawn after randomization and prior to receiving Olpasiran dose, the Sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic Case Report Form (eCRF). If a subject is withdrawn, efforts will be made to perform all EOS assessments, if possible (Appendix 9). Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the CRU. The Investigator (or designee) may also request that the subject return for additional follow-up visits. All withdrawn subjects will be followed until resolution of all their TEAEs or until the unresolved TEAEs are judged by the Investigator (or designee) to have stabilized.

Subjects who are withdrawn for reasons not related to study drug may be replaced following discussion between the Investigator and the Sponsor. Subjects withdrawn as a result of TEAEs thought to be related to the study drug will generally not be replaced.

4.6 Study Termination

The Sponsor 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 the Sponsor 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 Ethics Committee (EC) in writing of the study's completion or early termination and send a copy of the notification to the Sponsor.

In addition, the study may be terminated by the Sponsor at any time and for any reason. If the Sponsor decides to terminate the study, the Sponsor will inform the Investigator as soon as possible.

5. STUDY TREATMENTS

Study treatment is defined as the investigational product intended to be administered to a study subject according to the study protocol.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of the investigational medicinal product (IMP) shown in Table 2 and Appendix 8

5.1 Investigational Product

The IMP will be supplied by the Sponsor.

All supplies of investigational product, both bulk and subject-specific, will be stored in accordance with the manufacturer’s instructions or pharmacy instructions. Until dispensed to the subjects, the investigational products will be stored at the study site in a location that is locked with restricted access.

Table 2. Investigational Product

Amgen Investigational Medicinal Product[a]		
Study Treatment Name	**Olpasiran (Group A)**	**Olpasiran (Group B)**
Unit Strength and Formulation	[redacted] mg/mL vial[b] Olpasiran SC injection	[redacted] mg/mL vial[b] Olpasiran SC injections
Dosage Level	[redacted] mg ([redacted])	[redacted] mg ([redacted])
Route of Administration	SC injection	SC injection
Accountability	The date/time of administration, lot number, box number of investigational product is to be recorded on each subject's CRF(s). The Investigator or study physician must be available when the subject receives the dose of Olpasiran for immediate intervention in case of complication(s).	The date/time of administration, lot number, box number of investigational product is to be recorded on each subject's CRF(s)[redacted]. The Investigator or study physician must be available when the subject receives the dose of Olpasiran for immediate intervention in case of complication(s).

Abbreviations: CRF = case report form; SC = subcutaneous.
[a] Olpasiran will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.
[b] Provided as a [redacted], with maximum deliverable volume of up to [redacted] from each vial of [redacted] mg/mL Olpasiran. Each [redacted] mL).[redacted].

5.2 Treatment of Overdose

Treatment overdose is not applicable to this study.

5.3 Randomization

Subjects will be randomized in a 1:1 ratio to 1 of 2 groups (A or B) as shown in Table 1, in an open-label manner.

Labcorp will provide a computer-generated randomization schedule to the site to be used for treatment assignments. Subjects will be assigned a subject number based in sequential order in which they qualified to be randomized, in accordance with the randomization schedule. Subjects are considered randomized once a unique subject number has been assigned. Dosing should occur within 1 day (≤ 24 hours) of randomization. If dosing cannot occur within 1 day of randomization, the Medical Monitor may be contacted to approve dosing outside the 24-hour

window (up to an additional 24 hours after randomization). The randomization date is to be documented in the subject's medical record and on the enrollment CRF.

5.4 Blinding

This is an open label study; blinding procedures are not applicable.

5.5 Treatment Compliance

Treatment compliance is not applicable to this study.

5.6 Drug 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. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1 Concomitant Therapies

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for the following:

- Use of any over-the-counter or prescription medications within 14 days or 5 half-lives (whichever is longer), before dosing on Day 1 and during the study, unless to treat a TEAE
    - Use of any herbal medicines, vitamins, or dietary supplements known to affect lipid metabolism (e.g., fish oils $>$ 1000 mg/day, red yeast rice extract), within 30 days before dosing on Day 1 and for the duration of the study.

The following concomitant therapies are allowed:

- Acetaminophen (paracetamol) up to 2 g/day for analgesia
- Hormone replacement therapy (e.g., estrogen, thyroid) provided the subject is stable on replacement therapy
- Medication for the management of arterial hypertension, including, but not limited to, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers, or low dose thiazides, provided it is stable (i.e., no change in drug or dose) for at least 8 weeks prior to enrollment
- Use of anti-platelet therapy (low-dose acetylsalicylic acid [up to 162.5 mg daily], clopidogrel, or ticagrelor) is allowed, provided subjects have been on a stable dose for at least 6 weeks prior to enrollment and plan to be on the same dose for the duration of the study
- If subjects are on statin, subjects must be on a stable dose of the same statin for at least 6 weeks prior to enrollment, and plan to remain on the same dose (i.e., no change in medication or dosage) for the duration of the study
- Use of ezetimibe is allowed, provided subjects have been on a stable dose for at least 6 weeks prior to enrollment and plan to be on the same dose for the duration of the study

- Medication used to manage chronic conditions not excluded by other exclusion criteria, provided subjects have been on a stable dose for at least 6 weeks prior to enrollment and plan to be on the same dose for the duration of the study. Medication must be reviewed and approved by the Investigator (or designee) and acknowledged by the Sponsor. Written documentation of this review and Sponsor acknowledgement is required for subject participation.
- All herbal medicines (e.g., St. John's wort) and dietary supplements (with the exception of those known to affect lipid metabolism, which are excluded above) consumed by the subject within the 30 days prior to Check-in and continue use during the study, which are deemed acceptable by the Investigator (or designee) and in consultation with the Sponsor.

Concomitant therapies are to be collected from informed consent through the EOS. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

6.2 Diet

While confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities. Subjects will be fasted overnight (at least 10 hours) before collection of blood samples for clinical chemistry evaluations or lipids.

Alcohol consumption will not be allowed from 48 hours prior to Check-in until end of in-house residency period.

6.3 Exercise

Subjects will abstain from strenuous exercise for 72 hours before each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during the study (e.g., watching television, walking, reading).

6.4 Blood Donation

Subjects are required to refrain from donation of blood from 60 days prior to Check-in, plasma from 2 weeks prior to Check-in, and platelets from 6 weeks prior to Check-in until 3 months after the EOS visit.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving consideration to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The highest priority procedures will be performed closest to the nominal time. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- PK blood samples
- safety assessments (ECGs will be scheduled before vital signs measurements)
- any other procedures.

Where activities at a given timepoint coincide, consideration must be given to ensure that the following order of activities is maintained: blood samples, ECGs, vital signs, and other procedures.

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 Assessments, is essential and required for study conduct.

7.1 Study Procedures

7.1.1 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 screen the subject to assess eligibility for participation. The screening window is up to 40 days.

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 4.3 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 failure. Screen failed subjects may be eligible for re-screening 3 times.

Once the subject is registered as rescreened, a new 40-day screening window will begin. Subjects will retain the same unique identification number assigned at the original screening. If the rescreening period begins more than 40 days after the original signing of the ICF, all screening procedures, including informed consent, must be repeated as well.

Laboratory assessments used to determine subject eligibility may be repeated once for confirmation, allowing for up to a total of two assessments during the 40-day screening period, if necessary, before the subject is considered a screen failure. If any assessments are repeated

during the screening period, the value that is closest to the enrollment date will apply for the determination of eligibility.

If the initial BP measurement is elevated, the assessment may be repeated again at least 15 minutes later and the lower of the 2 readings may be used for Screening.

Subjects will be assigned a randomization number based in sequential order in which they qualified to be randomized, in accordance with the randomization schedule. Subjects are considered randomized once a unique subject randomization number has been assigned.

The point of enrollment occurs at the time of subject randomization number allocation. The enrollment date is the same as the randomization date.

7.1.2 Treatment Period

Dosing should occur within 1 day (≤ 24 hours) of randomization. Visits will occur per the Schedule of Assessments in Appendix 9. The date of the dose of Olpasiran is defined as Day 1. All subsequent study visits will be scheduled based on the Day 1 date.

7.1.3 End of Study

Subjects' participation in the study will conclude with the completion of the EOS procedures unless any study assessment demonstrates a significant clinical or laboratory abnormality. The subject will be followed until resolution of the abnormality or until the subject is considered clinically stable by the principal investigator. EOS procedures may be performed on subjects who are withdrawn early from the study.

7.2 General Assessments

7.2.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the EC approved ICF before any study-specific procedures are performed.

7.2.2 Demographics

Demographic data collection including sex and age will be collected.

7.2.3 Physical Examination

Physical examination will be performed and will include a neurological examination (breast, rectal and genital examination are not required). Physical examination findings should be recorded on the appropriate CRF (e.g., medical history, TEAE).

7.2.4 Physical Measurements

Height [in centimeters] should be measured without shoes. Weight [in kilograms] should be measured without shoes. Body Mass Index should be calculated using the following formula: BMI (kg/m^2) = weight (kg)/[height (cm)/100]^2.

7.2.5 Medical History

The Investigator or designee will collect a complete medical history at screening and an interim medical history at Check-in. Medical history will include information on the subject's concurrent medical conditions and subjects' use of tobacco, alcohol, and history of non-reproductive potential. Record all findings on the medical history CRF.

7.3 Pharmacokinetic Assessments

7.3.1 Pharmacokinetic Blood Sample Collection and Processing

All subjects enrolled will have PK samples assessed. Blood samples of approximately 4 mL will be collected for measurement of serum concentrations of Olpasiran by venipuncture or cannulation at the times indicated in the Schedule of Assessments in Appendix 9.

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.

7.3.2 Analytical Methodology

Serum concentrations of Olpasiran will be determined using validated analytical procedures. Specifics of the analytical method will be provided in a separate document.

7.4 Pharmacodynamic Assessments

7.4.1 Pharmacodynamic Blood Sample Collection and Processing

Venous blood samples (approximately 5 mL) will be collected for measurement of Lp(a) at times indicated in the Schedule of Assessments in Appendix 9.

Lipid panel will include triglycerides, VLDL-C, LDL-C, and HDL-C, total cholesterol, ApoA1, and total Apo B. At Screening, lipids will measure triglycerides only. Subjects will be fasted overnight (at least 10 hours) before collection of blood samples for lipids. Venous blood samples (approximately 8.5 mL) will be collected for measurement of lipids at the times indicated in the Schedule of Assessments in Appendix 9.

7.4.2 Analytical Methodology

Serum concentrations of Lp(a) and lipids will be determined using validated analytical procedures. Specifics of the analytical method will be provided in a separate document.

7.5 Anti-Olpasiran Antibody Assessments

Bioanalytical testing for anti-Olpasiran antibodies will be conducted on blood samples (approximately 4 mL) at times indicated in the Schedule of Assessments in Appendix 9, if there are unexpected PK or 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-Olpasiran antibodies during the study.

Subjects who test positive for binding antibodies at the final antibody-scheduled timepoint 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.

7.6 Safety and Tolerability Assessments

7.6.1 Treatment-Emergent Adverse Events and Serious Treatment-Emergent Adverse Events: Time Period and Frequency for Collecting and Reporting Safety Event Information

TEAE definitions, assignment of severity and causality, and procedures for reporting serious TEAEs are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF to EOS visit. Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as “How have you been feeling since you were last asked?”, at least once each day while resident at the study site and at each study visit. Subjects will also be encouraged to spontaneously report TEAEs occurring at any other time during the study.

Treatment-emergent adverse events

The TEAE grading scale to be used in this study is described in “Assessment of Severity” in Appendix 1.

The Investigator is responsible for ensuring that all non-serious TEAEs observed by the Investigator or reported by the subject (whether reported by the subject voluntarily or upon questioning or noted on physical examination) from Olpasiran dosing through EOS are recorded/reported using the appropriate eCRF.

Serious treatment-emergent adverse events

The Investigator is responsible for ensuring that all serious TEAEs observed by the Investigator or reported by the subject that occur after signing of the ICF through 30 days after the dosing or the EOS visit (whichever is later) are reported using the appropriate eCRF and reported on the Serious Treatment-Emergent Adverse Event Report Form (described in Appendix 1).

All serious TEAEs will be collected, recorded, and reported to the Sponsor within 24 hours of the Investigator's knowledge of the event. The Investigator will submit any updated serious TEAE data to the Sponsor within 24 hours of it being available.

Serious Treatment-emergent Adverse Events after the Protocol-Required Reporting Period

There is no requirement to monitor study subjects for serious TEAEs following the protocol required reporting period or after EOS. However, these serious TEAEs can be reported to Amgen. Per local requirements in some countries, Investigators are required to- report serious TEAEs that they become aware of after EOS. If serious TEAEs are reported, the Investigator is to report them to the Sponsor within 24 hours following the Investigator's knowledge of the event using the Serious Treatment-Emergent Adverse Event Report Form (Figure 2).

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

Method of Detecting Treatment-emergent adverse events and Serious Treatment-emergent adverse events

Care will be taken not to introduce bias when detecting TEAEs and/or serious TEAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about TEAE occurrence.

Follow-up of Treatment-emergent adverse events and Serious Treatment-emergent adverse events

After the initial TEAE/serious TEAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All TEAEs and serious TEAEs will be followed, where possible, until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up. This will be completed at the Investigator's (or designee's) discretion.

All new information for previously reported serious TEAEs 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 TEAE must be consistent with that recorded on the eCRF.

Regulatory Reporting Requirements for Serious Treatment-emergent adverse events

If subject is permanently withdrawn from protocol-required therapies because of a serious TEAE, this information must be submitted to the Sponsor.

Prompt notification by the Investigator to the Sponsor of serious TEAEs 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, ECs, 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 TEAE or other specific safety information (e.g., summary or listing of serious TEAEs) from the Sponsor will file it along with the IB and will notify the EC, if appropriate according to local requirements.

Safety Monitoring Plan

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

Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and pregnancies in female partners of male subjects will be collected until 90 days after Olpasiran dosing.

If a pregnancy and/or lactation 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 Appendix 5. Amgen Global Patient Safety will follow-up with the Investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (e.g., female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) are considered serious TEAEs.

Further details regarding pregnancy and lactation are provided in Appendix 5.

7.6.2 Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations (including coagulation panel, clinical chemistry, hematology, urinalysis, serology, and eGFR) at the times indicated in the Schedule of Assessments in Appendix 9. Clinical laboratory evaluations are listed in Appendix 2 Table 3. Blood will be collected after fasting at least 10 hours for clinical chemistry evaluations.

The Investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in CRF/eCRF. 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 TEAEs. However, laboratory value changes that require treatment or adjustment in current therapy are considered TEAEs. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the TEAE.

Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol urine test at the times indicated in the Schedule of Assessments in Appendix 9. For all female subjects, a pregnancy test and FSH screen for postmenopausal women will be performed at the times indicated in the Schedule of Assessments in Appendix 9.

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

Pregnancy test

A highly sensitive serum pregnancy test should be completed at screening for all female subjects. A urine pregnancy test should be completed at all other times. A positive urine pregnancy test will be confirmed with a serum pregnancy test. A pregnancy test should be performed at the end of the study. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Form, see Figure 3). Refer to Appendix 4 for contraceptive requirements. Additional on-treatment pregnancy testing may be performed at the investigator' discretion or as required per local laws and regulations.

eGFR

eGFR will be calculated using the MDRD equation.

7.6.3 12-Lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 9. If the subject is unable to be in the supine position, the subject should be in the most suitable recumbent position possible. The ECG must include the following measurements: heart rate, QRS, QT, QTc, and PR intervals. The ECG will be single trace (1 x 10-second tracing), prior to safety blood draws or invasive procedures.

Single 12-lead ECGs will be repeated twice (within a total of five minutes from the start of the first to the completion of the third), and an average taken of the 3 readings, if either of the following criteria apply:

- QTcF is > 500 ms
- QTcF change from the baseline (predose) is > 60 ms.

The Investigator (or designee [e.g., 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. Additional 12lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

7.6.4 Vital Signs

Systolic/diastolic BP, pulse rate, respiratory rate, and body temperature will be assessed in sitting position at the times indicated in the Schedule of Assessments in Appendix 9. Pulse rate and BP will be measured using the same arm for each reading after the subject has been resting in the sitting position for at least 5 minutes. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required. The position selected for a subject should be the same position used throughout the study and documented on the vital sign CRF.

All measurements will be performed singly and repeated once (within a total of 5 minutes) if outside the relevant clinical reference range.

Subjects must be sitting for at least 5 minutes before BP and pulse rate measurements. When vital signs are scheduled at the same time as blood draws, the blood draws will be obtained at the scheduled timepoint, and the vitals will be obtained as close to the scheduled blood draw as possible, but preferably prior to the safety blood draw.

8. SAMPLE SIZE AND DATA ANALYSIS

Data will be analyzed for all subjects who are randomized and receive Olpasiran. Descriptive statistics by treatment group will be provided for selected demographics, safety, PK and Lp(a) data. Descriptive statistics on continuous measurements will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. PK, Lp(a), lipids (as listed in Table 4 in Appendix 2), vital signs, ECG, and clinical laboratory data will be summarized at each scheduled visit per Schedule of Assessments.

Additional details will be included in the Statistical Analysis Plan (SAP).

8.1 Determination of Sample Size

Approximately 24 subjects (12 per group) will be enrolled in the study. No formal statistical hypothesis testing will be performed. The sample size of 12 subjects per group is based on studies of similar nature and is not based on power calculations. Considering a 33.3% drop-out rate, 8 subjects per cohort provides an approximately 90% confidence of observing a case of a TEAE in each cohort at an incidence of 25%.

8.2 Analysis Set

8.2.1 Pharmacokinetic Analysis Set

The PK analysis set will include all randomized subjects who received Olpasiran and have evaluable PK data.

8.2.2 Pharmacodynamic Analysis Set

The PD analysis set will include all randomized subjects who received Olpasiran and have evaluable PD data.

8.2.3 Safety Analysis Set

The safety analysis set will include all randomized subjects who received Olpasiran.

8.3 Pharmacokinetic Analyses

The serum PK parameters of Olpasiran will be calculated using standard noncompartmental methods. Pharmacokinetic parameters will be listed and summarized using descriptive statistics.

Additional statistical analyses may be performed as appropriate. Detailed descriptions of the statistical analysis and reporting of data will be provided in the SAP.

8.4 Pharmacodynamic Analyses

Absolute change and percent change in serum Lp(a) and lipids from baseline will be summarized by treatment groups.

Detailed descriptions of the statistical analysis and reporting of data will be presented in the SAP for this study.

8.5 Safety Analysis

The final safety analysis for the study will be performed at the end of the study. No imputation will be done for safety assessments and endpoints for clinical laboratory tests, 12-lead ECGs, and vital signs will be summarized using descriptive statistics. Each TEAE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Subject incidence of all TEAEs will be tabulated by system organ class and preferred term and by treatment group. Subject incidence tables of fatal TEAEs and serious TEAEs will be tabulated by treatment group. Subject-level data may be provided instead of tables if the subject incidence is low.

8.6 Interim Analysis

No interim analyses are planned for this study.

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10. APPENDICES

Appendix 1. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting of Treatment-emergent adverse event

Definition of Treatment-emergent adverse event

Treatment-emergent 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. • A treatment-emergent adverse event (TEAE) will be defined as an AE that starts during or after the first dose or starts prior to the first dose and increases in severity after the first dose.
Events Meeting the Treatment-emergent adverse event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., 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 (i.e., 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 a TEAE/serious TEAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae.
Events NOT Meeting the Treatment-emergent adverse event Definition
• Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the TEAE. • 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 Treatment-emergent adverse event

A Serious Treatment-emergent 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. For instance, drug induced-hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced-hepatitis can be fatal.
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 a TEAE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is considered serious. When in doubt as to whether “hospitalization” occurred or was necessary, the TEAE is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered a TEAE.
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 (e.g., 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 TEAE 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.

Recording Treatment-emergent adverse events and Serious Treatment-emergent adverse events

Treatment-emergent adverse event and Serious Treatment-emergent adverse event Recording

- When a TEAE or serious TEAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The Investigator will then record all relevant TEAE/serious TEAE information in the Event electronic Case Report Form (eCRF).
- The Investigator must assign the following TEAE attributes:
  - TEAE diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Dates of onset and resolution (if resolved);
  - Severity (or toxicity defined below);
  - Assessment of relatedness to the investigational product(s) and/or study-mandated procedures, and
  - Action taken.
- If the severity of a TEAE changes from the date of onset to the date of resolution, record the TEAE as a single event with the worst severity on the appropriate eCRF.
- It is not acceptable for the Investigator to send photocopies of the subject's medical records to Sponsor in lieu of completion of the appropriate eCRF 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 the Sponsor.
- 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 a TEAE/serious TEAE.

Evaluating Treatment-emergent adverse events and Serious Treatment-emergent adverse events

Assessment of Severity	
The Investigator will make an assessment of severity for each TEAE and serious TEAE reported during the study. The assessment of severity will use the following definitions:	
Grade	Definition
MILD	Aware of sign or symptom, but easily tolerated, usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
MODERATE	Discomfort enough to cause interference with usual activity causing discomfort but poses no significant or permanent risk of harm to the subject. Usually alleviated with additional specific therapeutic intervention.
SEVERE[a]	Incapacitating with inability to work or interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
[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 TEAE, NOT when it is rated as severe.	

Assessment of Causality

- The Investigator is obligated to assess the relationship between investigational product(s), protocol-required therapy and/or study-mandated procedure and each occurrence of each TEAE/serious TEAE.
- 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 TEAE/serious TEAE, the Investigator must document in the medical notes that he/she has reviewed the TEAE/serious TEAE and has provided an assessment of causality.
- There may be situations in which a serious TEAE 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 TEAE data.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a serious TEAE 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 Treatment-emergent adverse event and Serious Treatment-emergent 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 the Sponsor to elucidate the nature and/or causality of the TEAE or serious TEAE 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 TEAE, this information must be submitted to the Sponsor. • If a subject dies during participation in the study, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed eCRF. • The Investigator will submit any updated serious TEAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of Serious Treatment-emergent adverse event

Serious Treatment-Emergent Adverse Event Reporting Via Paper Serious Treatment-Emergent Adverse Event Report Form
• Facsimile transmission of the Serious Treatment-Emergent Adverse Event Report Form (see Figure 2) is the preferred method to transmit this information. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the Serious Treatment-Emergent Adverse Event Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the Serious Treatment-Emergent Adverse Event Report Form within the designated reporting time frames.

Figure 2. Sample Serious Treatment-Emergent Adverse Event Report Form

AMGEN
20190095
Covance
study #:
8424665
<<AMG 890>>

Clinical Trial Serious Adverse Event Report – Phase 1–4
Notify Amgen Within 24 Hours of knowledge of the event

❑New
❑Follow-up

svc-ags-in-cn@amgen.comsvc-ags-in-cn@amgen.comsvc-ags-in-cn@amgen.com

1. SITE INFORMATION

Site Number	Investigator	Country	Date of Report Day Month Year

Reporter	Phone Number ( )	Fax Number ( )

2. SUBJECT INFORMATION

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

3. SERIOUS TREATMENT-EMERGENT ADVERSE EVENT - *Information in this section must also be entered on the Serious Treatment-emergent adverse event Summary CRF*

Provide the date the Investigator became aware of this Serious Treatment-emergent adverse event Information: Day_____Month____Year_____

Serious Treatment-emergent adverse event Diagnosis or Syndrome **If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Treatment-emergent adverse event** *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	**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? **If yes see section 10** <AMG890> No✓ Yes✓ <IP/device> No✓ Yes✓ <IP/device> No✓ Yes✓ <IP/device> No✓ Yes✓ <IP/device> No✓ Yes✓	**Outcome of Event** **01** Resolved **02** Not resolved **03** Fatal **04** Unknown	Check only if event is related to study procedure *eg, biopsy*

Serious Criteria:	**01** Fatal **02** Immediately life- threatening	**03** Required hospitalization **04** Prolonged hospitalization	**05** Persistent or significant disability /incapacity **06** Congenital anomaly / birth defect	**07** Other medically important serious event

4. HOSPITALIZATION

	Date Admitted Day Month Year	**Date Discharged** Day Month Year
Was subject hospitalized or was a hospitalization prolonged due to this event? ❑No ❑Yes, If yes, please complete date(s):		

5. INVESTIGATIONAL PRODUCT (IP)

	Initial Start Date Day Month Year	**Prior to, or at time of Event**				**Action Taken with Product** **01** Still being Administered **02** Permanently discontinued **03** Withheld	**Lot # and Serial #**
		Date of Dose Day Month Year	**Dose**	**Route**	**Frequency**		
<<AMG890>> ✕Open Label							Lot # _____

	Site Number	Subject ID Number	

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

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

	Site Number	**Subject ID Number**	

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

Signature of Investigator or Designee _____ *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.*	Title	Date

Appendix 2. Clinical Laboratory Evaluations

Table 3. Safety Laboratory Evaluations

Clinical chemistry:	**Hematology:**	**Urinalysis:**
Alanine aminotransferase	Hematocrit	Bilirubin
Albumin	Hemoglobin	Blood
Alkaline phosphatase	Mean cell hemoglobin	Color and appearance
Aspartate aminotransferase	Mean cell hemoglobin-concentration	Glucose
Blood urea nitrogen or urea	Mean cell volume	Ketones
Calcium	Platelet count	Leukocyte esterase
Chloride	Red blood cell (RBC) count	Nitrite
Cholesterol	RBC distribution width	pH
Creatinine	White blood cell (WBC) count	Protein
Direct bilirubin[a]	WBC differential:	Specific gravity
Gamma-glutamyl transferase	Basophils	Urobilinogen
Glucose (fasting)	Eosinophils	Microscopic examination (if protein, leukocyte esterase, nitrite, or blood is positive)
Indirect bilirubin[a]	Lymphocytes	**Hormone panel - females only:**
Inorganic phosphate	Monocytes	Follicle-stimulating hormone[b] (postmenopausal females only)
Lactate[h]	Neutrophils	Serum pregnancy test (human chorionic gonadotropin)[d]
Magnesium		Urine pregnancy test[d]
Phosphorous		
Potassium		
Sodium		
Total bilirubin[a]		
Total cholesterol		
Total CO_2 (measured as: bicarbonate)		
Total creatine kinase		
Total protein		
Tryptase[g]		
Uric acid		

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Footnotes defined on last page of the table

Table 3. Safety Laboratory Evaluations

Serology[b]:	**Drug screen[c]:**	**Other Tests:**
Anti-hepatitis B surface antibody Anti-hepatitis B core antibody Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency virus antibodies	Including, but not limited to: Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine Methadone Phencyclidine Opiates K2 (Synthetic cannabinoids) Tricyclic antidepressants Cotinine test Alcohol urine test	Estimated glomerular filtration rate (eGFR) [b, f]
Coagulation Panel:		
International normalized ratio (INR)[e] Prothrombin time (PT) Activated partial thromboplastin time (APTT)		

[a] Direct and indirect bilirubin will be analyzed if total bilirubin is elevated.
[b] Only analyzed at Screening.
[c] Only analyzed at Screening and Check-in.
[d] Performed in serum at Screening and in urine at all other times for all females. A positive urine pregnancy test will be confirmed with a serum pregnancy test.
[e] International normalized ratio will be tested if hepatotoxicity is suspected guidelines presented in Appendix 7
[f] Estimated glomerular filtration rate will be calculated by the Modification of Diet in Renal Disease (MDRD) equation.
[g] Tryptase to be collected in the case of a suspected anaphylactic reaction. To be performed at the discretion of the Investigator or qualified designee.
[h] Lactate to be collected if an anion-gap acidosis is identified. To be performed at the discretion of the Investigator or qualified designee.

Table 4. Pharmacodynamic Laboratory Evaluations

Lipid panel:	**Additional test:**
Triglycerides [a, b] Very low-density lipoprotein cholesterol (VLDL-C) [b] Low-density lipoprotein cholesterol (LDL-C) [b] High-density lipoprotein cholesterol (HDL-C) [b] Total Cholesterol [b] Apolipoprotein A1 (Apo A1) [b] Total Apolipoprotein B (Apo B) [b]	Lipoprotein(a) (Lp[a]) [c]

[a] Only analyzed at Screening.
[b] After screening, on-study lipids will include triglycerides, VLDL-C, LDL-C, HDL-C, total cholesterol, Apo A1, and total Apo B.
[c] Part 1 and Part 2 screening, and on study serum Lp(a) samples will be analyzed by a Sponsor-designated laboratory.

Appendix 3. Approximate Total Blood Volume

The following blood volumes will be withdrawn for each subject.

Test	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Clinical Chemistry and Hematology	12	12	144
Coagulation	3	9	27
Serum Pregnancy[a]	5	1	5
FSH[b]	5	1	5
Serology	9	1	9
PK	4	17	68
PD: Lp(a)	5	14	70
PD: lipid panel	8.5	7	59.5
Anti-Olpasiran Antibody	4	3	12
Total:			**399.5**

Abbreviations: FSH = follicle-stimulating hormone; PK = pharmacokinetic(s); PD = pharmacodynamics(s).
Note:
[a] For female subjects only. A highly sensitive serum pregnancy test should be completed at screening for all female subjects. A urine pregnancy test should be completed at all other times. A serum pregnancy test will only be performed when the urine pregnancy test is positive.
[b] For postmenopausal female subjects only.

Appendix 4. Contraception Requirements

All subjects must receive pregnancy prevention counseling and be advised of the risk to the fetus if they conceive a child during treatment and for 90 days after the dose of Olpasiran.

Additional medications given during the study may alter the contraceptive requirements. The Investigator must discuss these contraceptive changes with the subject.

Definitions

Women of Childbearing Potential: premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

Women of Non-childbearing Potential:

1. **Surgically sterile:** females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the Investigator's discretion, prior to Screening.
2. **Postmenopausal**: Females with age of $\geq$ 55 years with no menses for at least 12 months; or with age of $<$ 55 years with no menses for at least 12 months AND with a follicle stimulating hormone (FSH) level $>$ 40 IU/L or according to the definition of "postmenopausal range" for the laboratory involved. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators.

Fertile male: a male that is considered fertile after puberty.

Infertile male: permanently sterile male via bilateral orchiectomy.

Contraception Requirements

Male Subjects:

Male subjects (even with a history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (i.e., male condom with spermicide) in addition to a second method of acceptable contraception by female partner from Check-in until 90 days after Olpasiran dosing. Acceptable methods of contraception for female partners include:

- hormonal injection
- combined oral contraceptive pill or progestin/progestogen-only pill
- combined hormonal patch
- combined hormonal vaginal ring

- surgical method (bilateral tubal ligation or regulatory approved method of hysteroscopic bilateral tubal occlusion)
- hormonal implant
- hormonal or non-hormonal intrauterine device
- over-the-counter sponge with spermicide
- cervical cap with spermicide
- diaphragm with spermicide.

Male subjects are required to refrain from donation of sperm from Check-in until 90 days after Olpasiran dosing.

Sexual Abstinence

Subjects who practice true abstinence, because of the subject's lifestyle choice (i.e., the subject should not become abstinent just for the purpose of study participation), are exempt from contraceptive requirements. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not acceptable methods of contraception.

For subjects who practice true abstinence, subjects must be abstinent for at least 6 months prior to Screening and must agree to remain abstinent from the time of signing the Informed Consent Form (ICF) until 90 days after Olpasiran dosing.

Same-sex Relationships

For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply.

A subject in a same-sex relationship at the time of signing the ICF must agree to refrain from engaging in a heterosexual relationship from the time of signing the ICF until 90 days after Olpasiran dosing.

Appendix 5. Collection of Pregnancy and Lactation Information

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 until 90 days after Olpasiran dosing
- Information will be recorded on the Pregnancy Notification Form (see Figure 3). 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 after Olpasiran dosing. 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 a treatment-emergent adverse event (TEAE) or serious TEAE, 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 a TEAE or serious TEAE. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered a TEAE, but still must be reported to the Sponsor as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious TEAE (e.g., 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 TEAE.
- Any serious TEAE occurring as a result of a poststudy pregnancy which is considered reasonably related to the study treatment by the Investigator will be reported to Amgen Global Patient Safety as described in Appendix 1. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious TEAE through spontaneous reporting.

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 Olpasiran dosing, the information will be recorded on the Pregnancy Notification Form. The form (see Figure 3) 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 after Olpasiran dosing.
- Information will be recorded on the Lactation Notification Form (Figure 4) and submitted to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge of event.

With the female subject's 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 the dose of Olpasiran.

Figure 3. Pregnancy Notification Form

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: 20190095 (Covance study #: 8424665)

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
				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

Figure 4. Lactation Notification Form

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: 20190095 (Covance study #: 8424665)

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
				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

Appendix 6. Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

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

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

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Ethics Committee (EC) by the Investigator and reviewed and approved by the EC before the study is initiated.

Any substantial protocol amendments, likely to affect the safety of the subjects or the conduct of the study, will require EC and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects or any non-substantial changes, as defined by regulatory requirements.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the EC annually or more frequently in accordance with the requirements, policies, and procedures established by EC.
- Notifying the EC of serious treatment-emergent adverse events (TEAEs) or other significant safety findings as required by EC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

An initial sample ICF will be provided for the Investigator (or designee) to prepare the informed consent document to be used at his or her site. Updates to the sample ICF are to be communicated formally in writing from the Study Manager to the Investigator. The written ICF is to be prepared in the language(s) of the potential study participant population.

The Investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, 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 or their legally authorized representative (defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study) will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, and the EC 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 ICF.

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 ICF 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.

Subjects must be re-consented to the most current version of the ICF during their participation in the study.

The original signed ICF is to be retained in accordance with institutional policy, and a copy of the ICF must be provided to the subject or the subject's legally authorized representative.

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 ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF 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 ICF if the rescreening occurs within 40 days from the previous ICF signature date.

Subject Data Protection

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

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

On the electronic Case Report Form (eCRF) demographics page, in addition to the unique subject number, include the age at time of enrollment.

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

Documents that are not submitted to the Amgen (e.g., signed ICFs) are to be kept in confidence by the Investigator, except as described below.

In compliance with ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the EC 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.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential information of the Sponsor, Amgen Inc. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor. The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written permission from the Sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, EC 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. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- A Study Monitor will perform ongoing source data verification to confirm that data entered into the eCRF 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.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in the study site archive for 15 years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 CFR Part 11 compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (e.g., laboratory and bioanalytical data), and transmitted to the Sponsor or designee electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each enrolled subject who undergoes any screening procedures, according to the eCRF completion instructions. The Sponsor, or Contract Research Organization, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

The policy for publication of data obtained during this study will be documented in the Clinical Study Agreement.

Appendix 7. Hepatotoxicity: Suggested Actions and Follow-up Assessments

Subjects with normal hepatic function at Screening who experience aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations > 3 x upper limit of normal (ULN) or subjects with elevated values before drug exposure who have a 2-fold increase above baseline values (as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009)[32] are to undergo clinical assessments and a period of "close observation" until abnormalities return to normal or to the subject's baseline level as described below.

Clinical Assessments and Observation

Assessments that are to be performed during this period include:

- Repeat AST, ALT, alkaline phosphatase, bilirubin (total and direct), and international normalized ratio (INR) within 24 hours
- In cases of total bilirubin (TBL) > 2 × ULN or INR > 1.5, retesting of liver tests, bilirubin (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.

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 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 PK 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 are considered stable by the Investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of Olpasiran.

The potential drug-induced liver injury (DILI) event and additional information such as medical history, concomitant medications, and laboratory results must be captured in the corresponding electronic Case Report Forms (eCRFs).

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

- Hepatobiliary tract disease
- Viral hepatitis (e.g., 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 (e.g., Gilbert's syndrome, Crigler Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (e.g., indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis
- Non-hepatic causes (e.g., rhabdomyolysis, hemolysis).

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, i.e., cases of AST or ALT $> 3 \times$ ULN and concurrent TBL $> 2 \times$ ULN or INR > 1.5 (for subjects not on anticoagulation therapy) without evidence of alternative cause of the elevations, the following is required:

- The event is to be reported to the Sponsor as a serious treatment-emergent adverse event (TEAE) within 24 hours of discovery or notification of the event (i.e., before additional etiologic investigations have been concluded)
- The appropriate eCRF (e.g., Event eCRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Sponsor.

Other events of hepatotoxicity and potential DILI are to be reported as serious TEAEs if they meet the criteria for a serious TEAE defined in Appendix 1.

Appendix 8. Sample Storage and Destruction

Any blood sample collected according to the Schedule of Assessments 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.

Appendix 9. Schedule of Assessments

Table 5. Schedule of Assessments

PROCEDURE	Screening	Check-in	Treatment Period												
Study Day	**-40 to -2**	**-1**	**1**									**2**		**3**	**4**
Study Time (Hours)			**Predose**	**0**	**1**		**2**	**3**	**6**	**9**	**12**	**24**	**36**	**48**	**72**
Study Time (Minutes)				**0**	**30**	**60**	**120**	**180**	**360**	**540**	**720**				
GENERAL AND SAFETY ASSESSMENTS															
Informed Consent	X														
In-house Residency[a]															
Physical Examination[b]	X	X													X
Medical History	X	X[c]													
Weight	X	X													
Height	X														
ECG[d]	X		X					X			X				
Vital Signs[e]	X	X	X			X		X			X	X		X	X
TEAEs[f]				◄											►
Serious TEAEs[f]															
Concomitant Therapy Review[g]															
LABORATORY ASSESSMENTS															
Pregnancy Test[h]	X	X													
Coagulation Panel	X	X										X			X
Chemistry & Hematology[i, o]	X	X										X			X
Serology	X														
Urinary Drug Screen	X	X													
Alcohol Urine Test	X	X													
Urinalysis	X	X													X
eGFR[j]	X														
FSH[k]	X														
Anti-Olpasiran Antibody			X												
PHARMACOKINETIC ASSESSMENTS															
Olpasiran Serum PK Collection[l]			X		X	X	X	X	X	X	X	X	X	X	X
PHARMACODYNAMIC ASSESSMENTS															
Lp(a)[m]	X		X									X			X
Lipid Panel[n, o]	X		X												

PROCEDURE	Screening	Check-in	Treatment Period														
Study Day	-40 to -2	-1	1										2		3	4	
Study Time (Hours)			Predose	0	1		2	3	6	9	12	24	36	48	72		
Study Time (Minutes)				0	30	60	120	180	360	540	720						
STUDY TREATMENT																	
Olpasiran administration				X													

Abbreviations: Apo A1 = apolipoprotein A1; Apo B = apolipoprotein B; ECG = electrocardiogram; eGFR = Estimated glomerular filtration rate; FSH = follicle-stimulating hormone; HLDL-C = High-density lipoprotein; LDL-C = low-density lipoprotein; Lp(a) = lipoprotein(a); TEAE = treatment-emergent adverse event; VLDL-C = very low-density lipoprotein.

[a] In-house residency from Day -1 through the completion of all assessments on Day 4.

[b] Physical examination to include neurologic examination.

[c] Interim medical history only.

[d] ECG will be single trace (1 × 10-second tracing), prior to safety blood draws or invasive procedures.

[e] Sitting blood pressure, sitting pulse rate, respiratory rate and temperature. Pulse rate and BP will be measured using the same arm for each reading after the subject has been resting in the sitting position for at least 5 minutes.

[f] TEAEs will be recorded from initiation of study treatment on Day 1 until EOS/ET completion. Serious TEAEs will be recorded from the time the subject signs the Informed Consent Form until 30 days after the last dose of study treatment or the EOS (whichever is later).

[g] Prior and concomitant medication administration will be recorded beginning at informed consent. Also, all Investigator-approved medications taken by a subject within 14 days or 5 half-lives (whichever is longer) before dosing on Day 1 for over-the-counter or prescription medications, and 30 days prior to Check-in for herbal medicines (e.g., St. John's wort), vitamins and dietary supplements (with the exception of those known to affect lipid metabolism, which are excluded), will be recorded on the subject's electronic Case Report Form.

[h] Performed in serum at Screening and in urine at all other times for all females. A positive urine pregnancy test will be confirmed with a serum pregnancy test.

[i] Clinical chemistry (fasted at least 10 hours).

[j] eGFR will be calculated using the Modification of Diet in Renal Disease (MDRD) equation.

[k] Performed in postmenopausal females only.

[l] Blood samples for determination of Olpasiran serum concentrations and PK parameters will be collected: Predose, 30 minutes, 60 minutes, 2, 3, 6, 9, 12, 24, and 36 hours postdose and on Study Days 3, 4, 7, 15, 29, 57, and 85 following administration of Olpasiran on Day 1. The PK samples collected on Day 1 will have a sampling window of ± 10 minutes, postdose samples collected on Day 2 through Day 4 will have a sampling window of ± 1 hour, postdose samples collected on Day 7 through Day 57 will have a sampling window of ± 48 hours, and postdose samples collected on Day 85 through EOS will have a sampling window of ± 5 days. Times of all PK samples will be recorded to the nearest minute.

[m] Part 1 and Part 2 screening, and on study serum Lp(a) samples will be analyzed by a Sponsor-designated laboratory.

[n] At screening, lipids will measure triglycerides only. After screening, on-study lipids will include triglycerides, VLDL-C, LDL-C, HDL-C, total cholesterol, Apo A1, and total Apo B.

[o] Subjects will be fasted overnight (at least 10 hours) before collection of blood samples for clinical chemistry evaluations or lipids.

Table 6. Schedule of Assessments

PROCEDURE	Treatment Period									EOS
Study Day	**7**	**15**	**29**	**57**	**85**	**113**	**155**	**183**	**211[a]**	**225**
Study Time (Hours)	144									
GENERAL AND SAFETY ASSESSMENTS										
Physical Examination[b]			X		X		X			X
Weight										X
ECG[c]		X	X		X		X			X
Vital Signs[d]	X	X	X	X	X	X	X	X		X
Concomitant Therapies Review[f]										
TEAEs[e]										
Serious TEAEs[e]										
Telephone Visit[a]									X	
LABORATORY ASSESSMENTS										
Pregnancy Test[g]										X
Coagulation Panel		X		X		X	X	X		
Chemistry & Hematology[h, l]		X	X	X	X	X	X	X		X
Urinalysis			X							X
Anti-Olpasiran Antibody			X							X
PHARMACOKINETIC ASSESSMENTS										
Olpasiran Serum PK Collection[i]	X	X	X	X	X					
PHARMACODYNAMIC ASSESSMENTS										
Lp(a)[j]	X	X	X	X	X	X	X	X		X
Lipid Panel[k, l]	X	X		X			X			X

Abbreviations: Apo A1 = apolipoprotein A1; Apo B = apolipoprotein B; ECG = electrocardiogram; EOS = end of study; HLDL-C = High-density lipoprotein; LDL-C = low-density lipoprotein; Lp(a) = lipoprotein(a); TEAE = treatment-emergent adverse event; VLDL-C = very low-density lipoprotein.

[a] A telephone visit will be scheduled for TEAE assessments on Day 211 with a visit window of ± 3 days. Subjects will be brought in only based on any safety concern(s) identified by the investigator.

[b] Physical examination to include neurologic examination.

[c] ECG will be single trace (1 × 10-second tracing), prior to safety blood draws or invasive procedures.

[d] Sitting blood pressure, sitting pulse rate, respiratory rate and temperature. Pulse rate and BP will be measured using the same arm for each reading after the subject has been resting in the sitting position for at least 5 minutes.

[e] TEAEs will be recorded from initiation of study treatment on Day 1 until EOS/ET completion. Serious TEAEs will be recorded from the time the subject signs the Informed Consent Form until 30 days after the last dose of study treatment or the EOS (whichever is later).

[f] Prior and concomitant medication administration will be recorded beginning at informed consent. Also, all Investigator-approved medications taken by a subject within 14 days or 5 half-lives (whichever is longer) before dosing on Day 1 for over-the-counter or prescription medications, and 30 days prior to Check-in for herbal medicines (e.g., St. John's wort), vitamins and dietary supplements (with the exception of those known to affect lipid metabolism, which are excluded), will be recorded on the subject's electronic Case Report Form.

[g] Performed in serum at Screening and in urine at all other times for all females. A positive urine pregnancy test will be confirmed with a serum pregnancy test.

[h] Clinical chemistry (fasted at least 10 hours).

[i] Blood samples for determination of Olpasiran serum concentrations and PK parameters will be collected at the following timepoints: predose, 30 minutes, 60 minutes, 2, 3, 6, 9, 12, 24, and 36 hours postdose and on Study Days 3, 4, 7, 15, 29, 57, and 85 following administration of Olpasiran on Day 1. The PK samples collected on Day 1 will have a sampling window of ± 10 minutes, postdose samples collected on Day 2 through Day 4 will have a sampling window of ± 1 hour, postdose samples collected on Day 7 through Day 57 will have a sampling window of ± 48 hours, and postdose samples collected on Day 85 through EOS will have a sampling window of ± 5 days. Times of all PK samples will be recorded to the nearest minute.

[j] Part 1 and Part 2 screening, and on study serum Lp(a) samples will be analyzed by a Sponsor-designated laboratory.

[k] At screening, lipids will measure triglycerides only. After screening, on-study lipids will include triglycerides, VLDL-C, LDL-C, HDL-C, total cholesterol, Apo A1, and total Apo B.

[l] Subjects will be fasted overnight (at least 10 hours) before collection of blood samples for clinical chemistry evaluations or lipids.

Summary of Amended Protocol Changes

An Open-label, Single-dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of Olpasiran in Chinese Subjects With Elevated Serum Lipoprotein(a)

Protocol Version 1.0 Date: 09 October 2020
Protocol Version 2.0 Date: 03 May 2021
Protocol Version 3.0 Date: 28 July 2021
Protocol Version 3.0 Status: Final

Investigational Medicinal Product: Olpasiran (AMG 890)

Amgen Protocol Reference Number: 20190095
Labcorp Study Number: 8424665

Sponsor:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320
USA

Protocol Version 2.0 (dated 03 May 2021) has been amended to implement the following changes:

1. The name of the Contract Research Organization (CRO) was updated to reflect the current official legal name.
2. The names and contact information for the Sponsor's Study Manager and CRO Project Manager have been updated in the Study Identification section.
3. Section 4.1, Inclusion Criteria, was updated to clarify that subject eligibility based on lipoprotein(a) (Lp[a]) levels is determined by the results from Part 1 of the screening period.
4. Section 4.2, Exclusion Criteria, was updated to allow investigator discretion in consultation with the study medical monitor in determining eligibility for subjects with prothrombin time (PT) and/or activated partial thromboplastin time (APTT) values that are outside of the laboratory's normal reference range at screening.
5. Section 4.2, Exclusion Criteria, was updated to correct the fasting glucose unit from nmol/L to mmol/L for Exclusion Criterion #4.

Minor changes:

1. The protocol version and date were updated throughout the protocol.
2. Typographical errors and formatting errors were corrected, as necessary.
3. Definitions of PT and APTT were added in the abbreviation list.

A detailed summary of changes is presented below:

Study Identification

Now reads:

Sponsor's Study Manager	[redacted] Global Early Clinical Development Manager Amgen Inc. One Amgen Center Drive Thousand Oaks, California 91320 USA Tel: [redacted] Email: [redacted]

Labcorp Project Manager	[redacted] Senior Project Manager Labcorp Clinical Pharmacology Services USA Tel: [redacted] Email: [redacted]

Section 4.1 Inclusion Criteria

Now reads:

Inclusion eligibility criteria will be evaluated in 2 parts during the screening period:

- **Part 1**: After written informed consent is obtained, subjects will provide a blood sample for a preliminary Lp(a) assessment to determine eligibility for Part 2 screening. Subjects with Lp(a) ≥ 70 nmol/L (or approximately ≥ 27 mg/dL) will be eligible to return to the CRU for Part 2 screening. Subjects not eligible to return for Part 2 screening will be screen failed.
- **Part 2**: Eligible subjects will complete all remaining screening procedures and tests that establish eligibility within 40 days prior to the Day 1 visit.

Section 4.2 Exclusion Criteria

Now reads:

4. History or clinical evidence of bleeding diathesis or any coagulation disorder, including prothrombin time (PT), activated partial thromboplastin time (APTT), or platelet count outside of the laboratory's normal reference range at screening. Subjects with PT and/or APTT values that are outside of the laboratory's normal reference range at screening may still be eligible to proceed to enrollment if the results are judged by the investigator in consultation with the study medical monitor to not be clinically significant.
5. History or clinical evidence of diabetes mellitus, including a fasting glucose ≥ 125 mg/dL (6.9 mmol/L) at Screening.

Sponsor approval of these changes is indicated by the signatures in the complete amended document, Protocol Version 3.0 for study 20190095.

Protocol Amendment 1.0

Summary of Changes

Title: An Open-label, Single-dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of Olpasiran in Chinese Subjects With Elevated Serum Lipoprotein(a)

Sponsor: Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320

No.	Page,	Original	Amendment	Rationale
1	Title page, Investigator agreement page	**An Open-label, Single-dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of AMG 890 in Chinese Subjects With Elevated Serum Lipoprotein(a)**	**An Open-label, Single-dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of ~~AMG 890~~Olpasiran in Chinese Subjects With Elevated Serum Lipoprotein(a)**	Updated product name in the study title and through the protocol.
2	Title page	Protocol Date: 09 October 2020 Protocol Version: 1.0 Investigational Product: AMG 890	Protocol Date: ~~09 October 2020~~**03 May 2021** Protocol Version: ~~1~~**2**.0 Investigational Product: **Olpasiran (**AMG 890**)**	Updated protocol date and version. Updated product name.
3	Page footer	Protocol Version 1.0, 09 October 2020	Protocol Version ~~1~~**2**.0, ~~09 October 2020~~**03 May 2021**	Updated protocol date and version.
4	Throughout the whole protocol	AMG 890	~~AMG 890~~**Olpasiran**	Updated product name through the protocol.

No.	Page,	Original	Amendment	Rationale
5	Throughout the whole protocol	eg	~~eg,~~**e.g.**	Editorial revision.
6	Throughout the whole protocol	ie	~~ie,~~**i.e.**	Editorial revision.
7	5	This will be an open-label, randomized, single-dose parallel group study in Chinese subjects with elevated serum Lp(a). Potential subjects will be screened within 28 days prior to the dose.	This will be an open-label, randomized, single-dose parallel group study in Chinese subjects with elevated serum Lp(a). Potential subjects will be screened within ~~28~~**40** days prior to the dose.	Updated screening period to 40 days.
8	5	Group B = [redacted] mg administered as [redacted] ([redacted] mg/mL) SC injections	Group B = [redacted] mg administered as [redacted] mL ([redacted] mg/mL) SC injections	Corrected the errors of Dosage Level of Olpasiran (Group B; number and volume of SC injections) for consistency with the Investigational Product Preparation and Administration (IPPA) document.
9	5	**Duration of subject participation in the study:** Planned Screening duration: approximately 4 **weeks**. Planned study duration (Screening to EOS): approximately 36 weeks.	**Duration of subject participation in the study:** Planned Screening duration: approximately ~~4~~**6** weeks. Planned study duration (Screening to EOS): approximately ~~36~~**38** weeks.	Updated screening period to 40 days and therefore also updated the

No.	Page,	Original	Amendment	Rationale
				study duration.
10	14	Currently, AMG 890 is being studied in two phase 1 studies in healthy subjects (first-in-human [FIH] Study 20170544 and Study 20180222). The FIH Study 20170544 is a blinded study in subjects with elevated plasma Lp(a), which is designed to evaluate safety and tolerability as primary endpoints, and to address PK and pharmacodynamics (PD) effects as secondary endpoints. Study 20180222 is an open-label study in Japanese and non-Japanese subjects to characterize AMG 890 PK as the primary endpoint and assess safety and tolerability as the secondary endpoint. AMG 890 was evaluated at dose ranges of [redacted] mg to [redacted] mg in both of these phase 1 studies.	Currently, ~~AMG 890~~**Olpasiran** is being studied in two phase 1 studies in healthy subjects (first-in-human [FIH] Study 20170544 and Study 20180222). The FIH Study 20170544 is ~~a blinded~~**an ongoing double-blind placebo-controlled** study in **healthy** subjects with elevated plasma Lp(a), which is designed to evaluate safety and tolerability as primary endpoints, and to address PK and pharmacodynamics (PD) effects as secondary endpoints. Study 20180222 is ~~an~~**a completed** open-label study in Japanese and non-Japanese subjects to characterize ~~AMG 890~~**Olpasiran** PK as the primary endpoint and assess safety and tolerability as the secondary ~~endpoint. AMG 890~~**endpoints. Olpasiran** was evaluated at dose ranges of [redacted] mg to [redacted] mg in both ~~of these~~ phase 1 studies.	Updated clinical study information according to the latest version 4.0 IB.
11	15-16	AMG 890 was well tolerated in the Sprague Dawley rat and cynomolgus monkey toxicology	~~AMG 890~~**Olpasiran** was well tolerated in the ~~Sprague Dawley~~**Investigational New Drug**	Updated toxicology according to

No.	Page,	Original	Amendment	Rationale
		studies. All dose levels in the monkey toxicology studies reduced serum Lp(a) by ≥ 90%. In the Investigational New Drug (IND)-enabling GLP 57-day rat and monkey toxicology studies and in the registrational GLP 6-month rat and 9-month monkey studies, AMG 890 was administered at 10, 30, and 150 mg/kg once monthly. In rats at 10 mg/kg, the only AMG 890 related change was minimal to mild accumulation of basophilic granular material in the proximal convoluted tubular epithelium of the renal cortex in the 6-month study. In monkeys at 10 mg/kg, the only AMG 890-related changes were Kupffer cell hypertrophy/hyperplasia (with cytoplasmic vacuolization and basophilia) in the liver and vacuolation of macrophages in the subcutis at the injection site and in the lymph nodes. AMG 890 related changes in the liver, kidneys, lymph nodes, and injection site were consistent with investigational product uptake, a known N-acetylgalactosamine (GalNAc) conjugated siRNA-related platform effect and not specific to AMG 890[18,19,20].	**(IND)-enabling (57-day** rat and ~~cynomolgus~~ monkey**) and registrational (6-month rat, 9-month monkey) GLP** toxicology studies. All dose levels in the monkey toxicology studies reduced serum Lp(a) by ≥ 90%. In the ~~Investigational New Drug (~~IND~~) -~~-enabling GLP 57-day rat and monkey toxicology studies and in the registrational GLP 6-month rat and 9-month monkey studies, ~~AMG 890~~**Olpasiran** was administered at 10, 30, and 150 mg/kg once monthly. In rats at 10 mg/kg, the only ~~AMG 890~~**Olpasiran** related change was minimal to mild accumulation of basophilic granular material in the proximal convoluted tubular epithelium of the renal cortex in the 6-month study. In monkeys at 10 mg/kg, the only ~~AMG 890~~**Olpasiran**-related changes were Kupffer cell hypertrophy/hyperplasia (with cytoplasmic vacuolization and basophilia) in the liver and vacuolation of macrophages in the subcutis at the injection site and in the lymph nodes~~. AMG 890~~ **; the vacuolation of macrophages in the subcutis at the injection site was not observed**	the latest version 4.0 IB.

No.	Page,	Original	Amendment	Rationale
		There were other AMG 890-related changes that occurred either at higher dose levels or a more frequent dosing regimen (eg, weekly in the exploratory studies) included transient changes in cholesterol (rats only), serum alanine aminotransferase (ALT), serum alkaline phosphatase (ALP), and bilirubin. The only AMG 890-related finding considered secondary to silencing of *LPA* gene expression was reduction in serum Lp(a) in monkeys. …… In an exploratory embryo fetal development toxicology study in the rat, there were no AMG 890 related mortalities, clinical signs, maternal ovarian or uterine abnormalities, or fetal external or visceral abnormalities.	**in the 9-month monkey toxicology study. Olpasiran-**related changes in the liver, kidneys, lymph nodes, and injection site were consistent with investigational product uptake, a known N-acetylgalactosamine (GalNAc) conjugated siRNA-related platform effect and not specific to ~~AMG 890~~**Olpasiran**[18,19,20]. There were other ~~AMG 890~~**Olpasiran**-related changes that occurred either at higher dose levels or a more frequent dosing regimen (~~eg,~~**e.g.,** weekly in the exploratory studies) included transient, **minimal to mild increases** changes in cholesterol (rats only), serum alanine aminotransferase (ALT), **and minimal to mild increases in** serum alkaline phosphatase (ALP), and bilirubin. **Additional Olpasiran-related changes occurring at higher dose levels or with increased frequency of dosing included basophilic granules in the proximal tubular epithelial cells of the kidney. Olpasiran-related liver changes at higher dose levels or increased frequency of dosing consisted of hepatocellular vacuolation, increased single cell necrosis and**	

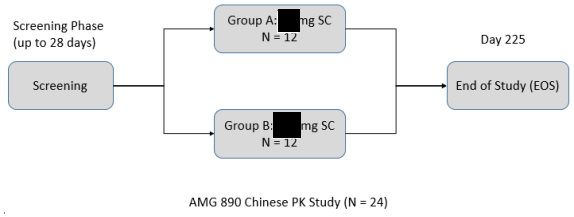
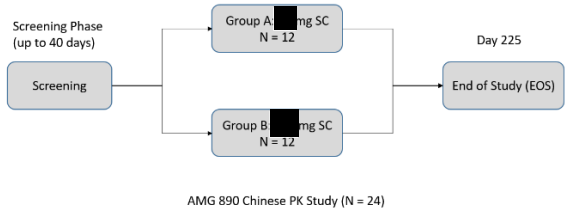
No.	Page,	Original	Amendment	Rationale
			mitoses of hepatocytes, and basophilic granular material in Kupffer cells in the liver in rats and hepatocellular hypertrophy with cytoplasmic rarefaction in monkeys. The only ~~AMG 890~~**Olpasiran**-related finding considered secondary to silencing of *LPA* gene expression was **a** reduction in serum Lp(a) in monkeys. …… In an exploratory embryo fetal development toxicology study in the rat, there were no ~~AMG 890~~ **Olpasiran-**related mortalities, clinical signs, maternal ovarian or uterine abnormalities, or fetal external or visceral abnormalities~~.~~ **when pregnant rats received up to 200 mg/kg Olpasiran SC daily on gestation Day (GD) 7 through GD 17.**	
12	17-18	**Study 20170544 (FIH)** As of the 19 March 2020 data snapshot date, AMG 890 or placebo had been administered to 64 subjects in Study 20170544; these subjects included 40 subjects with screening serum Lp(a) ≥ 70 to ≤ 200 nmol/L in 5 different single doses (cohorts 1 to 5[redacted] mg) and 24	**Study 20170544 (FIH)** As of the 19 March 2020 data snapshot date, ~~AMG 890~~**Olpasiran** or placebo had been administered to 64 subjects ~~in Study 20170544;~~**(48 Olpasiran and 16 placebo). Of** these ~~subjects included 40~~**30** subjects with screening ~~serum~~**plasma** Lp(a) **between** ≥ 70 to ≤	Updated clinical study information according to the latest version 4.0 IB.

No.	Page,	Original	Amendment	Rationale
		subjects with screening serum Lp(a) ≥ 200 nmol/L in 2 different single doses (high Lp[a] cohorts 6 and 7: [redacted] and [redacted] mg). No AMG 890 treated subjects in Study 20170544 had a serious adverse event (AE). One placebo subject in cohort 6 of Study 20170544 had grade 2 serious AEs of non-cardiac chest pain and cardiac telemetry abnormal on Study Day 128 that resolved. There have been no fatal or life-threatening AEs reported. No clinically relevant changes in liver function tests, platelets or coagulation parameters, or renal function (creatinine) have been detected. Overall, no notable trends in AEs, vital signs, or laboratory results have been observed to date. As of 19 March 2020, all 64 subjects enrolled in cohorts 1 to 7 of Study 20170544 had completed the treatment phase of the study. ……. **Study 20180222 (Japanese PK)** ……	~~200~~**199** nmol/L ~~in~~**received** 5 different single doses (cohorts 1 to 5: [redacted] mg) and ~~24~~**18** subjects with screening ~~serum~~**plasma** Lp(a) ≥ 200 nmol/L ~~in~~**received** 2 different single doses (high Lp[a] cohorts 6 and 7: [redacted] and [redacted] mg). ~~No AMG 890 treated~~ **Two additional cohorts were added to Study 20170544 and are ongoing (cohort 8 [redacted] mg] and cohort 9 [redacted] mg] included subjects with screening plasma Lp(a) ≥ 200 nmol/L). As of 19 March 2020, no data are available for reporting from cohorts 8 and 9. All 64** subjects ~~in~~ **enrolled in cohorts 1 to 7 of** Study 20170544 ~~had a serious adverse event (AE). One placebo subject in cohort 6 of Study 20170544 had grade~~**have completed the treatment phase of the study (cohorts 1 and** 2 ~~serious AEs of non-cardiac chest pain and cardiac telemetry abnormal on Study Day 128 that resolved.~~**: Day 113 and cohorts 3 to 7: Day 225).** There have been no ~~fatal or~~ life-threatening **or fatal adverse events (AEs) reported, and no serious** AEs reported **in subjects treated with Olpasiran**. No clinically relevant changes in liver	

No.	Page,	Original	Amendment	Rationale
		AMG 890 was administered to a total of 27 subjects; 21 subjects in 4 different single doses [redacted] mg) in Japanese subjects and to 6 subjects in 1 single dose ([redacted] mg) in non-Japanese subjects. No fatal, serious, or life-threatening AEs were reported. In general, AMG 890 was well tolerated at the doses tested. To date, all subjects have completed the study. [redacted]	function tests, platelets or coagulation parameters, or renal function (creatinine) have been detected. Overall, no notable trends in AEs, vital signs, or laboratory results have been observed to date. ~~As of 19 March 2020, all 64 subjects enrolled in cohorts 1 to 7 of Study 20170544 had completed the treatment phase of the study.~~ …… **Study 20180222 (Japanese PK)** …… ~~AMG 890~~**Olpasiran** was administered to a total of 27 subjects~~:~~**:** 21 subjects in 4 different single doses [redacted] mg) in Japanese subjects and to 6 subjects in 1 single dose ([redacted] mg) in non-Japanese subjects. ~~No fatal, serious, or life-threatening AEs were reported. In general, AMG 890 was well tolerated at the doses tested. To date, all subjects have completed the study.~~**Olpasiran was shown to be safe and well tolerated. No patterns indicative of clinically important adverse events, laboratory abnormalities, or vital sign abnormalities were**	

No.	Page,	Original	Amendment	Rationale
		[redacted]	**observed. No serious or fatal adverse events were reported from this study.** [redacted]	

No.	Page,	Original	Amendment	Rationale
			[redacted]	

No.	Page,	Original	Amendment	Rationale
			[redacted]	
13	23-24	 AMG 890 Chinese PK Study (N = 24) Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to dose administration. Subjects will be admitted into the phase I Clinical Research Unit (CRU) on Day -1 and be confined to the CRU until discharge on Day 4. Subjects will return to the CRU for outpatient visits on Days 7, 15, 29, 57,	 AMG 890 Chinese PK Study (N = 24) Potential subjects will be screened to assess their eligibility to enter the study within ~~28~~**40** days prior to dose administration. Subjects will be admitted into the phase I Clinical Research Unit (CRU) on Day -1 and be confined to the CRU until discharge on Day 4. Subjects will return to	Updated screening period to 40 days and therefore also updated the total study duration.

No.	Page,	Original	Amendment	Rationale
		85, 113, 155, and 183, and at the end of study (EOS) visit on Day 225. A telephone visit will be scheduled for TEAE assessments on Day 211. The total duration of study participation for each subject (from Screening through EOS visit) is anticipated to be approximately 253 days (36 weeks).	the CRU for outpatient visits on Days 7, 15, 29, 57, 85, 113, 155, and 183, and at the end of study (EOS) visit on Day 225. A telephone visit will be scheduled for TEAE assessments on Day 211. The total duration of study participation for each subject (from Screening through EOS visit) is anticipated to be approximately ~~253~~**265** days (~~36~~**about 38** weeks).	
14	25	**Part 2**: Eligible subjects will complete all remaining screening procedures and tests, including definitive determination of Lp(a) levels, that establish eligibility within 28 days prior to the Day 1 visit.	**Part 2**: Eligible subjects will complete all remaining screening procedures and tests, including definitive determination of Lp(a) levels, that establish eligibility within ~~28~~**40** days prior to the Day 1 visit.	Updated screening period to 40 days.
15	32	**AMG 890 (Group A)** [redacted] mg/mL vial[b] AMG 890 SC injection [redacted] mg [redacted]) SC injection	~~**AMG 890**~~**Olpasiran (Group A)** [redacted] mg/mL vial[b] ~~AMG 890~~**Olpasiran** SC injection [redacted] mg ([redacted]) SC injection	Removed irrelevant information.

No.	Page,	Original	Amendment	Rationale
		The amount dispensed, amount returned, date/time dispensed, lot number, box number of investigational product is to be recorded on each subject's CRF(s). The Investigator or study physician must be available when the subject receives the dose of AMG 890 for immediate intervention in case of complication(s).	The ~~amount dispensed, amount returned,~~ date/time ~~dispensed~~**of administration**, lot number, box number of investigational product is to be recorded on each subject's CRF(s). The Investigator or study physician must be available when the subject receives the dose of ~~AMG 890~~**Olpasiran** for immediate intervention in case of complication(s).	
16	32	**AMG 890 (Group B)** [redacted] mg/mL vial[b] AMG 890 SC injections [redacted] mg [redacted]) SC injection The amount dispensed, amount returned, date/time dispensed, lot number, box number of investigational product is to be recorded on each subject's CRF(s). [redacted]. The Investigator or study physician must be available when the subject receives the dose of AMG 890 for immediate intervention in case of complication(s).	**~~AMG 890~~Olpasiran (Group B)** [redacted] mg/mL vial[b] ~~AMG 890~~**Olpasiran** SC injections [redacted] mg ([redacted]) SC injection The ~~amount dispensed, amount returned,~~ date/time ~~dispensed~~**of administration**, lot number, box number of investigational product is to be recorded on each subject's CRF(s). [redacted] The Investigator or study physician must be available when the subject receives the dose of ~~AMG 890~~**Olpasiran** for immediate intervention in case of complication(s).	Corrected the errors of Dosage Level of Olpasiran (Group B; number and volume of SC injections) for consistency with the IPPA document. Removed irrelevant information.
17	32	[a] AMG 890 will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures. [b] Provided as a [redacted] deliverable volume of [redacted] mg/mL AMG 890.	[a] ~~AMG 890~~**Olpasiran** will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.	Corrected the errors of Dosage Level of Olpasiran (Group B; number and

No.	Page,	Original	Amendment	Rationale
			[b] Provided as a [redacted] **~~-~~maximum deliverable volume of** [redacted] **will be used to administer the [redacted] mg dose.**	volume of SC injections) for consistency with the IPPA document.
18	35	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 screen the subject to assess eligibility for participation. The screening window is up to 28 days. 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 4.3 as applicable. If a subject has not met all eligibility criteria at the end of the screening period, the subject will	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 screen the subject to assess eligibility for participation. The screening window is up to ~~28~~**40** days. 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 4.3 as applicable. If a subject has not met all eligibility criteria at the end of the screening period, the subject will	Updated the screening period to 40 days.

No.	Page,	Original	Amendment	Rationale
		be registered as a screen failure. Screen failed subjects may be eligible for re-screening 3 times. Once the subject is registered as rescreened, a new 28-day screening window will begin. Subjects will retain the same unique identification number assigned at the original screening. If the rescreening period begins more than 28 days after the original signing of the ICF, all screening procedures, including informed consent, must be repeated as well. Laboratory assessments used to determine subject eligibility may be repeated once for confirmation, allowing for up to a total of two assessments during the 28-day screening period, if necessary, before the subject is considered a screen failure. If any assessments are repeated during the screening period, the value that is closest to the enrollment date will apply for the determination of eligibility.	be registered as a screen failure. Screen failed subjects may be eligible for re-screening 3 times. Once the subject is registered as rescreened, a new ~~28~~**40**-day screening window will begin. Subjects will retain the same unique identification number assigned at the original screening. If the rescreening period begins more than ~~28~~**40** days after the original signing of the ICF, all screening procedures, including informed consent, must be repeated as well. Laboratory assessments used to determine subject eligibility may be repeated once for confirmation, allowing for up to a total of two assessments during the ~~28~~**40**-day screening period, if necessary, before the subject is considered a screen failure. If any assessments are repeated during the screening period, the value that is closest to the enrollment date will apply for the determination of eligibility.	
19	37	Venous blood samples (approximately 6 mL) will be collected for measurement of Lp(a) at times	Venous blood samples (approximately ~~6~~**5** mL) will be collected for measurement of Lp(a) at	Updated blood volumes for Lp(a) and lipid panel analyses.

No.	Page,	Original	Amendment	Rationale
		indicated in the Schedule of Assessments in Appendix 9. Lipid panel will include triglycerides, VLDL-C, LDL-C, and HDL-C, total cholesterol, ApoA1, and total Apo B. At Screening, lipids will measure triglycerides only. Subjects will be fasted overnight (at least 10 hours) before collection of blood samples for lipids. Venous blood samples (approximately 6 mL) will be collected for measurement of lipids at the times indicated in the Schedule of Assessments in Appendix 9.	times indicated in the Schedule of Assessments in Appendix 9. Lipid panel will include triglycerides, VLDL-C, LDL-C, and HDL-C, total cholesterol, ApoA1, and total Apo B. At Screening, lipids will measure triglycerides only. Subjects will be fasted overnight (at least 10 hours) before collection of blood samples for lipids. Venous blood samples (approximately ~~6~~**8.5** mL) will be collected for measurement of lipids at the times indicated in the Schedule of Assessments in Appendix 9.	
20	41	Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol breath test at the times indicated in the Schedule of Assessments in Appendix 9. For all female subjects, a pregnancy test and FSH screen for postmenopausal women will be performed at the times indicated in the Schedule of Assessments in Appendix 9	Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol ~~breath~~**urine** test at the times indicated in the Schedule of Assessments in Appendix 9. For all female subjects, a pregnancy test and FSH screen for postmenopausal women will be performed at the times indicated in the Schedule of Assessments in Appendix 9.	Switched the Alcohol Breath Test to the Alcohol Urine Test due to COVID-19 pandemic at screening and Check-in visits.
21	42	Systolic/diastolic BP, heart rate, respiratory rate, and body temperature will be assessed in sitting	Systolic/diastolic BP, ~~heart~~**pulse** rate, respiratory rate, and body temperature will be assessed in	Updated to pulse rate per

No.	Page,	Original	Amendment	Rationale
		position at the times indicated in the Schedule of Assessments in Appendix 9. Heart rate and BP will be measured using the same arm for each reading after the subject has been resting in the sitting position for at least 5 minutes. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required. The position selected for a subject should be the same position used throughout the study and documented on the vital sign CRF. All measurements will be performed singly and repeated once (within a total of 5 minutes) if outside the relevant clinical reference range. Subjects must be sitting for at least 5 minutes before BP and heart rate measurements. When vital signs are scheduled at the same time as blood draws, the blood draws will be obtained at the scheduled timepoint, and the vitals will be obtained as close to the scheduled blood draw as	sitting position at the times indicated in the Schedule of Assessments in Appendix 9. ~~Heart~~**Pulse** rate and BP will be measured using the same arm for each reading after the subject has been resting in the sitting position for at least 5 minutes. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required. The position selected for a subject should be the same position used throughout the study and documented on the vital sign CRF. All measurements will be performed singly and repeated once (within a total of 5 minutes) if outside the relevant clinical reference range. Subjects must be sitting for at least 5 minutes before BP and ~~heart~~**pulse** rate measurements. When vital signs are scheduled at the same time as blood draws, the blood draws will be obtained at the scheduled timepoint, and the vitals will be obtained as close to the scheduled blood draw as	site requirement.

No.	Page,	Original	Amendment	Rationale
		possible, but preferably prior to the safety blood draw.	possible, but preferably prior to the safety blood draw.	
22	45	Amgen Inc. AMG 890 – Investigator's Brochure. (Version 3.0). 06 November 2019.	1. Amgen Inc. **Olpasiran (**AMG 890**)** – Investigator's Brochure. (Version ~~3~~**4**.0). 06 ~~November 2019~~**January 2021**.	Updated reference according the latest version 4.0 IB.
23	58	**Drug screen[c]:** Including, but not limited to: Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol/ cannabinoids Tricyclic antidepressants Cotinine test Alcohol breath test	**Drug screen[c]:** Including, but not limited to: Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine ~~(metabolite)~~ Methadone Phencyclidine Opiates ~~Tetrahydrocannabinol/ cannabinoids~~ **K2 (Synthetic cannabinoids)** Tricyclic antidepressants Cotinine test Alcohol ~~breath~~**urine** test	Switched the Alcohol Breath Test to the Alcohol Urine Test due to COVID-19 pandemic at screening and Check-in visits. Updated other drug screening substances per site requirement.
24	58	[a] Only analyzed at Screening. [b] After screening, on-study lipids will include triglycerides, VLDL-C, LDL-C, HDL-C, total cholesterol, Apo A1, and total Apo B. [c] Part 1 and Part 2 screening, and on study serum Lp(a) samples will be analyzed by a central laboratory of Covance Shanghai.	[a] Only analyzed at Screening. [b] After screening, on-study lipids will include triglycerides, VLDL-C, LDL-C, HDL-C, total cholesterol, Apo A1, and total Apo B.	Changed from Covance Shanghai to a Sponsor designated lab

<table>
<tr><th>No.</th><th>Page,</th><th>Original</th><th>Amendment</th><th>Rationale</th></tr>
<tr><td></td><td></td><td></td><td>[c] Part 1 and Part 2 screening, and on study serum Lp(a) samples will be analyzed by a ~~central~~**Sponsor-designated** laboratory ~~of Covance Shanghai~~.</td><td></td></tr>
<tr><td>25</td><td>59</td><td>
<table>
<tr><th>Test</th><th>Volume per blood sample (mL)</th><th>Maximum number of blood samples</th><th>Total amount of blood (mL)</th></tr>
<tr><td>Clinical Chemistry and Hematology</td><td>12</td><td>12</td><td>144</td></tr>
<tr><td>Coagulation</td><td>3</td><td>9</td><td>27</td></tr>
<tr><td>Serum Pregnancy[a]</td><td>5</td><td>1</td><td>5</td></tr>
<tr><td>FSH[b]</td><td>5</td><td>1</td><td>5</td></tr>
<tr><td>Serology</td><td>9</td><td>1</td><td>9</td></tr>
<tr><td>PK</td><td>4</td><td>17</td><td>68</td></tr>
<tr><td>PD</td><td>6</td><td>21</td><td>126</td></tr>
<tr><td>Anti-AMG 890 Antibody</td><td>4</td><td>3</td><td>12</td></tr>
<tr><td>Total:</td><td></td><td></td><td>396</td></tr>
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</td><td>
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<tr><td>PD
Lp(a)</td><td>~~6~~5</td><td>~~21~~14</td><td>~~126~~70</td></tr>
<tr><td><u>PD: Lipid panel</u></td><td><u>8.5</u></td><td><u>7</u></td><td><u>59.5</u></td></tr>
</table>
</td><td>Updated total blood volumes to be collected.</td></tr>
</table>

No.	Page,	Original	Amendment	Rationale
			Anti-~~AMG 890~~**Olpasiran** Antibody 4 3 12 **Total:** ~~396~~**399.5**	
26	68	A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.	A subject who is rescreened is not required to sign another ICF if the rescreening occurs within ~~28~~**40** days from the previous ICF signature date.	Updated the screening period to 40 days.
27	69	• Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in the study site archive for 25 years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.	• Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in the study site archive for ~~25~~**15** years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.	Updated the archival period of documentation from 25 years to 15 years per the site requirement.

No.	Page,	Original	Amendment	Rationale
28	76	**-28 to -2**	**~~-28~~ 40 to -2**	Updated screening period to 40 days.
29	76	Alcohol Breath Test	Alcohol ~~Breath~~**Urine** Test	Updated the alcohol test in Table 5 Schedule of assessment.
30	76	Anti-AMG 890 Antibody tested at Day -1	Anti-~~AMG 890~~**Olpasiran** Antibody tested at Day 1 predose	Updated collection timepoint ensure subject ID designation on sample collection tube.
31	77	[e] Sitting blood pressure, sitting heart rate, respiratory rate and temperature. Heart rate and BP will be measured using the same arm for each reading after the subject has been resting in the sitting position for at least 5 minutes. ..... [m] Part 1 and Part 2 screening, and on study serum Lp(a) samples will be analyzed by a central laboratory of Covance Shanghai.	[e] Sitting blood pressure, sitting ~~heart~~**pulse** rate, respiratory rate and temperature. ~~Heart~~**Pulse** rate and BP will be measured using the same arm for each reading after the subject has been resting in the sitting position for at least 5 minutes. ..... [m] Part 1 and Part 2 screening, and on study serum Lp(a) samples will be analyzed by a ~~central~~**Sponsor-designated** laboratory ~~of Covance Shanghai~~.	Updated to pulse rate per site requirement. Changed from Covance Shanghai to a Sponsor designated lab.

No.	Page,	Original	Amendment	Rationale
32	79	[d] Sitting blood pressure, sitting heart rate, respiratory rate and temperature. Heart rate and BP will be measured using the same arm for each reading after the subject has been resting in the sitting position for at least 5 minutes. ..... [j] Part 1 and Part 2 screening, and on study serum Lp(a) samples will be analyzed by a central laboratory of Covance Shanghai.	[d] Sitting blood pressure, sitting ~~heart~~**pulse** rate, respiratory rate and temperature. ~~Heart~~**Pulse** rate and BP will be measured using the same arm for each reading after the subject has been resting in the sitting position for at least 5 minutes. ..... [j] Part 1 and Part 2 screening, and on study serum Lp(a) samples will be analyzed by a ~~central~~**Sponsor-designated** laboratory ~~of Covance Shanghai~~.	Updated to pulse rate per site requirement. Changed from Covance Shanghai to a Sponsor designated lab.