Title: A RaNdomized Double-blInd Placebo ConTrolled Study Characterizing THe Effects of PCSK9 Inhibition On Arterial Wall Inflammation in Patients With Elevated Lp(a) (ANITSCHKOW)

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Investigator's Agreement

I have read the attached protocol entitled "A RaNdomized Double-blInd Placebo ConTrolled Study Characterizing THe Effects of PCSK9 Inhibition On Arterial Wall inflammation in Patients with Elevated Lp(a) (ANITSCHKOW)", dated **08 February 2017**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on 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 one 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)

Protocol Synopsis

Title: A RaNdomized Double-blInd Placebo ConTrolled Study Characterizing THe Effects of PCSK9 Inhibition On Arterial Wall inflammation in Patients with Elevated Lp(a) (ANITSCHKOW)

Study Phase: 3b

Indication: Hyperlipidemia

Primary Objective:

- To evaluate the effect of evolocumab on arterial wall inflammation, as measured by percent change from baseline in target-to-background ratio (TBR) of an index vessel by fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) at week 16 in subjects with baseline lipoprotein (a) [Lp(a)] ≥ 50 mg/dL and low density lipoprotein-cholesterol (LDL-C) ≥ 100 mg/dL

Secondary Objectives:

- To evaluate the effect of evolocumab on Lp(a), as measured by percent change from baseline at week 16 in subjects with baseline Lp(a) ≥ 50 mg/dL and LDL-C ≥ 100 mg/dL
- To evaluate the effect of evolocumab on LDL-C, as measured by percent change from baseline at week 16 in subjects with baseline Lp(a) ≥ 50 mg/dL and LDL-C ≥ 100 mg/dL
- To evaluate the effect of evolocumab on Apolipoprotein B (ApoB), as measured by percent change from baseline at week 16 in subjects with baseline Lp(a) ≥ 50 mg/dL and LDL-C ≥ 100 mg/dL

Safety Objective: To evaluate the safety of evolocumab in subjects with baseline Lp(a) ≥ 50 mg/dL and LDL-C ≥ 100 mg/dL

Exploratory Objectives:

CCI

Hypotheses: The primary clinical hypothesis is that administration of evolocumab 420 mg subcutaneous (SC) monthly will result in greater change from baseline TBR at week 16 than placebo in subjects with elevated baseline Lp(a).

Primary Endpoint: Percentage change from baseline in TBR within the MDS of the index vessel (right carotid, left carotid, or thoracic aorta) by FDG-PET/CT at week 16.

Secondary Endpoint(s):

- Percentage change in Lp(a) from baseline at week 16
- Percentage change in LDL-C from baseline at week 16
- Percentage change in ApoB from baseline at week 16

Safety Endpoints: Subject incidence of treatment-emergent adverse events compared to placebo for the duration of the study

Exploratory Endpoints:

CCI

[redacted]

Study Design: This is a phase 3b, multi-center, double-blind, randomized, placebo-controlled study evaluating the effect of evolocumab on arterial wall inflammation as measured by FDG-PET/CT following 16 weeks of treatment in subjects with elevated levels of Lp(a).

Sample Size: Approximately 120 subjects will be enrolled in the study.

Summary of Subject Eligibility Criteria: The study will enroll adult subjects (≥ 50 years of age) with elevated levels of lipoprotein(a) and LDL-C and TBRmax > 1.6 of (carotid arteries or aorta) by FDG-PET/CT. Those subjects receiving lipid-lowering therapy (not required), including statin, must be on a dose that remained unchanged for ≥ 8 weeks prior to screening. For a full list of eligibility criteria, please refer to Section 4.1.

Investigational Product (IP): Evolocumab or matching placebo administered by prefilled autoinjector (AI)/pen

Amgen Investigational Product Dosage and Administration:

Evolocumab 420 mg or matching placebo will be administered once monthly (QM) for 12 weeks as a SC injection with a total volume of 3.0 mL, via 3 separate autoinjections of 1.0 mL. The SC injections with the AI/Pen should be administered in a consecutive fashion with all injections completed within 30 minutes.

Procedures:

After subjects complete the informed consent form, they will be screened. Two screening visits (screen 1 and screen 2) will be conducted. Subjects should complete all the required tests and procedures in screen 1 and the site will confirm that the subject meets the inclusion criteria based on these procedures before the subject proceeds to the procedures in screen 2.

Screening evaluations will include complete medical and medication history; vital signs; physical examination; measurement of body weight, waist circumference, and height; and laboratory tests (fasting lipids, Lp(a), chemistry, estimated glomerular filtration rate, hemoglobin A1C, and, if applicable, serum pregnancy and follicle-stimulating hormone**)**. FDG PET/CT will be conducted at the screen 2 visit. Subjects will receive a placebo administration with three 1.0 mL SC injections with the prefilled AI/Pen to confirm tolerance of SC administration at the screen 2 visit (considered the placebo run-in). At this time, the subject will receive instruction/training on AI/Pen use. The maximum total screening period is 56 days, including both screen 1 and screen 2.

Subjects who meet all eligibility criteria at the end of the screening period will be randomized and will return within 3 days of randomization for day 1 procedures. Those subjects receiving lipid lowering therapy (not required to participate in this study) will continue to receive the same dose of their background lipid-lowering treatment during the entire time of screening and throughout the study.

Baseline evaluations will be performed on day 1 of treatment before subjects receive the first dose of investigational product. Laboratory tests will be conducted at day 1 (fasting lipids, Lp(a), OxPL/ApoB, IL-6, hsCRP1, biomarkers, hematology, urinalysis, and Lp(a) isoform number, hematology, and urinalysis) and week 8 (fasting lipids and Lp(a)). Adverse events, serious adverse events, adverse device effects (ADE)s, disease-related events, and changes in concomitant medications will be recorded at each visit. At the end of study visit at week 16,

FDG-PET/CT and laboratory tests (fasting lipids, Lp(a), OxPL/ApoB, IL-6, hsCRP1, biomarkers [serum, plasma and cell], and Lp(a) isoform number) will be conducted and adverse events, serious adverse events, ADEs, disease-related events, and changes in concomitant medications will be recorded.

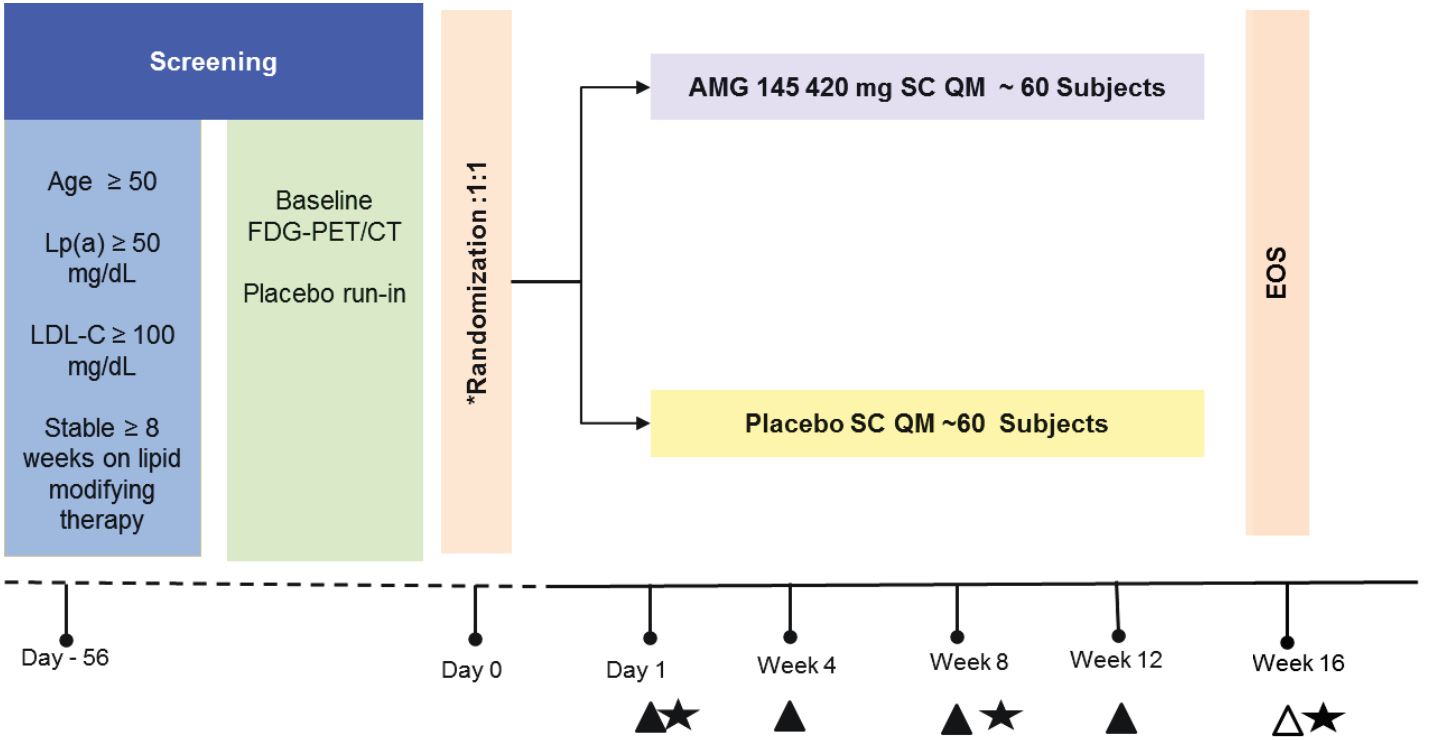
The overall study design is described by a study schema at the end of this synopsis section. For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 1).

Statistical Considerations: The superiority of evolocumab to placebo will be assessed for all efficacy endpoints on the full analysis set (FAS), which includes all randomized subjects who receive at least one dose of IP. The primary endpoint is the percentage change from baseline in MDS TBR at week 16. Percentage change for MDS TBR will be modeled as an analysis of covariance (ANCOVA) model with the treatment group and the stratification factor in the model. FDG-PET/CT observations made after an on-study cardiovascular event will be included in the primary analysis, and a sensitivity analysis excluding these observations will be conducted. To handle missing data, the correlations between the model errors as well as baseline values of MDS TBR and Lp(a) (and on-study percent change from baseline in Lp(a)) will be modeled. Analysis of the secondary endpoints Lp(a), ApoB and LDL-C will use a repeated measures model on the FAS including terms for treatment group, stratification factors, scheduled visit, and the interaction of treatment with scheduled visit. Safety endpoints will be summarized descriptively by treatment group. For a full description of statistical analysis methods, please refer to Section 10.

Sponsor: Amgen Inc.

Data Element Standards Version(s)/Date(s):	5: 20 March 2015

Study Design and Treatment Schema



Primary endpoint:

- **Arterial wall inflammation measured by FDG-PET/CT (percentage change in target-to-background ratio (TBR) within the most diseased segment (MDS) of the index vessel)**

▲ **SC IP Administration at study site and safety assessment**

△ **FDG-PET/CT**

★ **Blood draw**

*If FDG-PET/CT TBR max of index vessel >1.6

Study Glossary

Abbreviation or Term	Definition/Explanation
ADE	adverse device effect
AE	adverse event
AI	autoinjector
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
Apo(a)	apolipoprotein(a)
Apo(B)	apolipoprotein(B)
AST	aspartate aminotransferase
CHD	coronary heart disease
CI	confidence interval
CRF	case report form
CT	computed tomography
CTCAE	common terminology criteria for adverse events
DILI	drug induced liver injury
DRE	disease-related event
EDC	electronic data capture
eGRF	estimated glomerular filtration rate
End of Study (end of trial)	defined as the date when the last subject has completed all planned study procedures up to and including the End of Study visit as outlined in the Schedule of Assessments
End of Study (primary completion)	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)
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
EOS	end of study
FAS	full analysis set
FDG	fluorodeoxyglucose
FDG-PET/CT	fluorodeoxyglucose-positron emission tomography/computed tomography
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HDL-C	high-density lipoprotein cholesterol
hsCRP	high sensitivity C-reactive protein

Abbreviation or Term	Definition/Explanation
ICF	informed consent form
ICH	International Conference on Harmonisation
IL-6	Interleukin-6
IMP	investigational medicinal product
INR	international normalized ratio
IP	investigational product
IPIM	Investigational Product Instruction Manual
IRB/IEC	institutional review board/independent ethics committee
IVRS	interactive voice response system, telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.
IWRS	interactive web response system
LDL-C	Low-density lipoprotein-cholesterol
LDLR	low-density lipoprotein receptor
Lp(a)	lipoprotein(a)
MDS	most diseased segment
NSAID	nonsteroidal anti-inflammatory drug
OxPL	oxidized phospholipids
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
QM	once monthly
SAE	serious adverse event
SC	subcutaneous
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline (E6)). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study Day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
SUV	standardized uptake value
TBL	total bilirubin
TBR	target-to-background ratio
ULN	upper limit of normal

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1. OBJECTIVES

1.1 Primary

To evaluate the effect of evolocumab on arterial wall inflammation, as measured by percent change from baseline in target-to-background ratio (TBR) of an index vessel by fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) at week 16 in subjects with baseline lipoprotein (a) [Lp(a)] ≥ 50 mg/dL and low density lipoprotein-cholesterol (LDL-C) ≥ 100 mg/dL

1.2 Secondary

- To evaluate the effect of evolocumab on Lp(a), as measured by percent change from baseline at week 16 in subjects with baseline Lp(a) ≥ 50 mg/dL and LDL-C ≥ 100 mg/dL
- To evaluate the effect of evolocumab on LDL-C, as measured by percent change from baseline at week 16 in subjects with baseline Lp(a) ≥ 50 mg/dL and LDL-C ≥ 100 mg/dL
- To evaluate the effect of evolocumab on Apolipoprotein B (ApoB), as measured by percent change from baseline at week 16 in subjects with baseline Lp(a) ≥ 50 mg/dL and LDL-C ≥ 100 mg/dL

1.3 Safety

- To evaluate the safety of evolocumab in subjects with baseline Lp(a) ≥ 50 mg/dL and LDL-C ≥ 100 mg/dL

1.4 Exploratory

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2. BACKGROUND AND RATIONALE

2.1 Disease

Hyperlipidemia is a heterogeneous group of disorders characterized by an excess of lipids (ie, cholesterol, phospholipids, triglycerides) in the bloodstream. Primary hyperlipidemia is usually due to genetic causes (monogenetic or polygenetic) and environmental factors, such as diet and lifestyle. Primary nonfamilial hyperlipidemia is

hyperlipidemia that is not due to a specific genetic disorder, although there are polygenetic influences. Mixed dyslipidemia is generally defined as elevated LDL-C and high triglycerides and/or low high-density lipoprotein cholesterol (HDL-C). Data from epidemiologic studies show that LDL-C is a strong independent predictor of coronary heart disease (CHD) risk across diverse patient populations (The Emerging Risk Factors Collaboration, 2009).

Lipoprotein(a) [Lp(a)] is a modified form of LDL. It is composed of an LDL particle covalently bound to apolipoprotein(a) [apo(a)]. Lipoprotein (a) is distinctly different from other plasma lipoproteins given that it is an assembly of two critical elements; a central core linked by a disulfide bridge to a signature protein, apo(a). The first element shares similarities with LDL, is rich in cholesterol and contains ApoB. The other element, apo(a), consists of a number of pleated structures, kringles IV and V, of which kringle IV type 2 is repeated in a variable number, from 2 to more than 40 times. The variation in kringle IV type 2 repeats gives rise to considerable differences in the size and molecular weight of apo(a) and is the major determinant of Lp(a) plasma level (up to 90%) (Dube et al, 2012).

Serum levels of Lp(a) are primarily dependent on the production of apo(a), which is mainly regulated genetically. Lipoprotein (a) collects in the arterial wall and is subsequently scavenged by macrophages (Koschinsky and Marcovina, 2004). Additionally, Lp(a) is homologous to plasminogen and competitively inhibits binding of fibrin to plasminogen. Lipoprotein (a) may therefore enhance thrombosis due to endothelial damage by interfering with the conversion of plasminogen to plasmin (Rouy et al, 1991).

Serum levels of Lp(a) have a positive, continuous association with CHD risk, which is independent of LDL-C, non-HDL-C, and other cardiovascular risk factors (Nordestgaard et al, 2010, and Kamstrup et al, 2009). For instance, in a meta-analysis of 24 cohort studies, Erqou et al (2009) identified a 13% increase in CHD risk (95% confidence interval [CI] 9–18) per 3.5-fold elevation in Lp(a) concentrations. However, the beneficial effects of pharmacological intervention to reduce Lp(a) on cardiovascular risk remain to be determined. Despite a strong pathophysiologic rationale supporting reduction of Lp(a) as a therapeutic target, reliable pharmacologic means of reducing Lp(a) are still needed (Tziomalos et al, 2009). When low-density lipoprotein receptor (LDLR) is highly expressed and ApoB is low, the LDLR appears to play a key role in hepatic catabolism of Lp(a); proprotein convertase subtilisin/kexin type

9 (PCSK9) inhibits these processes, which provides a mechanism for direct reduction of Lp(a) with PCSK9 inhibition (Romagnuolo et al, 2015).

2.2 Amgen Investigational Product Background

Recycling of the hepatic cell surface LDLR plays a critical role in regulating serum LDL-C levels. Proprotein convertase subtilisin/kexin type 9 binds to the LDLR and downregulates hepatic cell surface LDLR, which, in turn, leads to increased levels of circulating LDL- C. Humans with PCSK9 loss-of-function mutations have cholesterol levels lower than normal and reduced incidence of CHD (Abifadel et al, 2009). Evolocumab (formerly referred to as AMG 145) is a fully human monoclonal immunoglobulin G2, developed at Amgen Inc., that specifically binds to PCSK9 preventing its interaction with the LDLR. The inhibition of PCSK9 by evolocumab leads to increased LDLR expression and subsequent decreased circulating concentrations of LDL-C.

Refer to the Evolocumab Investigator's Brochure for more information on evolocumab.

2.3 Rationale

Beyond the atherogenic potential of the Lp(a) LDL-like core, Lp(a) appears to be the preferential carrier of OxPL in the plasma and thus closely involved in atherosclerotic inflammation (Leibundgut et al, 2013). The inflammatory response to the accumulation of oxidized lipids in the artery wall plays a pivotal role in the atherosclerotic disease process, and plaque inflammation is associated with plaque rupture and atherothrombotic events (Tsimikas and Hall, 2012). It remains to be shown whether lowering Lp(a) can reverse these changes, providing a crucial link between lipid lowering and decreased inflammatory activity. Whereas, Lp(a) is relatively refractory to both lifestyle and drug intervention, evolocumab 420 mg once monthly (QM) reduced Lp(a) by approximately 28% compared to placebo measured using the mean of weeks 10 and 12, in phase 3 evolocumab studies (20110114, 20110115, and 20110117). The safety and efficacy of evolocumab 420 mg subcutaneous (SC) QM in adults has been extensively studied in phase 2 and phase 3 clinical trials.

Over the last decade FDG-PET/CT has shown great potential in visualizing, quantifying, and characterizing atherosclerotic inflammation non-invasively (Rosenbaum et al, 2012) and is a highly sensitive modality that can be utilized as a surrogate imaging marker for vessel wall inflammation (Joshi et al, 2011). FDG-PET/CT imaging has been shown to be reproducible for imaging of atherosclerotic plaque inflammation (Rudd et al 2007) and the FDG uptake signal correlates with macrophage content (Tawakol et al, 2006). In

quantitative PET/CT image analysis, the artery (right carotid, left carotid, or thoracic aorta) with the highest FDG uptake (highest mean of the maximum TBR at baseline) is identified as the index vessel. The maximum standardized uptake value (SUV) is calculated as a time- and dose- corrected tissue radioactivity divided by body weight for each region of interest and the TBR is calculated from the ratio of the SUV of the artery compared to mean background venous activity. FDG uptake signal is expressed as TBR of the whole index vessel or the MDS of the index vessel. The MDS is defined as the 1.5-cm arterial segment, centered on the slice of artery demonstrating the highest FDG uptake at baseline, and calculated as a mean of maximum TBR values derived from 3 contiguous axial segments (Fayad et al, 2011). These assessments have been used as standard endpoints in the most recent trials for the evaluation of arterial wall inflammation with various lipid-lowering treatments (van Wijk et al, 2014; Tawakol et al, 2013; Fayad et al, 2011).

The primary endpoints of this study are the percentage change from baseline in the arterial wall inflammation by FDG-PET/CT assessed as a TBR within the MDS of the index vessel (carotid arteries or aorta) at week 16.

2.4 Clinical Hypotheses

The primary clinical hypothesis is that administration of evolocumab 420 mg SC QM will result in greater change from baseline TBR at week 16 than placebo in subjects with elevated baseline Lp(a).

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 3b, multi-center, double-blind, randomized, placebo-controlled study evaluating the effect of evolocumab on arterial wall inflammation as measured by FDG-PET/CT following 16 weeks of treatment in subjects with elevated levels of Lp(a). Eligible subjects will have hyperlipidemia with Lp(a) $\geq$ 50 mg/dL and LDL-C $\geq$ 100 mg/dL. In addition, the subjects must have TBR max $>$ 1.6 on FDG PET/CT in order to qualify for enrollment. If subjects are on statin or other lipid-lowering therapy (not required to participate in this study), they must be on a stable dose for at least 8 weeks prior to screening and during the entire time of screening and throughout the study.

The study will include 2 screening visits (screen 1 and screen 2) during the screening period, which will be a maximum total of 56 days. Subjects will be randomized 1:1 into 2 treatment groups: evolocumab 420 mg QM SC or placebo QM SC. Randomization will be stratified for balance by baseline background statin therapy (on statin vs not on

statin) and by screening Lp(a) (< 175 mg/dL or ≥ 175 mg/dL). The treatment period will be 12 weeks in duration with study visits every 4 weeks. At the end of study (EOS) visit at week 16, FDG PET/CT will be conducted.

The overall study design is described by a study schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

Approximately 9 sites in the Netherlands will participate in this study. Other sites and countries may be added if required to meet recruitment goals.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as "subjects". Approximately 120 subjects will be enrolled.

3.4 Replacement of Subjects

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

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

Including the screening and study treatment, the maximum duration of study participation for a subject will be 24 weeks. After signing the informed consent form (ICF), subjects should be randomized within 56 days.

3.5.2 End of Study

The EOS and the primary completion date are defined as the date on which the last subject completes the week 16 EOS visit procedures or ends the study early.

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening). This log may be completed and updated via an interactive voice response (IVRS) system/interactive web response system (IWRS).

Before any study-specific activities/procedure, the appropriate written informed consent must be obtained (see Section 11.1).

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria – Assessed at Screening 1

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

102 Male or female, ≥ 50 years of age at the time of informed consent

103 Subject with fasting Lp(a) ≥ 50 mg/dL at screening 1

104 Subject with fasting LDL-C ≥ 100 mg/dL at screening 1

105 For those subjects receiving lipid lowering therapy (not required to participate in this study), lipid-lowering therapy, including statin dose, must be unchanged for ≥ 8 weeks prior to screening

4.1.2 Inclusion Criteria – Assessed at Screening 2

106 Subjects with TBRmax > 1.6 (either right carotid, left carotid or thoracic aorta) on FDG-PET/CT

4.1.3 Exclusion Criteria

201 Currently receiving, or less than 4 weeks since receiving, treatment in another investigational device or drug study(ies), or participating in other investigational procedures

202 Known diagnosis of diabetes mellitus or screening fasting serum glucose ≥ 126 mg/dL or HbA1C ≥ 6.5%

203 Subject with a history of homozygous familial hypercholesterolemia

204 Recent cardiovascular event (myocardial infarction, unstable angina, percutaneous coronary intervention (PCI), coronary artery bypass graft, or stroke) within 3 months prior to randomization, or planned cardiac surgery, PCI or carotid stenting, or planned major non-cardiac surgery during the course of the study period

205 Subject currently undergoing lipid apheresis

206 Known contraindications or limitations to FDG-PET/ CT (eg, scanner weight limit, devices that can cause image artifacts, or carotid/aortic stents/grafts)

207 Auto-immune disease/vasculitis, active inflammatory diseases, proven or suspected bacterial infections. Recent (< 1 month prior to screening) or ongoing serious infection requiring intravenous antibiotic therapy

208 Recent (< 6 weeks prior to screening) or current treatment with medications that may have a significant effect on plaque inflammation as measured by plaque TBR, including: oral, rectal, or injectable corticosteroids or immunosuppressive medications (eg, cyclosporine, methotrexate, tacrolimus, azathioprine, anti-thymocyte globulin, sirolimus, anti-TNF agents such as infliximab, anti-IL6 therapy such as tocilizumab, or anti-IL1 therapy)

209 Recent (< 6 weeks prior to screening) or current treatment with aspirin (> 325 mg/day) or nonsteroidal anti-inflammatory drugs (NSAIDs) (> 1000 mg/day)

210 Known sensitivity to any of the active substances or excipients (eg, carboxymethylcellulose) to be administered during dosing

211 Subject has taken a cholesterol ester transfer protein inhibitor (eg, anacetrapbib, dalcetrapib, evacetrapib) or mipomersen or lomitapide in the last 12 months prior to screening

212 Known systemic disorders such as hepatic, renal, hematologic, and malignant diseases or any clinically significant medical condition that could interfere with the conduct of the study

213 History of malignancy (except non-melanoma skin cancers, cervical in-situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma) within the last 5 years

214 Subject likely to not be available to complete all protocol-required study visits or procedures, or unreliability as a study participant (eg, alcohol or other drug abuse in the past year or psychosis), to the best of the subject's and investigator's knowledge

215 History or evidence of any other clinically significant disorder, condition or disease that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion

216 Subject has previously received evolocumab or any other therapy to inhibit PCSK9

217 Female subject who is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment with investigational medicinal product (IMP) (evolocumab or placebo) and for an additional 15 weeks after the last dose of IMP (evolocumab or placebo)

218 Female subject is not willing to use an acceptable method(s) of effective birth control during treatment with IMP (evolocumab or placebo) and for an additional 15 weeks after the end of treatment with IMP (evolocumab or placebo). Female subjects, who have had a hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or who are postmenopausal, are not required to use contraception

- Menopause is defined as 12 months of spontaneous and continuous amenorrhea in a female ≥ 55 years old; or age < 55 years but no spontaneous menses for at least 2 years; or age < 55 years and spontaneous menses within the past 1 year, but currently amenorrheic (eg, spontaneous or secondary to hysterectomy), and with postmenopausal gonadotropin levels (luteinizing hormone and follicle stimulating hormone levels > 40 IU/L) or postmenopausal estradiol levels (< 5 ng/dL) or according to the definition of "postmenopausal range" for the laboratory involved.

– Acceptable methods of effective birth control include: true sexual abstinence if this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception); surgical contraceptive methods (male partner who has had vasectomy with medical confirmation of surgical success or bilateral tubal ligation), use of hormonal birth control methods (oral, injectable, implantable transdermal, or intravaginal), intrauterine device, intrauterine hormone-releasing system, or 2 barrier methods (each partner must use 1 barrier method– males must use a condom with spermicide and females must choose either a diaphragm with spermicide, OR cervical cap with spermicide, OR contraceptive sponge with spermicide).

Note: Additional medications given during treatment with evolocumab may alter the contraceptive requirements. These additional medications may require an increase in the number of contraceptive methods and/or length of time that contraception is to be utilized or length of time breastfeeding is to be avoided after the last dose of protocol-required therapies. The investigator is to discuss these contraceptive changes with the study subject.

219 Subject has had exposure to investigational drugs targeting Lp(a) within the last 12 months, prior to Screening.

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, ICF, and all other subject information and/or recruitment material, if applicable (see Section 11.2). All subjects must personally sign and date the ICF before commencement of study specific activities/procedures.

Upon completion of the screening period the subject is evaluated by the investigator and providing the subject continues to meet the inclusion/exclusion criteria, the subject is subsequently eligible to be enrolled in the study and randomized. Subjects will be enrolled on the day they are randomized. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (defined as the point at which the subject signs the ICF) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by the IVRS/IWRS. 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 are unable to complete or meet the initial Part 1 eligibility criteria

(see Section 4.1.1) will be permitted to rescreen but any subject who does not meet the Part 2 criteria eligibility (Section 4.1.2) will not be allowed to rescreen.

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

5.1 Randomization/Treatment Assignment

Subjects who meet the eligibility requirements (Section 4.1) will be randomly assigned in a 1:1 allocation ratio to 2 treatment groups (evolocumab and placebo) in a double-blind manner. Randomization will be stratified by baseline background statin therapy (on statin vs not on statin) and by screening Lp(a) ($<$ 175 mg/dL or $\geq$ 175 mg/dL).

The randomization date is to be documented in the subject's medical record and on the enrollment CRF. Randomization numbers will be provided to the site through an IVRS/IWRS.

5.2 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject on this study. Unblinding at the study site for any other reason will be considered a protocol deviation. The investigator is strongly encouraged to contact the Amgen Clinical Study Manager before unblinding any subject's treatment assignment, but must do so within 1 working day after the event.

6. TREATMENT PROCEDURES

6.1 Classification of Product and Medical Device

The Amgen investigational product (IP) used in this study includes: evolocumab and matching placebo (IMP) in a prefilled autoinjector (AI)/Pen (investigational medical device).

Note: Ancillary device(s) (ie, medical device(s) not under study) are described in Section 6.5.

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

6.2 Investigational Product

6.2.1 Amgen Investigational Product

Evolocumab and matching placebo will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures.

Evolocumab will be supplied in a prefilled AI/Pen with a volume of 1.0 mL.

Placebo will be presented in identical containers and stored/packaged the same as evolocumab.

6.2.1.1 Dosage, Administration, and Schedule

6.2.1.1.1 Placebo Run-in

Subjects will receive a placebo administration with three 1.0 mL SC injections with the prefilled AI/Pen to confirm tolerance of SC administration at screening visit 2. The SC injections with the AI/Pen should be administered in a consecutive fashion with all injections completed within 30 minutes.

6.2.1.1.2 Randomized Treatment Period

The IP (420 mg evolocumab or matching placebo via AI/Pen) will be administered QM for 12 weeks on day 1, week 4 (± 7 days); week 8 (± 7 days); and week 12 (± 7 days).

The IP will be administered as an SC injection with a total volume of 3.0 mL QM, via 3 separate autoinjections of 1.0 mL administered consecutively with all injections completed within 30 minutes.

The IP will be administered in accordance with instructions in the IPIM and the Instructions for Use. All doses of evolocumab and placebo are mandated to be administered at the study site. Investigational product administration by SC injection must occur after after all other visit assessments are completed. After IP administration at the first dosing visit, subjects will be held for observation for at least 30 minutes before being discharged.

The date and completion time of administration, the body location of the injection, and whether the injection was fully or partially administered are to be recorded on each subject's CRF.

Overdose with this product has not been reported.

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

No dose adjustments are allowed in this study. If, in the opinion of the investigator, a subject is unable to tolerate a specific dose of IP, that subject will discontinue IP but will continue to return for all other study procedures and measurements until the EOS.

If a subject is late for administration of IP, administration should occur as soon as possible. A dose of IP should not be administered within less than 7 days of a previous dose. If a subject arrives for a visit with IP administration and IP was administered within the prior 7 days, the dose should not be administered but all other study procedures should be conducted. Administration of IP should occur as soon as possible but at least 7 days after the previous administration. Subjects who completely miss a dose of IP will continue in the study and receive the next dose of IP per their schedule of administration.

6.3 Hepatotoxicity Stopping and Rechallenge Rules

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

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

Evolocumab should be discontinued permanently and the subject should be followed according to the recommendations in Appendix A (Additional Safety Assessment Information) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:

- TBL > 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 TBL values include, but are not limited to:
  - Hepatobiliary tract disease
  - Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
  - Right sided heart failure, hypotension, or any cause of hypoxia to the liver causing ischemia
  - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms
  - Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
  - Alpha-one antitrypsin deficiency
  - Alcoholic hepatitis
  - Autoimmune hepatitis
  - Wilson's disease and hemochromatosis
  - Nonalcoholic fatty liver disease including steatohepatitis
  - Non-hepatic causes (eg, rhabdomylosis, hemolysis)

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

For subjects who do not meet the criteria for permanent discontinuation of evolocumab outlined above and have no underlying liver disease, and eligibility criteria requiring transaminases and TBL < 1.5x ULN at baseline or subjects with underlying liver disease and baseline abnormal transaminases, the following rules are recommended for withholding of Amgen IP and other protocol-required therapies:

- Elevation of either AST or ALT according to the following schedule:

Baseline AST or ALT value	AST or ALT elevation
Any	> 8x ULN at any time
Any	> 5x ULN but < 8x ULN for ≥ 2 weeks
Any	> 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule
Any	> 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice).

- OR: TBL > 3x ULN at any time
- OR: ALP > 8x ULN at any time

Evolocumab should be withheld pending investigation into alternative causes of DILI. If IP is withheld, the subject is to be followed according to recommendations in Appendix A for possible DILI. Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (Section 6.3.3).

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

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

If signs or symptoms recur with rechallenge, then evolocumab should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.3.1) should never be rechallenged.

6.4 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 6.7. If subjects are on statin or other lipid lowering therapy (not required to participate in this study), they must be on a stable dose for at least 8 weeks prior to screening and during the entire time of screening and throughout the study.

Concomitant therapies are to be collected in the CRF from the signing of the ICF through the EOS visit.

For concomitant therapies being taken for hyperlipidemia, collect therapy name, indication, dose, unit, frequency, route, start date, and stop date. For other medications being taken, collect therapy name, indication, unit, frequency, route, start date and stop date.

6.5 Medical Devices

The prefilled AI/Pen used in this study will be provided by Amgen. Additional details for the AI/Pen is to be provided in the IPIM.

Other medical devices, which are not considered test articles, may be used in the conduct of this study as part of standard care. These devices that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

6.6 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 drugs or devices provisioned and/or repackaged /modified by Amgen. Drugs or devices includes evolocumab/placebo and prefilled AI/Pen.

Any product complaint(s) associated with an IP or device supplied by Amgen is to be reported according to the instructions provided in the IPIM.

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

The following treatments are not permitted during the study:

- Treatments for inhibition of PCSK9 or any investigational therapies other than study provided IP
- Any lipid therapies not taken at the time of screening and enrollment
- Treatment with medications that may have a significant effect on plaque inflammation as measured by plaque TBR, including: oral, rectal, or injectable corticosteroids or immunosuppressive medications (eg, cyclosporine, methotrexate, tacrolimus, azathioprine, anti-thymocyte globulin, sirolimus, anti-TNF agents such as infliximab, anti- IL6 therapy such as tocilizumab, or anti-IL1 therapy).
- Treatment with aspirin (> 325 mg/day) or NSAIDs (> 1000 mg/day)

Please contact the Amgen medical monitor or designee if any of these therapies should be initiated during the study. Note that a change in lipid-lowering therapy does not necessarily require ending IP (except in case of non-study provided PCSK9 inhibition therapy).

The following treatments are not recommended because of their potential impact on metabolism of certain statins:

- Medications or foods that are known potent inhibitors of CYP3A (eg, itraconazole, ketoconazole, and other antifungal azoles, macrolide antibiotics erythromycin, clarithromycin, and the ketolide antibiotic telithromycin, human immunodeficiency virus or hepatitis C virus protease inhibitors, antidepressant nefazodone and grapefruit juice in large quantities [> 1 quart daily, ie, approximately 1 L]) should not be used during the study.

7. STUDY PROCEDURES

Screening assessments and study procedures outlined in this section and in Table 1 can only be performed after obtaining informed consent.

All on-study visits should be scheduled from day 1 (date of the first dose of evolocumab/placebo) on the study. It is very important to attempt to perform study procedures and obtain samples at the precise timepoints stipulated below. When it is not possible to perform the study visit at the exact time point, the visit may be performed within the acceptable visit window as defined in the visit-specific section below.

With the exception of the screening and rescreen visits, all study procedures for a visit should be completed on the same day. Any missed visits, tests not done, or examinations that are not conducted must be reported as such on the CRFs. Subsequent study visits should resume on the original schedule. Missed assessments at prior visits should not be duplicated at subsequent visits.

Refer to the applicable supplemental laboratory manuals for detailed collection and handling procedures.

7.1 Schedule of Assessments

Screening assessments and study procedures are outlined in this section and in Table 1 (Schedule of Assessments).

Table 1. Schedule of Assessments

Study Day / Week / Other time point	Screen 1	Screen 2	Visit 1	Visit 2	Visit 3	Visit 4	EOS
	-56 days from Day 1		Day 1	Week 4 (± 7d)	Week 8 (± 7d)	Week 12 (± 7d)	Week16 (-7d)
General Procedures							
Informed consent	X						
Medical history	X						
Vital signs	X						
Review for AEs/SAEs/ADEs/DREs	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X
Physical exam	X						
Body weight, waist circumference, and height	X						
Randomization			X				
Laboratory							
Central Laboratory							
Fasting lipids	X		X		X		X
Lp(a)	X		X		X		X
OxPL/ApoB, IL-6, hsCRP[a]			X				X
Biomarkers (serum, plasma and cell pellet[b])			X				X
Lp(a) Isoform number			X				X
Chemistry	X						
Hematology			X				
Urinalysis			X				
eGFR	X						
Hemoglobin A1C	X						
Serum pregnancy and FSH[c]	X						
Local Laboratory							
Serum pregnancy and FSH[c]						X	
Investigational Product							
Placebo run-in		X					
Investigational Product (office) administration			X	X	X	X	
FDG-PET/CT		X[d,e]					X[d]

ADE=adverse device effect; AE=adverse event; DRE=disease-related event; eGFR=estimated glomerular filtration rate; hsCRP=high sensitivity C-reactive protein; Lp(a)=lipoprotein(a); OxPL/ApoB=oxidized phospholipids/apolipoprotein(B); SAE=serious adverse event.

[a] UCSD (OxPL/apoB) and Amgen (IL-6).

[b] Cell pellet is collected only at day 1 (residual cell pellet from the plasma biomarker sample).

[c] FSH will be performed if needed per Exclusion 218 (see Section 4.1.3).

[d] Pregnancy testing (either serum or urine) will be performed locally prior to the FDG-PET/CT scan.

[e] FDG-PET CT images need to be approved by the Core lab before the subject can be randomized.

7.2 General Study Procedures

The procedures performed at each study visit are outlined Table 1. Details regarding each type of procedure are provided in subsequent sub-sections.

Refer to the applicable supplemental central laboratory, IVRS/IWRS, IPIM, and study manuals for detailed collection and handling procedures.

7.2.1 Screening Enrollment and/or Randomization

Informed consent must be obtained before completing any other screening procedure or discontinuation of standard therapy for any disallowed therapy. After signing the written ICF, site will register the subject in the IVRS/IWRS and screen the subject in order to assess eligibility for participation. The screening window is 56 days. If a subject has not met all eligibility criteria at the end of the 56-day window, the subject will be registered as a screen fail. Screen fail subjects may be eligible for rescreening once as described in Section 7.2.2.

7.2.2 Rescreening

Subjects who are unable to complete or meet eligibility on initial screening will be permitted to rescreen once. Rescreen subjects must first be registered as screen failed in IVRS/IWRS and subsequently registered as rescreened. Subjects will retain the same subject identification number assigned at the original screening. Subjects who are to be rescreened must be re-consented and repeat all screening 1 procedures. Subjects can only undergo 1 initial FDG-PET/CT during screen 2; therefore subjects who screen fail on the basis of the TBR criteria may not be rescreened.

7.2.3 Treatment

Visits will occur per the Schedule of Assessments (Table 1) during the treatment period from day 1 (week 1, baseline) through week 12. Visits during the treatment period must be completed within $\pm$ 7 days of the target visit date.

Evolocumab/placebo is to be administered at the site after blood draw procedures. IP administration should be the last procedure to be performed during each visit.

If a subject withdraws from the study early, all efforts should be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. The procedures for the EOS visit should be completed at the time of withdrawal (Section 7.2.4).

7.2.4 End of Study Visit

At week 16, subjects will return to the site for the EOS visit for the procedures specified in the Schedule of Assessments (Table 1).

End of Study is defined as the date when the last subject has completed all planned study procedures up to and including the EOS visit as outlined in the Schedule of Assessments (Table 1).

Subjects who do not complete their EOS visit and assessments are considered early termination. Subjects who terminate the study early prior to week 12 will not be eligible to perform the final FDG-PET/CT imaging.

7.3 Description of Study Procedures

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

7.3.1 Informed Consent

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

7.3.2 Demographics

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

7.3.3 Medical History

The investigator or designee will collect a complete medical and surgical history that started within 120 days prior to enrollment through the signing of the ICF. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF.

In addition to the medical history above, cardiovascular history and history of cancer and/or malignancy must date back to the original diagnosis. Record all findings on the medical history CRF.

7.3.4 Physical Examination

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

7.3.5 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. 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 possible. The position selected for a subject should be the same throughout the study and documented on the vital signs CRF. The arm with the highest systolic reading at screening will then be used for further BP readings throughout study. The appropriate sized cuff should be used.

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

If abnormalities are found and they are considered an adverse event, record on the Event CRF.

7.3.6 Height, Weight, and Waist Circumference

Height in inches and weight in pounds should be measured without shoes.

For measurement of waist circumference, subjects should wear minimal clothing to ensure that the measuring tape is correctly positioned. Subjects should stand erect with the abdomen relaxed, arms at the sides, feet together and with their weight equally divided over both legs. To perform the waist measurement, the lowest rib margin is first located and marked with a pen. The iliac crest is then palpated in the midaxillary line, and also marked. It is recommended to apply an elastic tape horizontally midway between the lowest rib margin and the iliac crest, and tie firmly so that it stays in position around the abdomen about the level of the umbilicus. The elastic tape thus defines the level of the waist circumference, which can then be measured by positioning the measuring tape over the elastic tape. Subjects are asked to breathe normally, and to breathe out gently at the time of the measurement to prevent them from contracting their muscles or from holding their breath. Measurements should be performed using the same procedure throughout the study. The reading is taken to the nearest centimeter or ½ inch and entered in the source document.

7.3.7 Adverse Events, Serious Adverse Events, Adverse Device Effects, and Disease-related Events

Adverse events, serious adverse events, adverse device effects (ADE)s, and disease-related events observed by the investigator or reported by the subject will be collected at all study visits from the signing of the ICF through the EOS visit.

7.3.8 Prior and Concomitant Medications

Prior therapies, which include general and targeted therapies (eg, statins and lipid lowering), taken 6 months prior to enrollment should be collected with the following information: therapy name, indication, dose, unit, frequency, route, start date, and stop date.

Concomitant therapies are to be collected from the signing of the ICF through the EOS visit, and should include the therapy name, indication, dose, unit, frequency, route, start date, and stop date. Concomitant medications include over-the-counter products and vitamins administered while the subject is on study.

7.4 FDG-PET/CT

Subjects must be fasting prior to the FDG-PET/CT. FDG-PET/CT images of the carotid arteries and ascending thoracic aorta will be obtained using the standard methods (Fayad et al, 2011) as outlined in the study 20130293 imaging training. The blinded images will be analyzed by a central core lab. The initial step of image analysis entails delineating the pre-defined sections of the target vessels (either right carotid, left carotid, or thoracic aorta).

Arterial FDG uptake is measured within pre-defined sections of the target vessels and measurements in the aorta, right and left carotids are made. The maximum SUV will be calculated as a time- and dose-corrected tissue radioactivity divided by body weight for each region of interest. The TBR is calculated from the ratio of the SUV of the artery compared to background venous activity. The superior vena cava will be used for correction of aortic values and the internal jugular veins will be used for correction of carotid values. Arterial FDG uptake (TBR) is evaluated in the 3 target arterial locations (right carotid, left carotid, or thoracic aorta). The artery with the highest FDG uptake (highest mean of the maximum TBR) at baseline will be identified as the index vessel. The average of the maximum TBR activity within the MDS of the index vessel (MDS TBR) will be defined as the 1.5-cm arterial segment, centered on the slice of artery demonstrating the highest FDG uptake at baseline, and calculated as a mean of maximum TBR values derived from 3 contiguous axial segments. The primary objective of the study is to determine the change in TBR of the MDS at 16 weeks compared to baseline in subjects taking evolocumab compared to placebo segments.

7.5 Laboratory Assessments

All screening and on-study laboratory samples will be processed and sent to the central laboratory with the exception of serum pregnancy after screen 1 visit (Section **7.5.2**).

The central laboratory will provide a study manual that outlines handling, labeling, and shipping procedures for all samples.

Subjects must be fasting for ≥ 9 hours before each study visit where fasting lipid samples are obtained.

All blood samples will be obtained by venipuncture before IP administration. The date and time of sample collection will be recorded in the source documents at the site. Specific analytes for serum chemistry, hematology, urinalysis, and other testing to be conducted on blood and urine samples are shown in Table 2. Although not specifically listed, additional components, abnormal, and/or atypical cells will also be reported if present.

As the laboratory testing requirement at each visit is different, total volumes ranging from approximately 5 to 70 mL of blood may be collected per visit, depending on the visit requirements. If a subject completes the entire study, the total amount of blood collected per protocol is estimated to be approximately 210 mL. However, additional blood draws and testing may be required for the care of the subject at the discretion of the investigator.

Table 2. Analyte Listing

Chemistry	Hematology	Urinalysis	Other Labs
Sodium Potassium Chloride Bicarbonate Total protein Albumin Calcium Magnesium Phosphorus Glucose (Fasting) BUN or Urea Creatinine Uric acid Total bilirubin Direct bilirubin CK ALP LDH AST (SGOT) ALT (SGPT)	Hemoglobin Hematocrit MCV MCH MCHC RDW Platelets RBC WBC Differential • Neutrophil • Bands • Eosinophils • Basophils • Lymphocytes • Monocytes	Specific Gravity pH Blood Protein Glucose Bilirubin WBC RBC Epithelial Cells Bacteria Casts Crystals	Fasting Lipids • Total cholesterol • HDL-C • LDL-C • Triglycerides • VLDL-C • non-HDL-C • Total Cholesterol/ HDL-C ratio • ApoA1 • ApoB/ApoA1 ratio • ApoB Lp(a) OxPL/ApoB IL-6 hsCRP Lp(a) isoform distribution Anti-evolocumab antibodies (drawn per investigator's discretion for safety assessments) HbA1c eGFR (calculated) Serum pregnancy test and FSH (if needed per Exclusion 218) Serum biomarkers for collection

7.5.1 Blinding of Laboratory Test Results

In order to protect the blinding of the double-blind treatment period, the following labs will be blinded to the Amgen study team and site staff from post-day 1 until unblinding of the clinical database and not reported to sites: fasting lipid panel (see Table 2), Lp(a), OxPL/ApoB, IL-6, hsCRP, and Lp(a) isoform distribution.

In addition, investigators and staff involved with this trial and all medical staff involved in the subject's medical care should not perform non-protocol testing of these analytes during a subject's study participation and until at least 12 weeks after the subject's last administration of IP or the end of the study, whichever is later, to prevent unblinding the patient and site to the treatment assignment, except when it is medically necessary.

If a local lipid panel is drawn, all reasonable steps must be undertaken to avoid informing the subject and study personnel of the results.

7.5.2 Serum Pregnancy Test

All females, except those who are confirmed surgically sterile or at least 2 years postmenopausal, must have a negative serum pregnancy test at baseline, prior to administering the first dose of evolocumab/placebo. The central laboratory will provide the baseline pregnancy tests. Pregnancy testing will be performed locally at each site prior to each FDG-PET/CT scan (serum or urine) and at visit 4 (week 12) (serum). If a pregnancy test is positive prior to the FDG-PET/CT scan, the subject should not undergo the procedure and the pregnancy should be reported in accordance with Section 9.3.

7.6 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biological 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. Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to evolocumab.

For all subjects in the study, 3 samples of EDTA-plasma and 3 serum of (3 vials of 500 μL each) will be collected vials at each time point of collection (prior to dosing on day 1 and at the end of the study [week 16]) for biomarker development. The samples must be kept at -70°C at all times and shipped in 1 batch on dry ice at the end of the study.

7.7 Pharmacogenetic Studies

In the pharmacogenetic portion of this study, DNA analyses may be performed. These pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of elevated Lp(a) and/or to identify subjects who may have positive or negative response to the IP.

For all subjects in the study who have consented to pharmacogenetic analyses, 1 cell pellet sample (ie, the residual pellet from the EDTA-plasma biomarker sample) of 500 μL will be collected at day 1. The samples must be kept at -70°C at all times and shipped in 1 batch on dry ice at the end of the study.

7.8 Sample Storage and Destruction

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

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

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

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

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

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as

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

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 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 IP 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 IP or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 1) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments (Table 1) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

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

8.2 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 IP and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

Subjects may be eligible for continued treatment with Amgen IP 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 12.1.

8.3 Reasons for Removal From Run-in, Treatment, or Study

8.3.1 Reasons for Removal From Treatment

A subject may be removed from study treatment or procedural assessments for any of the following reasons:

- Subject request
- Safety concern (eg, due to adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, or pregnancy)
- Decision by sponsor (other than subject request, safety concern, lost to follow-up)
- Death
- Lost to follow-up

8.3.2 Reasons for Removal From Study

A subject may be removed from the study for any of the following reasons:

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

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Disease-related Events

Disease-related events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease.

Disease-related events for the purposes of this study include manifestations and complications of atherosclerotic vascular disease such as coronary artery disease, angina, myocardial infarction, ischemic stroke, transient ischemic attack, carotid artery disease, peripheral vascular disease (including complications such as claudication or amputation), testing suggesting progression of atherosclerotic vascular disease, and treatment for atherosclerotic vascular disease and its complications such as revascularization procedures (coronary and non-coronary) and surgeries. Such events do not meet the definition of an adverse event unless assessed to be more severe than expected for the subject's condition.

Disease-related events and/or disease-related outcomes that do not qualify as serious adverse events:

- An event which is part of the normal course of disease under study (eg, disease progression in oncology or hospitalization due to disease progression) is to be reported as a disease-related event.
- Death due to the disease under study is to be recorded on the Event CRF.
- If the outcome of the underlying disease is worse than that which would normally be expected for the subject, or if the investigator believes there is a causal relationship between the IP /study treatment/protocol-required therapies and disease worsening, this must be reported as an adverse event or serious adverse event.

9.1.2 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.

An ADE is any adverse event related to the use of a medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

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 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

9.1.3 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria (unless it meets the definition of a disease-related event as defined in Section 9.1.1):

- 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

A disease-related event as described above is to be reported as a serious adverse event if:

- The subject's pre-existing condition becomes worse than what the investigator would consider typical for a patient with the same underlying condition, or
- If the investigator believes a causal relationship exists between the IMP/protocol-required therapies and the event,
- And the event meets at least 1 of the serious criteria above.

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, DILI (see Appendix A for DILI reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

The criteria for grade 4 in the Common Terminology Criteria for Adverse Events (CTCAE) grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events.

9.2 Safety Event Reporting Procedures

9.2.1 Reporting Procedures for Disease-related Events

The investigator is responsible for ensuring that all disease-related events observed by the investigator or reported by the subject that occur after the signing of the ICF through

the EOS visit are reported using the Event CRF. Additionally, the investigator is required to report a fatal disease-related Event on the Event CRF.

Events assessed by the investigator to be related to the IMP/study treatment/protocol-required therapies, and determined to be serious, require reporting of the event on the Event CRF.

9.2.2 Adverse Events

9.2.2.1 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 from the signing of the ICF through the EOS visit are reported using the Event CRF.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Severity (and/or toxicity per protocol),
- Assessment of relatedness to IP (evolocumab/placebo and/or the AI/Pen), or other protocol-required therapies/protocol-required procedure or activity, and
- Action taken.

The adverse event grading scale used will be the CTCAE. The grading scale used in this study is described in Appendix A.

The investigator must assess whether the adverse event is possibly related to the IMP (evolocumab or placebo) and/or the investigational device (AI/Pen). This relationship is indicated by a “yes” or “no” response to the question: “Is there a reasonable possibility that the event may have been caused by the IMP (evolocumab or placebo) and/or the investigational device (AI/Pen)?”

The investigator must assess whether the adverse event is possibly related to use of the investigational device (AI/Pen) or any study-mandated activity (eg, administration of IP, protocol-required therapies, device(s) and/or procedure [including any screening procedure(s)]. This relationship is indicated by a “yes” or “no” response to the question: “Is there a reasonable possibility that the event may have been caused by a study activity (eg, administration of IP, protocol-required therapies, device(s)), and/or procedure?”

If the severity of an adverse event worsens from the date of onset to the date of resolution, record a single event for each increased level of severity on the Event CRF.

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, 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.

9.2.2.2 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 ICF through 30 days after the last dose of IP or the EOS visit, whichever is later, 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 CRF.

The investigator must assess whether the serious adverse event is possibly related to any study-mandated activity or procedure. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity/procedure?"

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. The investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

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. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

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 (GCP).

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 procedures and statutes.

9.2.2.3 Reporting 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 the EOS. However, these serious adverse events can be reported to Amgen. In some countries (eg, European Union [EU] member states), investigators are required to report serious adverse events that they become aware of after the EOS. 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.

See Appendix B for a sample of the Serious Adverse Event Worksheet/electronic Serious Adverse Event Contingency Report Form.

In addition, if the electronic data capture (EDC) system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen via an electronic Serious Adverse Event (eSAE) Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix B for a sample of the Serious Adverse Event Worksheet/electronic Serious Adverse Event Contingency Report Form (a paper-based form). The data must be entered into the EDC system when the system is again available.

In addition to the attributes listed in Section 9.2.2.1, the investigator must also complete the serious adverse event section of the Event CRF.

9.3 Pregnancy and Lactation Reporting

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-required therapies report the pregnancy to Amgen as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur after the last dose of protocol-required therapies through 15 weeks after the end of treatment with evolocumab.

The pregnancy should be reported to Amgen's Global Patient Safety within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C).

If a lactation case occurs while the female subject is taking protocol-required therapies 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 after the last dose of protocol-required therapies through 15 weeks after the end of treatment with evolocumab/placebo.

Any lactation case should be reported to Amgen's Global Patient Safety within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C).

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoint

- Percentage change from baseline in TBR within the MDS of the index vessel (right carotid, left carotid, or thoracic aorta) by FDG-PET/CT at week 16

10.1.1.2 Secondary Endpoints

- Percentage change in Lp(a) from baseline at week 16
- Percentage change in LDL-C from baseline at week 16
- Percentage change in ApoB from baseline at week 16

10.1.1.3 Safety Endpoints

- Subject incidence of treatment emergent adverse events compared to placebo for the duration of the study

10.1.1.4 Exploratory Endpoints

CCI

[redacted]

10.1.2 Analysis Sets

The full analysis set (FAS) includes all randomized subjects who receive at least one dose of IP. This analysis set will be used in both efficacy and safety analyses. In efficacy analysis, subjects will be analyzed according to their randomized treatment group assignment. For safety analysis, subjects will be analyzed according to their randomized treatment group assignment except for the following case: if a subject receives a treatment that is different than the randomized treatment assignment throughout the study, then this subject will be analyzed by the treatment received.

10.1.3 Covariates and Subgroups

The primary endpoint analyses will be repeated by the individual stratification factors (on a statin vs not on a statin) and screening Lp(a) (< 175 mg/dL vs. ≥ 175 mg/dL) in subgroup analyses.

10.2 Sample Size Considerations

At present, PCSK9 inhibitors have not been evaluated for their ability to lower arterial wall inflammation. Therefore, we have used an efficacy study with atorvastatin aimed to lower LDL-C and arterial wall inflammation for our sample size estimation (Tawakol et al, 2013). The planned sample size is 120 subjects (60 in evolocumab and 60 in control). Based on Tawakol et al 2013, we make an assumption that each 10% reduction in LDL-C results in an approximate reduction of 2.4% in MDS TBR. Further assume that 70% of the subjects will be on a statin and 30% will not be on a statin. From the results of the phase 3 evolocumab studies, a treatment effect of evolocumab QM over placebo in the percentage reduction in LDL-C at week 16 is assumed to be 55% for subjects who are not on a statin and 60% for patients who are on a statin. From the assumption that 10% of LDL-C reduction induces an approximate 2.4% of TBR reduction, we expect to observe a combined reduction of 14.0% in MDS TBR at week 16 in the evolocumab

group compared to the control group. A combined standard deviation of 20.0% for the percentage change from baseline to week 16 is assumed for MDS TBR. After accounting for a dropout rate of 25%, the power is greater than 90% for testing superiority of evolocumab over placebo on the percentage change in MDS TBR at week 16.

10.3 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. Unblinding and potentially unblinding information should not be distributed to the study team, investigators, or subjects prior to the study being formally unblinded (eg, the formal unblinding may occur at the final analysis rather than during the primary analysis) except as specified (eg, Section 5.2 and Section 9.2.2.2).

10.4 Planned Analyses

10.4.1 Primary Analysis

The primary analysis will be conducted when all subjects have either completed all the scheduled study visits or have early terminated from the study.

10.5 Planned Methods of Analysis

10.5.1 General Considerations

Subject disposition, demographics, baseline characteristics, and exposure to IP will be summarized by treatment group.

Summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation or standard error, minimum, and maximum. For categorical variables, the frequency and percentage will be given. No adjustments for multiplicity will be applied.

Unless specified otherwise, the FAS will be the default analysis set in this study and data will be summarized by randomized treatment group. The superiority of evolocumab to placebo will be assessed for all efficacy endpoints. The primary analysis will include testing for the primary and secondary endpoints.

10.5.2 Primary Efficacy Endpoint

The primary endpoint is the percentage change from baseline in MDS TBR at week 16. In order to estimate the difference in mean percentage change from baseline in MDS TBR and to handle missing data for the primary endpoint, a multivariate regression model will be used. The response variables are percent change from baseline in MDS

TBR at week 16, baseline MDS TBR, percent change from baseline in Lp(a) at weeks 8 and 16, and baseline Lp(a). Each response follows its own regression model:

- Percent change in MDS TBR will be regressed on treatment group and the stratification factor;
- Baseline MDS TBR will be regressed on the stratification factor;
- Percentage change in Lp(a) will be regressed on the treatment group, stratification variable, visit, and treatment group by visit
- Baseline Lp(a) will be regressed on the stratification factor.

The variance-covariance matrix of the error terms from the response variables in the multivariate regression will be estimated. This analysis will use the FAS.

FDG-PET/CT observations made after an on-study cardiovascular event will be included in the primary analysis. A sensitivity analysis excluding these observations will be conducted.

10.5.3 Secondary Efficacy Endpoint(s)

Analysis of the secondary endpoints Lp(a), ApoB, and LDL-C will use a repeated measures model on the FAS including terms for treatment group, stratification factors, scheduled visit, and the interaction of treatment with scheduled visit.

10.5.4 Safety Endpoints

The current Medical Dictionary for Regulatory Activities version at the time of the data lock will be used to code all adverse events to a system organ class and a preferred term.

Subject incidence of all treatment emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from IP, device-related adverse events, and significant treatment-emergent adverse events will also be provided. Subject incidence of disease-related events and fatal disease-related events will be tabulated by system organ class and preferred term. Subject-level data may be provided instead of tables if the subject incidence is low.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample ICF 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 Clinical Study Manager to the investigator. The written

informed consent document 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 IP (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 ICF is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed ICF 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 ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF to attest that informed consent was freely given and understood.

11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed ICF, other written subject 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 ICF must be received by Amgen before recruitment of subjects into the study and shipment of Amgen IP.

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.

11.3 Subject Confidentiality

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

- Subjects are to be identified by a unique subject identification number.
- On the CRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.
- For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed ICFs) are to be kept in confidence by the investigator, except as described below.

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

11.4 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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

If Amgen amends the protocol, agreement from the investigator must be obtained. 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 to Amgen.

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 study contract. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination (ET) and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen IP 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 IP and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

12.2 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.

In this study, the IVRS/IWRS captures the following data points and these are considered source data: subject ID, enrollment date, IP dispensation date and IP box number dispensed.

Case report form entries may be considered source data if the CRF is the site of the original recording (ie, there is no other written or electronic record of data).

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 CRFs, ICFs, 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
- IP-related correspondence including Proof of Receipts, IP Accountability Record(s), Return of IP for Destruction Form(s), Final IP Reconciliation Statement, 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.

12.3 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 Amgen 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 CRFs must be maintained and readily available.
- Updates to 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 or the investigator applies an electronic signature in the EDC system if the study is set up to accept an electronic signature. This signature indicates that investigator inspected or reviewed the data on the CRF, the data queries, and agrees with the content.

Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical trial database, as documented in the Study Specific Self Evident Corrections Plan. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different visit-week 4 and early termination) and clarifying "other, specify" if data are provided (eg, race, physical examination). Each investigative site will be provided a list of the types of corrections applied to study data at the initiation of the trial and at study closeout.

12.4 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 (Table 1), the investigator can search publically 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.

12.5 Language

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

12.6 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), 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; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.
- 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 review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.7 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 ICF that is available as a separate document.

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

Refer to the NCI CTCAE Version 4.0 for AE grading and information. The CTCAE is available at the following link:http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation according to the criteria specified in Section 6.3 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 CRF (eg, Event CRF) 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 9.2.2.2.

Additional Clinical Assessments and Observation

All subjects in whom IP or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Sections 6.3.1 and 6.3.2 or who experience AST or ALT elevations > 3 x ULN are to 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 TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve

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

- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL:
  - Obtain complete blood count with differential to assess for eosinophilia

- Obtain **s**erum total immunoglobulin IgG, Anti-nuclear antibody (ANA), anti smooth muscle antibody, and liver kidney microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
- Obtain serum acetaminophen (paracetamol) levels
- Obtain 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
- Obtain viral serologies
- Obtain creatine phosphokinsase, haptoglobin, lactate dehydrogenase, and peripheral blood smear
- Perform appropriate liver imaging if clinically indicated

- Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all IP 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. Sample Serious Adverse Event Report Form (Sample eSerious Adverse Event Contingency Report Form – paper-based Form)

AMGEN Study # 20130293 evolocumab (AMG 145)	Electronic Adverse Event Contingency Report Form **For Restricted Use**

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

SELECT OR TYPE IN A FAX#

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day___ Month___ Year___

Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of eeath. 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/drug under study	Is event serious?	Is event a potential endpoint?	If serious, enter Serious Criteria code *(see codes below)*	Relationship Is there a reasonable possibility that theEvent may have been caused by IP/drug under study or an Amgen device used to administer the IP/drug under study?				Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
							evolocumab (AMG 145)		Autoinjector/ Pen(AIPen)			
							No✓	Yes✓	No✓	Yes✓		
				☐Yes ☐No	☐Yes ☐No							
				☐Yes ☐No	☐Yes ☐No							
				☐Yes ☐No	☐Yes ☐No							

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

FORM-056006 *Version 6.0 Effective Date 07 JUL 2014*

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AMGEN Study # 20130293 evolocumab (AMG 145)	**Electronic Adverse Event Contingency Report Form** **For Restricted Use**

Site Number	Subject ID Number

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

IP/Drug/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
evolocumab (AMG 145)	☒ blinded							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Prefilled Autoinjector/Pen (AI/Pen)	☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

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

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

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

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

Date Day Month Year	Test Unit											

AMGEN Study # 20130293 evolocumab (AMG 145)	Electronic Adverse Event Contingency Report Form **For Restricted Use**

Site Number	Subject ID Number

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

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

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

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20130293

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 DOB:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

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

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

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

5. Pregnancy Information

Pregnant female's LMP mm / dd / yyyy_____ ☐ Unknown

Estimated date of delivery mm / dd / yyyy_____ ☐ Unknown ☐ N/A

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:** _____

Effective Date: March 27, 2011

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AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: 20130293

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 Date of Birth:** mm_____ / dd_____/ yyyy_____

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:** _____

Effective Date: 03 April 2012, version 2.

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Amendment 3

Protocol Title: A RaNdomized Double-blInd Placebo ConTrolled Study Characterizing THe Effects of PCSK9 Inhibition On Arterial Wall Inflammation in Patients With Elevated Lp(a) (ANITSCHKOW)

Amgen Protocol Number (AMG145/Evolocumab) 20130293

EudraCT number 2015-003731-35

Amendment 3 Date: 08 February 2017

Rationale:

The intent of this amendment is to clarify the blinding of central laboratory test results during the double-blind treatment period and provide guidance in obtaining local lipid panels.

Table 1. Summary of Amendment Changes

Section	Text in Protocol	Amended Text	Rationale for Change
Header	Global	Replace: 25 August 2016 With: **08 February 2017**	Update to new date.
Front page		Add: **Amendment 3 Date 08 February 2017**	Update to new date.
Investigator's agreement	Paragraph 1	Replace: I have read the attached protocol entitled "A RaNdomized Double-blInd Placebo ConTrolled Study Characterizing THe Effects of PCSK9 Inhibition On Arterial Wall inflammation in Patients with Elevated Lp(a) (ANITSCHKOW)", dated 25 August 2016, and agree to abide by all provisions set forth therein. With: I have read the attached protocol entitled "A RaNdomized Double-blInd Placebo ConTrolled Study Characterizing THe Effects of PCSK9 Inhibition On Arterial Wall inflammation in Patients with Elevated Lp(a) (ANITSCHKOW)", dated **08 February 2017**, and agree to abide by all provisions set forth therein.	Update to new date
Section 7.5	Paragraph 1	Replace: All screening and on-study laboratory samples will be processed and sent to the central laboratory with the exception of serum pregnancy after screen 1 visit (Section 7.5.1). With: All screening and on-study laboratory samples will be processed and sent to the central laboratory with the exception of serum pregnancy after screen 1 visit (Section **7.5.2**).	Update to new Section number.

Table 1. Summary of Amendment Changes

Section 7.5	Page 34 - 35	**Add:** **7.5.1 Blinding of Laboratory Test Results** **In order to protect the blinding of the double-blind treatment period, the following labs will be blinded to the Amgen study team and site staff from post-day 1 until unblinding of the clinical database and not reported to sites: fasting lipid panel (see Table 2), Lp(a), OxPL/ApoB, IL-6, hsCRP, and Lp(a) isoform distribution.** **In addition, investigators and staff involved with this trial and all medical staff involved in the subject's medical care should not perform non-protocol testing of these analytes during a subject's study participation and until at least 12 weeks after the subject's last administration of IP or the end of the study, whichever is later, to prevent unblinding the patient and site to the treatment assignment, except when it is medically necessary.** **If a local lipid panel is drawn, all reasonable steps must be undertaken to avoid informing the subject and study personnel of the results.**	Provide guidance in obtaining local lipid panels and clarify the blinding of central laboratory test results during the double-blind treatment period.
Section 7.5	Page 35	Replace: 7.5.1 Serum Pregnancy Test With: **7.5.2** Serum Pregnancy Test	Update section numbering

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Amendment 1

Protocol Title: A RaNdomized Double-blInd Placebo ConTrolled Study Characterizing THe Effects of PCSK9 Inhibition On Arterial Wall inflammation in Patients With Elevated Lp(a) (ANITSCHKOW)

Amgen Protocol Number (AMG 145 / Evolocumab) 20130293

Protocol Date	18 September 2015
Amendment 1 Date:	**02 January 2016**

Rationale:

The protocol was amended to change the age of the patients included in the study from ≥ 45 to ≥ 50 years to meet the radiation dose limit required by the Dutch ethics committee. In addition, the study schema was updated for clarity. The primary and exploratory endpoints were reworded for clarity and the methods of analysis for the primary endpoint further detailed.

Amendment 2

Protocol Title: A RaNdomized Double-blInd Placebo ConTrolled Study Characterizing THe Effects of PCSK9 Inhibition On Arterial Wall Inflammation in Patients With Elevated Lp(a) (ANITSCHKOW)

Amgen Protocol Number (AMG 145 / Evolocumab) 20130293

EudraCT number 2015-003731-35

Amendment Date: 25 August 2016

Rationale:

- The protocol has been amended to provide clarification to minimize the risk of confounding the primary endpoint with prior therapies targeting Lp(a), an exclusion criterion has been added to exclude subjects with exposure to therapies targeting Lp(a) within the 12 months prior to Screening.
- The protocol was amended to clarify the timing and method of pregnancy testing. No additional testing or change in testing has been introduced. The ICF reflects this clarification in pregnancy testing.
- The protocol was amended to include additional detail regarding the volume of blood drawn to satisfy the existing protocol-specified laboratory testing. No additional testing has been introduced. The informed consent form (ICF) reflects this additional level of detail regarding blood volume.