Title: A Phase 1, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 890 in Subjects With Elevated Plasma Lipoprotein(a)

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Investigator's Agreement

I have read the attached protocol entitled, A Phase 1, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 890 in Subjects **W**ith Elevated Plasma Lipoprotein(a), dated **07 December 2021**, and agree to abide by all provisions set forth therein.

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

I agree to ensure that Financial Disclosure Statements will be completed by:

- *me (including, if applicable, my spouse [or legal partner] and dependent children)*
- *my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)*

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

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

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

1. Protocol Synopsis

Title: A Phase 1, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 890 in Subjects **W**ith Elevated Plasma Lipoprotein(a)

Study Phase: 1

Indication: Treatment of adults with atherosclerotic cardiovascular disease to reduce the risk of cardiovascular events

Primary Objective: To assess the safety and tolerability of AMG 890 when administered subcutaneously (SC) as a single dose to subjects with elevated plasma Lp(a).

Secondary Objectives:

- To characterize the pharmacokinetics (PK) of AMG 890 when administered SC as a single dose to subjects with elevated plasma Lp(a)
- To characterize the pharmacodynamics (PD) effects of AMG 890 on plasma Lp(a)
- To assess the safety, tolerability, and PD effects of AMG 890 when administered in combination with statins

Exploratory Objectives:

[redacted]

- To assess the effects of AMG 890 on total cholesterol and cholesterol fractions (very-low density lipoprotein cholesterol [VLDL-C], low-density lipoprotein cholesterol [LDL-C], and high-density lipoprotein cholesterol [HDL-C]), triglycerides, apolipoprotein A1 (ApoA1) and total apolipoprotein B (ApoB)
- To qualitatively assess AMG 890 urinary excretion following a single SC dose administration

[redacted]

Hypotheses:

- AMG 890 will be safe and well tolerated when administered SC as a single dose in subjects with elevated plasma Lp(a)
- AMG 890 PK and/or PD data from this study will support the selection of dose and frequency of AMG 890 administration for future multi-dose trials

Primary Endpoints:

- Subject incidence of treatment-emergent adverse events
- Safety laboratory analytes, vital signs, and electrocardiograms (ECGs)

Secondary Endpoints:

- AMG 890 PK parameters including, but not limited to, maximum observed concentration (C_{max}), the time of maximum observed concentration (t_{max}), and area under the concentration-time curve (AUC)
- Pharmacodynamic parameters:
    - Change and percent change in plasma Lp(a) levels at each scheduled visit up to the end of treatment visit

Study Design:

This is a randomized, double-blind, placebo-controlled, single ascending dose (SAD) study in subjects with elevated plasma Lp(a), which will be conducted at 3 to 10 sites in the United States and Australia. Additional sites and countries may be added.

Approximately [redacted] subjects will enroll in 9 SAD cohorts. As described in Table 1 below, for each cohort, subjects will be randomized to receive AMG 890 or placebo SC in a 3:1 ratio. As of Amendment 6, enrollment in cohorts 1 to 8 is closed. There were no safety concerns noted that would preclude enrollment into the higher dose cohorts 8 and 9.

Table 1. Planned Treatment by Cohort

Cohort	Number of Subjects	Investigational Product (SC administration)
1 [a]	6	AMG 890 3 mg
	2	Placebo
2 [a]	6	AMG 890 9 mg
	2	Placebo
3 [a]	6	AMG 890 30 mg
	2	Placebo
4 [a]	6	AMG 890 75 mg
	2	Placebo
5 [a]	6	AMG 890 225 mg
	2	Placebo
6 [b,s]	9	AMG 890 9 mg
	3	Placebo
7 [b,s]	9	AMG 890 75 mg
	3	Placebo
8 [b,s]	6	AMG 890 225 mg
	2	Placebo
9 [b,s]	6	AMG 890 675 mg
	2	Placebo

a = subjects with screening plasma Lp(a) ≥ 70 nmol/L and ≤ 199 nmol/L
b = subjects with screening plasma Lp(a) ≥ 200 nmol/L
s = at least 6 subjects must be on a stable dose of a statin for at least 6 weeks in each of cohorts 6 to 9

As described in the Eligibility Criteria, cohorts 1 to 5 will enroll subjects with plasma Lp(a) between 70 nmol/L and 199 nmol/L, inclusive. Cohorts 6 to 9 will enroll subjects with plasma Lp(a) equal to or greater than 200 nmol/L. At least 6 subjects in each of cohorts 6 to 9 will be on a stable dose of statin for at least 6 weeks.

For cohorts 1 to 5, the first 2 enrolled subjects will be randomized in a 1:1 ratio (sentinel pair) and will be dosed on the same day at the same study site, as will cohort 9. Within the pair and while maintaining treatment blind, 1 subject will receive AMG 890 and the other subject will receive placebo. If deemed safe by the investigator, and no less than 24 hours after sentinel pair dosing, the same dose will be administered to the remaining cohort subjects.

Enrollment into cohorts 1 to 5 will be staggered. Subsequent cohorts will be dosed after the dose regimen in the preceding cohort has been found by the Dose Level Review Team (DLRT) to be safe and reasonably tolerated based on available safety data through study day 15 for all subjects. Enrollment into cohorts 5 to 7 will be initiated after the dose regimen in cohort 4 has been found by the DLRT to be safe and reasonably tolerated based on available safety data through study day 15.

Enrollment into cohort 8 is closed. Enrollment into cohort 9 can be initiated after the dose regimen in cohort 5 has been found by the DLRT ("DLRM 5" in study schema) to be safe and reasonably tolerated based on available safety data through at least study day 15 for all subjects.

The planned dose escalation schedule may be modified based on treatment-emergent data (safety and/or PD). Dose adjustments (if any) will be made by Amgen on a treatment cohort and not on an individual basis. As of Amendment 6, enrollment in Cohorts 1 to 8 is closed. There were no safety concerns noted that would preclude enrollment into the higher dose cohorts, 8 and 9.

Sample Size:

The sample size is based on practical considerations. Approximately [redacted] subjects will be enrolled. With at least 6 subjects receiving AMG 890 in each cohort, there is at least a 74% chance of detecting an adverse event (AE) with a true incidence of 20% within each cohort. With at least 10 subjects receiving both AMG 890 and statin, there is at least a**n** 89% chance of detecting an adverse event with a true AE incidence rate of 20%. With [redacted] subjects receiving AMG 890 there is a 95% chance of detecting an adverse event with a true incidence of 5%.

Summary of Subject Eligibility Criteria:

Eligibility criteria include:

Across all study cohorts, women of non-reproductive potential and men, both with age between 18 and 60 years, inclusive, for cohorts 1 to 5; with age between 18 and 65 years, inclusive, for cohorts 6 to **8; and with age between 18 and 70 years, inclusive, for cohort** 9. Subjects without any clinically significant abnormality in medical history at the time of randomization.

For cohorts 1 to 5, plasma Lp(a) $\geq$ 70 nmol/L and $\leq$ 199 nmol/L, at screening

For cohorts 6 to 9, plasma Lp(a) $\geq$ 200 nmol/L, at screening; for cohorts 6 to 9, at least 6 subjects in each cohort must be on a stable dose of statin for at least 6 weeks at the time of enrollment

Investigational Product:

Amgen Investigational Product Dosage and Administration:

A total of [redacted] subjects will be randomized to receive AMG 890 or equal volume of placebo by SC injection as a single dose. The planned doses for AMG 890 are as follows: single SC doses of 3 mg, 9 mg, 30 mg, 75 mg, 225 mg, and 675 mg.

The planned dose escalation schedule may be modified based on treatment-emergent data (safety and/or PD). Dose adjustments (if any) will be made by Amgen on a treatment cohort and not on an individual basis. Each of cohorts 1 to 5 may be expanded up to [redacted] subjects, while applying the same eligibility criteria and the 3:1 AMG 890 to placebo randomization ratio.

Control Group: The control group will be those subjects who will be administered placebo. Within each cohort, 2 subjects (or 3 subjects if a cohort consists of [redacted] subjects) will receive an equal volume of placebo.

Procedures:

Screening

After written informed consent has been obtained, all screening procedures and tests that establish study eligibility will be performed within 28 days prior to day 1 visit. Study procedures are summarized in the Schedule of Assessments.

Serious Adverse Events will be collected from the time the Informed Consent Form (ICF) is signed.

Day -3 to Day -1

Subjects in cohorts 1 to 5 will be considered enrolled once the subject is deemed eligible by the investigator based on screening and day -1 assessments. Subjects enrolled will be admitted to the research facility at day -1.

Subjects in cohorts 6 to 9 will be considered enrolled once the subject is deemed eligible by the investigator based on screening and the day -3 to -1 assessments. The first 2 subjects enrolled in cohort 9 (sentinel pair) will be admitted to the research facility on day -1. Subjects enrolled in cohorts 6 to 8 and cohort 9 (other than the sentinel pair) will return to the clinic at day 1.

Treatment

After completion of all pre-dose procedures on day 1, subjects will receive their dose of AMG 890 or placebo.

For cohorts 1 to 5, subjects will stay in the research facility for a residency period from day -1 through day 4. For cohort 9, sentinel pair subjects will stay in the research facility for a residency period from day -1 through day 2. After completion of day 4 procedures for cohorts 1 to 5 or completion of day 2 procedures for the cohort 9 sentinel pair, subjects will be discharged and will return to the research facility at specified time points as per the schedule of assessments for additional collection of blood and urine samples for laboratory assessments, PK and PD measurements, and completion of safety assessments through the end of the study.

For cohorts 6 to 8 and cohort 9 (other than the sentinel pair), subjects will not have a required residency period, but will report to the research facility on day 1 for completion of the day 1 scheduled procedures according to the Schedule of Assessments (Table 4 to Table 9).

All adverse events (including serious adverse events) and use of concomitant medication will be collected throughout the study.

End of Treatment

Subjects will return to the research facility for an end of treatment visit according to the schedule below. If the subject is required to have a follow-up period due to plasma Lp(a) level, the end of study (EOS) visit for the subject will be as described under Follow-up, below.

- Cohorts 1 and 2 on day 113
- Cohorts 3 to 7 on day 225
- Cohorts 8 and 9 on day 365

The end of treatment visit will complete the subject's participation in this study unless a follow-up is required. The end of treatment visit for cohorts 8 and 9 will be the same as the end of study visit (day 365).

If there is a clinically significant clinical or laboratory abnormality that requires monitoring, subjects will be followed until resolution of the abnormality or until it is considered stable.

Follow-up

If at the day 113 visit for cohorts 1 and 2 and the day 225 visit for cohorts 3 to 7, the plasma Lp(a) level has not returned to ≥ 80% of baseline (mean of screening and day 1 predose), subjects will return to the clinical study site for follow-up. Cohorts 1 and 2 will return for safety and exploratory PD monitoring visits every 2 weeks until Lp(a) level returns to ≥ 80% of baseline. When the protocol amendment 2 is implemented, the follow-up visits will continue approximately monthly, as needed, and will include only Lp(a) monitoring as described below for cohorts 3 to 7.

For cohorts 3 to 7, subjects will return to the clinical study site for Lp(a) monitoring approximately monthly starting from when the site has been notified of the Lp(a) follow-up requirement until the Lp(a) level returns to ≥ 80% of baseline.

For cohorts 8 and 9, all subjects, regardless of the on-study Lp(a) level, will participate in the study through the EOS (day 365).

[redacted]

For a full list of study procedures, including the timing of each procedure, please refer to Section 10 and the Schedule of Assessments (Table 4 to Table 9).

Statistical Considerations:

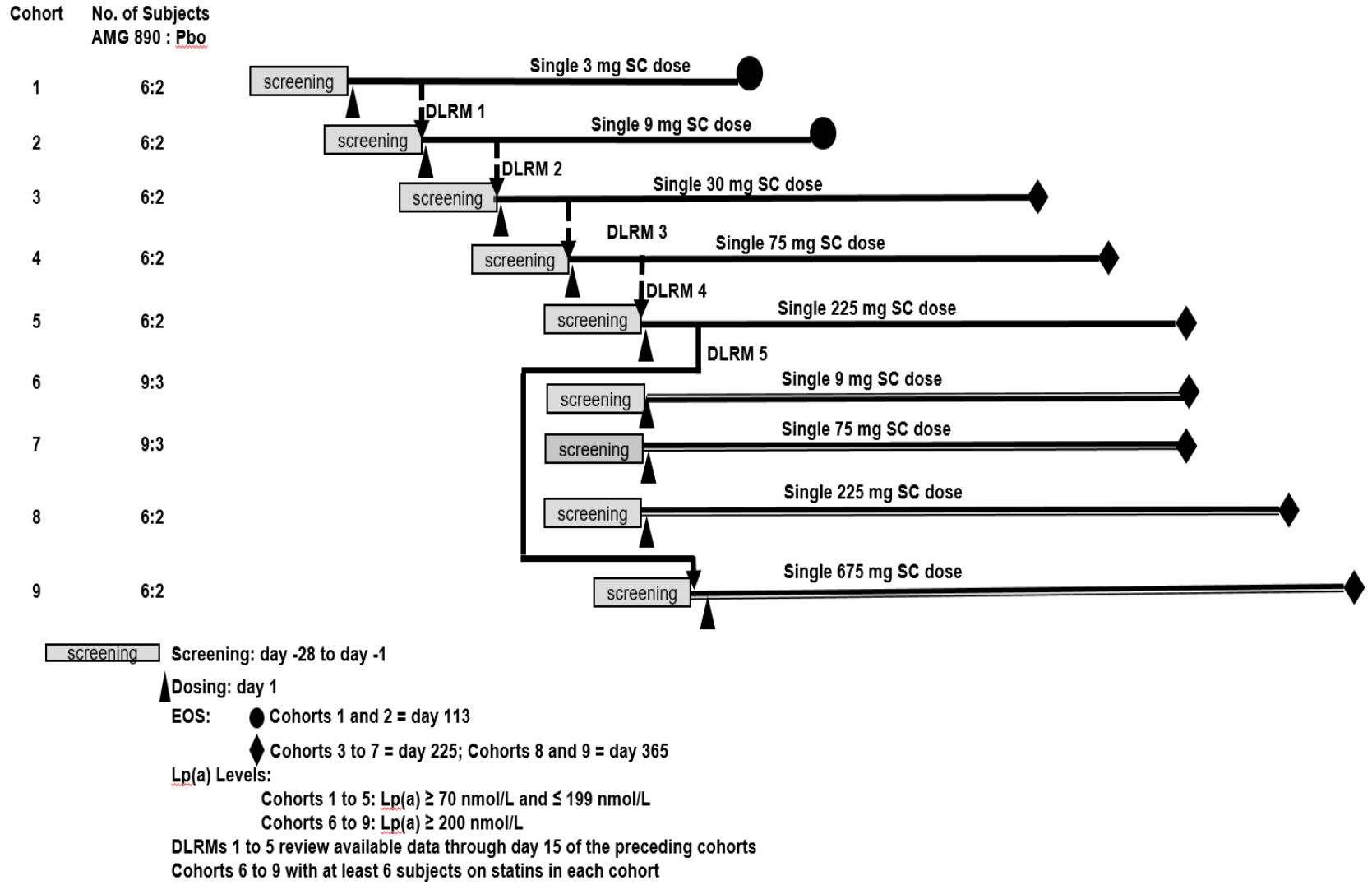
Descriptive statistics will be provided for selected demographics, safety, PK, and PD data. Data for subjects receiving placebo will be combined across all cohorts. Descriptive statistics on continuous measurements will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Data will be summarized by treatment group and at each time point when samples are collected.

The number and percent of subjects reporting any treatment-emergent adverse events will be tabulated by system organ class and preferred term and will be further classified by relationship to treatment.

For a full description of statistical analysis methods, please refer to Section 13.

Sponsor: Amgen Inc.

2. Study Design and Treatment Schema



3. Study Glossary

Abbreviation or Term	Definition/Explanation
ADA	anti-drug antibody
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Apo(a)	Apolipoprotein(a)
ApoA1	apolipoprotein A1
ApoB	apolipoprotein B
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{last}	area under the concentration-time curve from time zero to the last quantifiable concentration
BMI	**body mass index**
BP	blood pressure
C_{max}	maximum serum concentration
CRF	case report form
DILI	drug-induced liver injury
DLRM	Dose Level Review Meeting
DLRT	Dose Level Review Team
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
Enrolled	Defined as when the subject has fulfilled all conditions to be randomized and to receive study drug.
End of Study for Individual Subject	Defined as the last day that protocol-specified procedures are conducted for an individual subject.
EOS	end of study - Defined as when the last subject is assessed or receives an intervention for evaluation in the study; if the study includes multiple parts (eg, safety follow-up or survival assessment), the end of study would include these additional parts
EOT	end of treatment - defined as the last assessment for the protocol specified treatment phase of the study for an individual subject
FDA	Food and Drug Administration
FIH	first-in-human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice(s)
Heart rate	number of cardiac cycles per unit of time
HepCAb	hepatitis C virus antibody

Abbreviation or Term	Definition/Explanation
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International **Council for** Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IRB	institutional review board
IUD	intrauterine device
Lp(a)	Lipoprotein(a)
MRSD	maximum recommended starting dose
PD	pharmacodynamic(s)
PEF	peak expiratory flow
PK	pharmacokinetic(s)
PR interval	PR interval is measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by ECG
Primary Completion Date	Defined as when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint(s).
QRS interval	QRS interval the interval between the Q wave and the S wave in the heart's electrical cycle as measured by ECG; represents the time it takes for the depolarization of the ventricles
QT interval	QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by ECG.
QTc interval	QT interval corrected for heart rate
SAER	serious adverse event report
SCR	Screening
SiRNA	small interfering RNA
SOA	Schedule of assessments
Source Data	Information from an original record or certified copy of the original record containing information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
study day 1	defined as the first day that protocol specified investigational product(s)/protocol-required therapies is/are administered to the subject

Abbreviation or Term	Definition/Explanation
T_{max}, t_{max}	Time to maximum serum concentration
TBIL	total bilirubin
ULN	upper limit of normal

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4. OBJECTIVES

4.1 Primary

The primary objective of the study is to assess the safety and tolerability of AMG 890 when administered subcutaneously (SC) as a single dose to subjects with elevated plasma Lipoprotein(a) (Lp[a]).

4.2 Secondary

The secondary objectives are:

- To characterize the pharmacokinetics (PK) of AMG 890 when administered SC as a single dose to subjects with elevated plasma Lp(a)
- To characterize the pharmacodynamics (PD) effects of AMG 890 on plasma Lp(a)
- To assess the safety, tolerability, and PD effects of AMG 890 when administered in combination with statins

4.3 Exploratory

The exploratory objectives are:

[redacted]

- To assess the effects of AMG 890 on total cholesterol and cholesterol fractions (very-low density lipoprotein cholesterol [VLDL-C], low-density lipoprotein cholesterol [LDL-C], and high-density lipoprotein cholesterol [HDL-C]), triglycerides, apolipoprotein A1 (ApoA1) and total apolipoprotein B (ApoB)
- To qualitatively assess AMG 890 urinary excretion following a single SC dose administration

[redacted]

5. BACKGROUND AND RATIONALE

5.1 Disease

According to the World Health Organisation (WHO), cardiovascular disease is the leading cause of death and disability, accounting for approximately 31% of all deaths and 46% of deaths from noncommunicable diseases worldwide (WHO, 2014). Of the deaths related to cardiovascular disease (CVD), approximately 80% are from myocardial infarction or stroke (WHO, 2014). In the United States (US), more than 1 in 3 individuals have some form of CVD (Roger et al, 2012), and CVD is the leading cause of death (Xu et al, 2016). The morbidity associated with myocardial infarction and stroke continues to be serious and multifaceted, and reducing this morbidity is an important

treatment goal. Each year, it is estimated that 935,000 Americans have a myocardial infarction or coronary death, 155,000 have a silent first myocardial infarction, 610,000 have a new stroke (ischemic or hemorrhagic), and 185,000 have a recurrent stroke (Mozaffarian et al, 2015). After a cardiovascular (CV) 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 (Mendes de Leon et al, 1998; Simpson and Pilote, 2003; Brink et al, 2005; Schweikert et al, 2009; Bach et al, 2011).

The advances in identifying modifiable risk factors for cardiovascular disease (CVD), including smoking, hypertension, diabetes mellitus, obesity and dyslipidemias have allowed the development of evidence-based guidelines and therapeutic measures that significantly contributed to reduction of CVD burden and mortality (Egan et al, 2016). Notwithstanding, for more than 30% of all deaths occurring in the USA, CVD is still listed as the underlying cause.

While lipid lowering therapy research has historically focused on lowering LDL-C to reduce CV risk (Robinson et al, 2005), compelling evidence from epidemiologic studies characterizes elevated plasma lipoprotein(a) (Lp(a)) as a strong independent risk factor for atherosclerotic CVD (Danik et al, 2006; Bennet et al, 2008; Kamstrup et al, 2008; Emerging Risk Factors Collaboration, 2009; Dubé et al, 2012; Jacobson, 2013; Kamstrup et al, 2013; Willeit et al, 2014; Kassner et al, 2015). Further, Mendelian randomization studies (Ohro-Melander, 2015; Nordestgaard and Langsted, 2016) and an expert working group (Averna et al, 2017) suggest a causal link between elevated plasma Lp(a) levels and CVD.

Lp(a) has been strongly associated with the prevalence of coronary heart disease (CHD) (Hopewell et al, 2011) independently of ethnicity (Virani et al, 2012), LDL-C level (Gurdasani et al, 2012) and other traditional CV risk factors such as age, sex, smoking status, blood pressure, body mass index, total plasma cholesterol and history of diabetes (Erqou et al, 2009). Plasma Lp(a) levels have also been positively associated with CHD severity, as measured by the number of occluded coronary vessels (Habib et al, 2009), or the Global Registry of Acute Coronary Events (GRACE) risk score (Guler et al, 2013). Furthermore, Lp(a) apheresis was shown to stabilize coronary lesions, thus resulting in coronary atherosclerosis regression in chronic coronary disease patients (Safarova et al, 2013). In terms of clinical outcomes, Lp(a) concentrations at

1 year can predict the risk for future cardiovascular heart disease (CHD) and CV events in patients with stable CHD as shown in the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study (Nestel et al, 2013). Additionally, elevated Lp(a) concentrations were associated with worse prognosis (ie, cardiac death and non-fatal MI) in CHD patients followed-up for a period of an average of 4 years (Kwon et al, 2015). An independent positive relationship of Lp(a) with sudden cardiac death has been found (Kunutsor et al, 2016) with a further trend towards an inverse association between Lp(a) and total mortality being also reported (Onat et al, 2016). In this context, elevated Lp(a) levels were associated with an increased risk for HF in the general population as seen in the Copenhagen City Heart Study and the Copenhagen General Population Study (Katsiki et al, 2016; Kamstrup and Nordestgaard, 2016). Despite some conflicting results reporting the association of Lp(a) on stroke prevalence (Unal et al, 2013), previous studies and meta-analyses reported that higher Lp(a) concentrations were related to the presence and severity of ischemic stroke (Smolders et al, 2007; Nave et al, 2015); these associations were greater in men compared with women (Li et al, 2014), more pronounced in blacks (Boden-Albala et al, 2010), and events tend to be more severe in younger patients (ie, $\leq$ 55 years) compared with older ones (Nave et al, 2015). Hyperliporoteinemia (a) has been also linked to ischemic strokes in children and adolescents (Sultan et al, 2014; Akshintala et al, 2015). Finally, Lp(a) has been implicated in the development and progression of carotid artery disease (Ronald et al, 2011; Gardener et al, 2009), with the prevalence and severity of peripheral artery disease, and with the prevalence and progression of abdominal aortic aneurysm (Schillinger et al, 2002; Takagi et al, 2009; Stather et al, 2014; Poller et al, 2015; Kotani et al, 2017).

Studies show that either statins (Tziomalos et al, 2009; Nordestgaard et al, 2010; Khera et al, 2014; Kei et al, 2013) or ezetimibe (Moutzouri et al, 2013) have little impact on plasma Lp(a). On the other hand, nicotinic acid (niacin), besides exerting positive effects on cholesterol and triglycerides reduces Lp(a), with high doses (2-4 g) reducing it significantly (Carlson et al, 1989; Goldberg et al, 2000). Whether this holds true for individuals with high levels of Lp(a) has not been shown as yet. A meta-analysis of the beneficial effects of nicotinic acid on cardiovascular events (Bruckert et al, 2010) did not discriminate whether lowering plasma Lp(a) might have contributed to the positive results or not. More recently, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have been able to demonstrate reductions greater than 25% in plasma Lp(a)

concomitant with intensive LDL-C reductions (Desai et al, 2013; Raal et al, 2014; Gaudet et al, 2017; Sabatine et al, 2015). Interestingly, in patients with LDL-receptor negative homozygous familial hypercholesterolemia, evolocumab was, as expected, ineffective in reducing LDL-C, but Lp(a) was lowered by 20% (Raal et al, 2015). While the role of the LDL receptor in Lp(a) clearance is unclear, the upregulation of other receptors potentially involved in Lp(a) clearance may explain these findings, eg, the VLDL-receptor that mediates the uptake of Lp(a) into macrophages, an increased catabolic fraction rate or, a reduced synthesis (Desai et al, 2013). Another therapeutic approach to patients with very high plasma Lp(a) levels has been lipoprotein apheresis. Apheresis has been in clinical use for decades (Abel et al, 1914; Vogt, 2017) and reduces apoB100 containing lipoproteins (namely LDL-C and Lp[a]). A single treatment reduces both by about 60–70%, followed by a rapid return to baseline, making weekly treatment sessions necessary (Thompson et al, 2010). Retrospective evaluations of clinical data and analyses of the German Lipoprotein Apheresis Registry (GLAR) show that cardiovascular events were reduced significantly after establishing a regular apheresis schedule (von Dryander et al, 2013; Rosada et al, 2014; Schettler et al, 2015). A non-randomised prospective observational multicenter study in high-risk patients, showed a reduction of major adverse cardiac events and of major adverse non-cardiac events after 2 (Leebmann et al, 2013) as well as after 5 years (Roesler et al, 2016) of lipid apheresis therapy.

Although significant advances have been made in the understanding of the molecular, metabolic, epidemiological, pathobiological, clinical and analytic aspects of Lp(a), there is no definitive evidence that reduction in Lp(a) will impact cardiovascular risk (Ellis et al, 2017). Intensive pharmacologic lowering of high Lp(a) concentrations via alternative approaches must be investigated in order to demonstrate protection against cardiovascular disease (Witztum and Ginsberg, 2016).

5.2 Amgen Investigational Product Background

Small interfering (also called short interfering) RNA (siRNA) molecules are synthetic RNA duplexes that disrupt the expression of specific genes with complementary nucleotide sequences by degrading messenger RNA (mRNA) after transcription, preventing translation (Agrawal et al, 2003).

Once inside a cell, the antisense (guiding) strand of the siRNA double strand is loaded into an RNA-induced silencing complex (RISC), while the other 1 is degraded. The loaded RISC is then directed to an mRNA which has a perfectly complementary

sequence of the guide strand. Argonaute proteins present in RISC cleave the target mRNA, which is then further degraded by exonucleases. Dissociation of the target mRNA strand from RISC after the cleavage allow more mRNA to be silenced, enabling continual degradation of target mRNA and leading to efficient and potent gene silencing (Agrawal et al, 2003).

AMG 890 is an siRNA designed to target the mRNA transcribed from the LPA gene, which encodes apo(a) protein in liver cells. Thus, AMG 890 is able to specifically knock down hepatic Lp(a) production.

The siRNA molecule is formed by the hybridization of 2 partially complementary single-strands of ribonucleic acid (RNA) with 21 consecutive complementary base pairs. Nucleotide and sugar-phosphate backbone chemical modifications, such as 2-Fluro bases or phosphorodiester linkages, reduce off-target effects, and enhance metabolic stability and potency for SC administration. The sense strand sequence contains a tri-N-acetylgalactosamine (NAG) moiety conjugated to its 5' end, which directs trafficking of AMG 890 to hepatocytes. The triantennary NAG binds the asialoglycoprotein receptor (ASGPR) with high affinity (Tanowitz et al, 2017). ASGPR is an endocytic scavenger receptor which clears asialoglycoproteins from the circulation and it is almost exclusively expressed on liver cells (Grewal, 2010).

Refer to the specific section of the AMG 890 Investigator Brochure (IB) for additional information related to the physical, chemical, and pharmaceutical properties and formulation(s).

5.2.1 Pharmacology

AMG 890 is a synthetic, siRNA NAG-conjugated, liver-targeted therapy that inhibits apo(a) translation and Lp(a) production.

Amgen's nonclinical program showed that AMG 890 can achieve a sustained $>$ 80% reduction in plasma Lp(a) and is suitable for monthly SC administration. The studies supporting this conclusion included efficacy data collected from transgenic mice and cynomolgus monkeys demonstrating that Lp(a) levels can be specifically targeted with AMG 890 to inhibit apo(a) translation.

A summary of the AMG 890 nonclinical pharmacology studies is as follows:

- In double transgenic mice expressing the human apo(a) transgene and human ApoB, AMG 890 reduced Lp(a) and apo(a) levels by $>$ 80% for 36 days following administration of a single subcutaneous dose of 1 mg/kg. Levels of Lp(a) remained below pre-dose values at day 36.

- In lean cynomolgus monkeys, a single 2 mg/kg dose of AMG 890 significantly reduced Lp(a) and apo(a) levels by > 80% for up to 6 weeks. A recovery was observed thereafter with serum Lp(a) levels starting to rise after day 60 but they remained lower than pre-dose values up until day 100 of the study.
- A dose ranging study in lean cynomolgus monkeys showed a dose-dependent reduction in serum Lp(a) levels after treatment with AMG 890 at 0.1, 1, 3 or 10 mg/kg for 80 days although serum Lp(a) did not significantly differ between the 3 mg/kg and 10 mg/kg dose groups. Plasma AMG 890 PK levels were rapidly cleared within a range of 2 to 29 days after dosing, while suppression of Lp(a) levels persisted for up to 80 to 140 days. The effect of AMG 890 on the reduction of serum Lp(a) levels after a second dose was also evaluated and indicated similar Lp(a) reductions as observed after the first dose.

5.2.2 Pharmacokinetics

AMG 890 was administered subcutaneously to non-human primates at a single dose of 0.1, 1, 3 and 10 mg/kg. AMG 890 pharmacokinetics was linear over the dose range of 0.1 to 10 mg/kg SC; the dose normalized AUC_{last} and C_{max} were within 3-fold. Mean terminal half-life ($t_{1/2}$) values after SC administration ranged from 3.13 to 5.09 hours.

5.2.3 Toxicology

The Sprague-Dawley rat and cynomolgus monkey were selected as the toxicology species for AMG 890. The subcutaneous (SC) route of administration was chosen based on the intended clinical route of administration. The monkey is a pharmacologic relevant animal model, but the rat does not make apo(a) so is not.

In in vitro secondary pharmacodynamic studies, AMG 890 did not cause complement activation in human serum or cytokine stimulation or platelet activation in human whole blood.

In monkey safety pharmacology assessments, there were no AMG 890-related qualitative or quantitative electrocardiographic (ECG) changes or changes in blood pressure, heart rate, body temperature, respiratory rate or neurological function at up to 150 mg/kg, the highest dose level tested.

AMG 890 was well tolerated in the rat and monkey toxicology studies. All dose levels in the monkey toxicology studies reduced serum Lp(a) by ≥ 90%. In the GLP rat and monkey 57-day toxicology studies, AMG 890 was administered at 10, 30 and 150 mg/kg every 4 weeks on days 1, 29 and 57 (necropsy on day 58). At 10 mg/kg, there were no AMG 890-related changes in the rat. In the monkey at 10 mg/kg, the only AMG 890-related changes were vacuolation of Kupffer cells of the liver and vacuolation of macrophages in the subcutis at the injection site and in the lymph nodes; these

phagocytic cells contained basophilic material consistent with test article uptake (Frazier, 2014; Henry et al, 2008). 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, minimal increases in serum alanine aminotransferase (ALT), and minimal to mild increases in serum alkaline phosphatase (ALP) and bilirubin. Additional AMG 890-related changes occurring at doses greater than 10 mg/kg or with increased frequency of dosing, included the presence of basophilic granules in the proximal tubular cells of the kidney, and liver changes consisting of hepatocellular vacuolation, increased single cell necrosis and increased mitoses of hepatocytes in the rat and hepatocellular hypertrophy with cytoplasmic rarefaction in the monkey. The only AMG 890-related finding considered secondary to silencing of LPA gene expression was reduction in serum Lp(a) in monkeys. None of the AMG 890-related changes were considered adverse due to their low severity and absence of light microscopic evidence of tissue injury. All the AMG 890-related changes are anticipated to be reversible (recovery phases of the GLP rat and monkey studies were ongoing at the time of IND/CTA filing). In both the rat and monkey, the no adverse effect level (NOAEL) for the GLP toxicology studies was determined to be 150 mg/kg, the highest dose evaluated.

5.3 Risk Assessment

This is the first study in human subjects with AMG 890. The assessment of potential side effects is based on the pre-clinical studies conducted to date (Section 5.2.3) and the literature. Overall, safety data from the nonclinical studies support the proposed doses and dosing schedule in this FIH study.

Earlier therapeutic antisense oligonucleotide molecules relied on numerous phosphorothioate backbone modifications to increase metabolic stability and increase gene silencing effectiveness (Chi et al, 2017). However, such modifications have also been shown to elicit strong platelet activation, aggregation and thrombus formation (Flieri, 2015). The affinity of the phosphorothioate backbone for various cellular proteins also affects certain pathways, such as inhibition of the intrinsic coagulation pathway and activation of the alternative pathway of complement (Farman and Kornbrust, 2003; Henry et al, 2002). The most concerning proinflammatory changes seen in animal models include glomerulonephritis and vasculitis. These effects seem to relate to high doses and plasma exposures (Engelhardt et al, 2015). AMG 890 is a double strand siRNA of a novel generation, which contains a majority of phosphodiester backbone linkages and 2'-fluoro and 2'-metoxy nucleotide chemical modifications. In general,

these modifications provide enhanced resistance to degradation, lower toxicity and increased hybridization affinity (Judge et al, 2006; Wu et al, 2014; Crooke et al, 2016). Furthermore, the tri-N-acetylgalactosamine (NAG) moiety conjugated to 1 of the siRNA strands directs trafficking of AMG 890 to hepatocytes and mediates its internalization via the high affinity ASGPR, which may allow the use of lower effective doses and lower exposures (Chen et al, 2018). Therefore, the risks associated with earlier antisense oligonucleotides such as platelet and complement activation, and proinflammatory changes are considered low for AMG 890. In addition, organ toxicity related to intracellular accumulation and off-target effects of the siRNA are not expected at the doses administered. (Chi et al, 2017; Janas et al, 2018). Injection site reactions, hypersensitivity reactions, including anaphylaxis, and development of anti-drug antibodies (ADAs) are considered potential risks.

To minimize risk, a sentinel dosing strategy will be adopted for cohorts 1 to 5, and safety data will be reviewed in an accumulative manner during dose level review meetings (DLRM) prior to progressing to the next dose level in the study. Specific cohort dose stopping rules are specified in this protocol (Section 9.2.4). All study subjects will be closely monitored and frequently assessed for adverse events throughout the study. The laboratory safety monitoring includes evaluation of routine chemistry (including bicarbonate/CO_2 and liver function tests), hematology, and coagulation assessments. Lactate will be measured reflexively in the presence of an anion gap metabolic acidosis. Potential anaphylactic reactions will be assessed by Sampson criteria (Sampson et al, 2006). If Sampson criteria are positive, the potential anaphylactic reaction will be confirmed by measuring tryptase in blood plasma within 30 minutes of symptoms, if feasible. Bioanalytical testing for anti-AMG 890 antibodies will be conducted only if there are unexpected PD findings or a safety signal in this study or future studies that warrants further investigation. Additional blood samples may be obtained to rule out anti-AMG 890 antibodies during the study.

New onset or worsening neuropathy were reported during the clinical development program of an siRNA for the treatment of hereditary transthyretin amyloidosis. Neuropathy events have not been described in other recent human studies of antisense-based therapies (Chi et al, 2017), and safety pharmacology non-human primate studies did not disclose any evidence of neurologic effect of AMG 890 at all tested doses up to 150 mg/kg, the highest tested dose. However, clinical neurologic assessments are part of the safety evaluations throughout this study. If treatment

emergent neuropathy is suspected, dosing will be suspended and subjects will be directed to a specialist for further evaluation.

Low levels of Lp(a) have been associated with increased prevalence of type 2 diabetes mellitus (reviewed in Paige et al, 2017). There is uncertainty about the strength of this association, and available evidence does not suggest a causal link (Ye et al, 2014). Some evidence suggests that the hyperinsulinemia present in type 2 diabetes may lead to lower Lp(a) levels (Purnell et al, 1995; Neele et al, 1999). Fasting blood glucose will be monitored throughout the study.

The proposed risk assessment for the study is in accordance with the requirements of regulatory guidelines and strategies to identify and mitigate risks for FIH clinical trials with investigational medicinal products.

Refer to the AMG 890 IB, Section 10, for additional information.

5.4 Non-Amgen Non-investigational Medicinal Product

For cohorts 6 to 9, at least 6 subjects in each cohort are required to be on a stable dose of statin for at least 6 weeks prior to enrollment as defined in subject eligibility (Section 7.1). Specific product, dose and dosage schema should be defined by the subject's medical background and follow subject's health care provider instructions.

For additional information, refer to the manufacturer package insert.

Statins are not provided or reimbursed by Amgen (except if required by local regulation).

5.5 Rationale

A substantial body of evidence demonstrates the clear association between higher plasma Lp(a) levels and increased risk for cardiovascular atherosclerotic disease development. Furthermore, Mendelian randomization studies, experimental data and results from apheresis cohorts suggest a causal role for Lp(a) and vascular disease.

Nevertheless, there is yet a lack of evidence demonstrating that reduction in plasma Lp(a) is able to cause a significant reduction in cardiovascular risk. Currently available lipid-reducing medications, such as statins or PCSK9 inhibitors, are able to promote limited lowering of Lp(a). Therefore, the demonstration of effective and safe lowering of high Lp(a) concentrations by the inhibition of apo(a) translation through siRNA technology may provide a novel tool serving patients against cardiovascular atherosclerotic disease.

5.5.1 Dose Rationale

The starting dose and safety margins for this study were calculated based on the no observed adverse effect levels (NOAELs) determined in the 57-day GLP repeat-dose rat and cynomolgus monkey (NHP) toxicology studies [Q4W(x3) dosing, Section 5.2.3] and the predicted Lp(a) changes in humans, based on K-PD modeling analysis using single and multiple-dose PK and Lp(a) data in cynomolgus monkeys administered AMG 890 SC (Section 5.2.2). The NOAEL in the repeat-dose rat and NHP studies were both 150 mg/kg. The maximum recommended starting dose (MRSD), using the methodology described by the Food and Drug Administration Guidance for Starting Dose Estimation, "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" (US FDA, 2005) for calculating the human equivalent dose on a body surface area basis, was calculated to be 145 mg using a default safety factor of 10 and the rat NOAEL, as this was the lower value between the 2 species (290 mg based on cynomolgus NOAEL). Therefore, the proposed starting dose of 3 mg is 486-fold lower than the MRSD based on scaling using body surface area and assuming a human body weight of 60 kg.

Similarly, based on the rat and cynomolgus NOAEL of 150 mg/kg, the proposed starting dose of 3 mg is 3000-fold lower than the MRSD on a dose (mg/kg)-basis, assuming a human body weight of 60 kg. These calculated margins are conservative as only a single starting dose will be given, and the NOAEL was determined from Q4W (x3) repeat-dose studies over a 57-day period.

The selection of the doses being evaluated in this study are also supported by the calculated exposure safety margins derived from the 57-day GLP rat and monkey toxicology studies and the model-predicted human AMG 890 PK and Lp(a) profiles. Results from the population PK model indicate that the predicted mean human PK C_{max} and AUC values in the highest dose cohort (675 mg) are 2260 ng/mL and 43800 hr*ng/mL, respectively. These predicted human exposures are at least 11-fold and 21-fold lower than those observed at the NOAEL in the 57-day GLP rat and NHP toxicology studies, respectively (Table 2). In addition, the predicted human exposures at the proposed starting dose of 3 mg in humans are anticipated to be at least 2850-fold and 4660-fold lower than the NOAEL exposures in rat and NHPs, respectively. Therefore, the 3 mg starting dose was selected based on the conservative safety margins, as well as the low anticipated biological effect on Lp(a) suppression to support

evaluation of the AMG 890 dose-response relationship in subjects with elevated Lp(a) levels.

Table 2. Predicted AMG 890 Human Exposures After Single Dose Administration at the Proposed Clinical Doses and Margins Relative to Repeat-Dose Cynomolgus Monkey Exposures at the NOAEL

Dose (mg)	Predicted Exposure		Exposure Margins			
			C_{max}[a]		AUC_{last}[a]	
	C_{max} (ng/mL)	AUC_{last} (ng*hr/mL)	Rat	Cyno Monkey	Rat	Cyno Monkey
3	10.0	163	4420	4660	2850	5620
9	30.1	527	1470	1550	880	1730
30	100	1890	442	466	245	483
75	251	4820	176	186	96.3	190
225	753	14600	58.7	62.0	31.8	62.5
675	2260	43800	19.6	21.0	10.6	20.8

AUC_{last} – area under the concentration-time curve from time zero to the last quantifiable concentration;
C_{max} – maximum observed concentration
[a] Rat day 29 exposure at 150 mg/kg: C_{max} = 44200 ng/mL, AUC = 464000 ng*hr/mL;
Monkey day 29 exposure at 150 mg/kg: C_{max} = 46600 ng/mL, AUC = 913000 ng*hr/mL

Given the hepatic site target and rapid elimination of AMG 890 from systemic circulation, there is limited clinical relevance in correlating transient AMG 890 levels with the long-acting effects of Lp(a) reduction. Therefore, a K-PD model was also developed to predict Lp(a) levels in humans based on NHP efficacy data, and were simulated at the proposed clinical doses. Assuming similar potency in Lp(a) lowering effect between NHP and humans, the results from the K-PD model analysis indicate that for the proposed single starting dose of 3 mg, the maximum Lp(a) reduction from baseline is predicted to be 39%. In addition, a single dose of 75 mg is predicted to achieve Lp(a) reduction levels > 80% from baseline. These simulation results support the dose range to be evaluated in this study.

Subjects will be assessed across the proposed range of dose levels to evaluate the magnitude and durability of Lp(a) reduction, to determine if AMG 890 PK and PD translates from animal to humans, and to assess the safety and tolerability of the drug.

The proposed dose range for cohorts 1 to 9 (3, 9, 30, 75, 225, and 675 mg) allows for reasonable step increases in the dose escalation between the proposed starting dose and the highest dose. The doses were selected to allow for round mL injection volumes to circumvent any potential dosing errors due to extra dilution steps, as well as to evaluate specific dose levels (eg, 30 mg, 75 mg) that are anticipated to approach or achieve target Lp(a) reduction levels (≥ 80% decrease from baseline) in the majority of subjects based on the K-PD Lp(a) simulation results.

In cohorts 1 to 7 of this study, considerable variability has been observed in PK and Lp(a) response between low and high baseline Lp(a) subjects. Given this variability, the 225 mg and 675 mg cohorts in high baseline Lp(a) subjects (cohorts 8 and 9) will allow for more intensive and robust PK and Lp(a) data evaluation to support broader options for AMG 890 Ph 3 dose and regimen selection. The 675 mg dose (cohort 9) is also anticipated to provide a wide range of exposures with minimal overlap in exposure distributions across subjects with high baseline Lp(a) (~9 fold increase from 9 mg in cohort 6 to 675 mg in cohort 9), and to provide additional safety information at a higher dose and with longer durations of Lp(a) suppression.

Finally, for cohorts 1 to 5 and cohort 9, a sentinel dosing strategy ensures that only 1 subject will receive active drug at the start of each dose level and after being deemed safe by the investigator, the same dose will be administered to the remaining cohort subjects.

5.6 Clinical Hypotheses

AMG 890 will be safe and well tolerated when administered subcutaneously as a single dose to subjects with elevated plasma Lp(a).

The PK and/or PD data from this study will support the selection of dose and frequency of AMG 890 administration for future multi-dose trials.

6. EXPERIMENTAL PLAN

6.1 Study Design

This is a FIH randomized, double-blind, placebo-controlled, single ascending dose (SAD) study in subjects with elevated plasma Lp(a). AMG 890 will be evaluated as SC injections in adult subjects. Approximately [redacted] subjects will enroll in 9 SAD cohorts. As described in Table 1, for each cohort, subjects will be randomized to receive AMG 890 or placebo SC in a 3:1 ratio. As of Amendment 6, enrollment in cohorts 1 to 8

is closed. There were no safety concerns noted that would preclude enrollment into the higher dose cohorts, 8 and 9.

As described in the Eligibility Criteria (Section 7), cohorts 1 to 5 will enroll subjects with plasma Lp(a) between 70 nmol/L and 199 nmol/L, inclusive. Cohorts 6 to 9 will enroll subjects with plasma Lp(a) equal to or greater than 200 nmol/L. In cohorts 6 to 9, at least 6 subjects in each cohort will be on a stable dose of statin.

For cohorts 1 to 5, and cohort 9, the first 2 enrolled subjects will be randomized in a 1:1 ratio (sentinel pair) and will be dosed on the same day at the same study site. Within the pair and while maintaining treatment blind, 1 subject will receive AMG 890 and the other subject will receive placebo. If deemed safe by the investigator after review of available safety data at least 24 hours after the sentinel pair is dosed, the same dose will be administered to the remaining subjects of the cohort.

Enrollment into cohorts 1 to 5 will be staggered. Escalation to the next cohort will occur after the assessment of the safety and tolerability of each dose level. The recommendation to dose escalate will be based on the blinded review of safety data (including but not limited to vital signs, ECGs, treatment emergent adverse events, and clinical laboratory results) during the DLRM. Within each cohort, the safety data will be assessed after all 8 subjects have been enrolled and have been followed for 15 days. Emerging PD data may be reviewed in a blinded fashion at the DLRM as the data become available. The Dose Level Review Team (DLRT) will be responsible for dosing recommendations, which may include escalation to the next planned dose, adding additional cohorts, escalation to an intermediate dose (a dose lower than the next planned dose), de-escalation to a lower dose; continuation, delay, or termination of dosing; or repetition or expansion of a cohort.

Enrollment into cohorts 5 to 7 can be initiated after the dose regimen in cohorts 1 to 4 has been found by the DLRT to be safe and reasonably tolerated based on available safety data through study day 15 of cohort 4. Enrollment in cohort 8 is closed.

As of Amendment 6, enrollment in Cohorts 1 to 8 is closed. There were no safety concerns noted that would preclude enrollment into the higher dose cohorts, 8 and 9. **For cohort 9, t**he same randomization ratio (3:1) of AMG 890 to placebo will apply.

In consideration of the DLRT recommendations and review of emerging safety and/or PD data, dose adjustments (if any) will be made by Amgen on a treatment cohort basis and not on an individual basis.

The study endpoints are defined in Section 13.1

6.2 Number of Sites

This study will be conducted at 3 to 10 sites in the US and Australia. Additional sites in the same or in other countries may be added as necessary to complete enrollment.

Sites that do not enroll subjects within 1 month of site activation for enrollment may be closed.

6.3 Number of Subjects

Participants in this clinical investigation are referred to as "subjects."

The sample size is based on practical considerations. Sample size is discussed in Section 13.2. It is anticipated that an approximate total of [redacted] subjects in a total of 9 cohorts will be enrolled in this study.

6.4 Replacement of Subjects

In the event subjects are enrolled, but are withdrawn prior to IP administration, a replacement subject may be enrolled in the subject's place.

Additionally, subjects who are withdrawn from the study (Section 11) may be replaced at the discretion of the Amgen Medical Monitor in consultation with the investigator or designee. The replacement subject will be assigned to receive the identical treatment as the replaced subject, but will be assigned a replacement number associated with this new record. All data from the replaced subjects will be captured, identified, and kept in the clinical trial database.

6.5 Estimated Study Duration

6.5.1 Study Duration for Subjects

Subject participation will vary according to enrollment scheme. The duration of the follow-up period for each cohort was defined based on the simulation results from the population K-PD model describing the Lp(a) response to AMG 890 administration developed based on 57-day GLP repeat-dose cynomolgus monkey toxicology and PK/PD studies (Section 5.2.1). Data suggest that the lengths of study participation proposed will allow plasma Lp(a) levels to return at least to 80% of the baseline levels for each subject after administration across the proposed AMG 890 clinical doses.

For cohorts 1 and 2, planned subject participation will last up to 141 days, including a 28-day screening period prior to investigational product (IP) administration and on-study period (through the end of treatment visit) lasting 113 days.

For cohorts 3 to 7, planned subject participation will last up to 253 days, including a 28-day screening period prior to IP administration and on-study period (through the end of treatment visit) lasting 225 days.

For cohorts 8 and 9, planned subject participation will last up to 393 days, including a 28-day screening period prior to IP administration and on-study period (through the end of study visit) lasting 365 days.

For cohorts 1 to 7, the end of treatment visit will complete the subject's participation in this study unless a follow-up period is required. If there is a clinically significant clinical or laboratory abnormality that requires monitoring, subjects will be followed until resolution of the abnormality or until it is considered stable.

For cohorts 1 to 9, if at the end of treatment visit, the plasma Lp(a) level has not returned to ≥ 80% of baseline (mean of screening and day 1 predose), the follow-up period will be required.

The end of treatment visit for cohorts 8 and 9 will be the same as the end of study visit (day 365).

Subjects in cohorts 1 and 2 will return to the clinical study site approximately every 2 weeks until the Lp(a) level returns to ≥ 80% of baseline. Assessments during the follow-up period will include physical examination; vital signs; and collection of blood samples for chemistry, hematology, lipid, Lp(a), and biomarker development. When the protocol amendment 2 is implemented, the follow-up visits will continue approximately monthly, as needed, and will include only Lp(a) monitoring as described below for cohorts 3 to 7.

Subjects in cohorts 3 to 7 will return to the clinical study site for Lp(a) monitoring approximately monthly starting from when the site has been notified of the Lp(a) follow-up requirement until the Lp(a) level returns to ≥ 80% of baseline.

Lp(a) assessments in the follow-up period will be performed by Medpace.

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, 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 for day 365 of cohort 9.

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

End of Study: The end of study date is defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, follow-up period; long-term follow-up), as applicable.

7. SUBJECT ELIGIBILITY

Investigators are expected to maintain a screening log of all potential study candidates. Before any study-specific activities/procedure, the appropriate written informed consent must be obtained (see Section 14.1).

7.1 Inclusion Criteria

A subject that has provided written informed consent may be eligible for inclusion in this study only if the following criteria are met:

101 Men and women with ages between 18 and 60 years old, inclusive, for cohorts 1 to 5; and with ages between 18 and 65 years old, inclusive, for cohorts 6 to **8; and with ages 18 and 70 years old, inclusive, for cohort** 9.

102 Plasma Lp(a):

- ≥ 70 nmol/L and ≤ 199 nmol/L for cohorts 1 to 5
- ≥ 200 nmol/L for cohorts 6 to 9

103 For cohorts 6 to 9, 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 (ie, no change in medication or dosage) for the duration of the study

104 Body mass index (BMI) ≥ 18 and ≤ 32 kg/m^2, at screening**, for cohorts 1 to 8; BMI ≥ 18 and ≤ 40 kg/m^2, at screening, for cohort 9.**

105 Women must be of non-reproductive potential:

- Postmenopausal defined as:
  - Age ≥ 55 years with cessation of menses for 12 months or more, OR
  - Age < 55 years and no spontaneous menses for at least 12 months, AND with a follicle-stimulating hormone level > 40 IU/L or according to the definition of "postmenopausal range" for the laboratory involved, OR
- History of hysterectomy, OR
- History of bilateral oophorectomy

106 Men must agree to practice an acceptable method of effective birth control while on study or for 90 days after receiving investigational product (for subjects who withdraw prior to end of study). Acceptable methods of effective birth control include sexual abstinence; vasectomy; or a condom with spermicide (men) in combination with barrier methods (diaphragm, cervical cap or cervical sponge), hormonal birth control or IUD (female partner of male participant)

107 Men must be willing to abstain from sperm donation while on study or for 90 days after receiving investigational product (for subjects who withdraw prior to end of study)

7.2 Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

201 Currently receiving treatment in another investigational device or drug study, or less than 30 days or 5 half-lives (whichever is longer), since ending treatment on another investigational device or drug study(s) prior to receiving the first dose of investigational product

202 Women who are lactating/breastfeeding or who plan to breastfeed while on study or through 90 days after receiving investigational product (for subjects who withdraw prior to end of study)

203 Men with partners who are pregnant or planning to become pregnant while the subject is on study or through 90 days after receiving investigational product.

204 Positive pregnancy test at screening or at any pre-dose time point.

205 History or evidence of a clinically significant disorder, condition or disease (eg, symptomatic heart failure, documented previous myocardial infarction in the previous 12 months, active infection requiring antimicrobial therapy that will not be completed prior to randomization, or major surgery in the previous 3 months of screening) that, in the opinion of the investigator or Amgen Medical Monitor, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion. Exceptions include:

- Subjects with controlled and stable arterial hypertension, with a systolic blood pressure [SBP] < 150 mmHg or diastolic blood pressure [DBP] < 90 mmHg at screening and day -1 for cohorts 1 to 5 or day -3 to -1 for cohorts 6 to 9, with no change in medication and dosage for at least 6 weeks prior to enrollment, and expected to remain on this dose and medication for the entire duration of the study. Subjects not on medication are excluded from the study if systolic blood pressure [SBP] > 150 mmHg or diastolic blood pressure [DBP] > 90 mmHg at screening or day -1 for cohorts 1 to 5 or day -3 to -1 for cohorts 6 to 9. 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.
- For cohorts 6 to 9, at least 6 subjects in each cohort 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
- **For cohort 9, diagnosis of diabetes is not excluded provided diabetes is well-controlled according to treating physician's assessment and discretion, and the subject is on stable doses of diabetes medications for at least 6 weeks prior to enrollment**

206 Planned elective surgery to occur at any time from screening visit through the end of treatment visit for cohorts 1 to 7, and through the end of study visit for cohorts 8 and 9

207 Estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73 m^2, as defined by the local laboratory, at screening

208 Triglycerides ≥ 5.65 mmol/L (ie, 500 mg/dL) at screening

209 History or clinical evidence of liver disfunction, including total bilirubin > upper limit of normal (ULN) or ALT or AST > 1.1 ULN of the laboratory's reference at screening or at day -1 for cohorts 1 to 5, or day -3 to -1 for subjects not on statin in cohorts 6 to 9. For subjects on stable dose of statin in cohorts 6 to 9, ALT or AST > 1.5 ULN of the laboratory's reference at screening or at day -3 to -1.

210 History or clinical evidence of bleeding diathesis or any coagulation disorder, including prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT), or platelet count outside of the laboratory's normal reference range at screening

211 **For cohorts 1 to 8, h**istory or clinical evidence of diabetes mellitus, including a fasting glucose ≥ 125 mg/d**L** (6.9 mmol/L) at screening

212 History or clinical evidence of peripheral neuropathy

213 History of malignancy of any type, other than in situ cervical cancer or surgically excised non-melanomatous skin cancers occurring more than 5 years prior to randomization

214 Positive results for human immunodeficiency virus (HIV) antibodies, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C virus

ribonucleic acid (RNA). For hepatitis C, hepatitis C antibody (HepCAb) testing is done at screening, followed by hepatitis C virus RNA by polymerase chain reaction (PCR) if hepatitis C antibody is positive.

215 Subject was previously enrolled in this study or has been previously exposed to AMG 890

216 Use of any herbal medicines, vitamins or supplements known to affect lipid metabolism (eg, fish oils > **4**000 mg/day, red yeast rice extract), within 30 days prior to dosing on day 1

217 All herbal supplements and nutritional supplements (with the exception of those known to affect lipid metabolism, which are excluded as above) taken within 30 days prior to dosing on day 1 and continued use, if appropriate, must be reviewed and approved by the investigator and Amgen Medical Monitor. Written documentation of this review and Amgen acknowledgement is required for subject participation.

218 Use of any over-the-counter medications within 14 days or prior to dosing on day 1. Exceptions are listed below:

- Acetaminophen (paracetamol), up to 2 grams per day for analgesia
- For cohorts 6 to 9, use of low-dose acetylsalycilic acid (up to 162.5 mg daily) is allowed, provided it is stable for at least 6 weeks prior to enrollment and is planned to be the same dose for the duration of the study

219 Use of any prescription medications within 14 days or 5 half-lives (whichever is longer), prior to dosing on day 1. Exceptions are listed below:

- Hormone replacement therapy (eg, estrogen, thyroid) provided 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, calcium channel blockers, beta blockers, or low-dose thiazides, provided it is stable (ie, no change in drug or dose) for at least 6 weeks prior to enrollment
- For cohorts 6 to 9, use of antiplatelet therapy (low-dose acetylsalicylic acid, 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
- For cohorts 6 to 9, at least 6 subjects in each cohort must be on a stable dose of statin (ie, no change in drug or dose) for at least 6 weeks prior to enrollment and plan to be on the same dose for the duration of the study
- For cohorts 6 to 9, 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
- For cohorts 6 to 9, 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, and acknowledged by the Amgen Medical Monitor. Written documentation of this review and Amgen acknowledgement is required for subject participation.

- **For cohort 9, medication used to manage diabetes 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, and acknowledged by the Amgen Medical Monitor. Written documentation of this review and Amgen acknowledgement is required for subject participation.**

220 Currently receiving apheresis as lipid reducing therapy

221 Subject has known sensitivity to any of the products or components to be administered during dosing

222 Has donated or lost $\geq$ 500 mL of blood or plasma within 60 days of day 1

223 A corrected QT interval (QTc) at screening of $>$ 450 msec in men or $>$ 470 msec in women or history of long QT syndrome

224 History of substance abuse within 12 months before screening

225 Positive test for drugs of abuse at screening or on day -1 for cohorts 1 to 5 or day -3 to -1 for cohorts 6 to 9

226 Use of nicotine or tobacco containing products (including but not limited to: snuff, chewing tobacco, cigars, cigarettes, electronic cigarettes, pipes, or nicotine patches) during the 6 months before screening

227 Unwilling or unable to abstain from nicotine or tobacco containing products (including but not limited to: snuff, chewing tobacco, cigars, cigarettes, electronic cigarettes, pipes, or nicotine patches) throughout the course of the study

228 Subject is unwilling or unable to limit alcohol consumption throughout the course of the study:

- Alcohol is prohibited 48 hours prior to admission to the research facility (day -1 for cohorts 1 to 5 and the sentinel pair of cohort 9; day 1 for cohorts 6 to 9 (other than the sentinel pair) and during the residency periods, and
- Alcohol consumption is limited to no more than 1 drink per day for females and 2 drinks per day for males for the duration of the study (1 drink is equivalent to 12 ounces of regular beer, 8 to 9 ounces of malt liquor, 5 ounces of wine or 1.5 ounces of 80 proof distilled spirits)

229 Subject will not be available for protocol-required study visits or procedures (including the research facility residency period), to the best of the subject's and investigator's knowledge

230 Any other condition that might reduce the chance of obtaining data required by the protocol (eg, known poor compliance) or that might compromise the ability to give informed consent

8. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities and procedures, Amgen requires a copy of the site's written institutional review board or independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 14.2). All subjects and/or legally acceptable representatives must personally sign and date the informed consent form before commencement of study-specific activities/procedures. A subject is considered enrolled when study entry criteria are met. The investigator (or designee) will document the enrollment decision and date in the screening log, subject's medical record and in the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (defined as the time at which the subject signs the informed consent) receives a unique subject identification number before any study procedures are performed. The subject identification number will be assigned manually. The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment.

The unique subject identification number will consist of 11 digits. The first 3 digits will represent the last 3 digits of the protocol number (ie, 544). The next 5 digits will represent the country code and site number (eg, 66001) and will be identical for all subjects at the site. The next 3 digits will be assigned in sequential order as subjects are screened (eg, 001, 002, 003). To illustrate, the first subject to enter screening at site 66001 will receive the number 54466001001. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

Subjects who do not meet the eligibility criteria within the 28-day screening period will not be eligible for enrollment. Subjects may be re-screened up to 3 times upon discussion with and approval by the Amgen Medical Monitor. The subject must be re-consented if a re-screen occurs outside the 28-day screening period. Re-screen subjects will repeat all screening procedures.

Subjects not meeting study entry criteria will be documented as screen failures.

Subjects may be eligible to begin treatment once all screening tests and procedures are completed and results indicate that all eligibility criteria are met. A site representative will complete and send the enrollment eligibility worksheet to the sponsor or designee.

The Amgen representative will acknowledge receipt and send confirmation of cohort, dose level assignment, and randomization number.

8.1 Randomization/Treatment Assignment

An Amgen representative will notify the site(s) in writing when a cohort is open to screen new subjects. As of Amendment 6, enrollment in Cohorts 1 to 8 is closed. There were no safety concerns noted that would preclude enrollment into the higher dose cohorts, 8 and 9.

On day -1 for cohorts 1 to 5 or day -3 to -1 for cohorts 6 to 9 (or up to day 1), eligible and enrolled subjects will be randomized to a treatment assignment in a double-blind fashion. Within each cohort, subjects will be randomly assigned in a 3:1 ratio to receive either AMG 890 or placebo. They will be assigned a randomization number based in sequential order in which they qualified to be randomized. Subjects will be considered randomized once a unique subject randomization number has been assigned. For cohorts 1 to 5, dosing should occur within 24 hours of randomization; for cohorts 6 to 9, dosing should occur within 3 days (≤ 72 hrs) of randomization. If dosing cannot occur within the window for randomization, the Medical Monitor may be contacted to approve dosing outside the window (up to an additional 24 hours after randomization). The randomization date is to be documented in the subject's medical record and enrollment eCRF.

For cohorts 1 to 5, and cohort 9, the first 2 subjects (sentinel pair) will be randomized. One subject will receive AMG 890 and 1 subject will receive placebo. Subjects will be monitored for at least 24 hours before the remaining subjects in the cohort are dosed. Remaining subjects may be subsequently dosed provided there are no safety or tolerability concerns as assessed by the Principal Investigator.

For cohorts 6 to 9, at least 6 subjects in each cohort will be on a stable statin for 6 weeks prior to enrollment. Randomization in cohorts 6 to 8 will not use a sentinel dosing strategy. For cohorts 6 and 7, once 6 subjects not on a stable dose of statin are enrolled into cohort 6, then 6 subjects not on a stable dose of statin may be enrolled into cohort 7. Similarly, once 6 subjects on a stable dose of a statin are enrolled into cohort 6, then 6 subjects on a stable dose of a statin may be enrolled into cohort 7.

Enrollment in cohort 8 is closed, supported by the approval to dose escalate to the 225 mg dose of cohort 5 after the DLRT found that the previous dose regimen in cohorts

1 to 4 was safe and reasonably tolerated. In addition, the dose in cohort 5 was well tolerated with no safety signals observed in low Lp(a) level subjects.

Cohort 9 may be enrolled concurrently with cohort 8 or after cohort 8 has completed enrollment. If cohort 9 and cohort 8 are fully enrolled and there are additional subjects who have passed screening visit procedures, these subjects may be allowed to be enrolled and randomized in cohort 9 with approval of Amgen.

Amgen will provide a randomization schedule to the unblinded pharmacist at the site. The unblinded pharmacist will prepare all treatments accordingly. Subjects randomization will occur in accordance with the randomization schedule.

8.2 Site Personnel Access to Individual Treatment Assignments

The subjects and the investigative site staff, except for the unblinded pharmacist, will be blinded to treatment assignment.

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject which may potentially impact the safety of subjects currently enrolled or subjects in subsequent cohorts. Unblinding at the study site for any other reason will be considered a protocol deviation. The investigator is strongly encouraged to contact the Amgen Study Manager before unblinding any subject's treatment assignment, but must do so, in writing, within 1 working day after the event.

Treatment assignments will be unblinded after final database lock. After final database lock and receipt of written authorization from Amgen to unblind, the unblinded pharmacist will release the specified unblinded pharmacy records to site staff designated to enter the subject treatment into each subject's Unblinded Investigational Product Administration CRF.

9. TREATMENT PROCEDURES

9.1 Classification of Product(s), Medical Device(s), and/or Combination Product(s)

The Amgen Investigational Product(s) used in this study include: AMG 890 and placebo.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of AMG 890 and placebo.

9.2 Investigational Product

All investigational product(s) will be administered at the research facility by the investigator or designate.

A physician must be immediately available at the time of administration of Investigational Product in case of complication(s).

9.2.1 Amgen Investigational Product

AMG 890 will be distributed using Amgen clinical study drug distribution procedures. For cohorts 1 to 7, AMG 890 will be provided in a 6 mL sterile vial filled with 1 mL deliverable volume of 150 mg/mL AMG 890. For cohorts 8 and 9, AMG 890 will be provided in a 2 mL sterile vial filled with 1 mL deliverable volume of 75 mg/mL AMG 890.

For cohorts 1 to 7, placebo will be presented in 5 mL sterile vials filled with 1 mL deliverable volume; for cohorts 8 and 9, placebo will be provided in 2 mL sterile vials filled with 1 mL deliverable volume. Placebo will be stored under the same conditions as AMG 890.

9.2.2 Dosage, Administration, and Schedule

Subjects will receive AMG 890 or volume-matched placebo, respectively, via blinded SC injection in the abdomen according to the Schedule of Assessments (SOA) (Table 4, Table 5, Table 6, Table 7, Table 8, and Table 9). AMG 890 administration time should be chosen carefully to avoid any interference or inconvenience with time point of safety assessments or PK/PD measurements.

For cohorts 1 to 5, and the sentinel pair of cohort 9, subjects will be admitted to the clinical site on day –1. Subject residency is approximately 5 days for cohorts 1 to 5, and is approximately 3 days for the sentinel pair of cohort 9. Cohorts 6 to 9 (other than the sentinel pair) will report to the clinical site on day 1 and will not have a required residency period. At the Investigator's discretion, subjects may stay at the clinic overnight from the check-in visit and/or day 1 for subject's convenience. Subjects will be randomized in a 3:1 ratio to receive AMG 890 or placebo, respectively, via SC injection, according to the Schedule of Assessments (Table 4 to Table 9).

A single dose will be administered on day 1 following all required pre-dose procedures and confirmation of enrollment eligibility. For cohorts 1 to 5, and cohort 9, subjects will be dosed in a staggered fashion where 2 subjects will be dosed initially (randomized to AMG 890 or placebo in a 1:1 ratio), followed by the remaining subjects after a minimum of 24 hours and provided there are no safety or tolerability concerns as assessed by the

principal investigator. For cohorts 6 to 8, subjects may be dosed concurrently (see Section 8.1 for details).

The planned dose levels are, in milligrams (mg): 3, 9, 30, 75, 225 and 675.

Across all cohorts, the date, time, package lot number, and quantity administered are to be recorded on the individual subject's Investigational Product Administration eCRF prior to database lock.

The Investigator or study physician must be available when the subject receives the initial dose of AMG 890 for immediate intervention in case of complication(s). The subject's residency may be extended at the discretion of the investigator. During the residency periods, an immediately accessible emergency room with resuscitation equipment must be available.

Prior to discharge, clinical assessments per SOA (Table 4 to Table 9) will be completed.

9.2.3 Dosing Error

The effects of overdose/underdose of this product are not known. In case of dosing error, consultation with the Amgen medical monitor as soon as possible is recommended to discuss subject management and prompt reporting of clinically apparent or laboratory adverse events possibly related to the dosing error. Subjects should be monitored closely until symptom resolution. Adverse events should be reported and documented according to instructions available in Section 12.

9.2.4 Dose-cohort Study Escalation and Stopping Rules

The planned doses of AMG 890 are shown in Table 1.

The dosing schedule is described by the Schema in the Protocol Synopsis.

9.2.4.1 Dose Level Review Meetings

Dose level review meetings will be held to review subject data and monitor safety before escalation to the next higher dose cohort. The DLRT members will be composed of the investigators actively enrolling subjects at the time of the meeting (ie, have subjects in screening or already enrolled), the unblinded Amgen Medical Monitor, Amgen Global Safety Officer (GSO) or designated safety scientist, Clinical Study Manager, and Biostatistics representative. Additional members may be added as needed (eg, clinical pharmacologist). The DLRT voting members will include the investigator(s), Amgen Medical Monitor and Amgen GSO or designees. The DLRT is responsible for dosing recommendations, which may include escalation to the next planned dose, escalation to

an intermediate dose (a dose lower than the next planned dose), de-escalation to a lower dose; continuation, delay, or termination of dosing; or repetition or expansion of a cohort. Clear stopping rules will be followed, and ad hoc DLRMs will be held if necessary. All available study data, including demographics, medical history, concomitant medications, adverse events, electrocardiograms (if applicable), vital signs, and clinical laboratory test results will be reviewed. If available, emerging PK and PD data may also be reviewed in a manner that does not unblind individual treatment assignments.

Except for the unblinded Amgen Medical Monitor who will review data on an ongoing basis throughout the duration of study in an unblinded manner, data will be reviewed blinded (ie, treatment assignment will not be revealed) unless unblinding is deemed necessary for the review team to make dosing decisions. If deemed necessary, unblinding will be performed to assist dose change recommendations.

Investigators who are not actively enrolling subjects at the time of the DLRM will not participate in the DLRM. They will be informed of the decisions of the DLRT.

For cohorts 1 to 5, and cohort 9, escalation to a higher dose cohort will only proceed when the previous dose regimen has been found to be safe and reasonably tolerated based on available safety data through study day 15 for all subjects and upon unanimous recommendation of the DLRT. Available data from previous cohorts will also be considered. The next cohort will be open for enrollment immediately following the DLRT recommendation and Amgen decision.

Enrollment into cohorts 6 to 8 will be initiated after cohort 4 dose level has been found by the DLRT to be safe and reasonably tolerated based on available safety data through study day 15. Cohorts 5, 6 and 7 may be enrolled in parallel. For cohorts 6 and 7, eligible subjects will be first enrolled into cohort 6 and then into cohort 7. Cohort 8 will be enrolled after implementation of this protocol amendment. Enrollment into cohort 9 can be initiated after the preceding dose regimen has been found by the DLRT to be safe and reasonably tolerated based on available safety data through at least study day 15 of cohort 5. See Section 8.1 for details.

The planned dose escalation schedule may be modified based on treatment-emergent data (safety and/or PD). Dose adjustments, if any, will be made by Amgen on a treatment cohort and not on an individual basis.

The review of available safety data and dosing change decisions will be documented in meeting minutes. Amgen will issue a written notification of a dose change decision to investigators.

9.2.4.2 Dose Stopping Rules

Determination of the severity of adverse events will be as follows: mild (aware of sign or symptom, but easily tolerated), moderate (discomfort enough to cause interference with usual activity), and severe (incapacitating with inability to work or do usual activity).

Recommendations will be made by the DLRT to stop or modify dosing if suspected adverse drug reactions and/or changes in safety data (including but not limited to vital signs, electrocardiogram (ECG), or clinical laboratory results) are observed and these changes pose a significant health risk. The unblinded Amgen Medical Monitor will review data in an unblinded manner on an ongoing basis, and may suspend dosing and convene a DLRM at any time based on emerging safety data. In addition, dose escalation will be stopped or modified as shown in Table 3.

Clinically or medically significant suspected adverse drug reactions, and serious adverse events considered to be related to study procedures will be followed until resolved or considered stable.

Administration of any drug by any route can cause anaphylaxis. Anaphylaxis is a life-threatening medical emergency in which prompt intervention is critical. Therefore, in the case of a suspected event, monitoring, preferably continuous hemodynamic monitoring, is essential. Monitoring should include blood pressure, continuous pulse rate, pulse oximetry, and electrocardiographic monitoring. Intravenous access should be obtained as soon as possible. These measures should be used to monitor response to therapy and direct subsequent interventions. The decision to initiate specific treatment for anaphylaxis, which may include the prompt administration of parenteral epinephrine, requires clinical judgment, should not be delayed by other procedures, and should follow the World Allergy Organization Anaphylaxis Guidelines (Ronna et al, 2014) or the local institutional practices.

Any subject with suspected anaphylactic reaction should be evaluated using the clinical criteria for diagnosis of anaphylaxis below (Sampson et al, 2006). If the criteria for anaphylaxis is met, a blood tryptase test must be collected as soon as the effective treatment has been rendered. Treatment administration for a suspected anaphylaxis event should not be delayed by any clinical or laboratory test collection. The event and

test results should be documented in the subject's medical record and reported as an adverse event as appropriate (Section 12).

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosa, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least 1 of the following

a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen (minutes to several hours):

c. Involvement of the skin or mucosa (eg, generalized hives, itch, swollen lips-tongue-uvula)
d. Respiratory compromise (eg, dyspnea, bronchospasm, stridor, reduced PEF, hypoxemia)
e. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
f. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP after exposure to an allergen (minutes to several hours):

g. Systolic BP < 90 mmHg or greater than 30% decrease from that person's baseline

Table 3. Cohort Dose Stopping Rules

Scenario	Action
Any occurrence of a suspected adverse drug reaction classified as moderate in 2 or more subjects in the same cohort	• Stop dosing additional subjects and convene DLRM (if event occurs outside of the regularly scheduled DLRM) • Review adverse event and all relevant safety data for evidence of relationship to treatment and clinical or medical significance • Consider unblinding as appropriate[1] • Upon unanimous decision by the DLRT members, 1 of the following recommendations may be made: o stop enrollment of the cohort (if applicable) o resume enrollment of the cohort as planned o resume enrollment of the cohort at a lower dose o expand the cohort at the same dose o add a lower dose cohort to the study o escalate to an intermediate dose (a dose lower than the next planned dose) o escalate to the next planned dose
Any occurrence of a suspected adverse drug reaction classified as severe	• Stop dosing additional subjects and convene DLRM (if event occurs outside of the regularly scheduled DLRM) • Review adverse event and all relevant safety data for evidence of relationship to treatment and clinical or medical significance • Consider unblinding as appropriate[1] • If the adverse event is determined by unanimous decision of the DLRT members to be related to study drug (after breaking of the study blind) and clinically or medically significant, no further doses should be administered at this dose and no dose escalation should proceed. Enrollment of the study may continue at a lower dose or a lower dose cohort may be added to the study. • Otherwise (ie, if considered not related to study drug or not clinically relevant), upon unanimous decision of the DLRT members, 1 of the following recommendations may be made: o resume enrollment of the cohort as planned o resume enrollment of the cohort at a lower dose o expand the cohort at the same dose o add a lower dose cohort to the study o escalate to an intermediate dose (a dose lower than the next planned dose) o escalate to the next planned dose

[1] A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject, or may impact the safety of subjects currently enrolled, or subjects in subsequent cohorts.
The Amgen Medical Monitor will be unblinded to treatment assignment throughout the duration of the study.

9.3 Other Protocol-required Therapies

For cohorts 6 to 9, at least 6 subjects in each cohort are required to be on a stable dose of the same statin through EOS as defined in subject eligibility (Section 7).

Specific product, dose and dosage regimen should be defined by subject's health care provider, based on the individual medical background. Subject must be on stable dose of the same drug for 6 weeks prior to enrollment.

For additional information, refer to the manufacturer package insert.

Information about therapy name, indication, dose, unit, frequency, route, start date, and stop date should be collected in the concomitant medication eCRF.

Protocol required therapies that are commercially available are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-required therapies.

9.4 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (ie, ALP, AST, ALT, TBIL) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen IP or other protocol-required therapies (as specified in the FDA Guidance for Industry Drug-induced Liver Injury: Premarketing Clinical Evaluation, July 2009).

9.4.1 Criteria for Permanent Withholding of Amgen Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity

Investigational product and other protocol-required therapies, as appropriate, should be discontinued permanently and the subject should be followed according to the recommendation in the Appendix A (Additional Safety Assessment Information) for possible drug-induced liver injury (DILI), if ALL the criteria below are met:

- TBIL > 2x upper limit of normal (ULN) or INR > 1.5
- AND increased AST or ALT from the relevant baseline value as specified below:

Baseline AST or ALT value	AST or ALT elevation
< ULN	> 3x ULN

- AND no other cause for the combination of the above laboratory abnormalities is immediately apparent; important alternative causes for elevated AST/ALT and/or TBIL values include, but are not limited to:
  - Hepatobiliary tract disease
  - Viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and Parvovirus)
  - Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia.
  - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
  - Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
  - Alpha-1 antitrypsin deficiency
  - Alcoholic hepatitis
  - Autoimmune hepatitis
  - Wilson's disease and hemochromatosis
  - Nonalcoholic Fatty Liver Disease including Steatohepatitis (NASH)
  - Non-hepatic causes (eg, rhabdomylosis, hemolysis)

9.5 Concomitant Therapy

Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 12.

Concomitant therapies are to be collected from informed consent through the end of treatment visit for cohorts 1 to 7, and through the EOS for cohorts 8 and 9. Collect therapy name, indication, dose, unit, frequency, route, start date, and stop date. Concomitant medications will not be collected after the end of treatment visit for any subjects with additional safety follow-up in cohorts 1 to 7.

9.6 Alcohol and Tobacco Restrictions

Subjects must limit alcohol consumption throughout the course of study participation (refer to Exclusion Criteria, Section 7.2). Alcohol is prohibited for approximately 48 hours prior to admission to the research facility (day -1 for cohorts 1 to 5 and the sentinel pair of cohort 9; day -3 to -1 for cohorts 6 to 9 [other than the sentinel pair]), and throughout the residency period. Alcohol consumption is limited to no more than 2 drinks per day for males and 1 drink per day for females for the duration of the study (1 drink is equivalent to 12 ounces of regular beer, 8 to 9 ounces of malt liquor, 5 ounces of wine or 1.5 ounces of 80 proof distilled spirits).

Only non-nicotine or non-tobacco using subjects should be enrolled. Subjects should not have used any nicotine or tobacco containing products within the last 6 months prior to screening. Subjects must abstain from nicotine or tobacco containing products (including but not limited to: snuff, chewing tobacco, cigars, cigarettes, electronic cigarettes, pipes, or nicotine gum or nicotine patches) throughout the screening period and for the duration of the study.

9.7 Exercise

Subjects should abstain from strenuous exercise for 72 hours before each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during study.

9.8 Product Complaints

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

This includes any drug(s), device(s), or combination product(s) provisioned and/or repackaged or modified by Amgen. Drug(s) or device(s) includes investigational product, AMG 890 or placebo.

Any product complaint(s) associated with the investigational product supplied by Amgen are to be reported according to the instructions provided in the IPIM.

9.9 Excluded Treatments, Medical Device Use, and/or Procedures During Study Period

Use of any over-the-counter or prescription medications within 14 days or 5 half-lives (whichever is longer), prior to dosing on day 1 and during the study is not permitted, unless to treat an adverse event. Additionally, use of any herbal medicines, vitamins or supplements known to affect lipid metabolism (eg, fish oils $>$ **4**000 mg/day, red yeast rice extract), within 30 days prior to dosing on day 1 and for the duration of the study is not permitted.

Accepted exceptions are:

- Acetaminophen (or paracetamol) up to 2 grams per day for analgesia
- Hormone replacement therapy (eg, estrogen, thyroid) provided 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, calcium channel blockers, beta blockers, or low-dose thiazides, provided it is stable (ie, no change in drug or dose) for at least 6 weeks prior to enrollment, as defined in Exclusion Criterion 219 (Section 7.2)
- For cohorts 6 to 9, at least 6 subjects in each cohort 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 (ie, no change in medication or dosage) for the duration of the study, as defined in Inclusion Criterion 103 (Section 7.1)
- For cohorts 6 to 9, ezetimibe is permitted as long as subjects have been on a stable dose for at least 6 weeks prior to enrollment, and plan to remain on the same dose for the duration of the study, as defined in Exclusion Criterion 219 (Section 7.2)
- For cohorts 6 to 9, antiplatelet therapy (low-dose acetylsalycilic acid, clopidogrel or ticagrelor) is permitted as long as subjects have been on a stable dose for at least 6 weeks prior to enrollment, and plan to remain on the same dose for the duration of the study, as defined in Exclusion Criterion 219 (Section 7.2)
- For cohorts 6 to 9, medication used to manage chronic conditions not excluded by 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, and acknowledged by the Amgen Medical Monitor. Written documentation of this review and Amgen acknowledgement is required for subject participation, as defined in Exclusion 219 (Section 7.2)
- **For cohort 9, medication used to manage diabetes 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, and acknowledged by the Amgen Medical Monitor. Written documentation of this review and Amgen acknowledgement is required for subject participation, as defined in Exclusion 219 (Section 7.2).**

All herbal supplements and nutritional supplements (with the exception of those known to affect lipid metabolism, excluded above) should not be taken within 30 days prior to dosing on day 1 and should not be used during the study, unless reviewed and approved by the investigator and Amgen Medical Monitor. Written documentation of this review and Amgen acknowledgement is required for subject participation.

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

10. STUDY PROCEDURES

10.1 Schedule of Assessments

Table 4. Schedule of Assessments – Dosing Period for Cohorts 1 to 5

Activity	Screening	Check-in	Treatment Period														
Study Day	**-28 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**	**10**	**30**	**60**	**120**	**180**	**360**	**540**	**720**					
General and Safety Assessments																	
Informed Consent	X																
Admission to residency		X															
Residency		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Discharge from residency																X	
Medical history	X																
Physical examination[e]	X	X											X			X	
Weight	X	X															
Height	X																
Vital signs (BP, HR, RR, TEMP)	X	X	X				X	X		X		X	X	X	X	X	
ECG[d]	X	X						**X**									
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events				X	X	X	X	X	X	X	X	X	X	X	X	X	
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Investigational Product Administration																	
IP administration				X													
Laboratory assessments																	
Chemistry and hematology panels	X[a]	X[a]											X			X	
eGFR	X[a]	X															
Coagulation panel	X[a]	X											X			X	
Urinalysis	X[a]	X											X			X	
Urine pregnancy test	X[a]	X[a]															
FSH (postmenopausal females only)	X[a]																
HIV, HepCAb, HBsAg, HBcAb	X[a]																
Drug and cotinine screen	X[a]	X[a]															
Pharmacodynamic Assessments																	
Lp(a)[g]	X		X										X			X	
Lipid panel[f]	X[a,b]		X														
[redacted]																	
Pharmacogenomic sample (optional)			X													X	
[redacted]																	
Pharmacokinetic Assessments																	
AMG 890 serum PK collection			X		X	X	X	X	X	X	X	X	X	X	X	X	
AMG 890 pooled urine PK collection[c]					X	X	X	X	X	X	X	X	X	X	X		

Footnotes defined after Table 5

Table 5. Schedule of Assessments – Post-Dosing for Cohorts 1 to 5

Activity										Cohorts 1 and 2		Cohorts 3 to 5				
										End of Treatment	Follow-up				End of Treatment	Follow-up
Study Day	**7**	**15**	**18**	**22**	**29**	**43**	**57**	**71**	**85**	**113**	**Every 2 weeks**	**113**	**155**	**183**	**225**	**Monthly**
Study Time (Hours)	144															
General and Safety Assessments																
Informed Consent																
Medical history																
Physical examination[e]	X	X			X		X		X	X		X			X	
Weight										X					X	
Height																
Vital signs (BP, HR, RR, TEMP)	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
ECG[d]	X	X			X		X			X		X			X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X		X			X	
Adverse Events	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
Serious Adverse Events[h]	X	X	X	X	X	X	X	X	X	X	X[h]	X	X	X	X	X
Investigational Product Administration																
IP administration																
Laboratory assessments																
Chemistry and hematology panels	X	X		X	X		X		X	X		X	X	X	X	
eGFR	X				X		X		X	X		X			X	
Coagulation panel	X	X		X	X		X		X	X		X	X	X	X	
Urinalysis	X				X		X		X	X		X			X	
Urine pregnancy test										X[a]					X[a]	
FSH (postmenopausal females only)																
HIV, HepCAb, HBsAg, HBcAb																
Drug and cotinine screen										X[a]					X[a]	
Pharmacodynamic Assessments																
Lp(a)[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lipid panel[f]	X	X			X		X		X	X					X	
[redacted]																
Pharmacokinetic Assessments																
AMG 890 serum PK collection	X	X			X		X		X							
AMG 890 pooled urine PK collection[c]																

[a] Laboratory tests to be performed at the local laboratory. For eligibility determination on day -1, only ALT, AST, and TBIL in the chemistry panel will be performed at the local laboratory.
[b] For screening purposes, lipid panel will measure triglycerides only.
[c] Urine will be pooled for PK analysis as 12-hour samples from the time of dosing to day 4 (72 hours post-dose) for cohorts 3 to 5. Urine will be pooled for PK analysis as 24-hour samples for cohorts 1 and 2.

[d] ECG will be single trace for screening purposes. Baseline ECGs on day -1 will be composed of 3 triplicate tracings. On-study ECGs will be single triplicate tracings.
[e] Physical examination to include neurologic examination as specified in protocol Section 10.3.
[f] On-study lipid panel includes apolipoprotein A1 and apolipoprotein B.
[g] Plasma Lp(a) to be analyzed by Medpace.
[h] When the current protocol amendment is implemented, the follow-up visits will continue approximately monthly.

Table 6. Schedule of Assessments – Dosing Period for Cohorts 6 and 7

Activity	Screening	Dosing Precheck	Treatment Period										
Study Day	**-28 to -4**	**-3 to -1**	**1**								**2**	**4**	
Study Time (Hours)			**Predose**	**0**		**2**	**3**	**6**	**9**		**24**	**30**	**72**
Study Time (Minutes)				**0**	**30**	**60**	**120**	**180**	**360**	**540**			
General and Safety Assessments													
Informed Consent	X												
Medical history	X												
Physical examination[d]	X	X									X		X
Weight	X	X											
Height	X												
Vital signs (BP, HR, RR, TEMP)	X	X	X			X	X		X		X		X
ECG[c]	X	**X**					X						
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events				X	X	X	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Investigational Product Administration													
IP administration				X									
Laboratory Assessments													
Chemistry and hematology panels	X[a]	X[a]									X		X
eGFR	X[a]	X											
Coagulation panel	X[a]	X									X		X
Urinalysis	X[a]	X											
Urine pregnancy test	X[a]	X[a]											
FSH (postmenopausal females only)	X[a]												
HIV, HepCAb, HBsAg, HBcAb	X[a]												
Drug and cotinine screen	X[a]	X[a]											
Pharmacodynamic Assessments													
Lp(a)[f]	X		X								X		X
Lipid panel[e]	X[a, b]		X										
[redacted]													
Pharmacogenomic sample (optional)			X										
[redacted]													
Pharmacokinetic Assessments													
AMG 890 serum PK collection			X		X	X	X	X	X	X	X	X	X

Footnotes defined after Table 7

Table 7. Schedule of Assessments – Post-Dosing for Cohorts 6 and 7

Activity										End of Treatment	Follow-up
Study Day	**7**	**15**	**29**	**43**	**57**	**85**	**113**	**155**	**183**	**225**	**Monthly**
Study Time (Hours)	**144**										
General and Safety Assessments											
Informed Consent											
Medical history											
Physical examination[d]	X		X		X	X		X		X	
Weight										X	
Height											
Vital signs (BP, HR, RR, TEMP)	X	X	X	X	X	X	X	X	X	X	
ECG[c]	X		X		X			X		X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Investigational Product Administration											
IP administration											
Laboratory Assessments											
Chemistry and hematology panels	X		X		X	X	X	X	X	X	
eGFR										X	
Coagulation panel	X		X		X	X		X		X	
Urinalysis	X									X	
Urine pregnancy test										X[a]	
FSH (postmenopausal females only)											
HIV, HepCAb, HBsAg, HBcAb											
Drug and cotinine screen										X[a]	
Pharmacodynamic Assessments											
Lp(a)[f]	X	X	X	X	X	X	X	X	X	X	X
Lipid panel[e]			X		X	X		X		X	
[redacted]											
Pharmacokinetic Assessments											
AMG 890 serum PK collection	X	X									

[a] Laboratory tests to be performed at the local laboratory. For eligibility determination on day -3 to -1, only ALT, AST, and TBIL in the chemistry panel will be performed at the local laboratory.
[b] For screening purposes, lipid panel will measure triglycerides only.
[c] ECG will be single trace for the study for cohorts 6 and 7.
[d] Physical examination to include neurologic examination as specified in protocol Section 10.3.
[e] On-study lipid panel assessments includes apolipoprotein A1 and apolipoprotein B.
[f] Plasma Lp(a) to be analyzed by Medpace.

Table 8. Schedule of Assessments – Dosing Period for Cohorts 8 and 9

Activity	Screening	Dosing Precheck	Treatment Period										
Study Day	**-28 to -4**	**-3 to -1**	**1**								**2**	**4**	
Study Time (Hours)			**Predose**	**0**		**2**	**3**	**6**	**9**		**24**	**30**	**72**
Study Time (Minutes)				**0**	**30**	**60**	**120**	**180**	**360**	**540**			
General and Safety Assessments													
Informed Consent	X												
Admission to residency		X[h]											
Medical history	X												
Physical examination[d]	X	X									X		X
Weight	X	X											
Height	X												
Vital signs (BP, HR, RR, TEMP)	X	X	X			X	X		X		X		X
ECG[c]	X	X					X	X	X	X	X		X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events				X	X	X	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Investigational Product Administration													
IP administration				X									
Laboratory Assessments													
Chemistry and hematology panels	X[a]	X[a]									X		X
eGFR	X[a]	X											
Coagulation panel	X[a]	X									X		X
Urinalysis	X[a]	X											
Urine pregnancy test	X[a]	X[a]											
FSH (postmenopausal females only)	X[a]												
HIV, HepCAb, HBsAg, HBcAb	X[a]												
Drug and cotinine screen	X[a]	X[a]											
Pharmacodynamic Assessments													
Lp(a)[f]	X		X								X		X
Lipid panel[e]	X[a, b]		X										
[redacted]													
Pharmacogenomic sample (optional)			X										
[redacted]													
Pharmacokinetic Assessments													
AMG 890 serum PK collection			X		X	X	X	X	X	X	X	X	X

Footnotes defined after Table 9

Table 9. Schedule of Assessments – Post-Dosing for Cohorts 8 and 9

Activity															End of Study (End of Treatment)
Study Day	**7**	**15**	**29**	**43**	**57**	**85**	**113**	**155**	**183**	**225**	**253**	**281**	**309**	**337**	**365**
Study Time (Hours)	**144**														
General and Safety Assessments															
Informed Consent															
Medical history															
Physical examination[d]	X		X		X	X		X		X					X
Weight															X
Height															
Vital signs (BP, HR, RR, TEMP)	X	X	X	X	X	X	X	X	X	X					X
ECG[c]	X		X		X			X		X					X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Investigational Product Administration															
IP administration															
Laboratory Assessments															
Chemistry and hematology panels	X		X		X	X	X	X	X	X					X
eGFR										X					X
Coagulation panel	X		X		X	X		X		X					X
Urinalysis	X									X					X
Urine pregnancy test															X[a]
FSH (postmenopausal females only)															
HIV, HepCAb, HBsAg, HBcAb															
Drug and cotinine screen															X[a]
Pharmacodynamic Assessments															
Lp(a)[f]	X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**	**X**	X
Lipid panel[e]			X		X	X		X		X					X
[redacted]															
Pharmacokinetic Assessments															
AMG 890 serum PK collection	X	X	X		X	X	X	X[g]							

[a] Laboratory tests to be performed at the local laboratory. For eligibility determination on day -3 to -1 Precheck visit, only ALT, AST, and TBIL in the chemistry panel will be performed at the local laboratory.
[b] For screening purposes, lipid panel will measure triglycerides only.
[c] ECG will be single trace for screening purposes. Baseline ECGs on day -3 to -1 Precheck visit, will be composed of 3 triplicate tracings for a total of 9 ECGs (3 sets of triplicates). For 2, 3, 6, 9, 24, and 72 hours post-dose, ECGs will be performed in a standardized method, in triplicate. After the 72 hour post-dose ECG time point, ECG will be single trace. See Section 10.3 for details on ECGs.
[d] Physical examination to include neurologic examination as specified in protocol Section 10.3.

[e] On-study lipid panel assessments includes apolipoprotein A1 and apolipoprotein B.
[f] Plasma Lp(a) to be analyzed by Medpace.
[g] PK sample collection on day 155 is required for cohort 9 subjects only.
[h] Only the sentinel pair in cohort 9 is required to be admitted for a residency period (from day -1 to completion of day 2 procedures).

10.2 General Study Procedures

A signed and dated IRB/IEC approved ICF must be obtained prior to performing any study-specific procedures including discontinuing standard therapy for purposes of this study.

During the study, every effort should be made to perform the study procedures as indicated on the SOA (Table 4 to Table 9). Every effort should be taken to collect all biomarker and PK samples as described in the SOA. If sample processing/shipment on a weekend/holiday is not logistically feasible for a site, this needs to be documented and will not be considered a protocol deviation.

Subjects will be seen in the clinic for study evaluations. When electrocardiograms (ECGs), vital signs, blood sample collections, and biomarker sample collection occur at the same visit, ECGs and vital signs should be collected before blood samples. The time of blood sample collection must be recorded with the exact time of collection (do not use the time that samples were frozen or any other time point). The study specific manuals provide additional details regarding the requirements for these procedures.

Acceptable deviation windows applicable to visits and sample collections follow:

- ± 5 minutes on the first hour PK assessments on day 1, ± 10 minutes for the subsequent PK assessments on the same day (dosing day)
- ± 1 hour on days 2 to 4 for PK samples
- ± 1 day on days 7 through 29 for study visits
- ± 3 days from day 43 through the end of treatment visit for study visits of cohorts 1 to 7 and through the end study visit for cohorts 8 and 9

Laboratory samples will be analyzed according to the following:

- At screening, hematology, chemistry, triglycerides, coagulation assessments, FSH, HIV and hepatitis serology tests, eGFR, urine pregnancy test, and drug & cotinine tests will be analyzed at local laboratories.
- At day -1 for cohorts 1 to 5 or day -3 to -1 for cohorts 6 to 9, tests that will be analyzed at local laboratories for eligibility determination will be: alanine aminotransferase (ALT), aspartate aminotransferase (AST); and total bilirubin (TBIL) in the chemistry panel; urine pregnancy test; and drug & cotinine tests. The day -1 tests for cohorts 1 to 5 or day -3 to -1 tests for cohorts 6 to 9 that will be analyzed at a central laboratory will be: hematology, chemistry (including ALT, AST, and TBIL for baseline measurements), eGFR, coagulation assessments, and urinalysis.
- The on-study hematology, chemistry, lipid panel, eGFR, coagulation assessments, and urinalysis will be analyzed at a central laboratory.

- All Lp(a) assessments, including for screening purposes, will be performed by Medpace.
- Blood and urine PK, biomarker development, pharmacogenomic, and [redacted] samples will be sent to Amgen or its designee, for analysis (if applicable) and storage.
- On-study urine pregnancy tests and the drug and cotinine screen tests will be analyzed locally.
- Follow-up period chemistry and hematology for cohorts 1 and 2 will be performed at the central laboratory.

Refer to the provided laboratory manual for detailed collection, processing, and shipping procedures. Additional procedures deemed necessary as part of standard of care or as required by local laws and regulations may be performed at the Investigator's discretion.

10.2.1 Screening

After written informed consent is obtained, subjects will be screened in order to assess and confirm eligibility for study participation. All screening procedures must be performed within 28 days prior to start of investigational product (IP) administration, unless otherwise noted. Subject re-consent is required if subject signature exceeds 28 days before IP dosing on day 1.

Subjects who meet the study entry criteria will be eligible for enrollment. Subjects who do not meet the eligibility criteria within the 28-day screening period are not eligible for enrollment. Ineligible subjects will be documented as screen failures. If a subject is an alternate on day -1 for cohorts 1 to 5 or day -3 to -1 for cohorts 6 to 9, and is not enrolled in the study because he/she is not needed to fulfill the enrollment requirement, the subject would not be considered a screen failure. The subject could be enrolled subsequently if the day -1 for cohorts 1 to 5 or day -3 to -1 for cohorts 6 to 9, procedures are performed again, the subject meets eligibility criteria, and the subject is within the 28-day screening period. The latest day -1 for cohorts 1 to 5 or day -3 to -1 for cohorts 6 to 9, results would be reported. Subjects outside of the 28-day screening period could be considered for re-screening as described in the Re-screening section below.

Laboratory assessments used to determine subject eligibility may be repeated once for confirmation (up to a total of 2 times 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.

If the initial blood pressure 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.

The following procedures are to be completed during the screening period at the time points designated in the Schedules of Assessments (Table 4 to Table 9). Assessments that were performed as standard of care prior to signature of informed consent but within 28 days prior to start of treatment with AMG 890 can be used as screening assessments and do not need to be repeated to confirm subject eligibility. Hepatitis serology does not need to be repeated to determine eligibility if it was performed within 6 weeks prior to start of treatment with AMG 890.

- Confirmation that the ICF has been signed
- Medical history
- Physical examination
- Demographic data including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety
- Weight and height
- Vital signs (ie, blood pressure, heart rate, respiratory rate, temperature)
- ECG (in single trace, to confirm no medically significant condition, including corrected QT interval (QTc) equal to or shorter than 450 msec in men or 470 msec in women)
- Document concomitant medications
- Laboratory assessments: hematology, chemistry, and coagulation panel, eGFR, urinalysis, urine pregnancy test (females only), FSH (post-menopausal women only), triglycerides, HIV and hepatitis serology, and plasma Lp(a)
- Drug & cotinine screen
- Serious adverse event reporting

Re-screening:

A subject may be rescreened up to 3 times in consultation with the Amgen Medical Monitor. The subject must be re-consented if a re-screening attempt occurs outside the 28-day screening period.

Re-screened subjects must be documented as screen failed in the subject's medical record and subsequently documented as re-screened. Subjects will retain the same subject identification number assigned at the time of initial screening. Once the subject is recorded as re-screened, a new 28-day screening window will begin.

10.3 Description of Study Procedures

The sections below provide a description of the individual study procedures listed in the Schedule of Assessments (Table 4 to Table 9).

Informed Consent

A signed ICF must be obtained from each subject prior to any study-mandated procedures.

Subject Residency

Subjects in cohorts 1 to 5 will check-in at the research facility on day -1 and will stay in the research facility for a residency period through day 4. After completion of day 4 procedures, subjects will be discharged. The sentinel pair of cohort 9 will stay in the research facility from day -1 through day 2. After completion of day 2 procedures, subjects will be discharged.

Demographic Data

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study possible association with subject safety. Additionally, demographic data will be used to study the impact of protocol-required therapy on biomarker variability and PK.

Medical History

A complete medical history will be obtained at screening by the investigator or designated site physician. Medical history will include information on the subject's current health and surgical history. Relevant medical history findings will be recorded in the subject's source and on the appropriate pages of the CRF. Record all findings on the medical history eCRF.

Concomitant Medications

Concomitant therapies are to be collected from informed consent through the end of treatment visit in the source documents and eCRF for cohorts 1 to 7; for cohorts 8 and 9, concomitant therapies are to be collected through the EOS visit (day 365). If the case, statin use and medication for blood pressure control are to be collected as concomitant medications. Collect drug, therapy name, indication, dose, unit, frequency, route, start date, and stop date (if applicable).

Physical Examination

A complete physical examination (breast, rectal and genital examination are not required) will be performed by the investigator or designee at screening and at the time

points specified in the Schedules of Assessments (Table 4 to Table 9). The physical examination will include general appearance, including examination of the skin, spleen, and respiratory, cardiovascular, musculoskeletal, and neurological systems.

The individual performing the physical examination will characterize their findings as either normal or abnormal. Abnormal physical examination findings found during screening should be reported on the Medical History eCRF. Abnormal physical examination findings found during the study, if clinically significant, should be noted in the event eCRF.

A clinical neurologic examination will be performed at every physical examination as specified in the SOA. The clinical neurologic examination will be performed to access signs of new onset peripheral neuropathy. The examination should be reported in the subject records and must include the following assessments:

- muscle mass and tone, presence of tremor, fasciculation or paralysis
- strength in all 4 members, including proximal and distal muscular groups
- gait, by observation of a short regular walk, heel and toe walk.
- symmetry of sensitivity to pressure (dull tool), temperature and pain (sharp tool)
- proprioception in upper and lower extremities
- symmetry of reflexes assessed on the upper extremities (biceps, triceps and brachioradial) and lower extremities (patellar and achilles)

If there is clinical evidence of treatment-emergent neuropathy, dosing will be suspended, the subject will be directed to a neurology specialist for a complete neurologic assessment, and the unblinded medical monitor will be informed. The identified neurologic abnormality is to be reported on the adverse event CRF.

Height Measurements

Height in centimeters should be measured without shoes at screening.

Weight Measurements

Weight in kilograms should be measured without shoes.

Body Mass Index (BMI)

BMI will be calculated at screening using the following formula:

$$\text{BMI } (kg/m^2) = \text{weight } (kg)/[\text{height } (cm)/100]^2$$

Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. Record all measurements on the vital signs eCRF.

The subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital signs eCRF. If the initial blood pressure measurement is elevated, the assessment may be repeated again at least 15 minutes later and the lower of the 2 readings may be used.

The location for temperature measurement selected for a subject should be the same that is used throughout the study and documented on the vital signs eCRF.

Electrocardiograms

The subject must be in a supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible.

The Screening ECG will be performed as a single ECG for screening purposes.

For cohorts 1 to 5, day -1 pre-dose ECGs will be performed on 3 occasions separated by at least 30 minutes all in triplicate for a total of 9 ECGs (3 sets of triplicate). This is the baseline ECG. At all other time points, ECGs will be performed in a standardized method, in triplicate, and approximately 30 seconds apart, prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals.

For cohorts 6 and 7, all ECGs will be performed as a single ECG for all time points, and prior to blood draws or other invasive procedures. The ECG must include the following measurements: Heart Rate, QRS, QT, QTc, and PR intervals.

For cohorts 8 and 9, the screening ECG will be performed as a single trace. The day -3 to -1 pre-check visit ECG will be the Baseline ECG and will be performed on 3 occasions separated by at least 30 minutes, all in triplicate for a total of 9 ECGs (3 sets of triplicates). Each set of triplicate ECGs should be run consecutively and completed within a total of 5 minutes from the start of the first to the completion of the third. For ECGs at 2, 3, 6, 9, 24, and 72 hours post-dose, ECGs will be performed in a

standardized method, in triplicate and run consecutively (triplicate ECGs should be completed within a total of 5 minutes from the start of the first to the completion of the third). ECGs will be performed prior to blood draws or other invasive procedures. At all other time points after 72 hours post-dose, ECGs will be performed as a single trace and prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals.

The investigator or 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 or designee.

Standard ECG machines provided by the sponsor should be used for all study-related ECG procedures.

Clinical Laboratory Tests

The tests will be conducted on samples collected and analyzed by standard laboratory procedures at the time points specified in the Schedule of Assessments (Table 4 to Table 9). Blood will be collected after fasting at least 10 hours at all clinical laboratory time points. The test results are to be recorded on the eCRFs. All laboratory test results must be reviewed and signed by the Principal Investigator or qualified designee. Missed test(s) that are not done must be reported as such on the eCRFs.

At screening, chemistry, hematology, coagulation assessments, urinalysis, and triglycerides will be analyzed by the local laboratory. At day -1 for cohorts 1 to 5 or day -3 to -1 for cohorts 6 to 9, for eligibility determination, the local laboratory will test only AST, ALT, and TBIL in the chemistry panel; a central lab will analyze hematology, chemistry (including ALT, AST, and TBIL for baseline measurements), eGFR, coagulation assessments, and urinalysis. On-study and follow-up laboratory assessments, unless specifically noted to the contrary, will be analyzed by a central laboratory.

Additional procedures deemed necessary as part of standard of care, for safety reasons or as required by local laws and regulations may be performed at the investigator's discretion.

The following laboratory tests will be conducted on samples collected and analyzed by standard laboratory procedures:

Hematology

The following hematology tests will be performed:

- Red blood cell count
- Hemoglobin
- Hematocrit
- Platelet count
- White blood cell count with differential count:
  - Total neutrophils
  - Eosinophils
  - Basophils
  - Lymphocytes
  - Monocytes

Clinical Chemistry

A fasting (at least 10 hours) blood sample will be assessed at screening and will be analyzed at the local laboratory.

Fasting (at least 10 hours) blood samples will be assessed at all time points indicated as on-study in the SOA (Table 4 to Table 9) and analyzed at the central laboratory. The clinical chemistry tests listed below will be performed:

- Glucose
- Sodium
- Chloride
- Calcium
- Phosphorus
- Potassium
- Magnesium
- Bicarbonate or total CO_2
- Creatinine
- Blood urea nitrogen (BUN)
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Total bilirubin
- Direct bilirubin
- Alkaline phosphatase (ALP)
- Creatine Kinase
- Total protein
- Albumin
- Tryptase (to be performed at the discretion of the PI or qualified designee)[a]
- Lactate, (to be performed at discretion of the PI or designee)[b]
- Estimated glomerular filtration rate (eGFR)[c]

[a] Tryptase to be collected in the case of a suspected anaphylactic reaction
[b] Lactate to be collected if an anion-gap acidosis is identified
[c] eGFR for screening will be calculated at the local laboratory, and the formula used should be recorded in subject's source documents for future reference.

Coagulation Assessments

The following coagulation assessments will be performed:

- Prothrombin time (PT) in international normalized ratio (INR)
- Activated partial thromboplastin time (aPTT)
- Thrombin time (TT)

Urinalysis

The urinary tests listed below will be performed:

Bilirubin Blood Glucose Ketones pH Protein Specific gravity Urobilinogen	Microscopic exam (To be performed at the discretion of the PI or qualified designee): White blood cells Red blood cells Epithelial cells Casts Bacteria Crystals

Hepatitis B, Hepatitis C and HIV status

Hepatitis B surface antigen, HBcAb, HepCAb, and HIV status will be assessed. If the results show a positive HepCAb, hepatitis C virus RNA by PCR is necessary. The test must be confirmed negative at screening for the subject to be eligible for this study.

Pregnancy Test (Females Only)

A urinary pregnancy test will be performed on all female subjects at screening; day -1 for cohorts 1 to 5 or day -3 to day -1 for cohorts 6 to 9; for cohort 1 to 7 the end of treatment visit; and for cohorts 8 and 9 at Day 225 and the end of study, as specified in the SOA (Table 4 to Table 9). Pregnancy tests must be confirmed negative for the subject to be eligible for this study.

Serum Follicle Stimulating Hormone Test (Females Only)

Additional serum may be collected for an FSH test if required to ensure menopause in a female subject. Results must be consistent with postmenopausal status per local laboratory ranges for inclusion in this study. Postmenopausal status will be recorded on the medical history eCRF.

Drug Screen

A urine screen for drugs with a high potential of abuse (according to the local lab standards) will be performed at screening; day -1 for cohorts 1 to 5 or day -3 to

day -1 for cohorts 6 to 9; and at the end of treatment visit for cohorts 1 to 7; and for cohorts 8 and 9, on day 365. The following drugs will be tested:

- Tetrahydrocannabinol
- Benzodiazepines
- Cocaine
- Opiates
- Amphetamines
- Barbiturates

Subjects with a positive result at time points specified in the SOA will be excluded from the study at screening. The intention is to detect drugs of abuse and not those prescribed therapeutically. Subjects with a positive drug test may be retested once at the discretion of the Principal Investigator in consultation with the Amgen Medical Monitor. The result will be documented in the source document but will not be recorded on the CRF.

Lipid Panel

A fasting (at least 10 hours) blood sample triglycerides will be assessed at screening and analyzed at the local laboratory.

Fasting (at least 10 hours) blood samples will be collected at all time points indicated as the on-study lipid panel in the SOA (Table 4 to Table 9). The following analytes will be assessed:

- Total cholesterol
- LDL-C (by ultracentrifugation)
- HDL-C
- VLDL-C
- Triglycerides
- Apolipoprotein A1 (apoA1)
- Apolipoprotein B (apoB)

The following analytes will be collected per the Schedule of Assessments:

10.4 Pharmacokinetic and Pharmacodynamic Analysis

Blood samples for determination of AMG 890 serum concentrations and for the evaluation of plasma Lp(a) dynamic response will be assessed at time points indicated in the Schedule of Assessments (Table 4 to Table 9). Collection time points may be added or removed based on affluence of data informing the PK of AMG 890 and its PD effects.

For cohorts 1 to 5, urine PK samples for a qualitative assessment of AMG 890 levels will be assessed at the time points indicated in the Schedule of Assessments.

- After dosing, all urine passed (including urine passed during bowel movements) must be collected including the first voiding of the following day. Urine will be collected and pooled in 12-hour interval samples from the time of dosing through day 4 (72 hours post-dose) for cohorts 3 to 5, and through day 2 as a 24-hour interval sample after dosing for cohorts 1 and 2. The total volume of urine collected (mL) for each collection interval is to be reported.
- The start and stop time of each collection interval (to the minute) is to be reported.
- The entire interval specimen should be collected in a properly labeled urine container and refrigerated at 2°C to 8°C during collection.
- The subject should be informed that a normal intake of fluids during the collection period is desirable.

The PK and PD samples must be collected within the following windows:

- ± 5 minutes on the first hour assessments on day 1; ± 10 minutes for the subsequent assessments on the same day (dosing day)
- ± 1 hour on days 2 to 4
- ± 1 day on days 7 through 29
- ± 3 days from day 43 through the end of treatment visit for study visits of cohorts 1 to 7 and through the end study visit for cohorts 8 and 9

The precise time of all sample collection should be documented.

Detailed sample collection, processing, storage and shipping instructions are provided in the laboratory manual.

[redacted]

[redacted]

10.6 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Biomarker development can be useful in developing markers to identify disease subtypes, guide therapy, and/or predict disease severity.

[redacted]

10.7 Pharmacogenetic Studies

[redacted]

[redacted]

10.8 Sample Storage and Destruction

Laboratory samples collected can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand hyperlipoproteinemia(a), the dose response and/or prediction of response to AMG 890, characterize antibody response, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites) and additional insights into cardiovascular disease. Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

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

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood, biomarker, PK, and pharmacogenetic samples can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed.

However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.
See Section 14.3 for subject confidentiality.

11. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

11.1 Subjects' Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product, device or other protocol-required therapies and must discuss with the subject the options for continuation of the SOA (Table 4 to Table 9) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, and adverse events. Subjects who have discontinued investigational product and/or protocol required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible it is imperative that subjects remain on study to ensure safety surveillance and/or collection of outcome data. The investigator must document the level of follow-up that is agreed to by the subject.

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data

can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

11.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, protocol procedures, or the study as a whole at any time prior to study completion.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 15.1.

11.3 Reasons for Removal From Treatment, or Study

11.3.1 Reasons for Removal From Treatment

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

- subject request
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, or pregnancy)
- death
- lost to follow-up
- decision by sponsor (other than subject request, safety concern, lost to follow-up)

11.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up

12. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

12.1 Definition of Safety Events

12.1.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than would be expected and/or has an association with a significantly worse outcome than expected. A pre-existing condition that has not worsened more than anticipated (ie, more than usual fluctuation of disease) during the study, or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event. Abnormal laboratory findings without clinical significance are usually not considered adverse events. However, laboratory value changes that require treatment or adjustment in current therapy may be considered adverse events.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 11.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

12.1.2 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

An adverse event would meet the criterion of "requires hospitalization," if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event." Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug induced liver injury (DILI) (see Appendix A for DILI reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

12.2 Safety Event Reporting Procedures

12.2.1 Adverse Events

12.2.1.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after the first dose of investigational product through the end of treatment visit are reported using the Event eCRF.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- **Did the event start prior to the first dose of investigational product,**
- **Assessment of seriousness,**
- Dates of onset and resolution (if resolved),
- Severity,
- Assessment of relatedness to investigational product, protocol required therapies, and/or study mandated procedures
- Action taken**, and**
- **Outcome of event.**

The adverse event grading scale used will be the Amgen Standard Adverse Event Grading Scale: mild (aware of sign or symptom, but easily tolerated), moderate (discomfort enough to cause interference with usual activity), and severe (incapacitating with inability to work or do usual activity). The grading scale used in this study is described in the Appendix A.

The investigator must assess whether the adverse event is possibly related to the investigational product (AMG 890 or placebo*)*. Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.

The investigator must assess whether the adverse event is possibly related to any study mandated activity (eg, administration of investigational product, protocol-required therapies, use of medical device(s) and/or procedure (including any screening procedure(s)).

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment

or adjustment in current therapy are considered adverse events. Where applicable and preferentially, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

The investigator is expected to follow reported adverse events until stabilization or reversibility.

12.2.1.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through the end of study visit (last visit where data for primary endpoints are collected) are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the Event eCRF and using the paper based Serious Adverse Event Report (SAER) Form (see Table 10 and Appendix B).

The investigator must assess whether the serious adverse event is possibly related to the investigational product (AMG 890 or placebo). Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.

The investigator must assess whether the serious adverse event is possibly related to any study mandated activity (eg, administration of investigational product, protocol-required therapies, use of medical device(s) and/or procedure (including any screening procedure(s)).

The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

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

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

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities.

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and good clinical practice.

The investigator is to notify the appropriate IRB/IEC of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local regulatory requirements and procedures.

Table 10. Serious Adverse Event Reporting via Paper CRF

Serious Adverse Event Reporting via Paper CRF
• Facsimile transmission of the Serious Adverse Event Report Form (see Appendix B) 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 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 Adverse Event Report Form within the designated reporting time frames. • Once the study has ended, serious adverse event(s) should be reported to Amgen (regardless of causality) if the investigator becomes aware of a serious adverse event. The investigator should use the paper-based Serious Adverse Event Contingency Report Form to report the event.

12.2.1.3 Serious Adverse Events after the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events should be reported to Amgen (regardless of causality) if the investigator becomes aware of them. Per local requirements in some countries (eg, European Union [EU] member states), investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

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

12.2.1.4 Method of Detecting Adverse Events and Serious Adverse Events

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

12.3 Pregnancy and Lactation Reporting

If a female subject becomes pregnant, or a male subject fathers a child following exposure to the Amgen investigational product (AMG 890 or placebo) report the pregnancy to Amgen Global Patient Safety as specified below.

Investigators should report pregnancies that occur during the study or through 90 days after receiving the Amgen investigational product (AMG 890 or placebo), for subjects who withdraw prior to end of study.

The pregnancy should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of the pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a female subject becomes pregnant during the study, the investigator should attempt to obtain information regarding the birth outcome and health of the infant.

If the outcome of the pregnancy meets a criterion for immediate classification as a Serious Adverse Event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a Serious Adverse Event.

If a female breastfeeds following exposure to the Amgen Investigational Product (AMG 890 or placebo) report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should report lactation cases that occur through 90 days after receiving the Amgen Investigational Product (AMG 890 or placebo) for subjects who withdraw prior to end of study.

Any lactation case should be reported to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a male subject's female partner becomes pregnant, the investigator should discuss obtaining information regarding the birth outcome and health of the infant from the pregnant partner.

13. STATISTICAL CONSIDERATIONS

13.1 Study Endpoints, Analysis Sets, and Covariates

13.1.1 Study Endpoints

13.1.1.1 Primary Endpoints

- Subject incidence of treatment-emergent adverse events
- Safety laboratory analytes, vital signs, and electrocardiograms (ECGs)

13.1.1.2 Secondary Endpoints

- AMG 890 PK parameters including, but not limited to, maximum observed concentration (C_{max}), the time of maximum observed concentration (t_{max}), and area under the concentration-time curve (AUC)
- Pharmacodynamic parameters:
  - Change and percent change in plasma Lp(a) levels at each scheduled visit up to the end of treatment visit

13.1.1.3 Exploratory Endpoints

[redacted]

- Change and percent change in total cholesterol and cholesterol fractions (very-low density lipoprotein cholesterol [VLDL-C], low-density lipoprotein cholesterol [LDL-C], and high-density lipoprotein cholesterol [HDL-C]), triglycerides, apolipoprotein A1 (ApoA1) and total apolipoprotein B (ApoB) at each scheduled visit
- AMG 890 excretion in urine

[redacted]

13.1.2 Analysis Sets

For all analyses, subjects will be analyzed according to the dose and treatment they received, not the dose and treatment to which they were randomized.

13.1.2.1 Safety Analysis Set

The safety analysis set will consist of all study subjects who receive at least 1 dose of AMG 890 or placebo.

Subjects withdrawing prior to AMG 890 or placebo administration due to adverse events related to study procedure will not be included in the safety analysis set but those adverse events will be listed.

13.1.2.2 Pharmacokinetic (PK) Analysis Set

The PK analysis set will consist of all dosed subjects for whom at least 1 PK parameter or endpoint can be reliably estimated.

13.1.2.3 Pharmacodynamics (PD) Analysis Set

The PD analysis set will consist of all dosed subjects for whom at least 1 PD parameter has a baseline value and at least 1 post-baseline measurement available. Baseline values for Lp(a) are defined as the mean of screening and day 1 predose. If for any reason only 1 value is available, then that value will be used as baseline.

13.1.2.4 Covariates and Subgroups

Baseline values may be used as a covariate in analyses. For any variable, unless otherwise defined, baseline is defined as the last assessment taken prior to the first administration of AMG 890 or placebo.

No subgroup analyses are planned.

13.1.3 Handling of Missing and Incomplete Data

The frequency of missing and incomplete data is expected to be low in this study and therefore, missing data will not be imputed.

13.2 Sample Size Considerations

The sample size is based on practical considerations. Approximately [redacted] subjects will be enrolled. With at least 6 subjects receiving AMG 890 in each cohort, there is at least a 74% chance of detecting an adverse event (AE) with a true incidence of 20% within each cohort. With at least 10 subjects receiving both AMG 890 and statin, there is at least a**n** 89% chance of detecting an adverse event with a true AE incidence rate of 20%. With [redacted] subjects receiving AMG 890 there is a 95% chance of detecting an adverse event with a true incidence of 5%.

13.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Amgen staff and their designees involved in the study will not be blinded, but will only be given treatment assignments when there is a need to use the information for analysis, discussion and internal decision making. The Amgen Medical

Monitor will be unblinded to treatment assignment throughout the duration of the study. Access to treatment assignments and other restricted data are described in Amgen standard documents. Unblinded individuals are to ensure unblinding and potentially unblinding information should not be distributed to the investigators or subjects prior to the study being formally unblinded.

13.4 Planned Analyses

13.4.1 Data Monitoring Committee (DMC), Data Review Team (DRT) or Dose Level Review Team (DLRT)

The DLRT voting members are responsible for dose level recommendations. The key objectives of the DLRT are to review data, monitor safety, and make dose change recommendations. Except for the unblinded Amgen Medical Monitor who will review data in an unblinded manner, DLRMs will be conducted in a blinded manner. Please refer to Section 9.2.4.1 for details.

13.4.2 Primary Analysis

The primary analysis will occur after all subjects have completed the end of treatment visit.

13.4.3 Final Analysis

The final analysis will occur after all subjects have completed the study.

13.5 Planned Methods of Analysis

13.5.1 General Considerations

Descriptive statistics will be provided for selected demographics, adverse events, vital signs, ECG, PK, and selected laboratory measurements. Descriptive statistics on continuous measurements will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Data will be presented and summarized by treatment cohort and at each time point. Graphical summaries of the data may also be presented.

Data for subjects receiving placebo will be combined across cohorts 1 to 5 and separately across cohorts 6 to 9.

When data are summarized by time, the values recorded against the scheduled time points listed in the protocol will be used. When assessing minimum/maximum increases or decreases over the study, all assessments, including unscheduled assessments will be used. Unless stated otherwise in the statistical analysis plan, the data analysis will be conducted using subjects in the safety analysis set. For statistical analyses

comparing change from baseline, only subjects with both baseline and at least 1 post-baseline assessment will be included.

At the primary analysis, the primary, secondary, and exploratory endpoints (if applicable) will be analysed. All data up to each subject's end of treatment visit will be included in the primary analysis. The follow-up time points will be summarized at the final analysis.

13.5.2 Primary Endpoint(s)

13.5.2.1 Safety Endpoint(s)

13.5.2.1.1 Adverse Events

All subjects who receive a dose of AMG 890 or placebo in the safety analysis set will be included in the analysis of the primary endpoints. Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term according to the medical dictionary for regulatory activities (MedDRA) terminology. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from IP or other protocol-required therapies, and significant treatment emergent adverse events will also be provided if observed. The number and percentage of subjects reporting adverse events will be evaluated for each dose cohort and across dose cohorts.

13.5.2.1.2 Vital Signs

Vital signs will be listed and reviewed for each subject. Summaries of heart rate and blood pressure data over time and change from baseline will be provided. The analyses of vital signs will include summary statistics over time (for each protocol scheduled study visit) by cohort. Depending on the size and scope of changes, summaries of changes from baseline over time may be provided.

13.5.2.1.3 Electrocardiogram

For cohorts 1 to 5 and cohorts 8 and 9, summaries over time and/or changes from baseline over time will be provided for ECG parameters (eg, RR, PR, QRS, QTc). Subjects' maximum change from baseline in QTc will be categorized and the number and percentage of subjects in each group will be summarized. Subjects' maximum post-baseline values will also be categorized and the number and percentage of subjects in each group will be summarized. Baseline ECG recording is defined as the mean of the 3 sets of triplicate ECG results (a total of 9 assessments) at study day -1 for cohorts 1 to 5, and at the day -3 to -1 visit for cohorts 8 and 9.

For cohorts 6 and 7, the ECG measurements will be performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; summaries and statistical analyses of ECG measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other trials.

13.5.2.1.4 Clinical Laboratory

Analyses of laboratory values will include summary statistics over time (for each protocol scheduled visit) by cohort. Additional summaries may include descriptive statistics of changes from baseline over time.

13.5.3 Secondary Endpoint(s)

13.5.3.1 Pharmacokinetics (PK) Analysis

Serum samples will be analyzed for AMG 890 concentrations using a validated assay. Individual concentration-time plots for AMG 890 will be presented for each subject as well as mean concentration-time plots for each cohort. Pharmacokinetic parameters including but not limited to AUC, C_{max}, and t_{max} will be estimated using non-compartmental methods. Actual dosing and sampling times will be used for calculation of PK parameters. Summary statistics will be generated for each PK parameter for each dose cohort using the PK analysis set.

13.5.3.2 Pharmacodynamic (PD) Analysis

Change and percent change in plasma Lp(a) levels at each scheduled visit up to the end of treatment visit.

[redacted]

13.5.4.1 Total Cholesterol, Cholesterol Fractions, and Apolipoproteins

Summary statistics will be provided for total cholesterol, cholesterol fractions (very-low density lipoprotein cholesterol [VLDL-C], low-density lipoprotein cholesterol [LDL-C], and high-density lipoprotein cholesterol [HDL-C]), triglycerides, apolipoprotein A1 [ApoA1] and total apolipoprotein B [ApoB]) at each scheduled visit by cohort.

13.5.4.2 Qualitative Assessment of AMG 890 in Urine

Urine samples will be collected and AMG 890 in urine will be analyzed so that fractions of dose eliminated unchanged in urine may be determined. Subject-level data and cohort summary statistics may be presented as appropriate.

[redacted]

14. REGULATORY OBLIGATIONS

14.1 Informed Consent

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

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specific screening procedures or any investigational product(s) is/ are administered.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record. The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject.

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

14.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed informed consent form, other written subject-facing information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

The investigator must submit and, where necessary, obtain approval from the *IRB/IEC* for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator is responsible for obtaining annual IRB/IEC approval /renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen.

14.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained:

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the demographics page, in addition to the unique subject identification number, include the age at the time of enrollment.

- For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in strict confidence by the investigator, except as described below.

In compliance with governmental/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit named such individuals to have access to his/her study related records, including personal information.

14.4 Investigator Signatory Obligations

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

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

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

15. ADMINISTRATIVE AND LEGAL OBLIGATIONS

15.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. After Amgen amends the protocol, the Investigator is to return the signed Investigator's Signature page confirming agreement to continue participation in the study according to the amendment. The IRB/IEC must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

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

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

15.2 Study Documentation and Archive

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

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

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

Elements to include:

- Subject files containing completed CRF, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.
- Non-investigational product(s), and/or medical device(s) or combination product(s) documentation, as applicable.

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

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

15.3 Study Monitoring and Data Collection

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and,

upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

The Clinical Monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Clinical Monitor is to have access to subject medical records and other study related records needed to verify the entries on the CRFs.

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

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

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the electronic CRFs must be maintained and readily available.
- Updates to electronic CRFs will be automatically documented through the software's "audit trail."
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that the investigator inspected or reviewed the data on the CRF, the data queries, and agrees with the content.

15.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the

Schedule of Assessments (Section 10.1), the investigator can search publicly available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

15.5 Language

CRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language.

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

15.6 Publication Policy

To coordinate dissemination of data from this study, the investigator will obtain input and assistance from Amgen staff as appropriate.

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff as appropriate as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

15.7 Compensation

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

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17. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

For all adverse events, the investigator must assess the severity according to the Amgen Standard Adverse Event Scale depicted below:

	Amgen Standard Adverse Event Grading Scale
MILD	Aware of sign or symptom, but easily tolerated
MODERATE	Discomfort enough to cause interference with usual activity
SEVERE	Incapacitating with inability to work or do usual activity

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBIL and/or INR elevation according to the criteria specified in Section 9.4 require the following:

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

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 12.2.1.2.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Section 9.4 or who experience AST or ALT elevations $>$ 3 x ULN or 2-fold increase above baseline values for subjects with evaluated values before drug must undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels. Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBIL $>$ 2x 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 or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.
- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBIL. The following are to be considered depending on the clinical situation:
  - Complete blood count (CBC) with differential to assess for eosinophilia
  - Serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) 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
  - CPK, haptoglobin, LDH, and peripheral blood smear
  - Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBIL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

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

Appendix B. Serious Adverse Event Report Form

The following minimum fields must be completed prior to faxing the form:
1) Site Number; 2) Subject ID Number; 3) Serious Adverse Event Diagnosis; Serious Criteria Code; Start Date of Event; 10) Signature
Ensure both pages are faxed with each submission.

Note: Only events that meet serious criteria (regardless of causal relationship to IP) should be reported on this form. Submit a Serious Adverse Event Report (SAER) form within 24 hours of the Investigator's knowledge of the event. *Indicates a mandatory field.

Data on the AE Summary CRF (also known as Events CRF) must agree with data submitted on the SAER form in the following areas: adverse event term(s), serious criteria, and relationship of product to event.

Only include information that is relevant (pertinent) to the event(s) included on this SAER (eg, concomitant medications, medical history, laboratory and diagnostic tests)

Header Information

New / Follow-up – Indicate if this is a new adverse event, or a follow-up of a pre-reported event.

Follow-up – Send a follow-up report if additional data adds to or changes the clinical interpretation of the event. Some examples are:
- The initial reported event has changed and additional serious criteria have been met (such as if event outcome is now fatal).
- Signs and symptoms were reported at the time of the initial report and a final diagnosis has now been made.
- A change in relationship of a study procedure or activity has occurred from the initial report.
- A significant change has occurred in the start date of the event or start date of a suspect concomitant medication.
- Additional concomitant medications and/or diagnostics have been identified that may contribute to or explain the event.

When sending a follow-up report, either:
- On a photocopy of the prior report, add the additional information, re-sign and date, then fax in the follow-up form – or –
- Complete a new form with the new information. If the serious adverse event terms have not changed, please write, in section 3, the following: "No changes in serious adverse event terms from previous SAER form," then fax in the follow-up form.
- If a new serious adverse event term is to be added to the terms previously reported, add this new term to a photocopy of the initial form.
- If an earlier reported adverse event is being replaced by a new diagnosis or event term, on a photocopy of the initial report, strike through the term to be deleted, sign and date the deletion and add the updated event term.

1. Site Information

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

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

2. Subject Information

Subject ID Number* – Enter the entire number assigned to the subject **Age at event onset, Sex, and Race –** Enter the subject's demographic information
End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

3. Serious Adverse Event

Provide the date the Investigator became aware of this Serious Adverse Event Information

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

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

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

If event occurred before the first dose of investigational product, add a check mark in the corresponding box.

Serious Criteria Code* - This is a mandatory field for serious events – Enter reason why the reported event has met serious criteria:

- Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
- If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria,"**Other medically important serious event**"" may be the appropriate serious criterion.

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

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

Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**

- Resolved – End date is known
- Not resolved/Unknown – End date is unknown
- Fatal – Event led to death

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

4. Hospitalization

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

5. Investigational Product including Lot # and Serial # when known / available

Investigational Product – If applicable, indicate whether the Investigational Product is blinded or open-label

Initial Start Date – Enter date the product was first administered, regardless of dose.

Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.

Action Taken with Product – Enter the status of the product administration.

Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.

6. Concomitant Medications

Indicate if there are any concomitant medications, including protocol-specified diluents and challenge agents.

Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.

Co-suspect – Indicate if the medication is suspect for the event

Continuing – Indicate if the subject is still taking the medication

Event Treatment – Indicate if the medication was used to treat the event

7. Relevant Medical History

Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.

8. Relevant Laboratory Tests

Indicate if there are any relevant laboratory values.

For each test type, enter the test name, units, date the test was run and the results.

9. Other Relevant Tests

Indicate if there are any tests, including any diagnostics or procedures.

For each test type, enter the date, name, results and units (if applicable).

10. Case Description

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

Footer

Signature, Title and Date* – The Investigator or designee must sign the form and provide his or her title and date and fax form to Amgen. If the reporter is not the Investigator, Designee must be identified on the Delegation of Authority form.

AMGEN 20170544 AMG 890	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event*	☐New ☐Follow-up

<<Fax number to be populated by COM/Study Manager/ProtocolAuthor prior to providing to sites>> SELECT OR TYPE IN A FAX#

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	Race	If applicable, provide End of Study date
		☐F ☐M		

3. SERIOUS ADVERSE EVENT - *Information in this section must also be entered on the Serious Adverse Event Summary CRF*

Provide the date the Investigator became aware of this Serious Adverse Event Information: Day____Month___Year_____

Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as 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 — AMG 890 (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: Date of Dose (Day Month Year)	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
AMG 890 ☐Blinded ☐Open Label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unknown

AMGEN 20170544 AMG 890	Clinical Trial Serious Adverse Event Report – Phase 1–4 *Notify Amgen Within 24 Hours of knowledge of the event*	☐New ☐Follow-up

Site Number	Subject ID Number

6. CONCOMITANT MEDICATIONS (eg, 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

AMGEN 20170544 AMG 890	Clinical Trial Serious Adverse Event Report – Phase 1–4 *Notify Amgen Within 24 Hours of knowledge of the event*	❑New ❑Follow-up

	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 C. Pregnancy Notification Form

Amgen Proprietary - Confidential

AMGEN® Pregnancy Notification Form

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

1. Case Administrative Information

Protocol/Study Number: 20170544

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

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

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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

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

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

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

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

_____

_____

Form Completed by

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

Appendix D. 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: 20170544

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

Approval Signatures

Document Name: Protocol Amendment olpasiran 20170544 7

Document Description: AMG 890 Study 20170544 PA7 clean

Document Number: CLIN-000007686

Approval Date: 08 Dec 2021

Type of Study Protocol: Amendment

Protocol Amendment No.: 7

Document Approvals	
Reason for Signing: Management	Name: [redacted] Date of Signature: 07-Dec-2021 17:48:12 GMT+0000
Reason for Signing: Functional Area	Name: [redacted] Date of Signature: 08-Dec-2021 17:34:40 GMT+0000

Amendment 7

Protocol Title: A Phase 1, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 890 in Subjects With Elevated Plasma Lipoprotein(a)

Amgen Protocol Number (AMG 890) 20170544

Amendment Date: 07 December 2021

Rationale:

This protocol is being amended to enhance subject enrollment for cohort 9 by loosening eligibility restrictions on age, body mass index (BMI), and history of diabetes. Accumulated data thus far confirm that modifying these eligibility criteria are not expected to have an adverse impact on subject safety, pharmacokinetics, or pharmacodynamics.

Changes to the protocol text in Section 12 (safety) are in line with current Amgen protocol template.

Superseding Amendment 6

Protocol Title: A Phase 1, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 890 in Subjects With Elevated Plasma Lipoprotein(a)

Amgen Protocol Number (AMG 890) 20170544

IND number BB-IND 136605

Amendment Date: 25 March 2021

Rationale:

This protocol is being amended to:

- Update made to the protocol to the Schedule of Assessments for cohorts 1 to 9
- Update the Pregnancy Notification Form
- Administrative, typographical, and formatting changes were made throughout the protocol.

Amendment 6

Protocol Title: **A Phase 1, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 890 in Subjects with Elevated Plasma Lipoprotein(a)**

Amgen Protocol Number AMG890 20170544

Amendment Date: 21 December 2020

Rationale:

This protocol was amended because editorial updates were needed to align with current safety language in the new template, change the vendor providing laboratory analyses, add urinalysis at day 85 for cohorts 8 and 9, clarify the enrollment status of cohorts 1-8, and make other administrative/editorial updates.

Amendment #5

Protocol Title: A Phase 1, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 890 in Subjects With Elevated Plasma Lipoprotein(a)

Amgen Protocol Number AMG 890 20170544

Amendment Date: 13 December 2019

Rationale:

The protocol is being amended to add 2 SAD cohorts evaluating 225 mg (cohort 8) and 675 mg (cohort 9) in subjects with high baseline Lp(a) ≥ 200 nM. The highest doses of AMG 890 tested to date, which have been observed to be well tolerated with no safety signals, are 225 mg in low baseline Lp(a) subjects (cohort 5) and 75 mg in high baseline Lp(a) subjects (cohort 7). In cohorts 1 to 7 of this study, considerable variability has been observed in PK and Lp(a) response between low and high baseline Lp(a) subjects. Given these differences, the 225 mg and 675 mg cohorts in high baseline Lp(a) subjects (cohorts 8 and 9) will allow for more intensive and robust PK and Lp(a) data evaluation to support broader options for AMG 890 Ph 3 dose and regimen selection. The 675 mg dose (cohort 9), in turn, is also anticipated to provide a wide range of exposures with minimal overlap in exposure distributions across subjects with high baseline Lp(a) (~9 fold increase from 9 mg in cohort 6 to 675 mg in cohort 9), and to provide additional safety information at a higher dose and with longer durations of Lp(a) suppression.

Also, administrative and typographical changes were made.

Amendment #4

Protocol Title: A Phase 1, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 890 in Subjects With Elevated Plasma Lipoprotein(a)

Amgen Protocol Number AMG 890 20170544

Amendment Date: 17 May 2019

Rationale:

The protocol is being amended to clarify that Lp(a) samples are to be collected at days 155 and 183 for cohorts 3 to 5. Inadvertently, Lp(a) measurement collections were not noted on Table 5: Schedule of Assessments – Post-Dosing for Cohorts 1-5 on study days 155 and 183, and the number of times and blood volume collected were not correctly reflected in the Informed Consent Form (ICF). Table 3: Tests & Procedures of the ICF does correctly state that blood tests for Lp(a) will be collected at Screening, days 1, 2, 4, 7, 15, and all visits through end of treatment for cohorts 3 to 5.

Also, administrative and typographical changes were made.

Amendment #3

Protocol Title: A Phase 1, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 890 in Subjects With Elevated Plasma Lipoprotein(a)

Amgen Protocol Number AMG 890 20170544

Amendment Date: 02 May 2019

Rationale:

The protocol is being amended for the following reasons: to update key study contact personnel, to define the dose in cohort 7 as 75 mg and to update inclusion and exclusion criteria for cohorts 6 and 7. Exclusion criterion 209 was updated to exclude subjects on stable dose of statin in cohorts 6 and 7 if the ALT or AST is > 1.5 the upper limit of normal of the laboratory's reference at screening or at day -3 to -1. In addition, exclusion criterion 219 was updated to permit subjects in cohorts 6 and 7 to be on stable medications for chronic medical conditions not otherwise excluded. These updates are not expected to impact the safety of the subjects. Updates to the Schedule of Assessment tables were also made to correct the study hour for day 7 and to add vital sign measurements on day -3 to day -1 for cohorts 6 and 7.

Also, administrative, typographical and formatting changes were made throughout the protocol.

Amendment #2

Protocol Title: A Phase 1, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 890 in Subjects With Elevated Plasma Lipoprotein(a)

Amgen Protocol Number AMG 890 20170544

Amendment Date: 07 February 2019

Rationale:

As of 6 February 2019, AMG 890 was administered as a single subcutaneous dose of 3, 9, 30, 75, and 225 mg to 30 subjects (6 per dose level) with elevated Lp(a) levels subjects. Doses up to 75 mg were reviewed by the dose level review team and found to be safe and tolerated to date. At the time of this amendment, subjects in the 225 mg dose cohort have completed dosing and have been followed for 7 days without incident. Based on the preliminary pharmacodynamic results no further dose escalation (ie, to 675 mg) is necessary, and monthly dosing will not be selected as a dosing regimen in future AMG 890 studies. Therefore, the 675 mg single dose cohort and the multiple ascending dose cohorts (ie, AMG 890 or placebo Q4W x 3) have been removed from the protocol.

Changes implemented include:

- Removing the multiple ascending dose (MAD) cohorts and SAD cohort 6 (675 mg dose)
- Adding two new SAD cohorts (6 and 7) that will enroll the same population that would have been assessed in the removed MAD cohorts
- Increasing the number of sites participating in the study
- Updating of the definitions of end of treatment visit and end of study visit
- Updating the requirements for the follow-up of subjects who at the end of treatment visit have plasma Lp(a) levels that have not returned to ≥ 80% of baseline

- Updating the secondary endpoint to reflect that the assessment of change in Lp(a) levels will be through the end of treatment visit
- Specifying the planned primary and final analyses
- Updating the definition of baseline for Lp(a)
- Updating the inclusion and exclusion criteria
- Updating the Dose Level Review Team (DLRT)

The use of Self Evident Corrections is being removed according to current Amgen practice.

Current Amgen forms have been updated for the following forms: electronic SAE Contingency Form, Lactation Notification Form, Pregnancy Form.

Also, administration, typographical and formatting changes were made throughout the protocol.

Amendment #1

Protocol Title: A Phase 1, Randomized, Double-blind, Placebo-controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 890 in Subjects with Elevated Plasma Lipoprotein(a)

Amgen Protocol Number AMG 890 20170544

Amendment Date: 20 September 2018

Rationale:

This protocol is being amended to add additional safety laboratory and ECG assessments; to add two additional days for urine PK sampling; to clarify exclusion criteria; to implement operational changes; and to remove redundancy within the exploratory biomarker endpoints, [redacted]. These changes will refine the protocol's readability, allow for the implementation of operational changes, and will improve quality of data generation.

In addition, changes have been made to the protocol to improve the readability, the clarity, and the consistency throughout the protocol.

One of the Key Contacts for the study has been updated.