Supplementary Online Content 1


Study Protocol
Title: A Double-Blind, Randomized, Multi-center, Placebo-controlled, Parallel-group Study to Determine the Effects of Evolocumab (AMG 145) Treatment on Atherosclerotic Disease Burden as Measured by Intravascular Ultrasound in Subjects Undergoing Coronary Catheterization

Amgen Protocol Number: 20120153
EudraCT Number: 2012-004208-37

GLAGOV
(GLobal Assessment of plaque reGression with a PCSK9 antibOdy as measured by intraVascular ultrasound)

Clinical Study Sponsor: Amgen Inc
One Amgen Center Drive
Thousand Oaks, CA 91320, USA
Phone: +1-805-447-1000

Key Sponsor Contact(s): Moetaz Albizem, MD
One Amgen Center Drive
Thousand Oaks, CA 91320, USA
Phone: +1-805-447-2058
Fax: +1-805-480-9385
Email: malbizem@amgen.com

Date: 24 October 2012
Amendment 1 date: 30 April 2013
Amendment 2 date: 20 December 2013

Confidentiality Notice

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Investigator's Agreement

I have read the attached protocol entitled “A Double-Blind, Randomized, Multi-center, Placebo-controlled, Parallel-group Study to Determine the Effects of Evolocumab (AMG 145) Treatment on Atherosclerotic Disease Burden as Measured by Intravascular Ultrasound in Subjects Undergoing Coronary Catheterization”, dated 20 December 2013, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice and applicable national or regional regulations/guidelines.

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

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

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

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

________________________________________
Signature

________________________________________
Name of Principal Investigator   Date (DD Month YYYY)
Protocol Synopsis

Title: A Double-Blind, Randomized, Multi-Center, Placebo-Controlled, Parallel Group Study to Determine the Effects of Evolocumab (AMG 145) Treatment on Atherosclerotic Disease Burden As Measured By Intravascular Ultrasound in Subjects Undergoing Coronary Catheterization

Study Phase: 3
Indication: Coronary Atherosclerosis

Primary Objective
To evaluate the effect of AMG 145 on the change in burden of coronary atherosclerosis as measured by percent atheroma volume (PAV) in subjects with coronary artery disease (CAD) requiring angiography for a clinical indication who are taking statins.

Secondary Objectives
- To evaluate the effect of AMG 145 on the change in normalized total atheroma volume (TAV) and the percentage of subjects who demonstrate regression of coronary atherosclerosis.

Hypothesis: The primary hypothesis is that (low-density lipoprotein cholesterol) LDL-C lowering with AMG 145 420 mg subcutaneous (SC) will result in a greater change from baseline in PAV at week 78 than placebo in subjects with coronary artery disease taking background statin therapy.

Primary Endpoint
The nominal change in percent atheroma volume (PAV) from baseline to week 78 post randomization, as determined by intravascular ultrasound (IVUS)

Secondary Endpoints
The secondary endpoints are listed in the following sequential order to reflect the multiplicity adjustment method stated in Section 10.5.1.

- Nominal change in total atheroma volume (TAV) from baseline to week 78
- Regression (any reduction from baseline) in PAV
- Regression (any reduction from baseline) in TAV

Study Design
This is a Phase III, multi-center, double-blind, randomized, placebo-controlled study evaluating the effect of AMG 145 on coronary atherosclerotic disease burden as assessed by intravascular ultrasound (IVUS) at baseline and following 78 weeks of treatment in subjects with coronary artery disease. Subjects will be randomized 1:1 into 2 treatment groups: AMG 145 420 mg on a monthly basis (QM) SC or placebo QM SC. Randomization will be stratified for balance by geographic region.

Sample Size: Approximately 950 subjects (475 AMG 145 and 475 placebo) will be randomized.

Summary of Subject Eligibility Criteria
- Men and women >18 years of age
- Clinically indicated coronary angiogram, with evidence of coronary artery disease which fulfill the angiographic and IVUS entry criteria
- Subjects already taking statin therapy, regulatory-approved sustained-release niacin (eg Niaspan®) or ezetimibe at initial screening must have been on a stable dose for at least 4 weeks prior to the lipid panel used for the screening LDL-C. Subjects not currently taking lipid-regulating therapy can be screened but must enter the study via a lipid stabilization period.

OR
Subjects who are intolerant to statins (limited to no more than approximately 10% of total planned enrollment) must meet statin intolerance entry criteria in Appendix G.

- Subjects must have at least one eligible LDL-C level (as defined below) via local, central laboratory or point of care device at the initial screening visit and, if applicable, at the end of each lipid stabilization period. A pre-existing local LDL-C level may be used as the initial screening LDL-C value as long as it was drawn within 4 weeks of the screening visit and no interim changes to lipid-regulating therapy have occurred during that 4-week period:
  - LDL-C ≥ 80 mg/dL (2.07 mmol/L) with or without additional risk factors
  - OR
  - LDL-C ≥ 60 -<80 mg/dL (1.55-2.07 mmol/L) in the presence of one major or three minor risk factors as defined below. Enrollment of subjects with LDL-C between ≥ 60 mg/dL (1.55 mmol/L) and < 80 mg/dL (2.07 mmol/L) will be limited to no more than approximately 25% of total planned enrollment.

**Major Risk Factors (one required)**

1) Non-coronary atherosclerotic vascular disease as evidenced by one of the following: documented peripheral arterial disease (PAD), documented abdominal aortic aneurysm (AAA), or documented cerebrovascular disease (CD).
   - Documented peripheral arterial disease (one of the following primary criteria must be satisfied):
     - Current intermittent claudication (WHO criteria, eg, leg pain occurring only while walking and disappearing in less than 10 minutes on standing) of presumed atherosclerotic origin TOGETHER WITH ankle-brachial index equal to or less than 0.9 in either leg at rest.
     - History of intermittent claudication (WHO criteria as above) TOGETHER WITH either previous intervention by amputation, or reconstructive vascular surgery, or angioplasty in one or both legs because of atherosclerotic disease within the last 2 years.
   - Documented abdominal aortic aneurysm:
     - AAA is considered to be present when the minimum anteroposterior diameter of the aorta reaches 3.0 cm. The size of the aorta can be measured in any plane that is perpendicular to the vessel axis.
   - Documented cerebrovascular disease (eg. carotid artery disease or prior history of stroke or transient ischemic attack occurring within the last 2 years):
     - Stroke: ischemic stroke is defined as an infarction of central nervous system tissue not secondary to underlying congenital or valvular heart disease. Symptomatic ischemic strokes manifest by clinical signs of focal or global cerebral, spinal, or retinal dysfunction caused by central nervous system infarction. A silent stroke is a documented central nervous system infarction that was asymptomatic.
o Transient ischemic attack (TIA): a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction, not secondary to underlying congenital or valvular heart disease.

o Carotid artery disease: defined as stenosis > 50% or PSV > 125 cm/sec with plaque

2) Documented history of myocardial infarction or hospitalization for unstable angina within the last two years
3) Documented type 2 diabetes mellitus

OR

Minor Risk Factors (three required)
- Current cigarette smoker
- Hypertension (One documented blood pressure (BP) ≥ 140/90 mm Hg or current use of antihypertensive medication)
- Low HDL-cholesterol - men < 40 mg/dL (1.03 mmol/L); women < 50 mg/dL (1.29 mmol/L)
- Family history of premature coronary heart disease (first-degree male relative < 55 years of age, or first-degree female relative < 65 years of age)
- Age (men ≥ 50 years; women ≥ 55 years)
- High sensitivity C-reactive protein (hs-CRP) ≥ 2 mg/dL

Major exclusion criteria:
- Clinically significant heart disease which, in the opinion of the Principal Investigator, is likely to require coronary artery bypass graft (CABG) surgery, percutaneous coronary intervention (PCI) (does not apply to PCI deemed necessary by the initial screening angiogram), cardiac transplantation, surgical or percutaneous valve repair and/or replacement during the course of the study.
- New York Heart Association (NYHA) class III or IV or last known left ventricular ejection fraction < 30%
- Coronary artery bypass graft surgery < 6 weeks prior to the qualifying IVUS
- Cardiac arrhythmia within 3 months prior to randomization that is not controlled by medication
- Known hemorrhagic stroke
- Uncontrolled hypertension at randomization, defined as a resting systolic blood pressure of ≥ 180 mm Hg at rest
- Personal or family history of hereditary muscular disorders
- Fasting triglyceride (TG) level > 400mg/dL (4.5 mmol/L) at screening
- Type 1 diabetes or poorly controlled type 2 diabetes (HbA1c > 9%) at screening
- Thyroid stimulating hormone (TSH) < lower limit of normal (LLN) or TSH > 1.5x upper limit of normal (ULN). A subject taking thyroid replacement therapy may be enrolled with TSH level below LLN if, in the opinion of the investigator, the subject is in a clinically euthyroid state.
- Estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m²
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3x ULN at screening or at end of lipid stabilization period
- Creatine kinase (CK) > 3x ULN at screening or at end of lipid stabilization period
- Use of cholesteryl ester transfer protein (CETP) inhibitor, mipomersen or lomitapide within 12 months prior to screening
Any prior use of **proprotein convertase subtilisin/kexin type 9** (PCSK9) inhibitor therapy

Subjects are excluded if they have taken any of the following drugs for more than 2 weeks in the last 3 months prior to LDL-C screening: systemic cyclosporine, systemic steroids (eg. IV, intramuscular [IM], or PO) ) *(Note: hormone replacement therapy is permitted)*; systemic vitamin A and retinol derivatives for the treatment of dermatologic conditions (eg, Accutane) *(Note: vitamin A in topical and multivitamin preparations are permitted)*

History of malignancy (except non-melanoma skin cancers, cervical in-situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma).

Known major active infection, or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction

Baseline IVUS **does not meet** IVUS Core Lab technical standards

Female subjects cannot be pregnant or breastfeeding, planning to become pregnant or planning to breastfeed during the screening period, at the end of the lipid stabilization period (if applicable), while receiving treatment with Investigational Product (AMG 145 or placebo) and within 15 weeks after the end of treatment with Investigational Product (AMG 145 or placebo).

Premenopausal females of childbearing potential must be willing to use an acceptable method(s) of birth control during treatment with Investigational product (IP) (AMG 145 or placebo) and for an additional 15 weeks after the end of treatment with Investigational product (IP) (AMG 145 or placebo).

For a full list of eligibility criteria, please refer to **Section 4.1 and Section 4.2**.

**Amgen Investigational Product Dosage and Administration**

Subjects will receive investigational product (IP), comprising **evolocumab** (AMG 145) or placebo **as subcutaneous (SC) injections on a monthly basis (QM)**. SC AMG 145 will be administered in a fixed volume regimen:

- 420 mg QM SC at 3.0 mL via 3 **prefilled** autoinjectors (1.0 mL per autoinjector) or
- 420 mg QM SC at 3.5 mL via 1 **Personal Injector** injection

**Control Group**

Placebo will be administered in a fixed volume regimen:

- QM SC at 3.0 mL via 3 **prefilled** autoinjectors (1.0 mL per autoinjector) or one 3.5 mL **Personal Injector injection**

Subjects will have the opportunity to switch from autoinjectors to a personal injector provided the required approvals and supplies of IP are available at the study site.

**Procedures**

Written informed consent must be obtained before protocol-specific procedures are carried out. Subjects will be assessed for inclusion and exclusion criteria and medical and medication history will be obtained. **In order to minimize the chances of performing unnecessary IVUS procedures, investigators should ensure that subjects' initial screening LDL-C results are available prior to performing the baseline IVUS examination. Thereafter, subjects will undergo clinically-indicated coronary angiography for further clinical evaluation. If angiographic criteria for IVUS are met, the subject will have baseline IVUS completed. Subjects who require a PCI as a result of the qualifying angiography will have baseline IVUS performed immediately following the PCI. Any intervention to the proposed target IVUS vessel will exclude this vessel from being used as the target IVUS vessel. Delayed or staged IVUS procedures must be performed within 4 weeks after qualifying angiography. For subjects who undergo delayed or staged interventions, the baseline IVUS must be performed after the final planned intervention. Subjects will undergo all screening labs and receive a 3.0 mL placebo injection by SC administration, prior to randomization.**
At time of randomization, subjects must be on stable, optimized background statin therapy (per Protocol Appendix E) that is expected to be unchanged for the duration of study participation (up to 18 months). Optimal statin therapy is defined as an effective dose of at least atorvastatin 20 mg daily or equivalent titrated to achieve target LDL-C (reduction or goal) as defined by regional guidelines. Where locally approved, highly effective statin therapy, defined as at least atorvastatin 40 mg daily or equivalent, is recommended. For subjects with LDL-C > 100 mg/dL (2.6 mmol/L) who are not receiving highly-effective statin therapy (atorvastatin ≥ 40 mg daily or equivalent), the investigator must attest that higher dose statin therapy is not appropriate for this subject (e.g., dose not tolerated, dose not available in that country, other significant clinical concern). Subjects who, in the investigator's opinion, are already at LDL-C goal at initial screening and are on stable (≥ 4 weeks), allowable lipid lowering therapy (per Appendix E), with no changes planned or expected for the duration of the study, will be enrolled and proceed directly to IP randomization if all other eligibility criteria are met. These subjects may skip the lipid stabilization period. Subjects requiring any change to their lipid therapy will be enrolled and subsequently enter a two- to four-week lipid stabilization period for initiation or titration of statins with a maximum of one uptitration step utilized to achieve a target LDL-C as defined by regional guidelines.

Locally-determined LDL-C levels may be used to determine eligibility at initial screening and for LDL-C monitoring during the lipid stabilization period. At randomization, an interactive voice response system (IVRS) will allocate subjects to receive either AMG 145 or placebo. Administration of IP (AMG 145 or placebo) will be once every month. Final administration of IP (AMG 145 or placebo) will occur at week 76. Subjects taking study-provided atorvastatin should continue the drug until their week 78 visit. Similarly, subjects taking non-study provided statins and allowable non-statin therapies should continue such treatment until week 78. Beyond the week 78 assessment, use of statins and other lipid regulating therapies will be at the discretion of the investigator. Subjects who discontinue IP for any reason will be asked to continue to return for all other study procedures and measurements until the end of the study. Subjects whose central laboratory LDL-C values increase by more than a predefined trigger (see section 7.1.3.4) during the study will be automatically given a reminder to adhere to their assigned LDL-C lowering therapies and to the ATP III TLC-type diet. To avoid unblinding, the same reminder will be provided to additional subjects in each treatment arm.

During the 4, 12, 24, 36, 52, 64, 76, and 78 week visits vital signs will be obtained and adverse events (AEs), serious AEs (SAEs), and concomitant medications will be recorded. Physical exams, laboratory tests and other procedures will be performed during these visits. Subjects at increased risk for hepatitis C virus (HCV) infection or with ALT or AST > 2x ULN at any time during screening will be tested for prior or existing HCV infection and viral load will be evaluated in those who show evidence thereof. Investigators will be informed if triglycerides are > 1000 mg/dL (11.3 mmol/L) so that appropriate subject follow-up can be initiated (see Protocol Section 6.2.2.1). For subjects consenting to pharmacogenetics analyses, DNA will be extracted from some of the blood samples.

Subject will undergo the final IVUS assessment at the week 78 visit. End of study (EOS) for subjects is by contact (e.g., phone call) from the site at week 80 for any potential AEs or SAEs. For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and Appendix A.

An Executive Committee (EC) has been formed to advise Amgen on trial design and for assistance in the communication of trial results. The EC will be blinded. Details will be provided in a committee charter. An external independent Data Monitoring Committee (DMC) will formally review the accumulating data from this and other ongoing studies with AMG 145 to ensure there is no avoidable increased risk for harm to subjects. Analyses for the DMC will be provided by an independent biostatistical group (IBG), which is external to Amgen.
Statistical Considerations

General Considerations
The full analysis set (FAS) includes all randomized subjects who received at least 1 dose of IP.
The IVUS analysis set (IAS) contains FAS with a baseline IVUS and an IVUS measurement conducted after week 52 (IVUS data collected after week 52 is considered clinically meaningful to be used in the analysis). The IAS will be used for primary efficacy analysis of IVUS related endpoints.
Method of adjusting for multiplicity due to multiple endpoints (primary and secondary endpoints) is provided in Section 10.5.1.
Safety analyses set will be FAS.

Events of death, myocardial infarction (MI), hospitalization for unstable angina, coronary revascularization, stroke, transient ischemic attack (TIA), and hospitalization for heart failure will be adjudicated by an independent Clinical Events Committee (CEC). Subject incidence of exploratory endpoint events will be summarized for each treatment group.

Analyses of Primary Endpoint
The primary analysis of the primary endpoint will use the ANCOVA model, including terms for treatment group, stratification factor (region) and baseline PAV as covariates. Least-square means and corresponding 95% confidence intervals will be calculated for each treatment (AMG145 and placebo) and for the difference between the treatment groups.

Sensitivity Analysis of the Primary Endpoint
A key sensitivity analysis will be conducted using a multiple imputation procedure to impute the primary endpoint for those dosed subjects with missing endpoint data. The primary endpoint will also be analyzed for the completers population (adhered to the scheduled IP) using the same methodology as the primary analysis.

Analyses of Secondary Efficacy Endpoints
Analyses of secondary efficacy endpoints will be similar to the analyses of the primary endpoint. However, the secondary efficacy endpoints of percentage of subjects demonstrating regression (any reduction from baseline) will be analyzed using the Cochran-Mantel Haenszel (CMH) test adjusted by the stratification factor.

Safety Analyses
AEs will be coded using the current version of MedDRA. Subject incidence of treatment-emergent adverse events, serious adverse events, treatment-related adverse events and adverse events leading to discontinuation of IP will be tabulated by system organ class and preferred term by randomized treatment group.
Measurements of laboratory parameters, ECGs, and vital signs will be summarized over time. Lab shift tables will be provided. The incidence and percentages of subjects who develop anti-AMG 145 antibodies (binding and neutralizing) at any time will be tabulated.

Safety Monitoring
An external independent Data Monitoring Committee (DMC) will formally review the accumulating data with AMG 145 to ensure there is no avoidable increased risk for harm to subjects. Analyses for the DMC will be provided by a group which is external to Amgen. In addition, Amgen performs continuous monitoring of SAEs in a blinded manner.

For a full description of statistical analysis methods, please refer to Section 10.

Sponsor: Amgen
Screening and Placebo Run-in Injection

1. Clinically indicated coronary angiogram
2. IVUS based on coronary angiogram results (eligible LDL value required prior to IVUS)
3. Subcutaneous injection of 3 mL placebo

Up to 4 Week Lipid Stabilization Period

Assigned to Statin Background Therapy (if applicable)

Study Design and Treatment Schema

Placebo SC QM

AMG 145 420mg SC QM

EOS

2-4 weeks

6 weeks

Day 1, Week 4, Week 12, Week 24, Week 36, Week 52, Week 64, Week 76, Week 78, EOS/Week 80* Phone Call

QM SC IP (at clinic):

*Phone call for SAEs
### Study Glossary

<table>
<thead>
<tr>
<th>Abbreviation or Term</th>
<th>Definition/Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAA</td>
<td>Abdominal aortic aneurysm</td>
</tr>
<tr>
<td>ADE</td>
<td>Adverse device effect</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
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<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>AI</td>
<td>Autoinjector</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
</tr>
<tr>
<td>ALP</td>
<td>Alkaline phosphatase</td>
</tr>
<tr>
<td>ALT (SGPT)</td>
<td>Alanine aminotransferase (serum glutamic-pyruvic transaminase)</td>
</tr>
<tr>
<td>ApoA1</td>
<td>Apolipoprotein A-1</td>
</tr>
<tr>
<td>ApoB</td>
<td>Apolipoprotein B</td>
</tr>
<tr>
<td>AST (SGOT)</td>
<td>Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)</td>
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<tr>
<td>AUC</td>
<td>Area under the curve</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CABG</td>
<td>Coronary artery bypass graft</td>
</tr>
<tr>
<td>CAS</td>
<td>Complete analysis set</td>
</tr>
<tr>
<td>CBC</td>
<td>Complete blood count</td>
</tr>
<tr>
<td>CD</td>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>CEC</td>
<td>Clinical Events Committee</td>
</tr>
<tr>
<td>CETP</td>
<td>Cholesteryl ester transfer protein</td>
</tr>
<tr>
<td>CK</td>
<td>Creatine kinase</td>
</tr>
<tr>
<td>CHD</td>
<td>Coronary heart disease, includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia</td>
</tr>
<tr>
<td>CHD risk equivalents</td>
<td>Coronary heart disease risk equivalents, include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks or stroke of carotid origin or &gt; 50% obstruction of a carotid artery]), diabetes, and 2+ risk factors with 10-year risk for hard CHD &gt; 20%. Risk factors include cigarette smoking, hypertension (BP ≥ 140/90 mm Hg or on antihypertensive medication), low HDL cholesterol (&lt; 40 mg/dL), family history of premature CHD (CHD in male first-degree relative &lt; 55 years of age; CHD in female first-degree relative &lt; 65 years of age), and age (men ≥ 45 years; women ≥ 55 years).</td>
</tr>
<tr>
<td>C_{max}</td>
<td>Maximal concentration</td>
</tr>
<tr>
<td>CMH</td>
<td>Cochran-Mantel Haenszel</td>
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<tr>
<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>Abbreviation or Term</td>
<td>Definition/Explanation</td>
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<tr>
<td>---------------------</td>
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<tr>
<td>CTCAE</td>
<td>Common Terminology Criteria for AEs</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
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<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
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<tr>
<td>DHA</td>
<td>Docosahexaenoic acid</td>
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<tr>
<td>DILI</td>
<td>Drug-induced liver injury</td>
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<tr>
<td>DMC</td>
<td>Data monitoring committee</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic case report form</td>
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<tr>
<td><strong>EDC</strong></td>
<td><strong>Electronic Data Capture</strong></td>
</tr>
<tr>
<td>eGFR (by MDRD equation)</td>
<td>Estimated glomerular filtration rate (by Modification of Diet in Renal Disease equation to calculate eGFR [Levey et al, 1999]).</td>
</tr>
<tr>
<td>eSAE</td>
<td>Electronic SAE</td>
</tr>
<tr>
<td>EEM_{CSA}</td>
<td>External elastic membrane cross-sectional area</td>
</tr>
<tr>
<td><strong>End of study (EOS)</strong></td>
<td>The end of the study is defined as the last date on which a randomized subject has the end-of-study assessment performed or the date the subject terminates the study early.</td>
</tr>
<tr>
<td><strong>End of study for individual subject</strong></td>
<td>Defined as the last day that protocol-specified procedures are conducted for an individual subject.</td>
</tr>
<tr>
<td><strong>End of treatment</strong></td>
<td>Defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject</td>
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<tr>
<td>EPA</td>
<td>Eicosapentaenoic acid</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
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<tr>
<td>FAS</td>
<td>Full analysis set</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>FIH</td>
<td>First in Human</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>HCV</td>
<td>Hepatitis C virus</td>
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<tr>
<td>HDL-C</td>
<td>High density lipoprotein cholesterol</td>
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<td>HepG2 cells</td>
<td>Human hepatocellular carcinoma cell line</td>
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<td><strong>Human Immunodeficiency Syndrome</strong></td>
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<td>High sensitivity CRP</td>
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<td>Independent Biostatistical Group</td>
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<td>ICF</td>
<td>Informed consent form</td>
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<td>ICH</td>
<td>International Conference on Harmonization</td>
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<td>Definition/Explanation</td>
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<td>IEC/IRB</td>
<td>Independent Ethics Committee / Institutional Review Board</td>
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<td>IFU</td>
<td>Instructions for Use</td>
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<td>Intramuscular</td>
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<tr>
<td>INR</td>
<td>International Normalized Ratio</td>
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<tr>
<td>IP</td>
<td>Investigational product (AMG 145 or placebo)</td>
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<td>IPIM</td>
<td>Investigational Product Instruction Manual</td>
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<tr>
<td>IVRS</td>
<td>Interactive Voice Response System</td>
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<tr>
<td>IV</td>
<td>Intravenous</td>
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<tr>
<td>LDH</td>
<td>Lactate dehydrogenase</td>
</tr>
<tr>
<td>LDL-C</td>
<td>Low-density lipoprotein cholesterol</td>
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<tr>
<td>LDLR</td>
<td>LDL receptor</td>
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<td>LLN</td>
<td>Lower limit of normal</td>
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<tr>
<td>LLOQ</td>
<td>Lower limit of quantification</td>
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<td>LOCF</td>
<td>Last observation carried forward</td>
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<td>Loss of function</td>
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<td>Lp(a)</td>
<td>Lipoprotein(a)</td>
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<td>LSP</td>
<td>Lactation Surveillance Program</td>
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<tr>
<td>LUMEN&lt;sub&gt;C&lt;/sub&gt;</td>
<td>Luminal cross-sectional area</td>
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<td>Medical dictionary for regulatory activities</td>
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<tr>
<td>NASH</td>
<td>Nonalcoholic steatohepatitis</td>
</tr>
<tr>
<td>NCEP ATP III TLC</td>
<td>National Cholesterol Education Program Adult Treatment Panel III Therapeutic Lifestyle Changes</td>
</tr>
<tr>
<td>PAV</td>
<td>Percent atheroma volume</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
</tr>
<tr>
<td>PCSK9</td>
<td>Proprotein convertase subtilisin/kexin type 9</td>
</tr>
<tr>
<td>PEP</td>
<td>Potential endpoint</td>
</tr>
<tr>
<td>PKPD</td>
<td>Pharmacokinetic / pharmacodynamic</td>
</tr>
<tr>
<td>PO</td>
<td>Oral administration</td>
</tr>
<tr>
<td>Q4W</td>
<td>Every 4 weeks, (AMG 145 Background section)</td>
</tr>
<tr>
<td>QM</td>
<td>QM is defined as every 4 weeks with a window of ± 3 days for each visit</td>
</tr>
<tr>
<td>QD</td>
<td>Each day</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>SC</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>Abbreviation or Term</td>
<td>Definition/Explanation</td>
</tr>
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<td>----------------------</td>
<td>------------------------</td>
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<tr>
<td>Source Data</td>
<td>Information from an original record or a 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 ID, Randomization ID, and Stratification Value.</td>
</tr>
<tr>
<td>Study day 1</td>
<td>defined as the first day that protocol-specified investigational product is administered to the subject</td>
</tr>
<tr>
<td>TAV</td>
<td><strong>Total Atheroma Volume</strong></td>
</tr>
<tr>
<td>TBL</td>
<td>Total bilirubin</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient ischemic attack</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Time to maximum concentration</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumor necrosis factor</td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid Stimulating Hormone</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper limit of normal</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>Very low-density lipoprotein cholesterol</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood cell</td>
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1. OBJECTIVES

1.1 Primary
To evaluate the effect of AMG 145 on the change in burden of coronary atherosclerosis as measured by percent atheroma volume (PAV) in subjects with coronary artery disease requiring angiography for a clinical indication who are taking statins.

1.2 Secondary
To evaluate the effect of AMG 145 on the change in normalized total atheroma volume (TAV) and regression of coronary atherosclerosis either by PAV or TAV.

1.3 Exploratory
- To evaluate the effect of AMG 145 on plaque composition
- To assess the effects of AMG 145 on change and percent change from baseline in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, and ApoB/Apolipoprotein A-1 (ApoA1) ratio, Lipoprotein (a) [Lp(a)], triglycerides (TG), very low-density lipoprotein cholesterol (VLDL-C), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C)
- To evaluate cardiovascular event rates in subjects treated with AMG 145.

2. BACKGROUND AND RATIONALE

2.1 Cardiovascular Disease
Cardiovascular disease (CVD) remains the most important healthcare issue in the developed world and is rapidly becoming so in large parts of the developing world. The following facts from the American Heart Association (AHA) Heart and Stroke Facts Update from 2011 illustrate the magnitude of the problem in the US (Roger et al, 2011).

1) The 2005 overall death rate from CVD in the US was 278.9 per 100,000. Nearly 2,400 Americans die of CVD each day - an average of 1 death every 37 seconds. More than 150,000 Americans killed by CVD in 2005 were less than 65 years of age. In 2005, 32% of deaths from CVD occurred before the age of 75 years, which is well before the average life expectancy of 77.9 years. Preliminary mortality data from 2006 show that CVD accounted for 34.2% (829,072) of all 2,425,900 deaths in 2006, or 1 of every 2.9 deaths in the United States.

2) Coronary heart disease (CHD) caused 1 of every 5 deaths in the United States in 2005. Coronary heart disease mortality was 445,687. In 2009, an estimated 785,000 Americans will have a new coronary attack, and about 470,000 will have a recurrent attack. It is estimated that an additional 195,000 silent first myocardial infarctions occur each year. About every 25 seconds, an American will have a coronary event, and about every minute someone will die from one.

3) Each year, about 795,000 people experience a new or recurrent stroke. About 610,000 of these are first attacks, and 185,000 are recurrent attacks. Preliminary
data from 2006 indicate that stroke accounted for about 1 of every 18 deaths in the United States. On average, every 40 seconds someone in the United States has a stroke. From 1995 to 2005, the stroke death rate fell 29.7%, and the actual number of stroke deaths declined 13.5%.

4) Coronary artery disease (CAD) affects almost 17 million Americans. Of those 7,900,000 suffer from myocardial infarction; 9,800,000 from angina pectoris; 5,700,000 from congestive heart failure; and 6.5 million from stroke. One in 3 individuals in the US has some form of cardiovascular disease. The aging of the population will undoubtedly result in an increased incidence of coronary artery disease, heart failure, and stroke. There has been an explosive increase in the prevalence of obesity and type 2 diabetes and their related complications (hypertension, hyperlipidemia, and atherosclerotic vascular disease) will also increase. An alarming increase in unattended risk factors in the younger generations will continue to fuel the cardiovascular epidemic for years to come.

5) Cardiovascular disease claims more lives each year than the next 5 leading causes of death combined. Cardiovascular disease claimed 35.3% of all deaths in the United States in 2005. Since 1900, cardiovascular disease has been the No.1 killer in the United States every year but 1918.

In Europe, the situation is similar to the data reported for the United States. Coronary heart disease by itself remains the single most common cause of deaths in the European Union (EU) although the 2008 European cardiovascular disease statistics shows a reduction in the crude number of CHD deaths when compared with the 2005 edition (Allender et al, 2008). This reflects a general trend in Western, Northern and Southern European countries, where CHD mortality rates are falling steadily. The situation in some Central and Eastern European countries is very different, with CHD rates rising dramatically. This gradient is more marked for stroke mortality, where the crude number of deaths increased since 2005. Over 200,000 men and nearly 300,000 women die of stroke in the EU every year.

Each year CVD causes over 4.3 million deaths in Europe and over 2.0 million deaths in the European Union (EU). CVD causes nearly half of all deaths in Europe (48%) and in the EU (42%). CVD is the main cause of death in women in all countries of Europe and is the main cause of death in men in all countries except France, the Netherlands, and Spain. CVD is the main cause of the disease burden (illness and death) in Europe (23% of the entire disease burden) and the second main cause of the disease burden in those EU countries with very low child and adult mortality (17%). CVD mortality, incidence and case fatality are falling in most Northern, Southern and Western European countries but either not falling as fast or rising in Central and Eastern European countries.
Clearly, more effective primary and secondary CHD prevention measures are required. CHD prevention in the future will be the result of the ground breaking research that has been conducted over the past 25 years. For example, in the 1970s, data from the Framingham Epidemiological Study demonstrated that increases in serum cholesterol levels in the general population were associated with an increased risk of death from CHD (Kannel et al, 1974; Kannel et al, 1979; Kannel, 1995). In 1988, the National Cholesterol Education Program (NCEP) identified elevated low-density lipoprotein cholesterol (LDL-C) as a primary risk factor for CHD (NCEP, 1988). In the 1993 NCEP Adult Treatment Panel II Report, this conclusion was further strengthened by the addition of aggressive dietary and drug therapy recommendations for subjects with known CHD (NCEP, 1993). In 1995, Gould and associates reported meta-analysis data on 35 randomized clinical trials that lasted more than 2 years and were designed to reduce serum cholesterol levels. They concluded that for every 10 percentage points of cholesterol lowering, CHD mortality was reduced by 13% (p < 0.002) and total mortality by 10% (p < 0.03). According to the most recently reported United States National Health and Nutrition Examination Survey (NHANES III), an estimated 5.5 million Americans with CHD should be treated with lipid-lowering medications under the NCEP guidelines (Sempos et al, 1993).

Despite the availability of several classes of very effective drugs, the treatment of dyslipidemia and risk factor control are poorly served and there remains a large unmet medical need for new, effective and well tolerated therapies.

2.2 AMG 145 Background

Recycling of the hepatic cell surface LDL receptor (LDLR) plays a critical role in the maintenance of cellular and whole body cholesterol balance by regulating plasma LDL-C levels. Recently it has been shown that proprotein convertase subtilisin/kexin type 9 (PCSK9) plays an important role in the recycling and regulation of LDLR (Horton et al, 2007; Brown and Goldstein, 2006). PCSK9 is a member of the subtilisin family of serine proteases and is expressed predominantly in the liver, kidney, and intestine (Zaid et al, 2008). Following secretion, it causes post-translational downregulation of hepatic cell surface LDLR by a mechanism that involves direct binding to the LDL receptor (LDLR). Downregulation of hepatic LDLR in turn leads to increased levels of circulating LDL-C. Thus PCSK9 may represent a target for inhibition by novel therapeutics in the setting of dyslipidemia. The rationale for such an approach is available from studies in preclinical models, and from human genetic data that provide
strong validation for the role of PCSK9 in modulating LDL-C levels and the incidence of CHD in man. These human studies have identified gain-of-function mutations in the PCSK9 gene that are associated with elevated serum LDL-C levels (> 300 mg/dL [approximately 7.8 mmol/L]) and premature CHD (Abifadel et al, 2003); and loss-of-function (LOF) mutations that are associated with low serum LDL-C levels (≤ 100 mg/dL [approximately 2.6 mmol/L]) (Cohen et al, 2005). Strikingly, subjects with heterozygous LOF mutations exhibit lower serum PCSK9 levels and as much as 88% reduction in the incidence of CHD over a 15-year period compared with noncarriers of the mutations (Cohen et al, 2006). Moreover, despite complete loss of PCSK9 and associated very low serum LDL-C levels (< 20 mg/dL [approximately 0.5 mmol/L]), the 2 subjects who have been identified with compound heterozygote LOF mutations appear healthy (Hooper et al, 2007; Zhao et al, 2006).

AMG 145 is a fully human monoclonal immunoglobulin (Ig) G2 that binds specifically to human PCSK9 and prevents the interaction of PCSK9 with LDLR. Details of the biochemistry, nonclinical pharmacology, nonclinical pharmacokinetics (PK), and nonclinical toxicology with AMG 145 are contained in the Investigator’s Brochure, 2012. AMG 145 binds to human, monkey, and hamster PCSK9 with high affinity (K_d < 100 pM). AMG 145 caused a dose-dependent inhibition of PCSK9 binding to the LDLR and of PCSK9-mediated reduction in low-density lipoprotein (LDL) uptake in HepG2 cells (human hepatocellular carcinoma cell line) in culture. In cynomolgus monkeys and in hamsters, in vivo administration of AMG 145 resulted in reduced serum lipoprotein cholesterol levels in a dose-dependent manner. Based on a comprehensive package of PK, pharmacodynamics (PD), and toxicology studies (Investigator’s Brochure, 2012), a program to develop AMG 145 as a treatment for dyslipidemia was initiated.

2.2.1 First-in-Human (FIH) Study 20080397

The first-in-human (FIH) study of AMG 145, Study 20080397, was a randomized, double-blind, placebo-controlled, ascending-single-dose phase 1 study to evaluate the safety, tolerability, PK, pharmacodynamics (PD; as measured by LDL-C), and immunogenicity of AMG 145 in healthy subjects. AMG 145 was administered at doses of 7, 21, 70, 210, and 420 mg SC and 21 and 420 mg IV.

AMG 145 reduced LDL-C by an average of 55% to 60% at single doses ≥ 70 mg SC, with the duration of effect being dose dependent. The LDL-C nadir was observed within 2 weeks of dosing. Complete suppression of PCSK9 (inability to detect unbound
PCSK9) was observed at single doses ≥ 70 mg SC, which correlated well with the effects seen on circulating LDL-C.

AMG 145 exhibited nonlinear PK after single-dose SC and IV administrations, as is typical with monoclonal antibodies. Over the dose range of 7 to 420 mg; the exposure, measured by the mean maximum measured concentration (Cmax) and area under the concentration-time curve (AUC), increased in a more than dose-proportional manner. The apparent clearance following an SC dose reached a plateau at doses ≥ 210 mg SC indicating that the linear range of antibody elimination was attained.

For mean unbound PCSK9, the single administrations of AMG 145 produced decreases that were also dose-related with respect to magnitude and overall duration. Baseline PCSK9 values were in the range of approximately 200 to 280 ng/mL for all groups. In the 210 mg dose group and in the 420-mg groups (SC or IV), mean PCSK9 decreased within hours after dosing to values below the lower limit of quantitation (LLOQ) (15 ng/mL), remained below the LLOQ until day 11, and subsequently returned to or toward baseline.

Treatment-emergent adverse events were reported for 29 of the 42 subjects (69%) who received AMG 145 at any dose, and for 10 of the 14 subjects (71%) who received placebo. No relationship was apparent between the subject incidence of adverse events and the dose of AMG 145, or between the subject incidence of adverse events and the route of administration of AMG 145 (SC versus IV).

No adverse events were reported as serious and no subjects discontinued the study due to an adverse event. There were no deaths on study.

For further details on study 20080397, please consult the Investigator’s Brochure (2012).

2.2.2 Multiple-dose Phase 1b Study 20080398

Study 20080398 was a phase 1b, randomized, double-blind, placebo-controlled, ascending, multiple-dose study in hypercholesterolemic subjects currently on stable doses of a statin. Six doses of AMG 145 were administered at 14 or 35 mg QW; 3 doses at 140 or 280 mg Q2W; or 2 doses at 420 mg Q4W. Hypercholesterolemic subjects taking high doses of a statin received 3 doses of 140 mg SC Q2W. The study also included subjects with heterozygous familial hypercholesterolemia who received 3 doses of AMG 145 at 140 mg SC Q2W.

AMG 145 lowered LDL-C at all doses tested. The LDL-C nadir was dependent on the dose and regimen and was observed following the last dose. Although lower doses
(14 mg QW and 35 mg QW) led to mean reductions in LDL-C of 20% to 50%, the maximum mean reduction of LDL-C was 70% to 80% in the highest dose groups (140 mg Q2W, 280 mg Q2W, and 420 mg Q4W). The higher dose regimens were associated with near complete suppression of unbound PCSK9, and the degree of PCSK9 suppression correlated well with the effects seen on circulating LDL-C. Subjects receiving high-dose statins had a similar degree of PCSK9 suppression and LDL-C lowering compared with subjects on the lower doses of statins. Subjects with heterozygous familial hypercholesterolemia exhibited a similar degree of PCSK9 suppression and LDL-C reduction compared with subjects without heterozygous familial hypercholesterolemia. AMG 145 exhibited nonlinear behavior following multiple doses. The PK profile of AMG 145 in the highest dose groups (140 mg Q2W, 280 mg Q2W, and 420 mg Q4W) was consistent with the PK profiles of AMG 145 in the single-dose phase 1a study.

Treatment-emergent adverse events were reported by 28 of 43 subjects (65%) receiving AMG 145 and 9 of 14 subjects (64%) receiving placebo. No adverse events were reported as serious, and no subjects discontinued the study due to an adverse event. There were no deaths on study. No relationship was apparent between the subject incidence of treatment-emergent adverse events and the dose of AMG 145 or between the subject incidence of treatment-related adverse events and the dose of AMG 145. There were no trends indicative of clinically important effects of AMG 145 on hepatic function tests, ECGs, or vital signs. One subject who received 140 mg AMG 145 Q2W for 6 weeks with a high-dose statin tested positive for AMG 145-binding antibodies at day 29, but was negative for neutralizing antibodies.

For further details on study 20080398, please consult the Investigator’s Brochure (2012).

2.2.3 Completed Phase 2, 12 Week LDL-C Lowering Studies

- Study 20101154 (N = 411) evaluating AMG 145 as monotherapy
- Study 20101155 (N = 631) evaluating AMG 145 as combination therapy with statin (with or without ezetimibe)
- Study 20090158 (N = 168) evaluating AMG 145 in subjects with heFH
- Study 20090159 (N = 160) evaluating AMG 145 in statin-intolerant subjects.

2.2.4 Ongoing Phase 2 Studies

In addition to study 20120153 there are 5 other ongoing phase 2 AMG 145 studies.
• Study 20110109 (planned N = 905; enrollment closed) which is a randomized, double-blind, placebo-controlled study evaluating safety, tolerability, and efficacy of AMG 145 compared with placebo for 52 weeks in hypercholesterolemic subjects

• Study 20110110 (planned N ~ 1600; enrollment ongoing) which is a multicenter, controlled, open-label extension (OLE) study to assess the long-term safety and efficacy of AMG 145 that includes subjects from the aforementioned phase 2 studies

• Study 20110231 (N= 300; enrollment ongoing), which is a double-blind, randomized, placebo-controlled, multicenter study to evaluate tolerability and efficacy of AMG 145 on LDL-C in combination with stable statin therapy in Japanese subjects with hypercholesterolemia and high cardiovascular risk

• Study 20110233 (planned N = 57; enrollment ongoing) which is a 2-Part, Phase 2/3 study to assess the safety, tolerability and efficacy of AMG 145 in subjects with homozygous familial hypercholesterolemia

• Study 20110271 (planned N=125; enrollment ongoing), which is a multicenter, open-label study designed to assess the long-term safety, tolerability, and efficacy of AMG 145 in subjects with severe familial hypercholesterolemia

2.2.4.1 Phase 2 Aggregate Interim Analysis Results

On 15 March 2012, a protocol-specified interim analysis was performed to facilitate phase 3 dose selection via an assessment of the safety, tolerability, and efficacy of 6 AMG 145 dosing regimens from the ongoing phase 2 program. This interim analysis included safety, tolerability, and efficacy data from 5 studies (Table 1).
Table 1. Summary of Study Design of Four Parent Studies and Extension Study

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>20101154</th>
<th>20101155</th>
<th>20090158</th>
<th>20090159</th>
<th>20110110</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Size</td>
<td>411</td>
<td>631</td>
<td>168</td>
<td>165</td>
<td>~1100</td>
</tr>
<tr>
<td>Patient Population</td>
<td>Subjects not on statins</td>
<td>Subjects on statins + ezetimibe</td>
<td>Subjects with HeFH</td>
<td>Subjects with statin intolerance</td>
<td>Subjects from studies 20101154, 20101155, 20090158, 20090159</td>
</tr>
<tr>
<td>Fasting LDL-C</td>
<td>≥ 100 mg/dL and &lt; 190 mg/dL</td>
<td>≥ 85 mg/dL (≥ 85 to &lt;100 mg/dL limited to 20%)</td>
<td>≥ 100 mg/dL; Not at LDL-C goal (NCEP ATP III)</td>
<td>≥ 100 mg/dL; Not at LDL-C goal (NCEP ATP III)</td>
<td>≥ 75 mg/dL</td>
</tr>
<tr>
<td>Randomization Ratio</td>
<td>9 arms, equal allocation</td>
<td>8 arms, equal allocation</td>
<td>3 arms, equal allocation</td>
<td>5 arms, equal allocation</td>
<td>2:1</td>
</tr>
<tr>
<td>Treatment Duration</td>
<td>12 weeks</td>
<td>12 weeks</td>
<td>12 weeks</td>
<td>12 weeks</td>
<td>52 weeks</td>
</tr>
<tr>
<td>Treatment Groups</td>
<td>70mg Q2W</td>
<td>70mg Q2W</td>
<td>105mg Q2W</td>
<td>105mg Q2W</td>
<td>140mg Q2W</td>
</tr>
<tr>
<td></td>
<td>140mg Q2W</td>
<td>140mg Q2W</td>
<td>Placebo Q2W</td>
<td>Placebo Q2W</td>
<td>Placebo Q2W</td>
</tr>
<tr>
<td></td>
<td>280mg Q4W</td>
<td>280mg Q4W</td>
<td>350mg Q4W</td>
<td>350mg Q4W</td>
<td>350mg Q4W</td>
</tr>
<tr>
<td></td>
<td>420mg Q4W</td>
<td>420mg Q4W</td>
<td>420mg Q4W</td>
<td>420mg Q4W</td>
<td>420mg Q4W</td>
</tr>
<tr>
<td></td>
<td>Placebo Q4W</td>
<td>Placebo Q4W</td>
<td>Placebo Q4W</td>
<td>Placebo Q4W</td>
<td>Placebo Q4W</td>
</tr>
<tr>
<td></td>
<td>Ezetimibe QD</td>
<td>Ezetimibe QD</td>
<td>Placebo Q4W + Ezetimibe QD</td>
<td>Placebo Q4W + Ezetimibe QD</td>
<td>Placebo Q4W + Ezetimibe QD</td>
</tr>
</tbody>
</table>

The interim analysis included data from 1340 unique subjects enrolled and dosed in the 4 parent phase 2 LDL-C lowering 12-week studies (20090158, 20090159, 20101154, and 20101155). Of these, 1229 (92%) subjects completed at least 4 weeks on study (LDL-C values are week 4) and 692 (52%) subjects completed at least 12 weeks on study. The primary efficacy analysis was based on the 692 subjects who had observed or imputed values of % change of LDL-C at week 12 while the data at week 4 was used to verify these findings. Safety analyses were performed based on the entire sample of 1340 subjects with hypercholesterolemia in the interim analysis.

As of the snapshot dates, 606 subjects from the 4 phase 2 parent studies had rolled over into the long-term extension study (20110110). The mean time on study for subjects in study 20110110 was 1.4 months plus an additional three months from the parent study. This translates into approximately 31% and 10% of subjects being on study (ie, parent and extension studies) for ≥ 5 and ≥ 6 months, respectively.
In order to maintain blinding in the ongoing phase 2 studies, data presented herein were aggregated by dose and dosing regimen across the 4 parent studies.

### 2.2.4.2 Phase 2 Aggregate Interim Analysis Efficacy Results

Statistically significant decreases in LDL-C from baseline at week 12 relative to placebo were observed for each of the 6 AMG 145 treatment groups (p values <0.001; Figure 1). The reduction in LDL-C was dose dependent within each dosing frequency (Q2W and Q4W). The largest LDL-C reductions at week 12 were seen at the highest dose within each dosing frequency (ie, 140 mg Q2W and 420 mg Q4W). In the Q2W cohorts, decreases relative to placebo (treatment difference) ranged from 41% (70 mg) to 60% (140 mg) at week 12; reductions ranged from 44% (280 mg) to 56% (420 mg) at week 12 in the Q4W cohorts.

Figure 1. Aggregate Interim Analysis Percent Change from Baseline in Calculated LDL-C Over Time for Q2W and Q4W Administration of AMG 145 or Placebo.

Subgroup analyses performed on aggregate interim data showed a similar effect on the LDL-C treatment difference from baseline at week 12 across all subgroups within each dosing frequency, demonstrating a consistent treatment effect of AMG 145.

Integrated analyses of mean percent change from baseline to week 12 in other lipid parameters are presented in Table 2. Statistically significant decreases from baseline for all 6 AMG 145 treatment groups were observed for total cholesterol (p < 0.001), ApoB (p < 0.001), non-HDL-C (p < 0.001), VLDL-C (p < 0.03), Lp(a) (p < 0.001). Mean reductions from baseline to week 12 relative to placebo in total cholesterol (range: 25% to 37%), ApoB (range: 33% to 51%), non-HDL-C (range: 36% to 53%) were strictly dose-dependent within each dosing frequency (ie, Q2W or Q4W). Mean reductions from
baseline to week 12 relative to placebo in VLDL-C (14% to 44%) and Lp(a) (15% to 31%) concentrations were generally dose dependent, although a single deviation for each parameter was observed. Favorable trends in the mean reductions from baseline to week 12 relative to placebo for triglycerides (range: 7% to 25%) were also observed. Statistically significant increases in HDL-C and ApoA1 were seen in all AMG 145 dose groups except for the 280 mg Q4W cohort, and the 70 mg Q2W and 280 mg Q4W cohorts, respectively. AMG 145 treatment resulted in dose-dependent elevations in HDL-C (3% to 10%) and ApoA1 (2% to 5%) in all dose groups.

Table 2. Integrated Interim Analysis of Treatment Difference (Estimate and 95% CI) from Baseline Relative to Placebo at Week 12 in Select Lipid Parameters - Study 20101154, 20101155, 20090158, 20090159 - (Integrated Interim Full Analysis Set)

<table>
<thead>
<tr>
<th>Lipid parameter</th>
<th>AMG 145 Q2W vs Placebo Q2W</th>
<th>AMG 145 Q4W vs Placebo Q4W</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>70 mg (N = 43)</td>
<td>105 mg (N = 43)</td>
</tr>
<tr>
<td>Calc LDL-C</td>
<td>-40.96 (-46.82, -35.10)</td>
<td>-50.53 (-56.41, -44.65)</td>
</tr>
<tr>
<td>95% CI</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total Chol</td>
<td>-25.27 (-29.47, -21.06)</td>
<td>-30.75 (-34.97, -26.54)</td>
</tr>
<tr>
<td>95% CI</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ApoB</td>
<td>-33.04 (-38.05, -30.03)</td>
<td>-41.70 (-46.73, -36.68)</td>
</tr>
<tr>
<td>95% CI</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>non-HDL-C</td>
<td>-35.96 (-41.25, -30.67)</td>
<td>-43.60 (-48.91, -38.29)</td>
</tr>
<tr>
<td>95% CI</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VLDL</td>
<td>-27.73 (-37.89, -17.14)</td>
<td>-22.53 (-29.82, -15.22)</td>
</tr>
<tr>
<td>95% CI</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>-15.21 (-24.18, -6.24)</td>
<td>-24.12 (-33.12, -15.12)</td>
</tr>
<tr>
<td>95% CI</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-14.89 (-28.37, -1.41)</td>
<td>-12.18 (-25.71, 1.34)</td>
</tr>
<tr>
<td>95% CI</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C</td>
<td>5.72 (0.82, 10.61)</td>
<td>7.13 (2.22, 12.04)</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.022</td>
<td>0.005</td>
</tr>
<tr>
<td>ApoA1</td>
<td>2.98 (1.01, 6.96)</td>
<td>4.09 (1.00, 8.09)</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.140</td>
<td>0.045</td>
</tr>
</tbody>
</table>

Source: Modified from integrated analysis Tables 14-4.14.1, 14-4.15.6, 14-4.9.1, 14-4.8.1, 14-4.18.6, 14-4.24.6, 14-4.17.6, 14-4.16.6, and 14-4.20.6.
2.2.4.3 Phase 2 Interim Efficacy Analysis Results for the Randomized, Controlled, Open-label Extension

Interim results of this open-label extension study show that treatment with AMG 145 was effective in reducing LDL-C concentrations in all subjects who had not previously received AMG 145, regardless of whether or not they had received other lipid lowering therapies (Figure 2). Subjects who received AMG 145 in their parent study maintained their LDL-C reductions in the extension study at levels similar to that in the parent study. Furthermore, results demonstrate reversibility of the treatment effects of AMG 145. Subjects who had previously received AMG 145 in their parent study and who were randomized to standard of care in the extension study (ie, discontinued AMG 145 therapy), saw their LDL-C concentrations rise to that of subjects who had never received AMG 145 (ie, standard of care alone) by week 4 in the extension.

Figure 2. Aggregate Interim Analysis Percent Change from Baseline in Calculated LDL-C in Subjects Transitioning from AMG 145 (Q2W or Q4W) or Placebo to AMG 145 and Standard of Care or Standard of Care Alone.

2.2.4.4 Aggregate Safety Data from Completed Phase 2 Studies

Adverse event data from completed clinical studies demonstrate that AMG 145 has an acceptable safety profile up to the highest dose tested (420 mg). Specifically:

- In completed phase 2 studies, subjects treated with AMG 145 (n=961) experienced a higher overall incidence of treatment emergent adverse events compared with placebo (n=301) (57% and 48%, respectively); however, there was no relationship between the dose or dosing frequency of AMG 145 and the incidence of treatment emergent adverse events.

- In completed phase 2 studies, adverse events with a subject incidence of at least 2% in the AMG 145 group and exceeding the placebo incidence by at least 1% were as follows (AMG 145, placebo): nasopharyngitis (8.2%, 6.6%), myalgia (2.7%, 1.0%), and nausea (2.7%, 1.7%).
• In completed phase 2 studies, the overall incidence of serious adverse events was similar between the AMG 145 and placebo groups (2.1% and 1.3%, respectively). No individual serious adverse event was reported in more than 2 (0.2%) subjects treated with AMG 145 in these studies.

There was a higher incidence of creatine kinase (CK) elevations in the AMG 145 group compared with placebo. These elevations were generally associated with obvious precipitating events in the form of strenuous physical activity. All of these events were transient (one laboratory abnormality followed by normal laboratory values), resolved spontaneously, and did not lead to discontinuation of investigational product.

2.3 Rationale

Over the course of the last three decades, considerable technological advances in arterial imaging have permitted visualisation of the full extent of atherosclerotic plaque. Intravascular ultrasound (IVUS) involves the placement of high frequency ultrasound transducers within the coronary artery lumen, generating high resolution imaging of the full thickness of the artery wall. IVUS imaging within an anatomically matched arterial segment at multiple time points enables measurement of changes in atheroma burden. In general these studies have demonstrated disease progression, in direct association with LDL-C levels.

Multiple clinical trials have evaluated the impact of LDL-C lowering with statin therapy on disease progression. The REVERSAL study directly compared the effects of moderate lipid lowering with pravastatin 40 mg daily and intensive lipid lowering with atorvastatin 80 mg daily for 18 months. Lower achieved levels of LDL-C (79 vs 110 mg/dL) with atorvastatin were associated with halting of disease progression (Nissen et al, 2004). Subsequent analyses revealed a direct relationship between lowering of either LDL-C or CRP and slowing of disease progression (Nissen et al, 2005). The ASTEROID study evaluated the impact of rosuvastatin 40 mg daily for 24 months. A lower LDL-C level (61 mg/dL) was associated with regression of coronary atherosclerosis (Nissen et al, 2006). This finding was further supported by the SATURN trial, in which subjects were treated with rosuvastatin 40 mg daily or atorvastatin 80 mg daily for 24 months. Low levels of LDL-C (62 v 70 mg/dL) and higher levels of HDL-C (48 v 50 mg/dL) in both groups was associated with disease regression (Nicholls et al, 2011).

Analysis of all studies that have employed serial IVUS imaging demonstrates a consistent direct relationship between achieving lower LDL-C levels and favorable effects on disease progression, with evidence of regression at LDL-C levels less than
70 mg/dL (Puri et al, 2013). To date, there is no evidence of a lack of incremental benefit at lower LDL-C levels (Puri et al, 2013), leaving unanswered whether achieving even lower LDL-C levels than observed in previous trials might result in greater disease regression.

With increasing evidence of benefit in clinical trials, treatment guidelines for risk reduction in subjects with established coronary artery disease requires a LDL-C less than 100 mg/dL or 70 mg/dL in subjects deemed to be at particularly high risk. However, many subjects with CAD demonstrate suboptimal LDL-C levels despite use of established lipid modifying therapies. The benefit of additional lipid modification with PCSK9 inhibition on disease progression has not been evaluated.

Dose Selection

Selection of the proposed dose regimen (420 mg SC, Q4W) was based on analysis of pharmacokinetic (PK) and pharmacodynamic (PD) data obtained from our interim phase 2 analysis (Section 2.2.4) and bolstered by a single dose study of AMG 145 in healthy volunteers (Study 20080397). PK/PD analysis and simulations were performed to predict AMG 145 concentrations and LDL lowering in subjects following multiple SC administration. The dose of 420 mg Q4W was predicted to provide LDL changes from baseline of approximately 60% at steady-state, allowing robust characterization of the durability of AMG 145 PD effects.

The no-observed-adverse-effect level (NOAEL) observed in a 6-month cynomolgus monkey toxicology study (300 mg/kg weekly SC) provides significant exposure multiples (86x for exposure (AUC) and 254x for Cmax) over the anticipated human exposures.

2.4 Clinical Hypotheses
The primary hypothesis is that LDL-C lowering with AMG 145 420mg SC will result in a greater change from baseline in PAV at week 78 than placebo in subjects taking statin lipid lowering therapy.

3. EXPERIMENTAL PLAN
3.1 Study Design
This is a Phase III, multi-center, double blind, randomized, placebo-controlled study evaluating the effect of Evolocumab (AMG 145) upon coronary atherosclerotic disease burden as assessed by IVUS at baseline and following 78 weeks of treatment in subjects with coronary artery disease.
Subjects will be identified for eligibility on the basis of requiring coronary angiography for further clinical evaluation, LDL-C inclusion criteria, and completion of IVUS.

At randomization, subjects must be on stable, optimized background statin therapy (per Protocol Appendix E) that is expected to be unchanged for the duration of study participation (up to 18 months). Optimal statin therapy is defined as an effective statin dose of at least atorvastatin 20 mg daily or equivalent titrated to achieve target LDL-C (change or goal) as defined by regional guidelines. Where locally approved, highly effective statin therapy, defined as at least atorvastatin 40 mg daily or equivalent, is recommended. For subjects with LDL-C > 100 mg/dL (2.6 mmol/L) who are not receiving highly effective statin therapy (atorvastatin ≥ 40 mg daily or equivalent), the investigator must attest that higher dose statin therapy is not appropriate for this subject (eg, dose not tolerated, dose not available in that country, other significant clinical concern). Subjects who, in the investigator’s opinion, are already at LDL-C goal at initial screening and are on stable (≥ 4 weeks), allowable lipid lowering therapy (per Appendix E), with no changes planned or expected for the duration of the study, will be enrolled and proceed directly to randomization if all other eligibility criteria are met. These subjects may skip the lipid stabilization period.

Subjects who have an acceptable IVUS and are currently on an appropriate statin dose with an LDL-C level that meets the inclusion criteria will be eligible for randomization.

Subjects not on an optimal dose of a statin, in the opinion of the investigator, will enter a two to four week lipid stabilization period for initiation or titration of a statin with a maximum of one uptitration step for optimization. No changes to lipid lowering therapies will be allowed (except for clinically compelling reasons) once subjects are randomized.

Subjects who fail to meet eligibility criteria will be considered screen failures, and cannot be rescreened. However, certain subjects may be eligible for retesting without rescreening: please refer to section 7.1.1.2. The baseline IVUS examination may be performed only once for entry into the study. Repeating the baseline IVUS examination is prohibited.

Subjects will be randomized 1:1 into 2 treatment groups: AMG 145 420 mg QM SC or placebo QM SC. Randomization will be stratified for balance by region. Study visits will occur during screening, Day 1 (randomization) and week 4, 12, 24, 36, 52, 64, 76 (last
dose of IP) and 78 (final IVUS procedure). **During these visits**, investigational product (IP) **will be given via either self-administration or by a qualified staff member.** Between study visits, **IP can be administered at a location external to the study site**, unless **subjects** choose to visit the site to have IP administered by site personnel. At **applicable** visits, vital signs, AEs, SAEs, and concomitant medications will be recorded and laboratory tests will be performed. Dietary instruction will be given at each visit. Central laboratory results of the lipid panel, ApoA1, ApoB, high sensitivity C-reactive protein (hsCRP), and lipoprotein(a) (Lp(a)) will be blinded during the **IP** treatment period until unblinding of the clinical database and will not be reported to the investigator post-screening. Investigators 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 end-of-study visit. Investigators will be informed if triglycerides are > 1000 mg/dL (11.3 mmol/L) so that appropriate subject follow-up can be initiated (see Protocol Section 6.2.2.1). The primary efficacy measurement for this study is PAV and will be measured at baseline and week 78. The study includes collection of biomarker samples and, where approved by the independent ethics committee and/or institutional review board (IEC/IRB) and applicable regulatory and other authorities, all subjects will be invited to consent to pharmacogenetic analyses. Last IP will be administered at week 76. The **final** visit will occur at week 80 for all subjects. **During this final visit,** **sites** will contact (eg, phone call) subjects to assess any potential AEs or SAEs. Subjects will be encouraged to complete all planned visits regardless of their adherence to IP administration. The study includes adjudication of deaths and specific cardiovascular events potential endpoints (PEPs) by an independent Clinical Events Committee (CEC) and formal review of the accumulating data by an independent Data Monitoring Committee (DMC). An Executive Committee (EC) has been formed to advise Amgen on trial design and for assistance in the communication of trial results. The EC will be blinded. Details for each committee will be provided in a committee charter.

### 3.2 Number of Centers

This study will include approximately 230 sites in the US, Canada, Latin America, Asia, Australia, South Africa, and Europe. Other regions may be added for participation in this study. Sites that do not enroll subjects within 3 months of site initiation may be closed.
3.3 Number of Subjects
Participants in this clinical investigation shall be referred to as “subjects”. There will be approximately 950 subjects randomized in this study. Justification for the sample size can be found in Section 10.2.

3.4 Estimated Study Duration
3.4.1 Study Duration for Participants
After signing the informed consent, subjects should be randomized within 6 weeks. Including the screening, treatment, and follow-up periods, the maximal total duration of study participation for a subject will be up to approximately 86 weeks or approximately 21 months.

3.4.2 End of Study
The end of the study (EOS) for this trial is defined as the date on which the last randomized subject completes week 80 EOS. The primary completion date is the date that the last randomized subject completes the week 78 assessment.

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

4.1 Inclusion Criteria
4.1.1 Subject has provided informed consent.
4.1.2 Male or female ≥ 18 age at screening
4.1.3 Clinical indication for coronary angiography
4.1.4 Subjects already taking statin therapy, regulatory-approved sustained-release niacin (eg Niaspan®) or ezetimibe at initial screening must have been on a stable dose for at least 4 weeks prior to the lipid panel used for the screening LDL-C. Subjects not currently taking lipid-regulating therapy can be screened but must enter the study via a lipid stabilization period.

OR
4.1.4 Subjects who are intolerant to statins (limited to no more than approximately 10% of total planned enrollment) must meet statin intolerance entry criteria in Appendix G.

4.1.5 Subjects must have at least one eligible LDL-C level (as defined below) via local, central laboratory or point of care device at the initial screening visit and, if applicable, at the end of each lipid stabilization period. A pre-existing local LDL-C level may be used as the initial screening LDL-C value as long as it was drawn within 4 weeks of the screening visit and no interim changes to lipid-regulating therapy have occurred during that 4 week period.

LDL-C \( \geq 80 \text{ mg/dL (2.07 mmol/L)} \) with or without additional risk factors

OR

LDL-C \( \geq 60 - <80 \text{ mg/dL (1.55-2.07 mmol/L)} \) in the presence of one Major or three Minor Risk factors as defined below. Enrollment of subjects with LDL-C between \( \geq 60 \text{ mg/dL (1.55 mmol/L)} \) and \( < 80 \text{ mg/dL (2.07 mmol/L)} \) will be limited to no more than approximately 25% of total planned enrollment.

Major Risk Factors (one required)

1) Non-coronary atherosclerotic vascular disease as evidenced by one of the following: documented peripheral arterial disease (PAD), documented abdominal aortic aneurysm (AAA), or documented cerebrovascular disease (CD).

   ▪ Documented peripheral arterial disease (one of the following primary criteria must be satisfied):
     - Current intermittent claudication (WHO criteria, eg, leg pain occurring only while walking and disappearing in less than 10 minutes on standing) of presumed atherosclerotic origin TOGETHER WITH ankle-brachial index equal to or less than 0.9 in either leg at rest.
     - History of intermittent claudication (WHO criteria as above) TOGETHER WITH either previous intervention by amputation, or reconstructive vascular surgery, or angioplasty in one or both legs because of atherosclerotic disease within the last 2 years.

   ▪ Documented abdominal aortic aneurysm,
     - AAA is considered to be present when the minimum anteroposterior diameter of the aorta reaches 3.0 cm. The size of the aorta can be measured in any plane that is perpendicular to the vessel axis.
- Documented cerebrovascular disease (e.g. carotid artery disease or prior history of stroke or transient ischemic attack occurring within the last 2 years).
  
  - Stroke: ischemic stroke is defined as an infarction of central nervous system tissue not secondary to underlying congenital or valvular heart disease. Symptomatic ischemic strokes manifest by clinical signs of focal or global cerebral, spinal, or retinal dysfunction caused by central nervous system infarction. A silent stroke is a documented central nervous system infarction that was asymptomatic.

  - Transient ischemic attack (TIA): a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction, not secondary to underlying congenital or valvular heart disease.

  - Carotid artery disease: defined as stenosis > 50% or PSV > 125 cm/sec with plaque

2) Documented history of myocardial infarction or hospitalization for unstable angina within the last two years

3) Documented Type 2 diabetes mellitus

Minor Risk Factors (three required)

a. **Current** cigarette smoker

b. Hypertension (**One documented blood pressure** (BP) ≥ 140/90 mm Hg or current use of antihypertensive medication)

c. Low HDL cholesterol - men < 40 mg/dL (1.03 mmol/L) ; women < 50 mg/dl (1.29 mmol/L)

d. Family history of premature CHD (in first-degree male relative < 55 years of age; in first-degree female relative < 65 years of age

e. Age (men ≥ 50 years; women ≥ 55 years)

f. **High sensitivity C-reactive protein** (hs-CRP) ≥ 2 mg/dL

Subjects must meet all of the following criteria at the qualifying coronary catheterization procedure:

A. Entire Coronary Circulation:

  - Angiographic evidence of coronary heart disease as defined by at least one lesion in any of the three major native coronary arteries that has > 20% reduction in lumen diameter by angiographic visual estimation or prior history of **percutaneous coronary intervention** (PCI).

  - This vessel need not be the target coronary artery for IVUS.

  - Any vessel with previous PCI may not be used as the target coronary artery.

B. Left Main Coronary Artery:
- Must not have a > 50% reduction in lumen diameter by visual angiographic estimation.

C. Target Coronary Artery for IVUS:

- Must be accessible to the IVUS catheter.
- Must not have a >50% reduction in lumen diameter by angiographic visual estimation within the target segment, the target segment being at least 40 mm in length.
- A lesion, distal to the target segment, of up to 60% stenosis is permitted, provided that the stenosis is not a target for PCI or CABG.
- A single branch of the "target vessel" may have a narrowing of < 70% by visual estimation, provided that the branch in question is not a target for PCI or CABG.
- Has not undergone prior percutaneous coronary intervention or coronary artery bypass graft surgery.
- The target vessel is not currently a candidate for intervention or a likely candidate for intervention over the next 18 months.
- The target vessel may not be a bypass graft.
- The target vessel may not be a bypassed vessel.
- The target vessel may not be the culprit vessel for a previous MI.

4.2 Exclusion Criteria

4.2.1 Clinically significant heart disease which in the opinion of the Principal Investigator is likely to require coronary bypass surgery, PCI (does not apply to PCI deemed necessary by the initial screening angiogram), cardiac transplantation, surgical or percutaneous valve repair and/or replacement during the course of the study.

4.2.2 Coronary artery bypass graft surgery < 6 weeks prior to the qualifying IVUS.

4.2.3 NYHA III or IV heart failure, or last known left ventricular ejection fraction < 30%

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

4.2.5 Known hemorrhagic stroke.

4.2.6 Uncontrolled hypertension at randomization, defined as a systolic blood pressure of ≥ 180mmHg at rest.

4.2.7 Personal or family history of hereditary muscular disorders.

4.2.8 Fasting TGs ≥ 400 mg/dL (4.5 mmol/L) at screening.

4.2.9 Subject has taken a cholesterol ester transfer protein (CETP) inhibitor, (ie. anacetrapib, dalcetrapib, evacetrapib) or mipomersen or lomitapide in the last 12 months prior to LDL-C screening.
4.2.10 Type 1 diabetes or poorly controlled type 2 diabetes (HbA1c > 9%) at screening.

4.2.11 Treatment for more than 2 weeks in the last 3 months prior to LDL-C screening with any of the following drugs: systemic cyclosporine, systemic steroids (eg. IV, intramuscular [IM], or PO) (Note: hormone replacement therapy is permitted); systemic vitamin A and retinol derivatives for the treatment of dermatologic conditions (eg, Accutane) (Note: vitamin A in topical and multivitamin preparations are permitted).

4.2.12 Thyroid stimulating hormone (TSH) < lower limit of normal (LLN) or TSH > 1.5x upper limit of normal (ULN). A subject taking thyroid replacement therapy may be enrolled with TSH level below LLN if, in the opinion of the investigator, the subject is in a clinically euthyroid state.

4.2.13 Moderate to severe renal dysfunction, defined as an estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m² at screening, confirmed by a repeat measurement at least 1 week apart.

4.2.14 Active liver disease or hepatic dysfunction, defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 times the ULN as determined by analysis at screening or at end of lipid stabilization period.

4.2.15 CK > 3 times the ULN at screening or at end of lipid stabilization period.

4.2.16 Known active infection or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction in the judgment of the investigator.

4.2.17 Baseline IVUS does not meet IVUS Core Lab technical standards.

4.2.18 Unreliability as a study participant based on the investigator’s (or designee’s) knowledge of the subject (eg, alcohol or other drug abuse, inability or unwillingness to adhere to the protocol, or psychosis).

4.2.19 Currently enrolled in another investigational device or drug study, or less than 30 days since ending another investigational device or drug study(s), or receiving other investigational agent(s).

4.2.20 Female subject who has not used an acceptable method(s) of birth control for at least 1 month prior to screening, unless the female subject is sterilized or postmenopausal (see below).

4.2.21 Female subject is not willing to inform her partner of her participation in this clinical study and to use an acceptable method(s) of birth control during treatment with IP (AMG 145 or placebo) and for an additional 15 weeks after the end of treatment with IP (AMG 145 or placebo) unless the female subject is sterilized or postmenopausal (see below).

- A female is considered of childbearing potential unless sterilized or postmenopausal with menopause defined as:
  - 12 months of spontaneous and continuous amenorrhea in a female ≥ 55 years old or 12 months of spontaneous and continuous amenorrhea with a follicle-stimulating hormone (FSH)
level > 40 IU/L (or according to the definition of "postmenopausal range" for the laboratory involved) in a female < 55 years old unless the subject has undergone bilateral oophorectomy.

- **Acceptable** methods of preventing pregnancy include sexual abstinence, surgical contraceptive methods (vasectomy or bilateral tubal ligation), use of hormonal birth control methods (pills, shots, implants or patches), intrauterine devices (IUDs), or two (2) barrier methods (each partner must use one barrier method) with spermicide – males must use a condom with spermicide; females must choose either a Diaphragm with spermicide, OR Cervical cap with spermicide, OR Contraceptive sponge with spermicide.

  - **Note:** Additional medications given during the screening period, lipid stabilization period and during treatment with IP (AMG 145 or placebo) 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 after the last dose of protocol-required therapies. The investigator is to discuss these contraceptive changes with the study subject.

4.2.22 Subject is pregnant or breastfeeding, planning to become pregnant, or planning to breastfeed during the screening period, at the end of the lipid stabilization period (if applicable), while receiving treatment with IP (AMG 145 or placebo) and within 15 weeks after the end of treatment with IP (AMG 145 or placebo)

4.2.23 History of malignancy (except non-melanoma skin cancers, cervical in-situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma)

4.2.24 Subject has previously received AMG 145 or any other investigational therapy to inhibit PCSK9

4.2.25 Known sensitivity to any of the active substances or their excipients (eg. carboxymethylcellulose) to be administered during the study

4.2.26 Subject will not be available for protocol-required study visits or procedures, to the best of the subject and investigator’s knowledge.

4.2.27 Subject has any kind of disorder that, in the opinion of the investigator, may compromise the ability of the subject to give written informed consent and/or to comply with all required study procedures.

5. **SUBJECT ENROLLMENT**

Before subjects may be entered into the study, Amgen requires a copy of the site’s written independent ethics committee and/or institutional review board (IEC/IRB) approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable (see Section 11.2). All subjects must personally sign and date the consent form before commencement of study-specific
procedures. SAEs and study-related AEs will be collected upon signing the informed consent form.

All subjects who enter into the screening period for the study, defined as when the subject signs the IEC/IRB approved informed consent form, will receive a unique subject identification number before any study procedures are performed. The subject identification number will be assigned by the Interactive Voice Response System (IVRS). This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. The subject identification number must remain constant throughout the entire clinical study; it must not be changed at the time of retesting or randomization. Unique 11-digit subject identification numbers will be assigned in sequential order for each site in the format 153CCXXX### where “CC” refers to the country code of the site location, “XXX” refers to the site number within the country, and ### refers to the sequential subject ordering as each subject at a site is entered into IVRS (eg, 15312123001, 15312123002, etc.). This number will not necessarily be the same as the randomization number assigned for the subject. A subject will be considered enrolled once they start or are eligible for the lipid stabilization period.

5.1 Randomization

Assignment to the 2 treatment arms will be based on a computer-generated randomization schedule prepared by Amgen before the start of the study. Subjects will be randomized in a 1:1 ratio to one of the following double blind treatment arms:

- AMG 145 420 mg QM SC via a 3.5 mL Personal Injector or 3.0 mL via 3 prefilled autoinjectors
- Placebo, QM SC via a 3.5 mL Personal Injector or 3.0 mL via 3 prefilled autoinjectors

A subject may only receive 1 randomization number and each randomization number will only be assigned to 1 subject. Randomization will be stratified by region.

Once eligibility into the study has been confirmed, a site representative will make the randomization call to the IVRS to assign a randomization number to the subject. The randomization call to the IVRS is accomplished by entering the pertinent information detailed in the IVRS user manual. A confirmation fax will be sent to the site to verify that the correct information has been entered and to confirm the randomization number assigned.

A subject is considered randomized into the study when they are randomized to IP.
Please refer to Section 5.2 below for details on when and how the randomization code may be broken.

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. Unblinding at the study site for any other reason will be considered a protocol deviation.

Refer to the IVRS user manual for instructions on unblinding.

The principal investigator is strongly encouraged to contact the medical monitor before unblinding any subject's treatment assignment.

6. Treatment Procedures

AMG 145 and placebo are IPs in this study. An Investigational Product Instruction Manual (IPIM) containing detailed information regarding the storage, preparation, and administration of IP will be provided separately.

6.1 AMG 145

AMG 145 and placebo will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical IP distribution procedures. AMG 145 will be presented as a sterile, preservative-free solution in a single use, disposable, handheld mechanical (spring-based) 1.0 ml prefilled autoinjector/pen (AI/Pen) or 3.5 mL Personal Injector (Personal Injector) for fixed dose, subcutaneous injection. The prefilled AI/Pen contains a 1.0 mL deliverable volume of 140 mg/mL AMG 145 in 220 mM proline, 20 mM acetate, 0.01% (w/v) polysorbate 80, pH 5.0. The Personal Injector with prefilled cartridge assembly is a single-use, disposable, on-body electro-mechanical injection device that is co-packaged with a prefilled Crystal Zenith (CZ) cartridge assembly containing 3.5 mL deliverable volume of 120 mg/mL AMG 145 in 220 mM proline, 20 mM acetate, 0.01% (w/v) polysorbate 80, pH 5.0. The 3.5 mL Personal Injector will only be made available for use in this study once it has been determined that the intended user population for AMG 145 can safely and effectively use the device in clinical trials under the guidance of the study investigators. Respective placebo will be presented in an identical prefilled AI/Pen containing a 1.0 mL deliverable volume of 1.1% (w/v) sodium carboxymethylcellulose, 250 mM proline, 10 mM acetate, and 0.01% (w/v) polysorbate 80, pH 5.0 or in an identical Personal Injector containing a 3.5 mL deliverable
volume of 0.7% (w/v) sodium carboxymethylcellulose, 250 mM proline, 10 mM acetate, and 0.01% (w/v) polysorbate 80, pH 5.0.

AMG 145 and placebo should be stored refrigerated and protected from light according to the storage and expiration information provided on the label (where required). AMG 145 should be handled per the instructions provided in the IPIM and the Instructions for Use (IFU) for the prefilled AI/Pen or Personal Injector.

The prefilled AI/Pen or Personal Injector should be inspected for IP quality, expiry, and damage before using. Damaged, expired, or degraded product should not be used and any issues with the prefilled AI/Pen or Personal Injector should be reported to Amgen. Further details are provided in the IPIM and IFU.

6.1.1 Dosage, Administration, and Schedule

IP will be administered at the investigator site during scheduled visits via self-administration or by a qualified staff member. Between scheduled visits to the site, IP will be administered at home or other locations by subjects (or designee, which may include a qualified health care professional) in accordance with instructions in the IPIM. Subjects who prefer not to self-administer IP may return to the study site for administration by qualified site personnel.

IP administration at each on-site visit must be done after vital signs, ECG, and blood draw procedures, if applicable. The date, time, and volume of AMG 145 administered will be collected and recorded on the individual subject’s electronic Case Report Form (eCRF) for doses administered at the study site. During the first 2 IP administrations (day 1 and week 4), subjects will be instructed and supervised in the use of the prefilled AI/Pen or Personal Injector and, after administration of IP, will be kept for observation for at least 30 minutes before being discharged.

Self-administration, defined as SC administration of IP by the subject or designee, will occur on a monthly basis between visits to the investigator site (eg, at home). The patient (or designee) must have demonstrated competency at administration of SC injections before self-administration is permitted: the first two self-administered doses must be administered in a clinic by the patient or designee under the supervision of a healthcare provider.

IP will be administered with a total volume of 3.0 mL QM, via 3 separate autoinjections or with a total volume of 3.5 mL QM via 1 administration by a Personal Injector. Injection sites should be rotated throughout the study. The autoinjector SC injections
should be administered in a consecutive fashion with all injections completed within
30 minutes.

Details of preparing and administering all study products are included in the IPIM
provided by Amgen prior to the start of the study.

6.1.2 Dosage Adjustments
There will be no IP dose adjustments in this study. If, in the opinion of the investigator, a
subject is unable to tolerate investigational product and requires dosage adjustment,
that subject will discontinue IP but will continue to return for all other study procedures
and measurements until the end of the study.

Subjects Who are Late for a Scheduled Dose of Investigational Product
If a subject is late for administration of IP, administration should occur as soon as
possible. A QM dose of IP should not be administered within less than 7 days of a
previous dose. If a subject arrives for a visit and IP was administered within less than
7 days prior the dose should not be administered but all other study procedures should
be conducted and administration of IP should occur as soon as possible at least 7 days
after the previous administration.

Subjects Who Miss a Scheduled Dose of Investigational Product Completely
Subjects who completely miss a dose of SC IP will continue in the study and administer
the next dose of IP per their schedule of administration.

Subjects Who Miss a Scheduled Dose of Statin
Subjects who miss a dose of background statin will be advised to take the missed dose
as soon as they can; subsequent doses will be taken at the usual time. However, if the
next scheduled dose would be due in less than 6 hours, the subject will be advised to
omit the missed dose entirely and to take the next dose at the normal time.

If stopping or altering statin (or allowable non-statin therapy) dosing is medically
warranted during the trial, the subject should continue to receive IP, except as defined in
section 6.2.1 These situations should be discussed with the Amgen medical monitor as
soon as possible. In addition, if a medical decision is made to withhold IP during the
study, subjects should continue to receive statin (and allowable non-statin)
background therapy except as defined in section 6.2.1. The medical monitor should
be contacted prior to stopping IP.
6.2 Background Lipid-lowering Therapy

Considering the patient population enrolled in GLAGOV, subjects must receive optimized lipid-lowering therapy during the study. Lipid therapy should remain unchanged for the duration of study participation (up to 18 months); local guidelines should be taken into consideration when determining optimal levels of treatment. All subjects should receive effective statin therapy with a minimum dose of atorvastatin 20 mg daily or equivalent unless they meet criteria for statin intolerance (4.1.5). Subjects with LDL-C > 100 mg/dL should receive highly effective statin therapy with atorvastatin ≥ 40 mg daily or equivalent (see Appendix E). If not receiving atorvastatin ≥ 40 mg or equivalent, the investigator must attest that higher dose statin therapy has been considered but is not appropriate for this subject (e.g., dose not tolerated, dose not available in that country, other significant concern).

Subjects who receive atorvastatin during the study can elect to have it provided by the sponsor at doses of 20 mg, 40 mg, or 80 mg. Other statins and other doses of atorvastatin will not be provided by the sponsor.

If making any changes to this therapy after randomization, the reason for the change must be provided in the eCRF and the Amgen medical monitor or designee should be consulted before making the change, if possible.

Subjects taking niacin, regulatory-approved sustained-release niacin (e.g., Niaspan®) or ezetimibe therapy at initial screening should remain unchanged for the duration of study participation (up to 18 months).

Subjects taking study-provided atorvastatin should continue the drug until their week 78 visit. Similarly, subjects taking non-study provided statins and allowable non-statin therapies should continue such treatment until week 78. Beyond the week 78 assessment, use of statins and other lipid regulating therapies will be at the discretion of the investigator.

6.2.1 Criteria for Withholding of Investigational Product

Reports from the central laboratory after each visit must be reviewed as soon as possible after receipt and before the next administration of IP. If any of the criteria below are met for withholding IP, statin, or other applicable background lipid therapy, the subject must be instructed to stop the applicable treatment and an additional visit must be scheduled for the required laboratory evaluations. If a
subject is experiencing elevations of laboratory values and is receiving other lipid therapies that may result in such elevations, eg, ezetimibe, or niacin, the additional therapies should also be evaluated for a potential role in these elevations and considered for discontinuation. Ezetimibe or niacin can result in elevation of CK or liver function tests.

6.2.1.1 Elevation of Creatine Kinase (CK)

If CK is > 5x ULN, CK must be retested before statin and IP are administered. In addition, investigators will ask study subjects to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever. If such symptoms occur and no scheduled study laboratory assessments are performed, the subject’s CK levels should be measured by unscheduled assessment. If CK is > 5x ULN, the subject must be instructed as soon as possible to discontinue statin, other applicable lipid-regulating background therapy, and/or IP (AMG 145). CK must be retested before statin, other lipid background therapy, and/or IP (AMG 145) administration can be continued. A sample for urinalysis must be collected and sent to the central laboratory if CK is elevated > 10x ULN on retest as per table below.

The following rules apply for scheduled laboratory assessments and for unscheduled CK measurements:

<table>
<thead>
<tr>
<th>CK at scheduled or unscheduled visit</th>
<th>CK on retest</th>
<th>Investigational Product and/or Statin and/or other lipid lowering therapy Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 5x ULN</td>
<td>&gt; 10x ULN</td>
<td>Discontinue statin, other lipid lowering therapies, and IP. Collect urine sample for urinalysis. Contact Amgen Medical Monitor</td>
</tr>
<tr>
<td>&gt; 5x ULN</td>
<td>&gt; 5x to ≤ 10x ULN</td>
<td>Discontinue statin, other lipid lowering therapies, and retest CK before IP administration. Consider continuing IP if alternative explanation</td>
</tr>
<tr>
<td>≤ 5x ULN</td>
<td></td>
<td>Consider continuing statin, other lipid lowering therapies, and IP</td>
</tr>
</tbody>
</table>

* CK elevations >10x ULN that have been confirmed to be secondary to myocardial infarction do not require discontinuation statin, other lipid lowering therapies or IP

If muscular symptoms are severe and cause daily discomfort, even if the CK levels are elevated to ≤ 5x ULN, reduction of dose, discontinuation of allowed lipid-regulating therapy, or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.
6.2.1.2 Elevation of Liver Function Tests

Subjects with abnormal hepatic laboratory values (eg, alkaline phosphatase [ALP], AST, ALT, total bilirubin [TBL] or signs/symptoms of hepatitis may meet the criteria for withholding of IP, statin, and other applicable lipid-regulating background therapy. If the subject experiences an ALT or AST > 3X ULN, then they must be followed as detailed under section on close observation in Appendix B.

**IP, statin, and other applicable lipid-regulating background therapy** must be discontinued and the subject should be followed according to the recommendations in Appendix B (Additional Safety Assessment Information) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:

- TBL > 2x ULN or INR > 1.5 (testing determined per Appendix B)
- AST or ALT > 3x ULN
- no other cause for the combination of laboratory abnormalities is immediately apparent; important potential causes for abnormal AST/ALT or TBL values include, but are not limited to:
  - Obstructive gall bladder or bile duct disease
  - Viral or alcoholic hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, etc)
  - Progression of malignancy involving the liver (note that metastatic disease to the liver, by itself, should not be used as an explanation for significant AST/ALT elevations)
  - Hypoxic or ischemic hepatopathy or congestive hepatopathy in association with significant right sided heart failure
  - Concomitant administration of other hepatotoxins, including drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir, irinotecan) or herbal or dietary supplements
  - Heritable disorders causing impaired glucuronidation (eg, Gilbert’s Syndrome); alpha-one antitrypsin deficiency
  - Autoimmune hepatitis
  - Nonalcoholic steatohepatitis (NASH) or other “fatty liver disease”

**IP, statin, and other applicable lipid-regulating background therapy** should also be withheld and the subject should be evaluated for DILI if ANY of the following criteria are met:

- AST or ALT > 8x ULN at any time
- AST or ALT > 5x ULN but < 8x ULN for ≥ 2 weeks
- TBL > 3x ULN at any time
- ALP > 8x ULN at any time
- Clinical signs or symptoms that are, in the opinion of the investigator, consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice, rash or eosinophilia > 5%). If such signs or symptoms are coupled with ALT or AST elevations > 3x ULN, IP should be withheld.

If IP, statin and other applicable lipid-regulating background therapy are withheld due to any of the conditions above, the subject should be followed according to recommendations in Appendix B for possible DILI.

6.2.2 Criteria for Rechallenge After Withholding or Discontinuation of IP (AMG 145 or Placebo) Statin and Other Applicable Lipid-regulating Background Therapy

The decision to rechallenge the subject after therapy changes due to CK elevation or elevation of liver function tests should be discussed and agreed unanimously upon by the subject, Investigator, and Amgen.

If signs or symptoms recur with rechallenge of IP, then IP should be permanently discontinued. If signs or symptoms recur with rechallenge of statin background therapy, the statin may be substituted by another statin in consultation with the Amgen medical monitor, if possible, or the statin therapy should be discontinued. If signs or symptoms recur with rechallenge of other applicable lipid-regulating background therapy, this therapy should be discontinued.

6.2.2.1 Elevation of Triglycerides

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

6.3 Product Complaints, Including Device Complaints

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

Concerns or irregularities about the packaging, appearance or usage of the prefilled AI/Pen or Personal Injector or other Amgen provided, protocol-required product (ie, statin) in this study are to be reported to Amgen within 24 hours of discovery or notification of the concern or irregularity. Should any such concerns or irregularities
occur please do not use the IP or statin until Amgen confirms that it is permissible to use.

Examples of potential product complaints that need to be reported to Amgen include, but are not limited to:

- broken container or cracked container
- misuse of the Al/pen or Personal Injector due to misunderstanding of the IFU or error on the part of the user, or other inability to appropriately use the product (eg, due to malfunction of the Al/Pen)
- missing labels, illegible labels, incorrect labels, and/or suspect labels
- change in IP appearance, for example color change or visible presence of foreign material
- unexpected quantity or volume, for example number of tablets or amount of fluid in the prefilled Al/Pen or Personal Injector evidence of tampering or stolen material

If possible, please have the IP or other Amgen provided protocol-required suspect product available for examination when making a product complaint. Maintain IP or other Amgen provided protocol-required suspect product at appropriate storage conditions until further instructions are received from Amgen.

The investigator is responsible for ensuring that all product or device complaints observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 days after the last dose of IP or EOS, whichever is later, are reported to Amgen within 24 hours of discovery or notification of the product complaint.

For more details regarding the identification and reporting of product and device complaints, refer to the IPIM and the IFU.

6.4 Concomitant Therapy, Physical Exercise, and Diet

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.5.

It is anticipated that subjects will remain on a stable dose of statin and other allowed lipid-regulating therapies from screening until the EOS.

Over-the-counter drugs that may alter lipid levels should be stable for at least 4 weeks before screening and should remain constant through the study. Examples include: psyllium preparations including Metamucil® (> 2 tbs per day), plant stanols (such as Benecol), or omega-3 fatty acids (prohibited at entry if combined docosahexaenoic
acid (DHA) and eicosapentaenoic acid (EPA) > 1000mg/day). Doses of niacin commonly used as a multivitamin (≤ 200 mg/day) do not alter lipid levels and are permitted during the study period.

The use of antacids is not recommended within the period of 2 hours before and 2 hours after dosing with statins.

Subjects should adhere to an ATP III TLC-type diet. Throughout the study, the central laboratory will compare LDL-C concentrations with the subject’s prior assessed LDL-C without unblinding the study team, investigator, or site staff. If the LDL-C increases by 15 mg/dl (for LDL-C < 100 mg/dL (2.59 mmol/L) or increases more than 15% (for LDL-C > 100 mg/dL (2.59 mmol/L), the site will be notified by an automated system to instruct the patient on compliance (study drug, statin, any other allowed lipid-regulating therapies and diet). To maintain the blind, the same reminder will be provided to additional subjects in each treatment arm, using an appropriate algorithm to balance the frequency of alerts for both treatment groups, active and placebo.

Subjects should also maintain their current regimen of exercise. Subjects will be required to refrain from unaccustomed intensive exercise (eg, heavy lifting or long runs) 48 hours prior to each visit.

6.5 Prohibited Treatments During Study Period
The following treatments are not permitted during the study:

- Prescription lipid-regulating medications other than protocol-approved statins, regulatory-approved, sustained-release niacin (eg Niaspan®) and ezetimibe such as fibrates and derivatives and bile-acid sequestering resins
- Red yeast rice, niacin > 200 mg per day, omega-3 fatty acid (eg, DHA and EPA) > 1,000 mg per day
- Prescribed amphetamines, or amphetamine derivatives, and weight loss medications.

6.6 Non-recommended Treatments During Study Period
The treatments in Appendix F are not recommended because of their potential impact on metabolism of specific statins.

If a subject is enrolled and subsequently requires a treatment that is not recommended based on their particular statin (eg, a strong cytochrome P450 3A4 inhibitor in a patient on atorvastatin), the treating physician should give consideration to using an equivalent concomitant drug, eg, a drug that does not inhibit cytochrome P450 3A4 so that the subject can continue taking statin...
background therapy. If this is not possible, it may be necessary to withdraw or change statin background therapy while the concomitant drug is required.

There is no need to discontinue treatment with IP should a subject require a non-recommended drug, eg, a strong cytochrome P450 3A4 inhibitor since monoclonal antibody therapeutics are not metabolised through cytochrome P450 and, thus, are unaffected by the use of cytochrome P450 inhibitors.

7. STUDY PROCEDURES

7.1 General Study Procedures

This will be a multi-center, double blind, randomized, placebo-controlled trial. The study consists of 3 periods:

- Screening (a Placebo Run-in injection will be administered during the initial screening visit)
- Enrollment: Lipid Stabilization Period (if applicable)
- Double-blind Treatment Period

Written informed consent must be obtained and will be implemented before protocol specific procedures are carried out. The risks and benefits of participating in the study will be verbally explained to each potential subject prior to entering into the study. All subjects will be specifically asked if they also consent to Pharmacogenetic analyses of their blood samples. The procedures to be performed at each clinic visit are described below and are summarized in Appendix A. If SC IP is administered during a study visit, administration must be after completion of vital signs, ECG, and blood draw procedures, as applicable.

Subjects must be fasting for ≥9 hours before each study visit. For procedures if the subject is not fasting when presenting at the study site for a visit, please see Section 7.1.1 and Section 7.1.2 below.

7.1.1 Screening and Placebo Run-in Injection

Written informed consent must be obtained before protocol-specific procedures are carried out. In order to minimize the chances of performing unnecessary IVUS procedures, investigators should ensure that subjects’ initial screening LDL-C results are available prior to performing the baseline IVUS examination. Thereafter, subjects will undergo clinically-indicated coronary angiography for further clinical evaluation. If angiographic criteria for IVUS are met, the subject will have baseline IVUS completed. Subjects who require a PCI deemed necessary by the qualifying angiography will have baseline IVUS performed immediately following
the PCI. Any intervention to the proposed target IVUS vessel will exclude this vessel from being used as the target IVUS vessel. Delayed or staged IVUS procedures must be performed within 4 weeks after qualifying angiography. For subjects who undergo delayed or staged interventions, the baseline IVUS must be performed after the final planned intervention.

The accuracy and reproducibility of the IVUS endpoints of the study are dependent upon Investigator's commitment to rigorous image acquisition techniques. The IVUS Core Laboratory at the Cleveland Clinic will provide a separate IVUS guidance document to all participating sites. Adherence to these guidelines will ensure low observer variability and high quantitative.

Investigators may only utilize the Boston Scientific iLAB™ ultrasound system in conjunction with an Atlantis™ SR series 40 MHz imaging catheter OR the Volcano S5™ ultrasound imaging system in conjunction with the Revolution™ 45 MHz imaging catheter. For each patient all imaging conditions performed at the baseline imaging time point must be duplicated at the follow-up time point utilizing the same IVUS system either Boston Scientific iLab or the Volcano S5. The Boston Scientific and Volcano ultrasound systems cannot be interchanged between the baseline and follow-up time points. All baseline angiographic studies must be forwarded to the IVUS Core Laboratory at the Cleveland Clinic for informational review. IVUS imaging must be reviewed and approved by the IVUS Core Laboratory before subjects return for randomization visit.

Subjects will be assessed for inclusion and exclusion criteria and medical and medication history will be obtained. The following data will be obtained and procedures performed during screening:

- Written informed consent
- **Angiogram**
- IVUS
- Medical history
- **Physical exam**
  - Vital signs (see Section 7.1.3.1): sitting blood pressure (BP), heart rate (HR)
  - Review for AEs/SAEs (SAEs and study-related AEs are collected after signing informed consent)
  - Concomitant therapy
    - 12-lead ECG in triplicate using centralized ECG services equipment
Blood draw for fasting lipids and glucose (≥ 9 hour fasting sample), chemistry, hematology, HbA1c, TSH, eGFR, serum pregnancy (females of childbearing potential only) and FSH (only if required to ensure menopause in a female subject [see exclusion criteria]) by local laboratory. The central laboratory may be used if a local laboratory is not available.

Central blood draws for hepatitis C virus (HCV) antibodies in high risk subjects or subjects with AST or ALT > 2x ULN at any time during screening*

The subject will be instructed in the NCEP ATP IIITLC-type diet and lifestyle regimen (example, http://www.nhlbi.nih.gov/health/public/heart/index.htm#chol). The subject will also be counseled on the importance of maintaining good compliance with current lipid lowering medications

Subjects will receive a placebo administration with three 1.0 ml SC injections with the prefilled AI/pen to confirm tolerance of SC administration prior to randomization. In order to reduce the burden of unnecessary procedures on subjects who subsequently elect not to participate in the study or continue with study procedures. During this time the subject will receive instruction/training on AI/Pen use

*Please note that subjects with ALT or AST > 2x ULN must be screen failed unless the elevation is transient as confirmed by retesting per Section 7.1.1.2. High risk subjects are defined in Section 7.1.3.6.

7.1.1.1 Enrollment and Lipid Stabilization Period

Subjects who complete the screening procedures and who meet the inclusion/exclusion criteria will be enrolled and enter the lipid stabilization period (if applicable). At a minimum, subjects must receive an effective statin dose of at least atorvastatin 20 mg daily or equivalent (see Appendix E) titrated to achieve target LDL-C (change or goal) as defined by regional guidelines. Where locally approved, highly effective statin therapy, defined as at least atorvastatin 40 mg daily or equivalent (see Appendix E), is recommended. For subjects with LDL-C > 100 mg/dL (2.6 mmol/L) and not receiving highly effective statin therapy (atorvastatin ≥ 40 mg daily or equivalent), the investigator must attest that higher dose statin therapy is not appropriate for this subject (eg, dose not tolerated, dose not available in that country, other significant concern). Subjects who, in the investigator’s opinion, are already at LDL-C goal at initial screening and are on stable (≥ 4 weeks) and acceptable lipid lowering therapy (per Appendix E) during screening, with no changes planned or expected for the duration of the study will be enrolled directly, skip the lipid stabilization period, and, if eligible, randomized. Subjects requiring any change to their lipid therapy will be enrolled and then enter a two- to four-week lipid stabilization period. During this period subjects must be titrated to an optimal statin dose within one month and with a maximum of one
uptitration step, which will occur at week 2 (if necessary). Ensuring stable individualized LDL-C levels will be required as physicians will be blinded to LDL-C values at randomization and no changes to lipid medications will be allowed during the trial except for clinically-compelling reasons.

At the end of each 2 week lipid stabilization period, the following data will be obtained and procedures performed during screening:

- Review for AEs/SAEs
- Blood draw for fasting lipids, chemistry (CK, AST and ALT) and serum pregnancy (females of childbearing potential only). The central laboratory may be used if a local laboratory is not available.

LDL-C will be evaluated for eligibility and if applicable, for titration of background therapy.

Subjects who do not tolerate a statin or do not qualify for any other reason during the lipid stabilization period must not be randomized, unless they meet statin intolerant inclusion criteria 4.1.5 and 4.1.6. Rather, they should be early-terminated and labs for pregnancy, CK and LFT should be collected. If a fasting sample for a laboratory qualification LDL-C could not be obtained after the lipid stabilization period and the other screening laboratory assessments confirm eligibility for the study, an additional fasting lipid sample to determine eligibility must be obtained before the planned day 1 (randomization) visit. It is recommended to schedule collection of this fasting lipid sample as quickly as possible.

7.1.1.2 Retesting

If, in the investigator’s judgment, lab abnormalities are likely to be transient (ie, subject participated in vigorous exercise and CK is elevated immediately afterwards), laboratory tests can be retested. Triglycerides, CK, and liver function and other laboratory values, except LDL-C, can be retested during screening as long as the subject can be evaluated for eligibility and randomized within the allowed screening period.

7.1.1.3 Screen Fail

Subjects who fail any of the eligibility criteria prior to becoming eligible for or initiating the lipid stabilization period need to be screen failed in IVRS.

7.1.2 Treatment Period

Subjects must be fasting for ≥ 9 hours before each study visit. If the subject is not fasting for the scheduled study randomization visit, no visit procedures are performed. The subject must return as soon as possible in a fasting state for study randomization.
visit procedures. If the subject is not fasting for any visit after randomization, all visit procedures, including investigational product administration, should be completed except for the fasting lipid blood sample. Please make sure to schedule an extra visit for the fasting sample collection as soon as possible and if possible, within the window for the respective visit.

Final IVUS assessment and angiography will be performed at Week 78.

It is critical that the follow-up IVUS be obtained in subjects, regardless of whether or not they discontinued study drug prematurely.

Any subjects who require cardiac catheterization for clinically indicated reasons at Week 52 or later must have IVUS examination of the target vessel performed at that time. The Week 78 IVUS will not be required for these subjects. If PCI of a non-target vessel is required, subjects will undergo the final IVUS after PCI is completed. If PCI of the target vessel is required, the final IVUS should be completed prior to PCI if clinically appropriate. These subjects will continue IP and all study visits with the exception of the Week 78 IVUS.

For subjects requiring coronary angiography prior to Week 52, the final IVUS examination should not be performed in these subjects at this time. An IVUS performed prior to week 52 will not be accepted as the final study IVUS. Subjects will remain on study drug and complete all required visits, including the second IVUS examination at week 78. However, subjects requiring PCI to the IVUS target vessel prior to Week 52 will not undergo a final IVUS examination. These subjects will continue IP and all study visits with the exception of the Week 78 IVUS. If PCI to a non-target vessel is indicated prior to Week 52, the follow up IVUS should not be performed at this time. These subjects will remain on study drug and complete all required visits, including the second IVUS examination at week 78.

7.1.2.1 Day 1 Visit (Randomization)

Subjects that tolerate the placebo injection, complete the screening procedures successfully, satisfy the inclusion/exclusion criteria, have a negative pregnancy test (if applicable), do not have active liver disease or hepatic dysfunction (defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) < 3 times the ULN), and have a CK ≤ 3 times ULN at the end of the lipid stabilization period, will visit the study site for randomization, and initiate their first dose of IP. The first administration of IP should be on the day of randomization, if not, it should be no later than within 5 calendar days after randomization.
The following data will be obtained and procedures performed for the day 1 visit:

- Vital signs (sitting BP, HR)
- Review of concomitant therapy.
- Review for AEs/SAEs/ CV events
- Body height
- Body weight
- Waist circumference
- 12-lead ECG in triplicate using centralized ECG services equipment
- Encourage subject to maintain a stable diet
- Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, chemistry, Hba1c, hematology, PK (AMG 145) PCSK9, hs-CRP, Lp(a), biomarkers, anti-AMG 145 antibodies, fasting Vitamin E and glucose, viral load in subjects positive for HCV, and pharmacogenetic studies\textsuperscript{a} (if subject consented to pharmacogenetic analyses)
- Urine sample for urinalysis
- Retraining on AI/Pen or Personal Injector use
- Administer IP to all subjects (must be after completion of vital signs, ECG, and blood draw procedures)

No additional blood will be collected for the pharmacogenetic analyses. For subjects who have consented to the pharmacogenetic portion of this study, deoxyribonucleic acid (DNA) will be extracted from blood samples already collected on day 1 or another visit (see Section 7.1.3.5 “Blood Sample Use” and Section 7.4.2 “Pharmacogenetic Studies”.

The date of first administration of IP will be recorded in IVRS and will determine the schedule of subsequent study visits.

7.1.2.2 Week 4 (± 3 Days)
The following data will be obtained and procedures performed:

- Vital signs (sitting BP, HR)
- Review of concomitant therapy
- Review for AEs/SAEs/ CV events
- Encourage subject to maintain a stable diet
- Dispense AI/Pens or Personal Injector with instructions for use
- Administer IP to all subjects (must be after vital signs)
7.1.2.3 Week 12 (± 3 Days)
The following data will be obtained and procedures performed:

- Vital signs (sitting BP, HR)
- Review of concomitant therapy
- Review for AEs/SAEs/ CV events
- Encourage subject to maintain a stable diet
- Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, Lp(a) chemistry, HbA1c, hematology, and fasting glucose
- Urine sample for urinalysis and in females of childbearing potential, urine pregnancy testing
- Dispense AI/Pens or Personal Injector
- Observe IP administration at clinic (must be after vital signs, and blood draw procedures)

7.1.2.4 Week 24 (± 3 Days)
The following data will be obtained and procedures performed:

- Vital signs (sitting BP, HR)
- Review of concomitant therapy
- Review for AEs/SAEs/ CV events
- Encourage subject to maintain a stable diet
- Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, Lp(a), chemistry, HbA1c, hematology, PK (AMG 145), PCSK9, anti-AMG 145 antibodies, viral load in subjects positive for HCV, and fasting glucose
- Dispense AI/Pens or Personal Injector
- Observe IP administration at clinic (must be after vital signs, and blood draw procedures)

7.1.2.5 Week 36 (± 3 Days)
The following data will be obtained and procedures performed:

- Vital signs (sitting BP, HR)
- Review of concomitant therapy
- Review for AEs/SAEs/ CV events
- Encourage subject to maintain a stable diet
- Blood draw for chemistry, HbA1c, hematology, and fasting glucose
- Urine sample for urinalysis and in females of childbearing potential, urine pregnancy testing
- Dispense AI/Pens or Personal Injector
- Observe IP administration at clinic (must be after vital signs, and blood draw procedures)
7.1.2.6 Week 52 (± 3 Days)
The following data will be obtained and procedures performed:
- Vital signs (sitting BP, HR)
- Review of concomitant therapy
- Review for AEs/SAEs/ CV events
- Encourage subject to maintain a stable diet
- Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, Lp(a) chemistry, HbA1c, hsCRP, PK (AMG 145), PCSK9, hematology, anti-AMG 145 antibodies, and fasting Vitamin E and glucose
- Urine sample for urinalysis and in females of childbearing potential, urine pregnancy testing
- Dispense AI/Pens or Personal Injector
- Observe IP administration at clinic (must be after vital signs, and blood draw procedures)

7.1.2.7 Week 64 (± 3 Days)
The following data will be obtained and procedures performed:
- Vital signs (sitting BP, HR)
- Review of concomitant therapy
- Review for AEs/SAEs/ CV events
- Encourage subject to maintain a stable diet
- Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, Lp(a) chemistry, HbA1c, hs-CRP, hematology, viral load in subjects positive for HCV, and fasting glucose
- Dispense AI/Pens or Personal Injector
- Observe IP administration at clinic (must be after vital signs, and blood draw procedures)

7.1.2.8 Week 76 (± 3 Days)
The following data will be obtained and procedures performed:
- Vital signs (sitting BP, HR)
- Review of concomitant therapy
- Review for AEs/SAEs/ CV events
- Encourage subject to maintain a stable diet
- Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, Lp(a) chemistry, HbA1c, hematology, and fasting glucose
- Observe IP administration at clinic (must be after vital signs, and blood draw procedures)
7.1.2.9 Week 78 /ET Visit (+14 Days)

The following data will be obtained and procedures performed:

- Vital signs (sitting BP, HR)
- Review of concomitant therapy
- Review for AEs/SAEs/ CV events
- Body weight
- Waist circumference
- Physical exam
- 12-lead ECG in triplicate using centralized ECG services equipment
- **Angiogram**
- Final IVUS assessment
- Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, PK (AMG 145), PCSK9, chemistry, HbA1c, hematology, hs-CRP, Lp(a), biomarkers, fasting Vitamin E and glucose, viral load in subjects positive for HCV, and anti-AMG 145 antibodies, and, in females of childbearing potential, for serum pregnancy testing
- Urine sample for urinalysis

7.1.2.10 Week 80 EOS Phone Call (+14 Days)

Subjects will end the study once contacted by the site, (eg, by phone call). The following data will be obtained:

- AEs/SAEs/ CV events

Completion of the study is defined as the last day that protocol-specified procedures are conducted for an individual subject. Subjects who are not deceased, have not withdrawn consent, or are not lost to follow-up, should have at minimum an End of Study assessment for Vital Status (alive or deceased), Adverse Events and Potential Endpoints.

7.1.3 Standardization of Study Procedures

7.1.3.1 Measurement of Vital Signs

Blood pressure (BP) and heart rate (HR) will be measured at each visit. Use of an automated oscillometric device for BP measurement is preferred and recommended. BP will initially be recorded in both of the subject’s arms unless a concomitant condition favors the use of a particular arm. The arm with the higher systolic reading at screening will then be used for further BP determinations throughout the study. The appropriate size cuff should be used. BP and HR measurements will be determined after the subject has been seated for at least 5 minutes. The subject’s pulse should be measured for 30 seconds and the number multiplied by 2 to obtain heart rate. Before randomization,
BP measurement can be repeated if the previous reading is outside of the eligibility range. The repeat BP measure should be taken at least 2 minutes following the previous measure.

7.1.3.2 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.

7.1.3.3 Electrocardiograms
At each timepoint where ECGs are being obtained (day 1 [randomization], and EOS), three ECGs will be collected with each one performed approximately 1 minute apart. Using equipment supplied to each site, all protocol-specified ECGs will be acquired and transmitted to the centralized ECG services provider. The PI or designated physician will review acquired ECGs. One signed, original ECG tracing should be retained with the subject’s source documents. At the request of the sponsor, the original ECG should be made available to Amgen to be manually read by a central reader.

The centralized ECG services cardiologists will perform standard interpretations of all tracings. A cardiologist reviewed ECG report will be provided to the study site. Final ECG reports will be provided to the investigative site. Investigators must initial and date the ECG reports upon receipt. If the investigator’s interpretation of any protocol-specified or unscheduled ECG differs from that supplied by centralized ECG services provider, it is the responsibility of the investigator to make the final clinical decisions. The investigator’s interpretation does not need to be reconciled with that supplied by centralized ECG services cardiologists. Any clinical interventions based on these results need to be documented in the appropriate source documents and eCRF as
applicable. It is the responsibility of the investigator to obtain additional ECGs required for the clinical management of the subject, using centralized ECG services equipment or equipment on-site.

Further detail about the equipment provided and its use for this study will be provided in an Investigator ECG Manual distributed to the sites before start of enrollment.

7.1.3.4 Lipid Measurements

During the screening process either central or local laboratory LDL-C results may be utilized for eligibility criteria. Central laboratory results will be utilized for all lipid measurements on and following randomization. Central laboratory results of the lipid panel, as well as ApoA1, ApoB, lipoprotein(a), and high sensitivity C-reactive protein (hsCRP) will be blinded post-treatment until unblinding of the clinical database and will not be reported to the investigator post-screening. In addition, investigators and staff involved with this trial and all medical staff involved in the subject’s medical care should refrain from obtaining lipid panels between randomization and at least 12 weeks after the subject ends the study (to avoid potential unblinding). If a lipid panel is drawn, all reasonable steps must be undertaken to avoid informing the subject and study personnel of the results.

Throughout the study, the central laboratory will compare LDL-C concentrations with the subject’s prior assessed LDL-C without unblinding the study team, investigator, or site staff. If the LDL-C increases by 15 mg/dl (for LDL-C < 100 mg/dL (2.59 mmol/L)) or increases more than 15% (for LDL-C > 100 mg/dL (2.59 mmol/L), the site will be notified by an automated system to instruct the patient on compliance (study drug, statin and diet). To maintain the blind, the same reminder will be provided to additional subjects in each treatment arm, using an appropriate algorithm to balance the frequency of alerts for both treatment groups, active and placebo.

In addition, if there are 2 consecutive LDL-C values below 25 mg/dL for an individual subject during the trial, an independent non-program related Amgen safety physician will collate the appropriate data (eg, demographics, medical history, concomitant medications, laboratory data, AEs, SAEs) and provide this information to the DMC.

7.1.3.5 Blood Sample Use

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

Amgen may perform additional testing on remaining samples (ie, residual and back-up) to investigate and better understand hyperlipidemia or markers of cardiovascular disease, metabolic disorders, the dose response and/or prediction of response to AMG 145, characterize antibody response, and characterize aspects of the molecule (eg, metabolites). Results from this analysis will be documented and maintained, but may not be reported as part of this study.

7.1.3.6 Laboratory Assessments

All screening and on-study laboratory samples will be processed and sent to the central laboratory starting on Day 1. Prior to Day 1, sites can choose to use local laboratories. Amgen or designee will be responsible for PK (AMG 145 and PCSK9 serum levels), anti-AMG 145 antibody, and biomarker development assessments and the central laboratory will ship the samples to Amgen or a specialty laboratory for assay (depending on the assessment).

The central laboratory will provide a study manual that outlines handling, labeling, and shipping procedures for all blood samples. The date and time of sample collection will be recorded in the source documents at the site.

Table 3 below outlines the specific analytes for serum chemistry, hematology, urinalysis, and other testing to be conducted.
Table 3. Analyte Listing

<table>
<thead>
<tr>
<th>Chemistry</th>
<th>Coagulation</th>
<th>Urinalysis</th>
<th>Hematology</th>
<th>Other Labs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>PT/INR</td>
<td>Specific gravity</td>
<td>Hemoglobin</td>
<td>Fasting lipids</td>
</tr>
<tr>
<td>Potassium</td>
<td></td>
<td>pH</td>
<td>Hematocrit</td>
<td>• Total cholesterol</td>
</tr>
<tr>
<td>Chloride</td>
<td></td>
<td>Blood</td>
<td>MCV</td>
<td>• HDL-C</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td></td>
<td>Protein</td>
<td>MCH</td>
<td>• LDL-C</td>
</tr>
<tr>
<td>Total protein</td>
<td></td>
<td>Glucose</td>
<td>MCHC</td>
<td>• Triglycerides</td>
</tr>
<tr>
<td>Albumin</td>
<td></td>
<td>Bilirubin</td>
<td>RDW</td>
<td>• VLDL-C</td>
</tr>
<tr>
<td>Calcium</td>
<td></td>
<td>WBC</td>
<td>Platelets</td>
<td>• Non-HDL-C</td>
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<tr>
<td>Magnesium</td>
<td></td>
<td>RBC</td>
<td>WBC</td>
<td>ApoA1</td>
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<tr>
<td>Phosphorus</td>
<td></td>
<td>Epithelial cells</td>
<td>RBC</td>
<td>ApoB</td>
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<tr>
<td>Glucose (Fasting)</td>
<td></td>
<td>Bacteria</td>
<td></td>
<td>ApoB/ApoA1 ratio</td>
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<tr>
<td>BUN or Urea</td>
<td></td>
<td>Casts</td>
<td></td>
<td>Total Cholesterol/HDL-C ratio</td>
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<tr>
<td>Creatinine</td>
<td></td>
<td>Crystals</td>
<td></td>
<td>hs-CRP</td>
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<tr>
<td>Uric acid</td>
<td></td>
<td></td>
<td></td>
<td>Lp(a)</td>
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<tr>
<td>Total bilirubin</td>
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<td></td>
<td></td>
<td>Anti-AMG 145 antibodies</td>
</tr>
<tr>
<td>Direct bilirubin</td>
<td></td>
<td></td>
<td></td>
<td>AMG 145 (PK)</td>
</tr>
<tr>
<td>CK</td>
<td></td>
<td></td>
<td></td>
<td>PCSK9</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>HbA1c</td>
</tr>
<tr>
<td>LDH</td>
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<td></td>
<td></td>
<td>FSH (if needed per exclusion 4.2.19)</td>
</tr>
<tr>
<td>AST (SGOT)</td>
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<td></td>
<td>TSH</td>
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<tr>
<td>ALT (SGPT)</td>
<td></td>
<td></td>
<td></td>
<td>eGFR (calculated)</td>
</tr>
</tbody>
</table>

*HCV antibodies are measured before initiating treatment with investigational product in subjects at high risk for HCV infection and in subjects with ALT or AST > 2x ULN at any time during screening. Please note that subjects with ALT or AST > 2x ULN must be screen failed unless the elevation is transient as confirmed by retesting per Section 7.1.1.2. High risk subjects for this protocol are those who meet any of the following conditions:

- Ever injected illegal drugs
- Received clotting factors made before 1987
- Received a blood or organ donation before July 1992 or were exposed to blood known to be infected with HCV
- Were ever on chronic hemodialysis
- Are known to be infected with **Human Immunodeficiency Syndrome** (HIV)
- Have a known HCV-infected sexual partner
**Viral load will be tested at the time points indicated in Appendix A in subjects who are positive for HCV.

Some laboratory results may inadvertently unblind investigators to treatment assignment to AMG 145. Central laboratory results of the lipid panel, ApoA1, ApoB, Lp(a), and hs-CRP will not be reported to the investigator post-screening. Investigators should not perform non-protocol testing of these analytes during a subject’s study participation from first administration of IP until at least 12 weeks after the subject’s last administration of IP or at least 4 weeks after the subject ends the study, whichever is later.

7.2 Antibody Testing Procedures

Blood samples will be collected per Appendix A from all subjects for the measurement of anti-AMG 145 binding antibodies. All subjects who have received at least 1 administration of AMG 145 will have samples assayed for binding and, if positive, neutralizing antibodies. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity and presence of immune complexes. Sites will be notified of any positive neutralizing antibody results to AMG 145. If results are not provided, no neutralizing antibodies to AMG 145 have been detected. Additional blood samples may be obtained to rule out anti-AMG 145 antibodies during the study.

Subjects who test positive for neutralizing antibodies to AMG 145 at the final scheduled study visit will be asked to return for additional follow-up testing. This testing should occur approximately every 3 months starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable or (2) the subject has been followed for a period of at least 1 year (± 4 weeks). More frequent testing (eg, every month) or testing for a longer period of time may be requested in the event of safety-related concerns. Follow-up testing will not be required where it is established that the subject did not receive AMG 145. All follow-up results, both positive and negative will be communicated to the sites.

Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-AMG 145 antibody response may also be asked to return for additional follow-up testing.

7.3 AMG 145 and PCSK9 Pharmacokinetic Sampling

Blood samples will be collected as shown in the Schedule of Assessments (Appendix A) to determine AMG 145 and PCSK9 serum concentration. Approximately 5 mL blood will
be collected at each time point. Serum will be prepared as instructed and will be frozen within 1 hour of collection in 2 aliquots for PCSK9 and 2 aliquots for AMG145 at -70°C (-20°C if a -70°C freezer is not available). The site will be expected to complete a shipping log or requisition that will include subject identification information and the time and date of collection for each sample shipped. Missing samples must be clearly documented on the shipping log or requisition. Please refer to the laboratory manual for detailed instructions on sample collection, processing, and shipping of PK samples.

7.4 Biomarker Development and Pharmacogenetic Studies

7.4.1 Biomarker Development

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

It is expected that further advances will occur in the future in investigational techniques that look at markers of PCSK9 signaling, LDLR turnover, cholesterol metabolism, inflammation, and plaque stability. It is not possible at this stage to anticipate what these advances will be; however, considerable benefit could accrue to future sufferers of coronary artery disease if these markers can be correlated with the data from the study. It is also important to clarify any potential drug interactions in this population of subjects who will be on a number of other drugs. For biomarker analysis 14.5 mL of blood will be collected at selected visits so that biomarkers related to, but not limited to PCSK9 signaling, LDLR turnover, cholesterol metabolism, inflammation, and plaque stability such as certain glycosylated proteins, matrix metalloproteinases, additional markers of inflammation such as myeloperoxidase, bromo and nitro-tyrosine, and tumor necrosis factor (TNF) cellular adhesion molecules may be studied.

Refer to the laboratory manual for detailed collection and handling procedures for all biomarker development samples.

7.4.2 Pharmacogenetic Studies

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations such as those of the PCSK9 gene or the LDLR gene to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of cardiovascular disease, hyperlipidemia and other metabolic disorders and/or to identify subjects who may have positive or negative response to
AMG 145. No additional blood will be collected for this analysis. For subjects who have consented to the pharmacogenetic portion of this study, DNA will be extracted from blood samples already collected. Subjects can participate in the main trial irrespective of whether they do or do not consent to the pharmacogenetic portion of the study.

7.4.3 Sample Storage and Destruction

These biomarker development samples and any other components from the cells may be stored for up to 20 years from the end of the study to research scientific questions related to cardiovascular disease, hyperlipidemia, metabolic disorders, and/or AMG 145. The subject retains the right to request that the sample material be destroyed at any time by contacting the principal investigator. The sponsor is responsible for the destruction of the sample(s) at the request of the subject through the principal investigator or at the end of the storage period or shorter as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample).

Following the request from the subject, the principal investigator will provide the sponsor with the required study and subject numbers so that any remaining plasma and blood samples and any other components from the cells can be located and destroyed. See Section 11.3 for subject confidentiality.

8. REMOVAL AND REPLACEMENT OF SUBJECTS

8.1 Removal of Subjects

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

Withdrawal of full consent for a study means that the subject does not wish to receive further investigational treatment and does not wish to or is unable to continue further study participation including any follow-up in person, by phone, through 3rd parties including relatives or friends, via discussion with other treating physicians, and by use of medical records; subject data up to withdrawal of full consent will be included in the analysis of the study. Any subject may withdraw full consent to participate in the study at any time during the study. The investigator will discuss with the subject appropriate procedures for withdrawal from the study. The investigator should ask the subject’s consent to perform the procedures listed under the final study visit.

Subjects may decline to continue receiving IP or other protocol-required procedures at any time during the study. If this occurs, the investigator will discuss with the subject
appropriate procedures for discontinuation from IP or other protocol-required procedures and should encourage the subject to continue with collection of data, including endpoints and adverse events. These subjects, as well as those who have stopped receiving IP or other protocol-required procedures for other reasons (eg, investigator or sponsor concern) should continue the schedule of study observations. If the subject is unable or unwilling to continue the schedule of observation, the investigators should clarify what type of follow-up the subject is agreeable to: in person, by phone/mail, through family/friends, in correspondence/communication with other physicians, and/or from review of the medical records.

Should a subject (or a legally acceptable representative) request or decide to withdraw from the study, all efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information should be reported on the applicable eCRFs.

Reasons for removal from protocol-required investigational product might include:

- withdrawal of full consent
- subject request to end investigational product administration
- administrative decision by Amgen
- decision by the primary investigator / physician
- pregnancy in a female subject (report on Pregnancy Notification Worksheet; see Appendix D)
- safety concern (eg due to an adverse event)

8.2 Replacement of Subjects

There will be no replacement for randomized subjects.

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of 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 the pre-existing medical condition (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not
worsened 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 adverse device effect (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.

9.1.2 Reporting Procedures for Adverse Events

All adverse events (see Section 9.2) are reported after signing of the informed consent. The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through the EOS are reported using the applicable eCRF (e.g., Adverse Event Summary eCRF), including events that are also reported to the CEC for adjudication.

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 (AMG 145 or placebo)
- Assessment of relatedness to other protocol-required therapies
- Assessment of relatedness to the device (prefilled Al/Pen or Personal Injector), and
- Assessment of relatedness to study procedure, and
- Action taken.

The adverse event toxicity grading scale used will be the NCI Common Terminology Criteria for AEs (CTCAE) grading score. The toxicity grading scale used in this study is described in Appendix B.

The investigator must assess whether the adverse event is possibly related to IP (AMG 145 or placebo) and/or other protocol-required therapies (e.g. study-mandated statin background therapy). 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 IP and/or other protocol-required therapies?

The investigator must assess whether the adverse event is possibly related to the prefilled Al/Pen or Personal Injector device used to administer IP (AMG 145 or
placebo). The 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 device?

The investigator must assess whether the adverse event is possibly related to any other 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 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) should not 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) should be recorded as the adverse event.

The investigator’s clinical judgment is used to determine whether a subject is to be removed from treatment or from the study due to an adverse event. A subject, or subject’s parent/legal guardian, can also voluntarily withdraw from treatment due to an adverse event. If the subject withdraws full consent, the subject is encouraged to undergo, at a minimum, an end of study assessment. Refer to section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

The investigator is expected to follow reported adverse events, any Amgen-provided protocol-required product or device until resolved, improved to baseline, or stabilized.

9.2 Serious Adverse Events

9.2.1 Definition of Serious Adverse Events

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

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event
An adverse event would meet the criterion of “requires hospitalization”, if the event necessitated an admission to a health care facility (eg, overnight stay).

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

Since the criteria for the CTCAE grading scale differs from the regulatory criteria for serious adverse events, if adverse events correspond to grade 4 “life threatening” CTCAE toxicity grading scale criteria (eg, laboratory abnormality reported as grade 4 without manifestation of life threatening status), it will be left to the investigator’s judgment to also report these abnormalities as serious adverse events. For any adverse event that applies to this situation, comprehensive documentation of the event’s severity status must be recorded in the subject’s medical record.

9.2.2 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 informed consent through 30 days after the last dose of IP or EOS, whichever is later, are recorded in the subject’s medical records and are submitted to Amgen, including events that are also reported to the CEC for adjudication. All serious adverse events must be submitted to Amgen within 24 hours following the investigator’s knowledge of the event via the applicable eCRF.

After the protocol-required reporting period defined above, the investigator does not need to actively monitor subjects for serious adverse events. However, if the investigator becomes aware of a serious adverse event after this protocol-required reporting period, the investigator will report the event to Amgen within 24 hours following the investigator’s knowledge of the event. Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

If the electronic data capture (EDC) system is unavailable to the site staff to report a 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 D for a sample of the electronic Serious Adverse Event Contingency Report Form. If the first notification of a serious adverse event is reported to Amgen via the eSerious Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

The investigator must assess whether the serious adverse event is possibly related to IP (AMG 145 or placebo). 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 IP?

The investigator must assess whether the serious adverse event is possibly related to the prefilled Al/Pen or Personal Injector device used to administer IP. The 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 device?

The investigator must assess whether the serious adverse event is possibly related to protocol-required therapies (eg study-mandated statin background therapy). 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 study-mandated statin background therapy”?

The investigator must assess whether the serious adverse event is possibly related to any other 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 resolved, improved to baseline, or stabilized.

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 applicable eCRF (eg, Adverse Event Summary eCRF).
If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities. 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 IEC/IRBs in compliance with all reporting requirements according to local regulations and good clinical practice.

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

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 monitor for pregnancies that occur after the last dose of protocol-required therapies through 15 weeks after the end of treatment with IP.

The pregnancy should be reported to Amgen’s global Pregnancy Surveillance Program within 24 hours of the investigator’s knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix D). The Pregnancy Surveillance Program (PSP) will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

If a lactation case occurs while a female subject is taking protocol-required therapies, and for an additional 15 weeks after the end of treatment with IP, report the lactation case to Amgen as specified below.
Any lactation case should be reported to Amgen’s global Lactation Surveillance Program (LSP) within 24 hours of the investigator’s knowledge of the event. Report a lactation case on the Lactation Notification Worksheet (Appendix D).

10. STATISTICAL CONSIDERATIONS
10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Primary Efficacy Endpoint
- Nominal change in percent atheroma volume (PAV) from baseline to week 78

This is the nominal change (end of treatment minus pre-treatment) in percent atheroma volume (PAV) in a ≥40 mm segment of one targeted (imaged) coronary artery as measured by IVUS. It will be computed as follows:

\[
P_{\text{AV}} \text{(Week 78)} - P_{\text{AV}} \text{(baseline)}, \text{where PAV is calculated as:}
\[
\left[ \frac{\sum (EEM_{\text{CSA}} - LUMEN_{\text{CSA}})}{\sum EEM_{\text{CSA}}} \right]
\]

10.1.2 Secondary Efficacy Endpoints
The secondary endpoints are listed in the following sequential order to reflect the multiplicity adjustment method stated in Section 10.5.1.

- Nominal change in total atheroma volume (TAV) from baseline to week 78
- Regression (any reduction from baseline) in PAV
- Regression (any reduction from baseline) in TAV

10.1.3 Exploratory Endpoints
- Plaque composition in a subset of subjects:
  - Fibrous volume
  - Fibrofatty volume
  - Necrotic core
  - Dense calcium
- Subject incidence of adjudicated events
  - death by any cause
  - cardiovascular death
  - myocardial infarction
  - hospitalization for unstable angina
  - coronary revascularization
  - stroke
  - transient ischemic attack (TIA)
  - hospitalization for heart failure
Subject incidence of non-coronary revascularization

Change and percent change from baseline at each scheduled visit in each of the following parameters:
- LDL-C
- Total cholesterol
- non-HDL-C
- ApoB
- total cholesterol/HDL-C ratio
- ApoB/ApoA1 ratio
- Triglycerides
- VLDL-C
- HDL-C
- ApoA1
- Lp(a)

hs-CRP at each scheduled assessment

HbA1c at each scheduled assessment

PCSK9 change from baseline at each scheduled assessment

10.1.4 Safety Endpoints

Subject incidence of treatment emergent adverse events

Safety laboratory values and vital signs at each scheduled visit

ECG parameters (such as RR, PR, QRS, QT and QTc intervals) at each scheduled visit

Incidence of anti-AMG 145 antibody (binding and neutralizing) formation

10.1.5 Pharmacokinetics Endpoints

Serum concentration of AMG 145 at selected time points

10.1.6 Analysis Sets

The full analysis set (FAS) includes all randomized subjects who received at least 1 dose of IP. The IVUS analysis set (IAS) contains subjects in the FAS with a baseline IVUS and an IVUS measurement conducted after week 52 (IVUS data collected after week 52 is considered clinically meaningful to be used in the analysis). The IAS will be used for primary efficacy analysis of IVUS related endpoints. Analyses of non-IVUS endpoints will be performed in FAS.

The Completer Analysis Set (CAS) includes subjects in the IAS who adhered to the scheduled IP and have an observed IVUS value at week 78 for the primary endpoint. In
efficacy analyses, subjects will be grouped according to their randomized treatment group assignment.

Safety analysis set will be FAS. For safety analyses, subjects will be grouped according to their randomized treatment group assignment with the following exception: if a subject receives treatment throughout the study that is different than the randomized treatment group assignment, then the subject will be grouped by the actual treatment group.

10.1.7 Covariates and Subgroups
Baseline covariates include, but are not limited to the following.

- Stratification factor (region - North America, Europe, Latin America, Asia Pacific)
- Age: < 65 years, ≥ 65 years
- Sex
- Race
- LDL-C: < baseline median, ≥ baseline median
- Family history of premature coronary heart disease: yes, no
- PCSK9 level: < baseline median, ≥ baseline median
- PAV: < baseline median, ≥ baseline median
- NCEP risk category

Baseline covariates may be used for subgroup or covariate analyses with the subgroups as specified or in their original format.

10.2 Sample Size Considerations
The planned total sample size is 950 subjects (475 randomized to AMG 145 420 mg QM and 475 randomized to placebo QM). This sample size will provide sufficient power to determine whether there is a treatment effect of AMG 145 relative to placebo in the primary endpoint.

The assumptions in the sample size calculation are based on the study of coronary atheroma by intravascular ultrasound: effect of rosuvastatin versus atorvastatin (SATURN) (Nicholls, 2011). The SATURN study indicates that every 1 mg/dL reduction in LDL-C is estimated to be associated with change of 0.03026 in PAV at week 104. For this study, the assumed treatment effect is change of at least change of 0.706 in PAV at week 78, which is approximated from an expected treatment effect of > 31 mg/dL reduction in LDL-C from baseline to week 78. The assumed common standard deviation (SD) is 2.9.
Assuming 25% of randomized subjects will not be included in the primary analysis, the sample size of 950 subjects will provide approximately 712 subjects in the primary analysis to ensure 90% power to test the study hypothesis.

The sample size calculation was performed using a 2-sided t-test with a 0.05 significance level. The sample size calculation was derived using nQuery version 7.01.

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Unless otherwise specified in this section, subjects, site personnel, or Amgen staff and their designees will not have access to unblinding information until the study is formally unblinded. Unblinded individuals, as designated in this section, are to ensure unblinding information and potentially unblinding data are not distributed to blinded individuals until the study is formally unblinded. Any unplanned unblinding occurring during the study period will be documented and reported in the final clinical study report.

The independent DMC members, and Independent Biostatistical Group (IBG) will have access to treatment assignments and subject level data from the clinical trial database. Amgen staff members who are involved in randomization, biological sample management, performing PK, and anti-AMG 145 antibody assay analysis will have treatment assignment information, but will not have access to subject level data from the clinical trial database.

10.4 Planned Analysis

10.4.1 Data Monitoring Committee (DMC)

An external independent DMC will formally review the accumulating data to ensure there is no avoidable increased risk for harm to subjects. Analyses for the DMC are provided by the Independent Biostatistical Group (IBG), which is external to Amgen. Details are provided in the DMC charter.

10.4.2 Final Analysis

There will be no interim analysis for this study. The final analysis will be conducted after all subjects have either completed all the scheduled study visits or have early terminated from the study. The primary objective of the final analysis is for hypothesis testing of the primary endpoint.
10.5 Planned Methods of Analysis

10.5.1 General Considerations

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.

Statistical inferences will be provided for analyses of primary and secondary efficacy endpoints. Unless specified otherwise, all statistical tests are 2-sided with a significance level of 0.05; no statistical inference and imputation will be conducted for analyses of exploratory endpoints.

Multiplicity Adjustment Method

In order to preserve the family wise type I error rate at 0.05 for testing the primary and secondary endpoints, the primary analysis of primary endpoint will be tested 1st. If the treatment effect from the primary analysis of the primary endpoint is significant at a significance level of 0.05, the hierarchical statistical testing of the secondary endpoints will be tested with significance level of 0.05 in the sequential order as listed in Section 10.1.2.

10.5.2 Analysis of Primary Efficacy Endpoint

Primary analysis

For the primary endpoint of nominal change in PAV from baseline to week 78, the treatment effect of AMG 145 420 mg QM SC will be evaluated by comparing against placebo QM SC.

The primary analysis method of the primary endpoint is to use the analysis of covariance (ANCOVA) model, including terms for treatment group, stratification factor (region) and baseline PAV as covariates. Least-square means and corresponding 95% confidence intervals will be calculated for each treatment (AMG 145 and placebo) and for the difference between the treatment groups. IAS will be used.

Sensitivity Analysis of the Primary Endpoint

A key sensitivity analysis will be conducted using a multiple imputation procedure to impute the primary endpoint for those dosed subjects with missing endpoint data. The primary endpoint will also be analyzed for the complete analysis set using the same methodology outlined above. Nonparametric test will be used for the IAS.
10.5.3 Analysis of Secondary Efficacy Endpoints
The secondary IVUS efficacy endpoint of change in TAV from baseline to week 78 will be analyzed according to the same methodology as the primary endpoint. The secondary efficacy endpoint of percentage of subjects demonstrating regression (any reduction from baseline) in either PAV or TAV will be analyzed using the Cochran-Mantel Haenszel (CMH) test adjusted by the stratification factors.

10.5.4 Analyses of Safety Endpoints
Missing data will not be imputed for safety endpoints.

Adverse Events
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 investigational product or other protocol-required therapies, and significant treatment-emergent adverse events will also be provided.

Safety Laboratory Parameters
Laboratory parameters will be summarized for each treatment group using descriptive statistics at each scheduled visit. Laboratory shift tables for certain analytes will be provided using the CTCAE v.4 toxicity criteria. The results will be based on the maximum (ie, worst) shift from baseline to the EOS.

Vital Signs
Vital signs will be summarized for each treatment group using descriptive statistics at each measurement time point.

Electrocardiogram
Summaries over time will be provided for all ECG parameters. Subjects' maximum change from baseline in QTcF will be categorized and the number and percentage of subjects in each group will be summarized.

Subjects' maximum post baseline values will also be categorized and the number and percentage of subjects in each group will be summarized.

Concomitant Medications
Concomitant medications of interest and lipid-lowering therapy will be summarized for each treatment group.
Anti-AMG 145 Antibodies
The incidence and percentages of subjects who develop anti-AMG 145 antibodies
(binding and neutralizing) at anytime will be tabulated.

10.5.5 Analysis of Exploratory Endpoints
Exploratory endpoints related to changes in plaque composition and lipid parameters will
be summarized by treatment group and by scheduled visit using descriptive statistics.

Death, myocardial infarction, hospitalization for unstable angina, coronary
revascularization, stroke, TIA, and hospitalization for heart failure will be adjudicated by
an independent CEC. Non-coronary revascularizations will be collected on the eCRF
and will not be adjudicated. Subject incidence of exploratory endpoint events will be
summarized for each treatment group.

11. REGULATORY OBLIGATIONS
11.1 Informed Consent
An initial generic informed consent form is provided for the investigator to prepare the
informed consent document to be used at his or her site. Updates to the template will be
communicated by letter from the Amgen study manager to the investigator. The written
informed consent document should be prepared in the language(s) of the potential
patient 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 IPs are administered.

The acquisition of informed consent should be documented in the subject’s medical
records, and the informed consent form should be signed and personally dated by the
subject and by the person who conducted the informed consent discussion. The original
signed informed consent form should be retained in accordance with institutional policy,
and a copy of the signed consent form should be provided to the subject.

If a potential subject is illiterate or visually impaired and does not have a legally
acceptable representative, these subjects can be enrolled provided this is in accordance
with the local IEC/IRB and state, federal and regional regulations.
11.2 Independent Ethics Committee/Institutional Review Board

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

The investigator must submit and, where necessary, obtain approval from the IEC/IRB for all subsequent protocol amendments and changes to the informed consent document. The investigator should notify the IEC/IRB 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 will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the investigator’s reports and the IEC/IRB continuance of approval must be sent to Amgen.

11.3 Subject Confidentiality

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

- On the eCRFs or other documents submitted to Amgen, subjects should be identified by a subject identification number only, with a complete and accurate date of birth on the demographics eCRF.
- For Serious Adverse Events reported to Amgen, subjects should be identified by their initials, date of birth, and a subject identification number.
- Documents that are not for submission to Amgen (eg, signed informed consent forms) should be kept in strict confidence by the investigator.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the subject’s original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records, including personal information, without violating the confidentiality of the subject.
11.4 Pharmacogenetics Confidentiality (for subjects who sign a separate consent only)

All pharmacogenetics samples will be no less than single coded prior to their being utilized and will be stored independent of the subject’s identification number for the study. Similarly, all results will be no less than single coded and stored in a secure database to ensure confidentiality while enabling destruction of the samples when requested. Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results will not be placed in the subject’s medical records and will not be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

11.5 Investigator Signatory Obligations

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

The coordinating investigator, identified by Amgen, will either be:

- 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 IEC/IRB must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IEC/IRB 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 should notify the IEC/IRB in writing of the study’s completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen 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 trial and before it is available commercially.
12.2 Study Documentation and Archive

The investigator should 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 eCRFs will be included on the Amgen Delegation of Authority Form.

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

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

- Subject files containing completed study-related worksheets, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator’s Brochure, copies of prestudy documentation, and all correspondence to and from the IEC/IRB and Amgen
- If kept, proof of receipt/delivery sheet, Investigational Product Accountability Record, Return of Investigational Product for Destruction, Final Investigational Product Reconciliation Statement (if applicable), and all drug-related correspondence

In addition, all original source documents supporting entries in the eCRFs 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 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, eCRFs and other pertinent data) provided that subject confidentiality is respected.

The Amgen monitor is responsible for verifying the eCRFs 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 monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs.
The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, 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, drug 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 eCRFs must be maintained and readily available.
- Updates to eCRFs 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 will be performed on subject data received at Amgen. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications will be created in the EDC system database for site resolution and closed by Amgen reviewer.
- The principal investigator signs only the Investigator Verification Form for this electronic data capture study. This signature will indicate that the principal investigator inspected or reviewed the data on the eCRF, the data queries, and the site notifications, 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 Language

eCRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language.
All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood. Consult the country-specific requirements for language requirements.

12.5 Publication Policy
To coordinate dissemination of data from this study, Amgen encourages the formation of a publication committee. The EC chair and EC members shall participate in a study publication committee, which shall be comprised of at least the following members: the EC chair and the study Principal Investigator and at least 2 members from Amgen. Additional members may be added as agreed upon in the study publication committee charter.

The study publication committee shall be responsible for oversight of the multicenter publication of primary results for the study and all publications of secondary research, in medical and scientific literature. A decision to proceed with any publication must be approved by the majority of the publication committee. If third party investigators are utilized during the course of this study, they must also adhere to publication requirements and obtain approval from the publication committee. Amgen shall be given an opportunity to corroborate any statistical analyses and may comment upon the results and conclusions set forth in such papers, abstracts, presentations, or similar publications. While reasonable consideration of company comments shall be given, the study publication committee shall not be obligated to address such comments; provided, however, that notwithstanding anything herein to the contrary, Amgen shall have the right to remove any confidential information from such proposed publications.

Any proposed publications which are to make public any findings, data, or results of the study shall be developed in accordance with standard good publication practices and submitted to the sponsor for its review and comment at least 45 days prior to submission of a manuscript for scientific publication or an abstract for scientific presentation. However, Amgen may delay such presentation for an additional 60 days in the event action must be taken to protect its intellectual property, such as filing a patent application. If the company chooses to do so, it must notify the publication committee in writing.

12.6 Compensation
Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent.
Depending on the type of study, and if permitted under applicable regional laws or regulatory guidelines, subjects may be compensated for other inconveniences not associated with study-related injuries (eg, travel costs).
13. REFERENCES


Amgen. AMG 145 Investigator’s Brochure, Edition 5.0. 01 February 2012.


14. APPENDICES
### Appendix A. Schedule of Assessments

**ALL SUBJECTS**

<table>
<thead>
<tr>
<th>Study Day / Timepoint</th>
<th>Screening &amp; Placebo Run-in</th>
<th>End of Each 2 Week Lipid Stabl. Period</th>
<th>D1</th>
<th>Week 4</th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 36</th>
<th>Week 52</th>
<th>Week 64</th>
<th>Week 76</th>
<th>Week 78/Early Term</th>
<th>EOS Week 80</th>
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<td>Vital Signs (sitting BP, HR)</td>
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<tr>
<td>Review for AEs/SAEs/CV events</td>
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</table>

*Footnotes defined on next page*
a At the end of the *initial* 2 week lipid stabilization period the subject will be assessed for early termination, up titration or randomization. Subjects with qualifying LDL-C levels (*a local LDL-C level drawn within 4 weeks of screening visit may be used for the initial screening value*) who are on stable doses of a statin per the investigators discretion will not be required to undergo lipid stabilization

b D1 = day of first administration of IP

c AEs/SAEs collected from the time of informed consent

d Concomitant therapy collected in all subjects entering lipid stabilization period

e IVUS imaging needs to be approved by the Core Lab before a subject can be randomized

f At the end of each 2 week lipid stabilization period a blood draw for LDL-C, chemistry (CK, AST and ALT only) and serum pregnancy (females of childbearing potential only) is required. These laboratory results apply to relevant exclusion criteria

g If the subject consented to pharmacogenetics analyses, DNA will be extracted from some of the blood samples, eg. biomarker samples

h HCV antibodies only in high risk subjects (see Section 7.1.3.6) or if ALT or AST > 2x ULN at any time during screening; viral load only in subjects positive for HCV

i FSH = in applicable subjects for study entry only – see exclusion criteria

j Last IP will be given at week 76. IP must be administered after vital signs, ECG, and blood sampling procedures

* Local labs may be used for fasting lipids, chemistry, hematology, fasting glucose/HbA1c, TSH, and assessing eGFR during screening. In addition, at the end of the lipid stabilization period, local labs may be used to assess both fasting lipids and chemistry. Starting on Day 1 all labs will be analyzed via the central laboratory only.
Appendix B. Additional Safety Assessment Information

**Adverse Event Toxicity Grading Scale**

Refer to the NCI Common Terminology Criteria for AEs (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.

When an AE cannot be graded by CTCAE v4.0 the following severity grade may be used:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Amgen Standard Adverse Event Severity Scoring System</th>
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<tbody>
<tr>
<td>1</td>
<td>MILD: Aware of sign or symptom, but easily tolerated</td>
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<tr>
<td>2</td>
<td>MODERATE: Discomfort enough to cause interference with usual activity</td>
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<tr>
<td>3</td>
<td>SEVERE: Incapacitating with inability to work or do usual activity</td>
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<tr>
<td>4</td>
<td>LIFE-THREATENING: Refers to an event in which the subject was, in the view of the investigator, at risk of death at the time of the event. (This category is not to be used for an event that hypothetically might have caused death if it were more severe.)</td>
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<td>5</td>
<td>FATAL</td>
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</table>

**Drug-induced Liver Injury Reporting & Additional Assessments Reporting**

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST/ALT and TBL elevation according to the criteria specified in Section 6.2.1 (3x ULN for AST/ALT and 2x ULN for TBL) require the following:

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

Other events of hepatotoxicity and potential DILI should be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.2.1.

**Additional Clinical Assessments and Observation**

All subjects in whom IP and/or background lipid therapy is withheld due to potential DILI or who experience AST/ALT elevations >3x ULN should undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels. Assessments that should be performed during this period include:

- Repeat liver chemistries within 24-48 hours (ALT, AST, ALP, TBL); in cases of TBL >2x ULN or AST/ALT much greater than 3x ULN, retesting should be performed within 24 hours
− Subjects should be monitored at least twice weekly; testing frequency may decrease to once per week or less if laboratory abnormalities stabilize or the IP has been discontinued AND the subject is asymptomatic

• Obtain PT/INR, fractionated bilirubin and any other potentially relevant laboratory evaluations of liver function or disease
• Obtain complete blood count (CBC) with differential to assess for eosinophilia
• Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
• 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 medications (including non-prescription medicines & herbal and dietary supplements)
• Initiate full viral and autoimmune hepatitis evaluation (serologies for hepatitis A, B, C, D, E, Epstein-Barr Virus, Herpes Simplex Virus, etc); evaluate for other potential causes of DILI including but not limited to: NASH, hypoxic/ischemic hepatopathy, and biliary tract disease
• Obtain gastroenterology or hepatology consult
• Perform appropriate liver imaging or biopsy if clinically indicated; strongly consider these tests in cases of concurrent transaminase and TBL elevation as specified in Section 6.2.1
• Follow the subject until all laboratory abnormalities return to baseline or normal. The “close observation period” should continue for a minimum of 4 weeks after drug discontinuation.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in corresponding eCRFs.
Appendix C. Example Serious Adverse Event Form (Do not use)

**Electronic Serious Adverse Event (eSAE) Contingency Reporting Form**
**For Restricted Use**

Complete either Section A or Section B and follow the instructions provided:

**Section A**
- EDC system (e.g., Rave) is active for this study but is not accessible to allow reporting within 24 hours of the investigator’s knowledge of the event. I am submitting (check all that apply):
  - An event that applies to a specialty CRF page titled (e.g., clinical fracture)
  - Screening event (as defined by the protocol) OR On-study event (as defined by the protocol)
  - Complete ONLY Sections 1, 2 and 3 (page 1)
  - Sign and date the signature section following Section 3
  - Fax completed page of the form to the number noted in the header above Section 1

**Section B**
- Access to the EDC system (e.g., Rave) has either not begun or has ended for this study. I am submitting (check all that apply):
  - Screening event (as defined by the protocol) OR Event after access to the EDC system (e.g., Rave) has ended (provide subject’s End of Study date in Section 2)
  - This is a new event report
  - This is follow-up information for a previously reported event
  - Complete ALL sections of the form (all 3 pages)
  - Sign and date the signature section at the end of the form
  - Fax completed form (all 3 pages) to the number noted in the header above Section 1

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

1. **SITE INFORMATION**
   - Site Number
   - Investigator
   - Phone Number
   - Country
   - Fax Number

2. **SUBJECT INFORMATION**
   - Subject ID Number
   - Date of Birth
   - Sex
   - Race
   - If applicable, provide End of Study date
   - [ ] If this is a follow-up to an event reported in the EDC system (e.g., Rave)

3. **SERIOUS ADVERSE EVENT**
   - Provide the date the investigator became aware of this Serious Adverse Event Information: Date/ Month/ Year
   - Date Started
   - Date Ended
   - Enter Serious Event code
   - Relationship: If event is fatal, please indicate Event of Event
   - Outcome of Event
   - Check only if event is related to study procedure
   - eg, biopsy

**Serious Event Criteria**
- 01 Fatal
- 02 Immediately life-threatening
- 03 Required prolonged hospitalization
- 04 Persistent or significant disability / incapacity
- 06 Other medically important serious event

I confirm by signing this report that the information on this form, including seriousness and causality assessment, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.

Signature of Investigator or Designee: ________________________________  Title: ____________________  Date: ____________________

FORM.056006  Version 2.0  Effective Date: 07-May-2012

Page 1 of 3
### Electronic Serious Adverse Event (eSAS) Contingency Reporting Form
For Restricted Use

If access to the EDC system (e.g., Rave) has either not begun or has ended for this study, complete the remainder of this form.

#### 4. Was subject hospitalized or was a hospitalization prolonged due this event?

- [ ] No
- [x] Yes, if yes, please complete all of Section 4

<table>
<thead>
<tr>
<th>Site Number</th>
<th>Subject ID Number</th>
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<table>
<thead>
<tr>
<th>Date Admitted (Day, Month, Year)</th>
<th>Date Discharged (Day, Month, Year)</th>
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</thead>
</table>

#### 5. Was IMP administered prior to this event?

- [ ] No
- [x] Yes, if yes, please complete all of Section 5

**IMP:**

- [ ] Blinded
- [x] Open Label

#### 6. RELEVANT CONCOMITANT MEDICATIONS (e.g., chemotherapy)

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<th>Stop Date (Day, Month, Year)</th>
<th>Co-suspect</th>
<th>Continuing</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
<th>Action Taken with Product</th>
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</thead>
</table>

- 01: Still being administered
- 02: Permanently discontinued
- 03: Withheld

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

- 

#### 8. RELEVANT LABORATORY VALUES (include baseline values)

<table>
<thead>
<tr>
<th>Test</th>
<th>Date (Day, Month, Year)</th>
<th>Unit</th>
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Any Relevant Laboratory values?

- [ ] No
- [x] Yes, if yes, please complete.
### Electronic Serious Adverse Event (eSAE) Contingency Reporting Form

**Study # 20120153**

**AMG 145**

#### Site Number

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**9. OTHER RELEVANT TESTS (diagnostics and procedures)**

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</tbody>
</table>

**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**

I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.

**Title**

**Date**

---

**FORM-056006**

**Page 3 of 3**

**Version 2.0 Effective Date** 07-May-2012
Appendix D. Sample Pregnancy and Lactation Notification Worksheets

Pregnancy Notification Worksheet
Fax Completed Form to the Country-respective Safety Fax Line

1. Case Administrative Information
Protocol/Study Number: 
Study Design: [ ] Interventional [ ] Observational (t Observational [ ] Prospective [ ] Retrospective)

2. Contact Information
Investigator Name: 
Phone (___) ______ Fax (___) ______ Email: 
Institution: 
Address: 

3. Subject Information
Subject ID #: ______ Subject Gender: [ ] Female [ ] Male Subject DOB: mm/dd/yyyy

4. Amgen Product Exposure

<table>
<thead>
<tr>
<th>Amgen Product</th>
<th>Dose at time of conception</th>
<th>Frequency</th>
<th>Route</th>
<th>Start Date</th>
</tr>
</thead>
</table>

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 UMP: 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 [ ] Unknown [ ] N/A

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: ___________________

Amgen maintains a Pregnancy Surveillance Program that collects data about pregnancy of women who have been exposed to an Amgen product directly or via male sexual partner. Information from this program and from other sources of information, will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during pregnancy.

Effective Date: March 27, 2011
AMGEN® Lactation 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: 
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

<table>
<thead>
<tr>
<th>Amgen Product</th>
<th>Dose at time of breast feeding</th>
<th>Frequency</th>
<th>Route</th>
<th>Start Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mm/dd/yyyy</td>
</tr>
</tbody>
</table>

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
Currently breast feeding? □ 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: ____________________________

Amgen maintains a Lactation Surveillance Program that collects data about women who have been exposed to a Amgen product prior to conception, during pregnancy, and during lactation. Information from this program and from other sources of information will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during lactation.

Effective Date ___________
Appendix E. Acceptable Statin Lipid Lowering Background Therapy

Background lipid lowering therapy should be optimized for the individual subject consistent with local professional society guidelines. At randomization, all subjects that tolerate statins must receive at least an effective statin dose, i.e., at least atorvastatin 20 mg daily or equivalent. Where locally approved, highly effective statin therapy, defined as at least atorvastatin 40 mg daily or equivalent, is recommended. For subjects with LDL-C > 100 mg/dL (> 2.6 mmol/L) and not receiving highly effective statin therapy (atorvastatin ≥ 40 mg daily or equivalent), the investigator must attest that higher dose statin therapy is not appropriate for this subject (e.g., dose not tolerated, dose not available in that country, other significant concern).

<table>
<thead>
<tr>
<th>Background statin</th>
<th>Atorvastatin</th>
<th>Simvastatin</th>
<th>Rosuvastatin</th>
<th>Pravastatin</th>
<th>Lovastatin</th>
<th>Pitavastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acceptable doses</td>
<td>20 MG</td>
<td>40 MG</td>
<td>5 MG</td>
<td>80 MG</td>
<td>80 MG</td>
<td>4 MG</td>
</tr>
<tr>
<td></td>
<td>40 MG</td>
<td>80 MG</td>
<td>10 MG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>80 MG</td>
<td>20 MG</td>
<td>40 MG</td>
<td></td>
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</tr>
</tbody>
</table>

For subjects enrolled with LDL-C > 100 mg/dL, confirmation is required that the selected dose of statin therapy was optimized and is appropriate for the duration of the study. Highly effective therapy includes atorvastatin 40 mg or 80 mg, rosuvastatin 10 mg, 20 mg or 40 mg, and simvastatin 80 mg monotherapy. Use of simvastatin 80 mg was associated with myopathy and is not commonly recommended for use. Simvastatin 80 mg is not available in all countries participating in this study. Approval of simvastatin 80 mg by the local regulatory authority is required for patients using simvastatin 80 mg in this study.

No other lipid therapy is required for the GLAGOV trial. Statins other than atorvastatin, are not provided or reimbursed by Amgen (except if required by local regulation). Background statin therapy received at randomization and other approved lipid lowering background therapies (niacin and/or ezetimibe, if applicable) should remain unchanged throughout the entire duration of the study (up to approximately 18 months).
Appendix F. Drugs With Known Major Interactions With Statin Background Therapy

Atorvastatin:
- strong Cyp3A4 inhibitors (eg, Itraconazole, ketoconazole, and other antifungal azoles, erythromycin, clarithromycin, telithromycin, HIV or HCV protease inhibitors, systemic cyclosporine nefazodone and grapefruit juice in large quantities [> 1 quart or approximately 1 Liter daily])
- colchicine

Simvastatin:
- strong Cyp3A4 inhibitors (eg, Itraconazole, ketoconazole, and other antifungal azoles, erythromycin, clarithromycin, telithromycin, HIV or HCV protease inhibitors, systemic cyclosporine nefazodone and grapefruit juice in large quantities [> 1 quart or approximately 1 Liter daily])
- verapamil
- diltiazem
- danazol
- colchicine
- if simvastatin dose > 20 mg
  - amlodipine
  - amiodarone
  - ranolazine

Rosuvastatin:
- systemic cyclosporine
- and if rosuvastatin > 10 mg, HIV or HCV protease inhibitors

Pravastatin:
- colchicine
- if pravastatin dose > 40 mg:
  - clarithromycin
- if pravastatin dose > 20 mg:
  - systemic cyclosporine

Lovastatin:
- strong Cyp3A4 inhibitors (eg, Itraconazole, ketoconazole, and other antifungal azoles, erythromycin, clarithromycin, telithromycin, HIV or HCV
protease inhibitors, systemic cyclosporine, nefazodone and grapefruit juice in large quantities (> 1 quart or approximately 1 Liter daily))

- colchicine
- ranolazine
- if lovastatin dose > 40 mg:
  - amiodarone
- if lovastatin dose > 20 mg:
  - verapamil
  - diltiazem
  - danazol

Pitavastatin:

- systemic cyclosporine
- combination protease inhibitor therapy with lopinavir and ritonavir
- erythromycin
- rifampin
Appendix G. Statin Intolerance Criteria

4.1.5 Subjects who are intolerant to statins (limited to no more than approximately 10% of total planned enrollment) as evidenced by both of the following (per subject or physician report):

a) Tried at least 2 statins and was unable to tolerate any dose or increase statin dose above the total weekly maximum doses listed below due to intolerable myopathy, ie, myalgia (muscle pain, ache, or weakness without CK elevation), myositis (muscle symptoms with increased CK levels), or rhabdomyolysis (muscle symptoms with marked CK elevation)

b) Symptoms resolved or improved when statin dose was decreased or discontinued

The following maximum total prescribed weekly dosages for statins are:

i. atorvastatin - 70 mg or less
ii. simvastatin - 140 mg or less
iii. pravastatin - 140 mg or less
iv. rosuvastatin - 35 mg or less
v. pitavastatin – 7 mg or less
vi. lovastatin - 140 mg or less
vii. fluvastatin - 280 mg or less
Amendment 2

Protocol Title: A Double-Blind, Randomized, Multi-center, Placebo-controlled, Parallel-group Study to Determine the Effects of Evolocumab (AMG 145) Treatment on Atherosclerotic Disease Burden as Measured by Intravascular Ultrasound in Subjects Undergoing Coronary Catheterization

Amgen Protocol Number: 20120153
EudraCT Number: 2012-004208-37

GLAGOV
(GLobal Assessment of plaque reGression with a PCSK9 antibOdy as measured by intraVascular ultrasound)

Amendment Date: 20 December 2013

Rationale:

This document provides the rationale and detailed list of changes for Amendment 2, dated 20 December 2013, from protocol Amendment 1, dated 30 April 2013.

The purpose of the amendment is to:

- Allow additional statins beyond atorvastatin
- Allow stain intolerant subjects (up to 10%)
- Allow niacin and ezetimibe background therapy, provided it is stable for 4 weeks prior to screening
- Change nomenclature from Q4W to QM
- Add additional device language so that subjects can use the new personal injector when available
- Update safety sections per the new Amgen safety template
Description of Changes:

Section: Title page

Replace:

A Randomized, Multi-center, Placebo-controlled, Parallel-group Study to Determine the Effects of AMG 145 Treatment on Atherosclerotic Disease Burden as Measured by Intravascular Ultrasound in Subjects Undergoing Coronary Catheterization

With:

A **Double-Blind**, Randomized, Multi-center, Placebo-controlled, Parallel-group Study to Determine the Effects of **Evolocumab** (AMG 145) Treatment on Atherosclerotic Disease Burden as Measured by Intravascular Ultrasound in Subjects Undergoing Coronary Catheterization

Replace:

Amendment 1 Date: 30 April 2013

With:

**Amendment 2 Date:** 20 December 2013

Section: Investigator's Agreement

Replace:

I have read the attached protocol entitled “A Randomized, Multi-center, Placebo-controlled, Parallel-group Study to Determine the Effects of AMG 145 Treatment on Atherosclerotic Disease Burden as Measured by Intravascular Ultrasound in Subjects Undergoing Coronary Catheterization”, dated 30 April 2013, and agree to abide by all provisions set forth therein.

With:

I have read the attached protocol entitled “A **Double-Blind**, Randomized, Multi-center, Placebo-controlled, Parallel-group Study to Determine the Effects of **Evolocumab** (AMG 145) Treatment on Atherosclerotic Disease Burden as Measured by Intravascular Ultrasound in Subjects Undergoing Coronary Catheterization”, dated **20 December 2013**, and agree to abide by all provisions set forth therein.
Section: Protocol Synopsis

Replace:

Protocol Synopsis

Title: A Randomized, Multi-Center, Placebo-Controlled, Parallel Group Study to Determine the Effects of AMG 145 Treatment on Atherosclerotic Disease Burden As Measured By Intravascular Ultrasound in Subjects Undergoing Coronary Catheterization

Study Phase: 3

Indication: Coronary Atherosclerosis

Primary Objective

To evaluate the effect of AMG 145 on the change in burden of coronary atherosclerosis as measured by percent atheroma volume (PAV) in subjects with coronary artery disease requiring angiography for a clinical indication who are taking atorvastatin.

Secondary Objectives

To evaluate the effect of AMG 145 on the change in normalized total atheroma volume (TAV) and the percentage of subjects who demonstrate regression of coronary atherosclerosis.

Hypothesis: The primary hypothesis is that (low-density lipoprotein cholesterol) LDL-C lowering with AMG 145 420 mg SC will result in a greater change from baseline in PAV at week 78 than placebo in subjects with coronary artery disease taking atorvastatin lipid lowering therapy.

Primary Endpoint

The nominal change in percent atheroma volume (PAV) from baseline to 78 weeks post randomization, as determined by intravascular ultrasound (IVUS)

Secondary Endpoints

The secondary endpoints are listed in the following sequential order to reflect the multiplicity adjustment method stated in Section 10.5.1

- Percentage of subjects demonstrating regression (any reduction from baseline) in PAV
- Nominal change in normalized TAV from baseline to 78 weeks
- Percentage of subjects demonstrating regression (any reduction from baseline) in TAV
Study Design

This is a Phase III, multi-center, double-blind, randomized, placebo-controlled study evaluating the effect of AMG 145 on coronary atherosclerotic disease burden as assessed by intravascular ultrasound (IVUS) at baseline and following 78 weeks of treatment in subjects with coronary artery disease. Subjects will be randomized 1:1 into 2 treatment groups: AMG 145 420 mg Q4W SC or placebo Q4W SC. Randomization will be stratified for balance by geographic region.

Sample Size: Approximately 950 subjects (475 AMG 145 and 475 placebo) will be randomized.

Summary of Subject Eligibility Criteria

- Men and women >18 years of age
- Clinically indicated coronary angiogram, with evidence of coronary artery disease which fulfill the angiographic and IVUS entry criteria
- Subjects already taking statin therapy at initial screening must be on a stable dose of statin for at least 4 weeks prior to screening.
- Subjects must meet one of the following LDL-C criteria determined by local laboratory at both the initial screening visit (a local LDL-C level may be used for the initial screening LDL-C level as long as it was drawn within 4 weeks of screening visit) and if applicable, at the end of the lipid stabilization period:
  - LDL-C ≥ 80 mg/dL (2.07 mmol/L)
  OR
  - LDL-C ≥ 60 -<80 mg/dL (1.55-2.07 mmol/L) in the presence of one major or three minor risk factors. Enrollment of subjects with LDL-C between ≥ 60 mg/dL (1.55 mmol/L) and < 80 mg/dL (2.07 mmol/L) will be limited to no more than approximately 25% of total planned enrollment.

Major Risk Factors (one required)

1) Non-coronary atherosclerotic vascular disease as evidenced by one of the following: documented peripheral arterial disease (PAD), documented abdominal aortic aneurysm (AAA), or documented cerebrovascular disease (CD).
   - Documented peripheral arterial disease (PAD one of the following primary criteria must be satisfied):
     - Current intermittent claudication (WHO criteria, e.g., leg pain occurring only while walking and disappearing in less than 10 minutes on standing) of presumed atherosclerotic origin TOGETHER WITH ankle-brachial index equal to or less than 0.9 in either leg at rest.
o History of intermittent claudication (WHO criteria as above) TOGETHER WITH either previous intervention by amputation, or reconstructive vascular surgery, or angioplasty in one or both legs because of atherosclerotic disease within the last 2 years.

- Documented abdominal aortic aneurysm,
  o AAA is considered to be present when the minimum anteroposterior diameter of the aorta reaches 3.0 cm. The size of the aorta can be measured in any plane that is perpendicular to the vessel axis.

- Documented cerebrovascular disease (e.g. carotid artery disease or prior history of stroke or transient ischemic attack occurring within the last 2 years)
  o Stroke: ischemic stroke is defined as an infarction of central nervous system tissue not secondary to underlying congenital or valvular heart disease. Symptomatic ischemic strokes are manifest by clinical signs of focal or global cerebral, spinal, or retinal dysfunction caused by central nervous system infarction. A silent stroke is a documented central nervous system infarction that was asymptomatic.
  o Transient ischemic attack (TIA): a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction, not secondary to underlying congenital or valvular heart disease.
  o Carotid artery disease: defined as stenosis > 50% or PSV >125 cm with plaque

1) Documented history of myocardial infarction or hospitalization for unstable angina within the last two years
2) Documented type 2 diabetes mellitus

OR

**Minor Risk Factors (three required)**
1) Cigarette smoking current
2) Hypertension (BP ≥ 140/90 mm Hg or current use of antihypertensive medication)
3) Low HDL-cholesterol - men < 40 mg/dL (1.03 mmol/L) ; women < 50 mg/dl (1.29 mmol/L)
4) Family history of premature coronary heart disease (first-degree male relative < 55 years of age, or first-degree female relative < 65 years of age)
5) Age (men ≥ 50 years; women ≥ 55 years)
6) hs-CRP ≥ 2 mg/L
Major exclusion criteria:

- Clinically significant heart disease which, in the opinion of the Principal Investigator, is likely to require coronary bypass surgery, percutaneous coronary intervention (PCI), cardiac transplantation, surgical valve repair and/or replacement during the course of the study.
- Heart failure of New York Heart Failure Association (NYHA) class III or IV or last known left ventricular ejection fraction < 30%
- Coronary artery bypass surgery < 6 weeks prior to the qualifying IVUS
- Cardiac arrhythmia within 3 months prior to randomization that is not controlled by medication
- **Known hemorrhagic stroke**
- Uncontrolled hypertension at day 1, defined as a resting systolic blood pressure of ≥ 180 mm Hg
- **Personal or family history of hereditary muscular disorders;**
  - Triglyceride (TG) level > 400mg/dL (4.5 mmol/L) at screening
  - Type 1 diabetes or poorly controlled type 2 diabetes (HbA1c > 9%) at screening
  - Thyroid stimulating hormone (TSH) < lower limit of normal (LLN) or TSH > 1.5x upper limit of normal (ULN)
  - Estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m²
  - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2x ULN
  - Creatine kinase (CK) > 3x ULN
- Use of cholesterylster transfer protein (CETP) inhibition treatment within 12 months prior to randomization
- Any prior use of PCSK9 inhibitor therapy
- Subjects are excluded if they have taken any of the following drugs for more than 2 weeks in the last 3 months prior to LDL-C screening: systemic cyclosporine, systemic steroids, isotretinoin (eg, Accutane)
- History of malignancy (except non-melanoma skin cancers, cervical in-situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma).
- Known major active infection, or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction
- Baseline IVUS study determined to be of unacceptable quality by IVUS Core Lab
- Female subjects cannot be pregnant or breast feeding. Premenopausal females must be willing to use at least 1 highly effective method of birth control during treatment and for an additional 15 weeks after the end of treatment

For a full list of eligibility criteria, please refer to Section 4.1 and Section 4.2

**Amgen Investigational Product Dosage and Administration**

Subjects will receive investigational product (IP = AMG 145 or placebo) SC Q4W SC AMG 145 will be administered at 1 fixed volume regimen:

- 420 mg Q4W SC at 3.0 mL via 3 autoinjectors (1.0 mL per autoinjector)

**Control Group**

Placebo will be administered at 1 fixed volume regimen:

- Q4W SC at 3.0 mL via 3 autoinjectors (1.0 mL per autoinjector)
Procedures

Written informed consent must be obtained before protocol specific procedures are carried out. Subjects will be assessed for inclusion and exclusion criteria and medical and medication history will be obtained. Subjects will undergo clinically indicated coronary angiography for further clinical evaluation. If angiographic criteria for IVUS (at least one vessel with 20% stenosis and a target vessel for imaging with less than 50% obstruction) is met, the subject will have baseline IVUS completed. Subjects will undergo screening labs and will receive a 3.0 mL placebo injection by SC administration.

Subjects must be on an optimal dose of atorvastatin (20 mg, 40 mg, or 80 mg), titrated to achieve target LDL-C as defined by regional guidelines. Subjects not on an optimal dose of atorvastatin, in the opinion of the investigator, will enter a two to four week lipid stabilization period for initiation or titration of atorvastatin with a maximum of one up titration step for optimization. Only subjects on a stable (ie, at least 4 weeks), optimal dose of atorvastatin and at their LDL-C goal at the initial screening visit can forgo the lipid stabilization period.

Eligibility LDL-C for randomization will be based upon locally determined LDL-C.

At randomization, an interactive voice response system (IVRS) will allocate subjects to receive either 3.0 mL of AMG 145 or placebo. Administration of IP (AMG 145 or placebo) will be every 4 weeks. Final administration of IP (AMG 145 or placebo) will occur at week 76. Subjects who discontinue IP for any reason will be asked to continue to return for all other study procedures and measurements until the end of the study.

Subjects whose central laboratory LDL-C values increase by more than a predefined trigger (see section 7.1.3.4) during the study will be automatically given a reminder to adhere to their assigned LDL-C lowering therapies and to the ATP III TLC-type diet. To avoid unblinding, the same reminder will be provided to additional subjects in each treatment arm.

During the 4, 12, 24, 36, 52, 64, 76, and 78 week visits vital signs will be obtained and AEs, SAEs, and concomitant medications will be recorded. Physical exams, laboratory tests and other procedures will be performed during these visits. Subjects at increased risk for hepatitis C virus (HCV) infection or with ALT or AST > 2x ULN at any time during screening will be tested for prior or existing HCV infection and viral load will be evaluated in those who show evidence thereof. Investigators will be informed if triglycerides are > 1000 mg/dL (11.3 mmol/L) so that appropriate subject follow-up can be
initiated (see Protocol Section 6.1.3.3). For subjects consenting to pharmacogenetics analyses, DNA will be extracted from some of the blood samples

Subject will undergo the final IVUS assessment at the week 78 visit. EOS for subjects is by contact (eg, phone call) from the site at week 80 for any potential AEs or SAEs.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and Appendix A

An Executive Committee (EC) has been formed to advise Amgen on trial design and for assistance in the communication of trial results. The EC will be blinded. Details will be provided in a committee charter.

Statistical Considerations

General Considerations

The full analysis set (FAS) includes all randomized subjects who received at least 1 dose of IP.

The IVUS analysis set (IAS) contains FAS with a baseline IVUS and an IVUS measurement conducted after week 52 (IVUS data collected after week 52 is considered clinically meaningful to be used in the analysis). The IAS will be used for primary efficacy analysis of IVUS related endpoints.

Method of adjusting for multiplicity due to multiple endpoints (primary and secondary endpoints) is provided in Section 10.5.1

Safety analyses set will be FAS.

Events of death, myocardial infarction (MI), hospitalization for unstable angina, coronary revascularization, stroke, transient ischemic attack (TIA), and hospitalization for heart failure will be adjudicated by an independent Clinical Events Committee (CEC). Subject incidence of exploratory endpoint events will be summarized for each treatment group.

Analyses of Primary Endpoint

The primary analysis of the primary endpoint will use the ANCOVA model, including terms for treatment group, stratification factor (region) and baseline PAV as covariates. Least-square means and corresponding 95% confidence intervals will be calculated for each treatment (AMG145 and placebo) and for the difference between the treatment groups.
Sensitivity Analysis of the Primary Endpoint

A key sensitivity analysis will be conducted using a multiple imputation procedure to impute the primary endpoint for those dosed subjects with missing endpoint data. The primary endpoint will also be analyzed for the completers population (adhered to the scheduled IP) using the same methodology as the primary analysis.

Analyses of Secondary Efficacy Endpoints

Analyses of secondary efficacy endpoints will be similar to the analyses of the primary endpoint. However, the secondary efficacy endpoints of percentage of subjects demonstrating regression (any reduction from baseline) will be analyzed using the Cochran-Mantel Haenszel (CMH) test adjusted by the stratification factor.

Safety Analyses

AEs will be coded using the current version of MedDRA. Subject incidence of treatment-emergent adverse events, serious adverse events, treatment-related adverse events and adverse events leading to discontinuation of IP will be tabulated by system organ class and preferred term by randomized treatment group.

Measurements of laboratory parameters, ECGs, and vital signs will be summarized over time. Lab shift tables will be provided. The incidence and percentages of subjects who develop anti-AMG 145 antibodies (binding and neutralizing) at any time will be tabulated.

Safety Monitoring

An external independent Data Monitoring Committee (DMC) will formally review the accumulating data with AMG 145 to ensure there is no avoidable increased risk for harm to subjects. Analyses for the DMC will be provided by a group which is external to Amgen. In addition, Amgen performs continuous monitoring of SAEs in a blinded manner.

For a full description of statistical analysis methods, please refer to Section 10

With:

Protocol Synopsis

Title: A Double-Blind, Randomized, Multi-Center, Placebo-Controlled, Parallel Group Study to Determine the Effects of Evolocumab (AMG 145) Treatment on Atherosclerotic Disease Burden As Measured By Intravascular Ultrasound in Subjects Undergoing Coronary Catheterization
Study Phase: 3

Indication: Coronary Atherosclerosis

Primary Objective

To evaluate the effect of AMG 145 on the change in burden of coronary atherosclerosis as measured by percent atheroma volume (PAV) in subjects with coronary artery disease (CAD) requiring angiography for a clinical indication who are taking statins.

Secondary Objectives

- To evaluate the effect of AMG 145 on the change in normalized total atheroma volume (TAV) and the percentage of subjects who demonstrate regression of coronary atherosclerosis.

Hypothesis: The primary hypothesis is that (low-density lipoprotein cholesterol) LDL-C lowering with AMG 145 420 mg subcutaneous (SC) will result in a greater change from baseline in PAV at week 78 than placebo in subjects with coronary artery disease taking background statin therapy.

Primary Endpoint

The nominal change in percent atheroma volume (PAV) from baseline to week 78 post randomization, as determined by intravascular ultrasound (IVUS)

Secondary Endpoints

The secondary endpoints are listed in the following sequential order to reflect the multiplicity adjustment method stated in Section 10.5.1

- Nominal change in total atheroma volume (TAV) from baseline to week 78
- Regression (any reduction from baseline) in PAV
- Regression (any reduction from baseline) in TAV

Study Design

This is a Phase III, multi-center, double-blind, randomized, placebo-controlled study evaluating the effect of AMG 145 on coronary atherosclerotic disease burden as assessed by intravascular ultrasound (IVUS) at baseline and following 78 weeks of treatment in subjects with coronary artery disease. Subjects will be randomized 1:1 into 2 treatment groups: AMG 145 420 mg on a monthly basis (QM) SC or placebo QM SC. Randomization will be stratified for balance by geographic region.

Sample Size: Approximately 950 subjects (475 AMG 145 and 475 placebo) will be randomized.
Summary of Subject Eligibility Criteria

- Men and women ≥18 years of age
- Clinically indicated coronary angiogram, with evidence of coronary artery disease which fulfill the angiographic and IVUS entry criteria
- Subjects already taking statin therapy, regulatory-approved sustained-release niacin (eg Niaspan®) or ezetimibe at initial screening must have been on a stable dose for at least 4 weeks prior to the lipid panel used for the screening LDL-C. Subjects not currently taking lipid-regulating therapy can be screened but must enter the study via a lipid stabilization period.

OR

Subjects who are intolerant to statins (limited to no more than approximately 10% of total planned enrollment) must meet statin intolerance entry criteria in Appendix G.

- Subjects must have at least one eligible LDL-C level (as defined below) via local, central laboratory or point of care device at the initial screening visit and, if applicable, at the end of each lipid stabilization period. A pre-existing local LDL-C level may be used as the initial screening LDL-C value as long as it was drawn within 4 weeks of the screening visit and no interim changes to lipid-regulating therapy have occurred during that 4-week period:
  - LDL-C ≥ 80 mg/dL (2.07 mmol/L) with or without additional risk factors
  OR
  - LDL-C ≥ 60 -<80 mg/dL (1.55-2.07 mmol/L) in the presence of one major or three minor risk factors as defined below. Enrollment of subjects with LDL-C between ≥ 60 mg/dL (1.55 mmol/L) and < 80 mg/dL (2.07 mmol/L) will be limited to no more than approximately 25% of total planned enrollment.

Major Risk Factors (one required)

1) Non-coronary atherosclerotic vascular disease as evidenced by one of the following: documented peripheral arterial disease (PAD), documented abdominal aortic aneurysm (AAA), or documented cerebrovascular disease (CD).

   - Documented peripheral arterial disease (one of the following primary criteria must be satisfied):
     - Current intermittent claudication (WHO criteria, e.g., leg pain occurring only while walking and disappearing in less than 10 minutes on standing) of presumed atherosclerotic origin TOGETHER WITH ankle-brachial index equal to or less than 0.9 in either leg at rest.
• History of intermittent claudication (WHO criteria as above) TOGETHER WITH either previous intervention by amputation, or reconstructive vascular surgery, or angioplasty in one or both legs because of atherosclerotic disease within the last 2 years.

- Documented abdominal aortic aneurysm:
  - AAA is considered to be present when the minimum anteroposterior diameter of the aorta reaches 3.0 cm. The size of the aorta can be measured in any plane that is perpendicular to the vessel axis.

- Documented cerebrovascular disease (e.g. carotid artery disease or prior history of stroke or transient ischemic attack occurring within the last 2 years):
  - Stroke: ischemic stroke is defined as an infarction of central nervous system tissue not secondary to underlying congenital or valvular heart disease. Symptomatic ischemic strokes manifest by clinical signs of focal or global cerebral, spinal, or retinal dysfunction caused by central nervous system infarction. A silent stroke is a documented central nervous system infarction that was asymptomatic.
  - Transient ischemic attack (TIA): a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction, not secondary to underlying congenital or valvular heart disease.
    - Carotid artery disease: defined as stenosis > 50% or PSV > 125 cm/sec with plaque

2) Documented history of myocardial infarction or hospitalization for unstable angina within the last two years

3) Documented type 2 diabetes mellitus

OR

Minor Risk Factors (three required)

- Current cigarette smoker
- Hypertension (One documented blood pressure (BP) ≥ 140/90 mm Hg or current use of antihypertensive medication)
- Low HDL-cholesterol - men < 40 mg/dL (1.03 mmol/L) ; women < 50 mg/dL-I (1.29 mmol/L)
- Family history of premature coronary heart disease (first-degree male relative < 55 years of age, or first-degree female relative < 65 years of age)
- Age (men ≥ 50 years; women ≥ 55 years)
- **High sensitivity C-reactive protein** (hs-CRP) ≥ 2 mg/dL

**Major exclusion criteria:**

- Clinically significant heart disease which, in the opinion of the Principal Investigator, is likely to require coronary artery bypass **graft (CABG)** surgery, percutaneous coronary intervention (PCI) *(does not apply to PCI deemed necessary by the initial screening angiogram)*, cardiac transplantation, surgical or percutaneous valve repair and/or replacement during the course of the study.
- New York Heart Association (NYHA) class III or IV or last known left ventricular ejection fraction < 30%
- Coronary artery bypass **graft** surgery < 6 weeks prior to the qualifying IVUS
- Cardiac arrhythmia within 3 months prior to randomization that is not controlled by medication
- Known hemorrhagic stroke
- Uncontrolled hypertension at **randomization**, defined as a resting systolic blood pressure of ≥ 180 mm Hg **at rest**
- Personal or family history of hereditary muscular disorders
- **Fasting** triglyceride (TG) level > 400mg/dL (4.5 mmol/L) at screening
- Type 1 diabetes or poorly controlled type 2 diabetes (HbA1c > 9%) at screening
- Thyroid stimulating hormone (TSH) < lower limit of normal (LLN) or TSH > 1.5x upper limit of normal (ULN). **A subject taking thyroid replacement therapy may be enrolled with TSH level below LLN if, in the opinion of the investigator, the subject is in a clinically euthyroid state.**
- Estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m²
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3x ULN at screening or at end of lipid stabilization period
- Creatine kinase (CK) > 3x ULN **at screening or at end of lipid stabilization period**
- Use of cholesteryl ester transfer protein ( CETP) inhibitor, mipomersen or lomitapide within 12 months prior to screening
- Any prior use of **proprotein convertase subtilisin/kexin type 9** (PCSK9) inhibitor therapy
- Subjects are excluded if they have taken any of the following drugs for more than 2 weeks in the last 3 months prior to LDL-C screening: systemic cyclosporine, systemic steroids *(e.g. IV, intramuscular [IM], or PO)* *(Note: hormone replacement therapy is permitted)*; systemic vitamin A and retinol derivatives for the treatment of dermatologic conditions *(e.g., Accutane)* *(Note: vitamin A in topical and multivitamin preparations are permitted)*
- History of malignancy *(except non-melanoma skin cancers, cervical in-situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma).*
- Known major active infection, or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction
- Baseline IVUS **does not meet** IVUS Core Lab technical standards
Female subjects cannot be pregnant or breastfeeding, planning to become pregnant or planning to breastfeed during the screening period, at the end of the lipid stabilization period (if applicable), while receiving treatment with Investigational Product (AMG 145 or placebo) and within 15 weeks after the end of treatment with Investigational Product (AMG 145 or placebo).

Premenopausal females of childbearing potential must be willing to use an acceptable method(s) of birth control during treatment with Investigational product (IP) (AMG 145 or placebo) and for an additional 15 weeks after the end of treatment with Investigational product (IP) (AMG 145 or placebo).

For a full list of eligibility criteria, please refer to Section 4.1 and Section 4.2

Amgen Investigational Product Dosage and Administration

Subjects will receive investigational product (IP), comprising evolocumab (AMG 145) or placebo as subcutaneous (SC) injections on a monthly basis (QM). SC AMG 145 will be administered in a fixed volume regimen:

- 420 mg QM SC at 3.0 mL via 3 prefilled autoinjectors (1.0 mL per autoinjector) or
- 420 mg QM SC at 3.5 mL via 1 Personal Injector injection

Control Group

Placebo will be administered in a fixed volume regimen:

QM SC at 3.0 mL via 3 prefilled autoinjectors (1.0 mL per autoinjector) or one 3.5 mL Personal Injector injection

Subjects will have the opportunity to switch from autoinjectors to a personal injector provided the required approvals and supplies of IP are available at the study site.

Procedures

Written informed consent must be obtained before protocol-specific procedures are carried out. Subjects will be assessed for inclusion and exclusion criteria and medical and medication history will be obtained. In order to minimize the chances of performing unnecessary IVUS procedures, investigators should ensure that subjects’ initial screening LDL-C results are available prior to performing the baseline IVUS examination. Thereafter, subjects will undergo clinically-indicated coronary angiography for further clinical evaluation. If angiographic criteria for IVUS are met, the subject will have baseline IVUS completed. Subjects who require a PCI as a result of the qualifying angiography will have baseline IVUS performed immediately following the PCI. Any intervention to the proposed target IVUS vessel will exclude this vessel from being used as the target IVUS vessel. Delayed or staged IVUS procedures must be performed within 4 weeks after qualifying angiography. For subjects who undergo delayed or staged interventions, the baseline IVUS must be performed after the final planned intervention. Subjects will undergo all screening labs and receive a 3.0 mL placebo injection by SC administration, prior to randomization.

At time of randomization, subjects must be on stable, optimized background statin therapy (per Protocol Appendix E) that is expected to be unchanged for the duration of study participation (up to 18 months). Optimal statin therapy is defined as an effective dose of at least atorvastatin 20 mg daily or equivalent titrated to achieve target LDL-C (reduction or goal) as defined by regional
guidelines. Where locally approved, highly effective statin therapy, defined as at least atorvastatin 40 mg daily or equivalent, is recommended. For subjects with LDL-C > 100 mg/dL (2.6 mmol/L) who are not receiving highly-effective statin therapy (atorvastatin ≥ 40 mg daily or equivalent), the investigator must attest that higher dose statin therapy is not appropriate for this subject (eg, dose not tolerated, dose not available in that country, other significant clinical concern). Subjects who, in the investigator's opinion, are already at LDL-C goal at initial screening and are on stable (≥ 4 weeks), allowable lipid lowering therapy (per Appendix E), with no changes planned or expected for the duration of the study, will be enrolled and proceed directly to IP randomization if all other eligibility criteria are met. These subjects may skip the lipid stabilization period. Subjects requiring any change to their lipid therapy will be enrolled and subsequently enter a two- to four-week lipid stabilization period for initiation or titration of statins with a maximum of one up titration step utilized to achieve a target LDL-C as defined by regional guidelines.

Locally-determined LDL-C levels may be used to determine eligibility at initial screening and for LDL-C monitoring during the lipid stabilization period. At randomization, an interactive voice response system (IVRS) will allocate subjects to receive either AMG 145 or placebo. Administration of IP (AMG 145 or placebo) will be once every month. Final administration of IP (AMG 145 or placebo) will occur at week 76. Subjects taking study-provided atorvastatin should continue the drug until their week 78 visit. Similarly, subjects taking non-study provided statins and allowable non-statin therapies should continue such treatment until week 78. Beyond the week 78 assessment, use of statins and other lipid regulating therapies will be at the discretion of the investigator. Subjects who discontinue IP for any reason will be asked to continue to return for all other study procedures and measurements until the end of the study. Subjects whose central laboratory LDL-C values increase by more than a predefined trigger (see section 7.1.3.4) during the study will be automatically given a reminder to adhere to their assigned LDL-C lowering therapies and to the ATP III TLC-type diet. To avoid unblinding, the same reminder will be provided to additional subjects in each treatment arm.

During the 4, 12, 24, 36, 52, 64, 76, and 78 week visits vital signs will be obtained and adverse events (AEs), serious AEs (SAEs), and concomitant medications will be recorded. Physical exams, laboratory tests and other procedures will be performed during these visits. Subjects at increased risk for hepatitis C virus (HCV) infection or with ALT or AST > 2x ULN at any time during screening will be tested for prior or existing HCV infection and viral load will be evaluated in those who show evidence thereof. Investigators will be informed if triglycerides are > 1000 mg/dL (11.3 mmol/L) so that appropriate subject follow-up can be initiated (see Protocol Section 6.1.3.3). For subjects consenting to pharmacogenetics analyses, DNA will be extracted from some of the blood samples

Subject will undergo the final IVUS assessment at the week 78 visit. End of study (EOS) for subjects is by contact (eg, phone call) from the site at week 80 for any potential AEs or SAEs.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and Appendix A.

An Executive Committee (EC) has been formed to advise Amgen on trial design and for assistance in the communication of trial results. The EC will be blinded. Details will be provided in a committee charter. An external independent Data Monitoring Committee (DMC) will formally review the accumulating data from this and other
ongoing studies with AMG 145 to ensure there is no avoidable increased risk for harm to subjects. Analyses for the DMC will be provided by an independent biostatistical group (IBG), which is external to Amgen.

**Statistical Considerations**

**General Considerations**

The full analysis set (FAS) includes all randomized subjects who received at least 1 dose of IP.

The IVUS analysis set (IAS) contains FAS with a baseline IVUS and an IVUS measurement conducted after week 52 (IVUS data collected after week 52 is considered clinically meaningful to be used in the analysis). The IAS will be used for primary efficacy analysis of IVUS related endpoints.

Method of adjusting for multiplicity due to multiple endpoints (primary and secondary endpoints) is provided in Section 10.5.1

Safety analyses set will be FAS.

Events of death, myocardial infarction (MI), hospitalization for unstable angina, coronary revascularization, stroke, transient ischemic attack (TIA), and hospitalization for heart failure will be adjudicated by an independent Clinical Events Committee (CEC). Subject incidence of exploratory endpoint events will be summarized for each treatment group.

**Analyses of Primary Endpoint**

The primary analysis of the primary endpoint will use the ANCOVA model, including terms for treatment group, stratification factor (region) and baseline PAV as covariates. Least-square means and corresponding 95% confidence intervals will be calculated for each treatment (AMG145 and placebo) and for the difference between the treatment groups.

**Sensitivity Analysis of the Primary Endpoint**

A key sensitivity analysis will be conducted using a multiple imputation procedure to impute the primary endpoint for those dosed subjects with missing endpoint data. The primary endpoint will also be analyzed for the completers population (adhered to the scheduled IP) using the same methodology as the primary analysis.

**Analyses of Secondary Efficacy Endpoints**

Analyses of secondary efficacy endpoints will be similar to the analyses of the primary endpoint. However, the secondary efficacy endpoints of percentage of subjects demonstrating regression (any reduction from baseline) will be analyzed using the Cochran-Mantel Haenszel (CMH) test adjusted by the stratification factor.

**Safety Analyses**

AEs will be coded using the current version of MedDRA. Subject incidence of treatment-emergent adverse events, serious adverse events, treatment-related adverse events and adverse events leading to discontinuation of IP will be tabulated by system organ class and preferred term by randomized treatment group.

Measurements of laboratory parameters, ECGs, and vital signs will be summarized over time. Lab shift tables will be provided. The incidence and percentages of subjects who develop anti-AMG 145 antibodies (binding and neutralizing) at any time will be tabulated.

**Safety Monitoring**
An external independent Data Monitoring Committee (DMC) will formally review the accumulating data with AMG 145 to ensure there is no avoidable increased risk for harm to subjects. Analyses for the DMC will be provided by a group which is external to Amgen. In addition, Amgen performs continuous monitoring of SAEs in a blinded manner.

For a full description of statistical analysis methods, please refer to Section 10

Section: Study Design and Treatment Schema

Replace:

With:
Study Glossary

Add:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAA</td>
<td>Abdominal aortic aneurysm</td>
</tr>
<tr>
<td>ADE</td>
<td>Adverse device effect</td>
</tr>
<tr>
<td>AI</td>
<td>Autoinjector</td>
</tr>
<tr>
<td>CD</td>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>CEC</td>
<td>Clinical Events Committee</td>
</tr>
<tr>
<td>CETP</td>
<td>Cholesteryl ester transfer protein</td>
</tr>
<tr>
<td>EDC</td>
<td>Electronic Data Capture</td>
</tr>
<tr>
<td>eSAE</td>
<td>Electronic SAE</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Syndrome</td>
</tr>
<tr>
<td>IFU</td>
<td>Instructions for Use</td>
</tr>
<tr>
<td>IM</td>
<td>Intramuscular</td>
</tr>
<tr>
<td>INR</td>
<td>International Normalized Ratio</td>
</tr>
<tr>
<td>LSP</td>
<td>Lactation Surveillance Program</td>
</tr>
<tr>
<td>PAV</td>
<td>Percent atheroma volume</td>
</tr>
<tr>
<td>PEP</td>
<td>Potential endpoint</td>
</tr>
<tr>
<td>Q4W</td>
<td>Every 4 weeks, <em>(AMG 145 Background section)</em></td>
</tr>
<tr>
<td>QM</td>
<td>QM is defined as every 4 weeks with a window of ± 3 days for each visit</td>
</tr>
<tr>
<td>TAV</td>
<td>Total Atheroma Volume</td>
</tr>
</tbody>
</table>

Section: 1.1 and 1.2 Primary and Secondary Objectives

Replace:

1.1 Primary

To evaluate the effect of AMG 145 on the change in burden of coronary atherosclerosis as measured by percent atheroma volume (PAV) in subjects with coronary artery disease requiring angiography for a clinical indication who are taking atorvastatin.

1.2 Secondary

To evaluate the effect of AMG 145 on the change in normalized total atheroma volume (TAV) and the percentage of subjects who demonstrate regression of coronary atherosclerosis.

With:

1.1 Primary

To evaluate the effect of AMG 145 on the change in burden of coronary atherosclerosis as measured by percent atheroma volume (PAV) in subjects with coronary artery disease requiring angiography for a clinical indication who are taking statins.
1.2 Secondary

To evaluate the effect of AMG 145 on the change in normalized total atheroma volume (TAV) and regression of coronary atherosclerosis either by PAV or TAV.

Section: 2.3 Rationale

Add references

Section: 3.1 Study Design

Replace:

Subjects will be identified for eligibility on the basis of requiring coronary angiography for further clinical evaluation, completion of IVUS, and LDL-C inclusion criteria.

Subjects must be on an optimal dose of atorvastatin (20 mg, 40, mg, or 80 mg), defined as the dose at which desired LDL-C goal is reached.

Subjects who have an acceptable IVUS and are currently on an appropriate atorvastatin dose with an LDL-C level that meets the inclusion criteria will be eligible for randomization.

Subjects not on an optimal dose of atorvastatin, in the opinion of the investigator, will enter a two to four week lipid stabilization period for initiation or titration of atorvastatin with a maximum of one up titration step for optimization. No changes in lipid lowering therapies will be allowed once subjects are randomized.

Subjects who do not meet inclusion criteria or meet any exclusion criteria at any time prior to becoming eligible for or initiating the lipid stabilization period will be considered screen failures, and cannot be rescreened.

Subjects will be randomized 1:1 into 2 treatment groups: AMG 145 420 mg Q4W SC or placebo Q4W SC. Randomization will be stratified for balance by region. Study visits will occur during screening, Day 1 (randomization) and week 4, 12, 24, 36, 52, 64, 76 (last dose of IP) and 78 (final IVUS procedure). Subjects will self-administer investigational product (IP) while under observation at the site, and those who wish to have IP administered by site personnel may do so. Between study visits subjects will self-administer IP monthly at home, unless they choose to visit the site to have IP administered by site personnel. At each visit, vital signs, AEs, SAEs, and concomitant medications will be recorded and laboratory tests will be performed. Dietary instruction will be given at each visit. Central laboratory results of the lipid panel, ApoA1, ApoB, high sensitivity C-reactive protein (hsCRP), and lipoprotein(a) (Lp(a)) will be blinded during the treatment period until unblinding of the clinical database and will not be reported to the investigator post-screening. Investigators 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 end-of-study visit. Investigators will be informed if triglycerides are > 1000 mg/dL (11.3 mmol/L) so that appropriate subject follow-up can be initiated (see Protocol Section 6.1.3.3). The primary efficacy measurement for this study is PAV and will be measured at baseline and week 78. The study includes collection of biomarker samples and, where approved by the independent ethics committee and/or institutional review board (IEC/IRB) and applicable regulatory and other authorities, all subjects will be invited to consent to pharmacogenetic analyses. The end-of-study (EOS) visit will occur at week 78 for all subjects. Last IP will be administered at week 76. Sites will contact (eg, phone call) subjects at week 80 to assess any potential AEs or SAEs. Subjects will be encouraged to complete all planned visits regardless of their adherence to IP administration. The study includes adjudication
of deaths and specific cardiovascular events potential endpoints (PEPs) by an independent Clinical Events Committee (CEC) and formal review of the accumulating data by an independent Data Monitoring Committee (DMC). An Executive Committee (EC) has been formed to advise Amgen on trial design and for assistance in the communication of trial results. The EC will be blinded. Details for each committee will be provided in a committee charter

With:

This is a Phase III, multi-center, double blind, randomized, placebo-controlled study evaluating the effect of Evolocumab (AMG 145) upon coronary atherosclerotic disease burden as assessed by IVUS at baseline and following 78 weeks of treatment in subjects with coronary artery disease.

Subjects will be identified for eligibility on the basis of requiring coronary angiography for further clinical evaluation, LDL-C inclusion criteria, and completion of IVUS.

At randomization, subjects must be on stable, optimized background statin therapy (per Protocol Appendix E) that is expected to be unchanged for the duration of study participation (up to 18 months). Optimal statin therapy is defined as an effective statin dose of at least atorvastatin 20 mg daily or equivalent titrated to achieve target LDL-C (change or goal) as defined by regional guidelines. Where locally approved, highly effective statin therapy, defined as at least atorvastatin 40 mg daily or equivalent, is recommended. For subjects with LDL-C > 100 mg/dL (2.6 mmol/L) who are not receiving highly effective statin therapy (atorvastatin ≥ 40 mg daily or equivalent), the investigator must attest that higher dose statin therapy is not appropriate for this subject (eg, dose not tolerated, dose not available in that country, other significant clinical concern). Subjects who, in the investigator’s opinion, are already at LDL-C goal at initial screening and are on stable (≥ 4 weeks), allowable lipid lowering therapy (per Appendix E), with no changes planned or expected for the duration of the study, will be enrolled and proceed directly to randomization if all other eligibility criteria are met. These subjects may skip the lipid stabilization period.

Subjects who have an acceptable IVUS and are currently on an appropriate statin dose with an LDL-C level that meets the inclusion criteria will be eligible for randomization.

Subjects not on an optimal dose of a statin, in the opinion of the investigator, will enter a two to four week lipid stabilization period for initiation or titration of a statin with a maximum of one up titration step for optimization. No changes to lipid lowering therapies will be allowed (except for clinically compelling reasons) once subjects are randomized.

Subjects who fail to meet eligibility criteria will be considered screen failures, and cannot be rescreened. However, certain subjects may be eligible for retesting without rescreening: please refer to section 7.1.1.2. The baseline IVUS examination may be performed only once for entry into the study. Repeating the baseline IVUS examination is prohibited.

Subjects will be randomized 1:1 into 2 treatment groups: AMG 145 420 mg QM SC or placebo QM SC. Randomization will be stratified for balance by region. Study visits will occur during screening, Day 1 (randomization) and week 4, 12, 24, 36, 52, 64, 76 (last dose of IP) and 78 (final IVUS procedure). During these visits, investigational product (IP) will be given via either self-administration or by a qualified staff member. Between study visits, IP can be administered at a location external to the study site, unless subjects choose to visit the site to have IP administered by site personnel. At
applicable visits, vital signs, AEs, SAEs, and concomitant medications will be recorded and laboratory tests will be performed. Dietary instruction will be given at each visit. Central laboratory results of the lipid panel, ApoA1, ApoB, high sensitivity C-reactive protein (hsCRP), and lipoprotein(a) (Lp(a)) will be blinded during the IP treatment period until unblinding of the clinical database and will not be reported to the investigator post-screening. Investigators 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 end-of-study visit. Investigators will be informed if triglycerides are > 1000 mg/dL (11.3 mmol/L) so that appropriate subject follow-up can be initiated (see Protocol Section 6.1.3.3). The primary efficacy measurement for this study is PAV and will be measured at baseline and week 78. The study includes collection of biomarker samples and, where approved by the independent ethics committee and/or institutional review board (IEC/IRB) and applicable regulatory and other authorities, all subjects will be invited to consent to pharmacogenetic analyses. Last IP will be administered at week 76. The final visit will occur at week 80 for all subjects. During this final visit, sites will contact (eg, phone call) subjects to assess any potential AEs or SAEs. Subjects will be encouraged to complete all planned visits regardless of their adherence to IP administration. The study includes adjudication of deaths and specific cardiovascular events potential endpoints (PEPs) by an independent Clinical Events Committee (CEC) and formal review of the accumulating data by an independent Data Monitoring Committee (DMC). An Executive Committee (EC) has been formed to advise Amgen on trial design and for assistance in the communication of trial results. The EC will be blinded. Details for each committee will be provided in a committee charter.

Section: 4.1 Inclusion Criteria

Replace:

Subject has provided informed consent.

Male or female ≥ 18 age at screening

Clinical indication for coronary angiography.

Subjects must meet all of the following IVUS criteria at the qualifying coronary catheterization procedure:

A. Entire Coronary Circulation:
   - Angiographic evidence of coronary heart disease as defined by at least one lesion in any of the three major native coronary arteries that has > 20% reduction in lumen diameter by angiographic visual estimation or prior history of PCI.
   - This vessel need not be the target coronary artery for IVUS.
   - Any vessel with previous PCI may not be used as the target coronary artery.

B. Left Main Coronary Artery:
   - Must not have a > 50% reduction in lumen diameter by visual angiographic estimation.

C. Target Coronary Artery for IVUS:
   - Must be accessible to the IVUS catheter.
Must not have a >50% reduction in lumen diameter by angiographic visual estimation within the target segment, the target segment being at least 40 mm in length.

A lesion, distal to the target segment, of up to 60% stenosis is permitted, provided that the stenosis is not a target for PCI or CABG.

A single branch of the “target vessel” may have a narrowing of <70% by visual estimation, provided that the branch in question is not a target for PCI or CABG.

Has not undergone prior percutaneous coronary intervention or coronary artery bypass graft surgery.

The target vessel is not currently a candidate for intervention or a likely candidate for intervention over the next 18 months.

The target vessel may not be a bypass graft.

The target vessel may not be a bypassed vessel.

The target vessel may not be the culprit vessel for a previous MI.

Subjects already taking a statin at the time of the initial screening LDL-C assessment must be on a stable dose of statin therapy for at least 4 weeks prior to the initial screening LDL-C assessment.

Fasting LDL-C as determined by local laboratory both at the initial screening visit (a local LDL-C level may be used for the initial screening LDL-C level as long as it was drawn within 4 weeks of screening visit) and if applicable at the end of the lipid stabilization period:

LDL-C ≥ 80 mg/dL (2.07 mmol/L)

OR

LDL-C ≥ 60 -<80 mg/dL (1.55-2.07 mmol/L) in the presence of one Major or three Minor Risk factors. Enrollment of subjects with LDL-C between ≥ 60 mg/dL (1.55 mmol/L) and < 80 mg/dL (2.07 mmol/L) will be limited to no more than approximately 25% of total planned enrollment.

Major Risk Factors (one required)

1) Non-coronary atherosclerotic vascular disease as evidenced by one of the following: documented peripheral arterial disease (PAD), documented abdominal aortic aneurysm (AAA), or documented cerebrovascular disease (CD).

   - Documented peripheral arterial disease (one of the following primary criteria must be satisfied):
     - Current intermittent claudication (WHO criteria, eg, leg pain occurring only while walking and disappearing in less than 10 minutes on standing) of presumed atherosclerotic origin TOGETHER WITH ankle-brachial index equal to or less than 0.9 in either leg at rest.

     - History of intermittent claudication (WHO criteria as above) TOGETHER WITH either previous intervention by amputation, or reconstructive vascular surgery, or
angioplasty in one or both legs because of atherosclerotic disease within the last 2 years.

- Documented abdominal aortic aneurysm,
  - AAA is considered to be present when the minimum anteroposterior diameter of the aorta reaches 3.0 cm. The size of the aorta can be measured in any plane that is perpendicular to the vessel axis.

- Documented cerebrovascular disease (e.g. carotid artery disease or prior history of stroke or transient ischemic attack occurring within the last 2 years).
  - Stroke: ischemic stroke is defined as an infarction of central nervous system tissue not secondary to underlying congenital or valvular heart disease. Symptomatic ischemic strokes are manifest by clinical signs of focal or global cerebral, spinal, or retinal dysfunction caused by central nervous system infarction. A silent stroke is a documented central nervous system infarction that was asymptomatic.
  - Transient ischemic attack (TIA): a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction, not secondary to underlying congenital or valvular heart disease.
  - Carotid artery disease: defined as stenosis > 50% or PSV > 125 cm with plaque

2) Documented history of myocardial infarction or hospitalization for unstable angina within the last two years
3) Documented Type 2 diabetes mellitus

Minor Risk Factors (three required)
- Cigarette smoking current
- Hypertension (BP ≥ 140/90 mm Hg or current use of antihypertensive medication)
- Low HDL cholesterol - men < 40 mg/dL (1.03 mmol/L) ; women < 50 mg/dl(1.29 mmol/L)
- Family history of premature CHD (in first-degree male relative < 55 years of age; in first-degree female relative < 65 years of age
- age (men ≥ 50 years; women ≥ 55 years)
- hs-CRP ≥ 2 mg/L

With:

4.1.1 Subject has provided informed consent.
4.1.2 Male or female ≥ 18 age at screening
4.1.3 Clinical indication for coronary angiography.
4.1.4 Subjects already taking statin therapy, regulatory-approved sustained-release niacin (eg Niaspan®) or ezetimibe at initial
screening must have been on a stable dose for at least 4 weeks prior
to the lipid panel used for the screening LDL-C. Subjects not
currently taking lipid-regulating therapy can be screened but must
enter the study via a lipid stabilization period.

OR

4.1.5 Subjects who are intolerant to statins (limited to no more than
approximately 10% of total planned enrollment) must meet statin
intolerance entry criteria in Appendix G.

4.1.6 Subjects must have at least one eligible LDL-C level (as defined
below) via local, central laboratory or point of care device at the
initial screening visit and, if applicable, at the end of each lipid
stabilization period. A pre-existing local LDL-C level may be used as
the initial screening LDL-C value as long as it was drawn within
4 weeks of the screening visit and no interim changes to lipid-
regulating therapy have occurred during that 4 week period.

LDL-C ≥ 80 mg/dL (2.07 mmol/L) with or without additional risk factors

OR

LDL-C ≥ 60 - <80 mg/dL (1.55-2.07 mmol/L) in the presence of one Major
or three Minor Risk factors as defined below. Enrollment of subjects
with LDL-C between ≥ 60 mg/dL (1.55 mmol/L) and < 80 mg/dL
(2.07 mmol/L) will be limited to no more than approximately 25% of total
planned enrollment.

Major Risk Factors (one required)

1) Non-coronary atherosclerotic vascular disease as evidenced by one
of the following: documented peripheral arterial disease (PAD),
documented abdominal aortic aneurysm (AAA), or documented
cerebrovascular disease (CD).

- Documented peripheral arterial disease (one of the following
primary criteria must be satisfied):
  - Current intermittent claudication (WHO criteria, eg, leg pain
occurring only while walking and disappearing in less than
10 minutes on standing) of presumed atherosclerotic origin
TOGETHER WITH ankle-brachial index equal to or less
than 0.9 in either leg at rest.

  - History of intermittent claudication (WHO criteria as above)
TOGETHER WITH either previous intervention by
amputation, or reconstructive vascular surgery, or
angioplasty in one or both legs because of atherosclerotic
disease within the last 2 years.

- Documented abdominal aortic aneurysm,
  - AAA is considered to be present when the minimum
anteroposterior diameter of the aorta reaches 3.0 cm. The
size of the aorta can be measured in any plane that is
perpendicular to the vessel axis.
- Documented cerebrovascular disease (eg. carotid artery disease or prior history of stroke or transient ischemic attack occurring within the last 2 years).
  - Stroke: ischemic stroke is defined as an infarction of central nervous system tissue not secondary to underlying congenital or valvular heart disease. Symptomatic ischemic strokes are manifest by clinical signs of focal or global cerebral, spinal, or retinal dysfunction caused by central nervous system infarction. A silent stroke is a documented central nervous system infarction that was asymptomatic.
  - Transient ischemic attack (TIA): a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction, not secondary to underlying congenital or valvular heart disease.
  - Carotid artery disease: defined as stenosis > 50% or PSV > 125 cm/sec with plaque
  2) Documented history of myocardial infarction or hospitalization for unstable angina within the last two years
  3) Documented Type 2 diabetes mellitus

**Minor Risk Factors (three required)**

a. **Current cigarette smoker**

b. Hypertension (*One documented blood pressure* (BP) ≥ 140/90 mm Hg or current use of antihypertensive medication)

c. Low HDL cholesterol - men < 40 mg/dL (1.03 mmol/L) ; women < 50 mg/dl (1.29 mmol/L)

d. Family history of premature CHD (in first-degree male relative < 55 years of age; in first-degree female relative < 65 years of age

e. age (men ≥ 50 years; women ≥ 55 years)

f. hs-CRP ≥ 2 mg/dL

Subjects must meet all of the following criteria at the qualifying coronary catheterization procedure:

A. Entire Coronary Circulation:

- Angiographic evidence of coronary heart disease as defined by at least one lesion in any of the three major native coronary arteries that has > 20% reduction in lumen diameter by angiographic visual estimation or prior history of **percutaneous coronary intervention** (PCI).

- This vessel need not be the target coronary artery for IVUS.

- Any vessel with previous PCI may not be used as the target coronary artery.

B. Left Main Coronary Artery:

- Must not have a > 50% reduction in lumen diameter by visual angiographic estimation.

C. Target Coronary Artery for IVUS:
Must be accessible to the IVUS catheter.

- Must not have a >50% reduction in lumen diameter by angiographic visual estimation within the target segment, the target segment being at least 40 mm in length.
- A lesion, distal to the target segment, of up to 60% stenosis is permitted, provided that the stenosis is not a target for PCI or CAGB.
- A single branch of the “target vessel” may have a narrowing of <70% by visual estimation, provided that the branch in question is not a target for PCI or CAGB.
- Has not undergone prior percutaneous coronary intervention or coronary artery bypass graft surgery.
- The target vessel is not currently a candidate for intervention or a likely candidate for intervention over the next 18 months.
- The target vessel may not be a bypass graft.
- The target vessel may not be a bypassed vessel.
- The target vessel may not be the culprit vessel for a previous MI

Section: 4.2 Exclusion Criteria

Replace:

4.2.1 Clinically significant heart disease which in the opinion of the Principal Investigator is likely to require coronary bypass surgery, PCI, cardiac transplantation, surgical valve repair and/or replacement during the course of the study.

With:

4.2.1 Clinically significant heart disease which in the opinion of the Principal Investigator is likely to require coronary bypass surgery, PCI (does not apply to PCI deemed necessary by the initial screening angiogram), cardiac transplantation, surgical or percutaneous valve repair and/or replacement during the course of the study.

Replace:

4.2.6 Uncontrolled hypertension at Randomization visit, defined as a resting systolic blood pressure of ≥ 180mmHg

With:

4.2.6 Uncontrolled hypertension at randomization, defined as a systolic blood pressure of ≥ 180mmHg at rest

Delete:

4.2.8 and at end of lipid stabilization period

Replace:

4.2.9 Subject has taken a cholesterol ester transfer protein (CETP) inhibitor in the last 12 months prior to LDL-C screening, such as: anacetrapib, dalcetrapib or evacetrapib.

With:
4.2.9 Subject has taken a cholesterol ester transfer protein (CETP) inhibitor, (ie anacetrapib, dalcetrapib, evacetrapib) or mipomersen or lomitapide in the last 12 months prior to LDL-C screening.

Add:

4.2.11 For more than 2 weeks
(e.g. IV, intramuscular [IM], or PO) (Note: hormone replacement therapy is permitted); systemic vitamin A and retinol derivatives for the treatment of dermatologic conditions (e.g., Accutane) (Note: vitamin A in topical and multivitamin preparations are permitted)

Replace:

4.2.12 Hyperthyroidism or hypothyroidism as defined by thyroid stimulating hormone TSH below the lower limit of normal (LLN) or > 1.5 times the upper limit of normal (ULN), respectively, at screening

With:

4.2.12 Thyroid stimulating hormone (TSH) < lower limit of normal (LLN) or TSH > 1.5x upper limit of normal (ULN). A subject taking thyroid replacement therapy may be enrolled with TSH level below LLN if, in the opinion of the investigator, the subject is in a clinically euthyroid state.

Replace:

4.2.14 2 times

With:

4.2.14 3 times

Replace:

4.2.20 Female subject who is not willing to use at least 1 highly effective method of birth control during treatment and for an additional 15 weeks after the end of treatment unless subject is sterilized or postmenopausal;

- Menopause is defined as 12 months of spontaneous and continuous amenorrhea in a female ≥ 55 years old or 12 months of spontaneous and continuous amenorrhea with a follicle-stimulating hormone (FSH) level > 40 IU/L (or according to the definition of "postmenopausal range" for the laboratory involved) in a female < 55 years old unless the subject has undergone bilateral oophorectomy

- Highly effective methods of birth control include abstinence, birth control pills, shots, implants, or patches, intrauterine devices (IUDs), sexual activity with a male partner who has had a vasectomy, condom or occlusive cap (diaphragm or cervical/vault caps) used with spermicide.

With:

4.2.20 Female subject who has not used an acceptable method(s) of birth control for at least 1 month prior to screening, unless the female subject is sterilized or postmenopausal (see below)
4.2.21 Add:

Female subject is not willing to inform her partner of her participation in this clinical study and to use an acceptable method(s) of birth control during treatment with IP (AMG 145 or placebo) and for an additional 15 weeks after the end of treatment with IP (AMG 145 or placebo) unless the female subject is sterilized or postmenopausal (see below)

- **A female is considered of childbearing potential unless sterilized or postmenopausal** with menopause defined as:
  - 12 months of spontaneous and continuous amenorrhea in a female ≥ 55 years old or 12 months of spontaneous and continuous amenorrhea with a follicle-stimulating hormone (FSH) level > 40 IU/L (or according to the definition of "postmenopausal range" for the laboratory involved) in a female < 55 years old unless the subject has undergone bilateral oophorectomy.

- **Acceptable methods of preventing pregnancy** include sexual abstinence, surgical contraceptive methods (vasectomy or bilateral tubal ligation), use of hormonal birth control methods (pills, shots, implants or patches), intrauterine devices (IUDs), or two (2) barrier methods (each partner must use one barrier method) with spermicide – males must use a condom with spermicide; females must choose either a Diaphragm with spermicide, OR Cervical cap with spermicide, OR Contraceptive sponge with spermicide.

*Note: Additional medications given during the screening period, lipid stabilization period and during treatment with IP (AMG 145 or placebo) 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 after the last dose of protocol-required therapies. The investigator is to discuss these contraceptive changes with the study subject.*

4.2.22 Add: planning to become pregnant, or planning to breastfeed during the screening period, at the end of the lipid stabilization period (if applicable), while receiving treatment with IP (AMG 145 or placebo) and within 15 weeks after the end of treatment with IP (AMG 145 or placebo)

4.2.24 Add: (eg carboxymethylcellulose)

**Section: 5.1 Randomization**

Replace:

- 420 mg Q4W SC at 3.0 mL via 3 autoinjectors
- Placebo, Q4W SC at 3.0 mL via 3 autoinjectors

With:

- AMG 145 420 mg QM SC via aat 3.5 mL Personal Injector or 3.0 mL via 3 prefilled autoinjectors
- Placebo, QM SC via a 3.5 mL Personal Injector or 3.0 mL via 3 prefilled autoinjectors
Section: 6.1 AMG 145

Replace:

AMG 145 and placebo will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical IP distribution procedures. AMG 145 will be presented as a sterile, preservative-free solution in a single use, disposable, handheld mechanical (spring-based) prefilled autoinjector/pen (Al/Pen) for fixed dose, subcutaneous injection. The prefilled Al/Pen contains a 1.0 mL deliverable volume of 140 mg/mL AMG 145 in 220 mM proline, 20 mM acetate, 0.01% (w/v) polysorbate 80, pH 5.0. Placebo will be presented in an identical prefilled Al/Pen containing a 1.0 mL deliverable volume of 1.1% (w/v) sodium carboxymethylcellulose, 250 mM proline, 10 mM acetate, and 0.01% (w/v) polysorbate 80, pH 5.0.

AMG 145 and placebo should be stored refrigerated and protected from light according to the storage and expiration information provided on the label (where required). AMG 145 should be handled per the instructions provided in the IPIM and the Instructions for Use (IFU) for the prefilled Al/Pen.

The prefilled Al/Pen should be inspected for IP quality, expiry, and damage before using. Damaged, expired, or degraded product should not be used and any issues with the prefilled Al/Pen should be reported to Amgen. Further details are provided in the IPIM and IFU.

With:

AMG 145 and placebo will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical IP distribution procedures. AMG 145 will be presented as a sterile, preservative-free solution in a single use, disposable, handheld mechanical (spring-based) 1.0 ml prefilled autoinjector/pen (Al/Pen) or 3.5 mL Personal Injector (Personal Injector) for fixed dose, subcutaneous injection. The prefilled Al/Pen contains a 1.0 mL deliverable volume of 140 mg/mL AMG 145 in 220 mM proline, 20 mM acetate, 0.01% (w/v) polysorbate 80, pH 5.0. The Personal Injector with prefilled cartridge assembly is a single-use, disposable, on-body electro-mechanical injection device that is co-packaged with a prefilled Crystal Zenith (CZ) cartridge assembly containing 3.5 mL deliverable volume of 120 mg/mL AMG 145 in 220 mM proline, 20 mM acetate, 0.01% (w/v) polysorbate 80, pH 5.0. The 3.5 mL Personal Injector will only be made available for use in this study once it has been determined that the intended user population for AMG 145 can safely and effectively use the device in clinical trials under the guidance of the study investigators. Respective placebo will be presented in an identical prefilled Al/Pen containing a 1.0 mL deliverable volume of 1.1% (w/v) sodium carboxymethylcellulose, 250 mM proline, 10 mM acetate, and 0.01% (w/v) polysorbate 80, pH 5.0 or in an identical Personal Injector containing a 3.5 mL deliverable volume of 0.7% (w/v) sodium carboxymethylcellulose, 250 mM proline, 10 mM acetate, and 0.01% (w/v) polysorbate 80, pH 5.0.

AMG 145 and placebo should be stored refrigerated and protected from light according to the storage and expiration information provided on the label (where required). AMG 145 should be handled per the instructions provided in the IPIM and the Instructions for Use (IFU) for the prefilled Al/Pen or Personal Injector.

The prefilled Al/Pen or Personal Injector should be inspected for IP quality, expiry, and damage before using. Damaged, expired, or degraded product should not be used and any issues with the prefilled Al/Pen or Personal Injector should be reported to Amgen. Further details are provided in the IPIM and IFU.
Section: 6.1.1 Dosage, Administration, and Schedule

Replace:

IP will be administered SC at the investigator site during scheduled visits either by self-administration or by a qualified staff member and at home monthly by subjects between visits in accordance with instructions in the IPIM. For subjects that prefer not to self-administer IP, IP may be administered at the site.

IP administration at each on-site visit must be done after vital signs, ECG, and blood draw procedures, if applicable. The date, time, and volume of IP withdrawn from the vial and injected will be recorded on the individual subject’s worksheet and/or eCRF. After IP administration at each dosing visit, subjects will be kept for observation for at least 30 minutes before being discharged.

Self-administration, defined as SC administration of IP by the patient or designee, will occur monthly between visits (eg, at home). The patient (or designee) must have demonstrated competency at administration of SC injections before self-administration is permitted: the first two self-administered doses must be administered in a clinic by the patient or designee under the supervision of a healthcare provider.

IP will be administered with a total volume of 3.0 mL Q4W, via 3 separate autoinjections. Injection sites should be rotated throughout the study. The SC injections should be administered in a consecutive fashion with all injections completed within 30 minutes. For further details regarding the injection procedures, the IPIM should be consulted.

Details of preparing and administering all study products are included in the IPIM provided by Amgen prior to the start of the study.

With:

IP will be administered at the investigator site during scheduled visits via self-administration or by a qualified staff member. **Between scheduled visits to the site, IP will be administered** at home or other locations by subjects (or designee, which may include a qualified health care professional) in accordance with instructions in the IPIM. **Subjects who prefer not to self-administer IP may return to the study site for administration by qualified site personnel.**

IP administration at each on-site visit must be done after vital signs, ECG, and blood draw procedures, if applicable. The date, time, and **volume of AMG 145 administered will be collected and recorded on the individual subject’s eCRF for doses administered at the study site.** During the first 2 IP administrations (day 1 and week 4), subjects will be instructed and supervised in the use of the prefilled AI/Pen or Personal Injector and, after administration of IP, will be kept for **observation** for at least 30 minutes before being discharged.

Self-administration, defined as SC administration of IP by the patient or designee, will occur on a monthly basis between visits to the investigator site (eg, at home). The patient (or designee) must have demonstrated competency at administration of SC injections before self-administration is permitted: the first two self-administered doses must be administered in a clinic by the patient or designee under the supervision of a healthcare provider.

IP will be administered with a total volume of 3.0 mL **QM**, via 3 separate autoinjections **or with a total volume of 3.5 mL QM via 1 administration by a Personal Injector.** Injection sites should be rotated throughout the study. The **autoinjector** SC injections should be administered in a consecutive fashion with all injections completed within 30 minutes.
Section: 6.1.2 Dosage Adjustments

Replace:

There will be no dose adjustments in this study. If, in the opinion of the investigator, a subject is unable to tolerate a specific dose of placebo or AMG 145 and requires dosage adjustment, that subject will discontinue IP but will continue to return for all other study procedures and measurements until the end of the study.

Subjects Who are Late for a Scheduled Dose of Investigational Product

If a subject is late for administration of IP, administration should occur as soon as possible. A Q4W dose of IP should not be administered within less than 7 days of a previous dose. If a subject arrives for a visit and IP was administered within less than 7 days prior the dose should not be administered but all other study procedures should be conducted and administration of IP should occur as soon as possible at least 7 days after the previous administration.

Subjects Who Miss a Scheduled Dose of Investigational Product Completely

Subjects who completely miss a dose of SC IP will continue in the study and administer the next dose of IP per their schedule of administration.

Subjects Who Miss a Scheduled Dose of Statin

Subjects who miss a dose of background statin will be advised to take the missed dose as soon as they can; subsequent doses will be taken at the usual time. However, if the next scheduled dose would be due in less than 6 hours, the subject will be advised to omit the missed dose entirely and to take the next dose at the normal time.

If stopping or altering atorvastatin dosing is medically warranted during the trial, the subject should continue to receive IP, except as defined in section 6.1.3.1. These situations should be discussed with the Amgen medical monitor as soon as possible. In addition, if a medical decision is made to withhold IP during the study, subjects should continue to receive atorvastatin background therapy. The medical monitor should be contacted prior to stopping IP.

With:

There will be no IP dose adjustments in this study. If, in the opinion of the investigator, a subject is unable to tolerate investigational product and requires dosage adjustment, that subject will discontinue IP but will continue to return for all other study procedures and measurements until the end of the study.

Subjects Who are Late for a Scheduled Dose of Investigational Product

If a subject is late for administration of IP, administration should occur as soon as possible. A QM dose of IP should not be administered within less than 7 days of a previous dose. If a subject arrives for a visit and IP was administered within less than 7 days prior the dose should not be administered but all other study procedures should be conducted and administration of IP should occur as soon as possible at least 7 days after the previous administration.

Subjects Who Miss a Scheduled Dose of Investigational Product Completely

Subjects who completely miss a dose of SC IP will continue in the study and administer the next dose of IP per their schedule of administration.
Subjects Who Miss a Scheduled Dose of Statin

Subjects who miss a dose of background statin will be advised to take the missed dose as soon as they can; subsequent doses will be taken at the usual time. However, if the next scheduled dose would be due in less than 6 hours, the subject will be advised to omit the missed dose entirely and to take the next dose at the normal time.

If stopping or altering statin (or allowable non-statin therapy) dosing is medically warranted during the trial, the subject should continue to receive IP, except as defined in section 6.2.1 These situations should be discussed with the Amgen medical monitor as soon as possible. In addition, if a medical decision is made to withhold IP during the study, subjects should continue to receive statin (and allowable non-statin) background therapy except as defined in section 6.2.1. The medical monitor should be contacted prior to stopping IP.

Add new

Section: 6.2 Background lipid-lowering therapy

Considering the patient population enrolled in GLAGOV, subjects must receive optimized lipid-lowering therapy during the study. Lipid therapy should remain unchanged for the duration of study participation (up to 18 months); local guidelines should be taken into consideration when determining optimal levels of treatment. All subjects should receive effective statin therapy with a minimum dose of atorvastatin 20 mg daily or equivalent unless they meet criteria for statin intolerance (4.1.5). Subjects with LDL-C > 100 mg/dL should receive highly effective statin therapy with atorvastatin ≥ 40 mg daily or equivalent (see Appendix E). If not receiving atorvastatin ≥ 40 mg or equivalent, the investigator must attest that higher dose statin therapy has been considered but is not appropriate for this subject (eg, dose not tolerated, dose not available in that country, other significant concern).

Subjects who receive atorvastatin during the study can elect to have it provided by the sponsor at doses of 20 mg, 40 mg, or 80 mg. Other statins and other doses of atorvastatin will not be provided by the sponsor.

If making any changes to this therapy after randomization, the reason for the change must be provided in the eCRF and the Amgen medical monitor or designee should be consulted before making the change, if possible.

Subjects taking niacin, regulatory-approved sustained-release niacin (eg Niaspan®) or ezetimibe therapy at initial screening should remain unchanged for the duration of study participation (up to 18 months).

Subjects taking study-provided atorvastatin should continue the drug until their week 78 visit. Similarly, subjects taking non-study provided statins and allowable non-statin therapies should continue such treatment until week 78. Beyond the week 78 assessment, use of statins and other lipid regulating therapies will be at the discretion of the investigator.

Section: 6.2.1 Criteria for Withholding of Investigational Product

Replace:

Reports from the central laboratory after each visit must be reviewed as soon as possible after receipt and before the next administration of IP, irrespective of whether the next dose is to occur at the site or via self-administration at home. If any of the criteria below are met for withholding IP or atorvastatin, the subject
must be instructed to stop treatment and an additional visit must be scheduled for the required laboratory evaluations.

With:

Reports from the central laboratory after each visit must be reviewed as soon as possible after receipt and before the next administration of IP. If any of the criteria below are met for withholding IP, statin, or other applicable background lipid therapy, the subject must be instructed to stop the applicable treatment and an additional visit must be scheduled for the required laboratory evaluations. If a subject is experiencing elevations of laboratory values and is receiving other lipid therapies that may result in such elevations, eg, ezetimibe, or niacin, the additional therapies should also be evaluated for a potential role in these elevations and considered for discontinuation. Ezetimibe or niacin can result in elevation of CK or liver function tests.

Section: 6.2.1.1 Elevation of Creatine Kinase (CK)

Replace:

If CK is > 5x ULN, CK must be retested before atorvastatin and IP are administered. In addition, investigators will ask study subjects to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever. If such symptoms occur and no scheduled study laboratory assessments are performed, the subject’s CK levels should be measured by unscheduled assessment. If the subject’s CK level on retesting is > 5x ULN to ≤ 10x ULN, the investigator will be required to discontinue atorvastatin administration. If the subject’s CK level on retesting is >10x ULN, the investigator will be required to stop both atorvastatin and IP.

The following rules apply for scheduled laboratory assessments and for unscheduled CK measurements:

<table>
<thead>
<tr>
<th>CK at scheduled or unscheduled visit</th>
<th>CK on retest</th>
<th>Investigational Product and/or Atorvastatin Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 5x ULN</td>
<td>&gt; 10x ULN</td>
<td>Discontinue both atorvastatin and IP⁸. Contact Amgen Medical Monitor</td>
</tr>
<tr>
<td>&gt; 5x to ≤ 10x ULN</td>
<td>&gt; 5x ULN</td>
<td>Discontinue atorvastatin and retest CK before IP administration. Consider continuing IP if alternative explanation</td>
</tr>
<tr>
<td>≤ 5x ULN</td>
<td>≤ 5x ULN</td>
<td>Consider continuing atorvastatin and IP⁸</td>
</tr>
</tbody>
</table>

⁸ CK elevations >10x ULN that have been confirmed to be secondary to myocardial infarction do not require discontinuation of atorvastatin or of IP

With:

If CK is > 5x ULN, CK must be retested before statins and IP are administered. In addition, investigators will ask study subjects to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever. If such symptoms occur and no scheduled study laboratory assessments are performed, the subject’s CK levels should be measured by unscheduled assessment. If CK is > 5x ULN, the subject must be instructed as soon as possible to discontinue statin,, other applicable
lipid-regulating background therapy, and/or IP (AMG 145). CK must be retested before statin, other lipid background therapy, and/or IP (AMG 145) administration can be continued. A sample for urinalysis must be collected and sent to the central laboratory if CK is elevated > 10x ULN on retest as per table below.

The following rules apply for scheduled laboratory assessments and for unscheduled CK measurements:

<table>
<thead>
<tr>
<th>CK at scheduled or unscheduled visit</th>
<th>CK on retest</th>
<th>Investigational Product and/or Statin and/or other lipid lowering therapy Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 10x ULN</td>
<td>Discontinue statin, other lipid lowering therapies, and IP. Collect urine sample for urinalysis. Contact Amgen Medical Monitor</td>
</tr>
<tr>
<td>&gt; 5x ULN</td>
<td>&gt; 5x to ≤ 10x ULN</td>
<td>Discontinue statin, other lipid lowering therapies, and retest CK before IP administration. Consider continuing IP if alternative explanation</td>
</tr>
<tr>
<td></td>
<td>≤ 5x ULN</td>
<td>Consider continuing statin, other lipid lowering therapies, and IP</td>
</tr>
</tbody>
</table>

* CK elevations >10x ULN that have been confirmed to be secondary to myocardial infarction do not require discontinuation statin, other lipid lowering therapies or IP.

If muscular symptoms are severe and cause daily discomfort, even if the CK levels are elevated to ≤ 5x ULN, reduction of dose, discontinuation of allowed lipid-regulating therapy, or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.

Section: 6.2.1.2 Elevation of Liver Function Tests

Replace:

Subjects with abnormal hepatic laboratory values (eg, alkaline phosphatase [ALP], AST, ALT, total bilirubin [TBL] or international normalized ratio [INR]) or signs/symptoms of hepatitis may meet the criteria for withholding of IP and atorvastatin. If the subject experiences an ALT or AST > 3X ULN, then they must be followed as detailed under section on close observation in Appendix B.

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

- TBL > 2x ULN or INR > 1.5 (testing determined per Appendix B) AND
- AST or ALT > 3x ULN AND
- no other cause for the combination of laboratory abnormalities is immediately apparent; important potential causes for abnormal AST/ALT or TBL values include, but are not limited to:
  - Obstructive gall bladder or bile duct disease
Viral or alcoholic hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, etc)

Progression of malignancy involving the liver (note that metastatic disease to the liver, by itself, should not be used as an explanation for significant AST/ALT elevations)

Hypoxic or ischemic hepatopathy or congestive hepatopathy in association with significant right sided heart failure

Concomitant administration of other hepatotoxins, including drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir, irinotecan) or herbal or dietary supplements

Heritable disorders causing impaired glucuronidation (eg, Gilbert’s Syndrome); alpha-one antitrypsin deficiency

Autoimmune hepatitis

Nonalcoholic steatohepatitis (NASH) or other “fatty liver disease”

IP should also be withheld and the subject should be evaluated for DILI if ANY of the following criteria are met:

- AST or ALT > 8x ULN at any time
- AST or ALT > 5x ULN but < 8x ULN for ≥ 2 weeks
- TBL > 3x ULN at any time
- ALP > 8x ULN at any time
- Clinical signs or symptoms that are, in the opinion of the investigator, consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice, rash or eosinophilia > 5%). If such signs or symptoms are coupled with ALT or AST elevations > 3x ULN, IP should be withheld.

If IP is withheld due to any of the conditions above, the subject should be followed according to recommendations in Appendix B for possible DILI

With:

Subjects with abnormal hepatic laboratory values (eg, alkaline phosphatase [ALP], AST, ALT, total bilirubin [TBL]) or signs/symptoms of hepatitis may meet the criteria for withholding of IP, statin, and other applicable lipid-regulating background therapy. If the subject experiences an ALT or AST > 3X ULN, then they must be followed as detailed under section on close observation in Appendix B.

IP, statin, and other applicable lipid-regulating background therapy must be discontinued and the subject should be followed according to the recommendations in Appendix B (Additional Safety Assessment Information) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:

- TBL > 2X ULN or INR > 1.5 (testing determined per Appendix B)

AND

- AST or ALT > 3X ULN

AND

- no other cause for the combination of laboratory abnormalities is immediately apparent; important potential causes for abnormal AST/ALT or TBL values include, but are not limited to:
Obstructive gall bladder or bile duct disease
Viral or alcoholic hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, etc)
Progression of malignancy involving the liver (note that metastatic disease to the liver, by itself, should not be used as an explanation for significant AST/ALT elevations)
Hypoxic or ischemic hepatopathy or congestive hepatopathy in association with significant right sided heart failure
Concomitant administration of other hepatotoxins, including drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir, irinotecan) or herbal or dietary supplements
Heritable disorders causing impaired glucuronidation (eg, Gilbert’s Syndrome);
alpha-one antitrypsin deficiency
Autoimmune hepatitis
Nonalcoholic steatohepatitis (NASH) or other “fatty liver disease”

IP, statin, and other applicable lipid-regulating background therapy should also be withheld and the subject should be evaluated for DILI if ANY of the following criteria are met:

- AST or ALT > 8x ULN at any time
- AST or ALT > 5x ULN but < 8x ULN for ≥ 2 weeks
- TBL > 3x ULN at any time
- ALP > 8x ULN at any time
- Clinical signs or symptoms that are, in the opinion of the investigator, consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice, rash or eosinophilia > 5%). If such signs or symptoms are coupled with ALT or AST elevations > 3x ULN, IP should be withheld.

If IP, statin and other applicable lipid-regulating background therapy are withheld due to any of the conditions above, the subject should be followed according to recommendations in Appendix B for possible DILI.

Add new
Section: 6.2.2 Criteria for Rechallenge After Withholding or Discontinuation of IP (AMG 145 or Placebo) Statin and Other Applicable Lipid-regulating Background Therapy

The decision to rechallenge the subject after therapy changes due to CK elevation or elevation of liver function tests should be discussed and agreed unanimously upon by the subject, investigator, and Amgen.

If signs or symptoms recur with rechallenge of IP, then IP should be permanently discontinued. If signs or symptoms recur with rechallenge of statin background therapy, the statin may be substituted by another statin in consultation with the Amgen medical monitor, if possible, or the statin therapy should be discontinued. If signs or symptoms recur with rechallenge of other applicable lipid-regulating background therapy, this therapy should be discontinued.
Section: 6.3 Product Complaints, including Device Complaints
Add: or personal injector after Al/Pen

Section: 6.4 Concomitant therapy, physical exercise, and diet
Add:

statin and other allowed lipid-regulating therapies
combined docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)
, any other allowed lipid-regulating therapies

Section: 6.5 Prohibited treatments during study period
Replace:

- Prescription lipid-regulating medications other than protocol-assigned atorvastatin, such as ezetimibe, fibrates and derivatives, and bile-acid sequestering resins

With:

- Prescription lipid-regulating medications other than protocol-approved statins, regulatory-approved, sustained-release niacin (eg Niaspan®) and ezetimibe such as fibrates and derivatives and bile-acid sequestering resins

Section: 6.6 Non-recommended Treatments During Study Period
Replace:

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

Drugs or foods that are known potent inhibitors of CYP3A (Itraconazole, ketoconazole, and other antifungal azoles, macrolide antibiotics erythromycin, clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors, antidepressant nefazodone and grapefruit juice in large quantities [> 1 quart (0.95 liters)daily]) should not be used during the study. Should there be a clinical need to prescribe one of these treatments, the investigator should call the Amgen Medical Monitor to discuss

With:

The treatments in Appendix F are not recommended because of their potential impact on metabolism of specific statins.

If a subject is enrolled and subsequently requires a treatment that is not recommended based on their particular statin (eg, a strong cytochrome P450 3A4 inhibitor in a patient on atorvastatin), the treating physician should give consideration to using an equivalent concomitant drug, eg, a drug that does not inhibit cytochrome P450 3A4 so that the subject can continue taking statin background therapy. If this is not possible, it may be necessary to withdraw or change statin background therapy while the concomitant drug is required.

There is no need to discontinue treatment with IP should a subject require a non-recommended drug, eg, a strong cytochrome P450 3A4 inhibitor since
monoclonal antibody therapeutics are not metabolised through cytochrome P450 and, thus, are unaffected by the use of cytochrome P450 inhibitors.

Section: 7.1.1 Screening and Placebo Run-in Injection

Replace:

Written informed consent must be obtained before protocol specific procedures are carried out. Subjects who satisfy all available inclusion and exclusion criteria should have the IVUS performed immediately following the qualifying angiography. Subjects who require a PCI as a result of the qualifying angiography will have baseline IVUS performed immediately following the PCI. Any intervention to the proposed target IVUS vessel will exclude this vessel from being used as the target IVUS vessel. Delayed or staged IVUS procedures must be performed within 4 weeks after qualifying angiography.

The accuracy and reproducibility of the IVUS endpoints of the study are dependent upon Investigator’s commitment to rigorous image acquisition techniques. The IVUS Core Laboratory at the Cleveland Clinic will provide a separate IVUS guidance document to all participating sites. Adherence to these guidelines will ensure low observer variability and high quantitative.

Investigators may only utilize the Boston Scientific iLAB™ ultrasound system in conjunction with an Atlantis™ SR series 40 MHz imaging catheter or the Volcano S5™ ultrasound imaging system in conjunction with the Revolution™ 45 MHz imaging catheter. For each patient all imaging conditions performed at the baseline imaging time point must be duplicated at the follow-up time point utilizing the same IVUS system either Boston Scientific iLab or the Volcano S5. The Boston Scientific and Volcano ultrasound systems cannot be interchanged between the baseline and follow-up time points. All baseline angiographic studies must be forwarded to the IVUS Core Laboratory at the Cleveland Clinic for informational review. IVUS imaging must be reviewed and approved by the IVUS Core Laboratory before subjects return for randomization visit.

Subjects will be assessed for inclusion and exclusion criteria and medical and medication history will be obtained. The following data will be obtained and procedures performed during screening:

- Written informed consent
- IVUS
- Medical history
- Vital signs (see Section 7.1.3.1): sitting blood pressure (BP), heart rate (HR)
- Review for AEs/SAEs (SAEs and study-related AEs are collected after signing informed consent)
- Concomitant therapy
- Blood draw for fasting lipids and glucose (≥ 9 hour fasting sample), ApoA1, ApoB, Lp(a), chemistry, hematology, PCSK9, HbA1c, TSH, serum pregnancy (females of childbearing potential only) and FSH (only if required to ensure menopause in a female subject [see exclusion criteria]) by local laboratory. A central laboratory may be used if a local laboratory is not available.
- Blood draws for hepatitis C virus (HCV) antibodies in high risk subjects or subjects with AST or ALT > 2x ULN at any time during screening*
• The subject will be instructed in the NCEP ATP TLC-type diet and lifestyle regimen (example, http://www.nhlbi.nih.gov/health/public/heart/index.htm#chol). The subject will also be counseled on the importance of maintaining good compliance with current lipid lowering medications

• Subjects will receive a placebo administration with three 1.0 ml SC injections with the AI pen to confirm tolerance of SC administration prior to randomization. In order to reduce the burden of unnecessary procedures on subjects who subsequently elect not to participate in the study or continue with study procedures. During this time the subject will receive instruction/training on AI/Pen use

*Please note that subjects with ALT or AST > 2x ULN must be screen failed unless the elevation is transient as confirmed by retesting per Section 7.1.1.2. High risk subjects are defined in Section 7.1.3.6.

With:

Written informed consent must be obtained before protocol-specific procedures are carried out. In order to minimize the chances of performing unnecessary IVUS procedures, investigators should ensure that subjects’ initial screening LDL-C results are available prior to performing the baseline IVUS examination. Thereafter, subjects will undergo clinically-indicated coronary angiography for further clinical evaluation. If angiographic criteria for IVUS are met, the subject will have baseline IVUS completed. Subjects who require a PCI deemed necessary by the qualifying angiography will have baseline IVUS performed immediately following the PCI. Any intervention to the proposed target IVUS vessel will exclude this vessel from being used as the target IVUS vessel. Delayed or staged IVUS procedures must be performed within 4 weeks after qualifying angiography. For subjects who undergo delayed or staged interventions, the baseline IVUS must be performed after the final planned intervention.

The accuracy and reproducibility of the IVUS endpoints of the study are dependent upon Investigator’s commitment to rigorous image acquisition techniques. The IVUS Core Laboratory at the Cleveland Clinic will provide a separate IVUS guidance document to all participating sites. Adherence to these guidelines will ensure low observer variability and high quantitative.

Investigators may only utilize the Boston Scientific iLAB™ultrasound system in conjunction with an Atlantis™ SR series 40 MHz imaging catheter OR the Volcano S5™ ultrasound imaging system in conjunction with the Revolution™ 45 MHz imaging catheter. For each patient all imaging conditions performed at the baseline imaging time point must be duplicated at the follow-up time point utilizing the same IVUS system either Boston Scientific iLab or the Volcano S5. The Boston Scientific and Volcano ultrasound systems cannot be interchanged between the baseline and follow-up time points. All baseline angiographic studies must be forwarded to the IVUS Core Laboratory at the Cleveland Clinic for informational review. IVUS imaging must be reviewed and approved by the IVUS Core Laboratory before subjects return for randomization visit.

Subjects will be assessed for inclusion and exclusion criteria and medical and medication history will be obtained. The following data will be obtained and procedures performed during screening:

• Written informed consent
• Angiogram
• IVUS
• Medical history
• **Physical exam**
  • Vital signs (see Section 7.1.3.1): sitting blood pressure (BP), heart rate (HR)
  • Review for AEs/SAEs (SAEs and study-related AEs are collected after signing informed consent)
  • Concomitant therapy
    12-lead ECG in triplicate using centralized ECG services equipment
  • Blood draw for fasting lipids and glucose (≥ 9 hour fasting sample), chemistry, hematology, HbA1c, TSH, eGFR, serum pregnancy (females of childbearing potential only) and FSH (only if required to ensure menopause in a female subject [see exclusion criteria]) by local laboratory. The central laboratory may be used if a local laboratory is not available.
  • **Central** blood draws for hepatitis C virus (HCV) antibodies in high risk subjects or subjects with AST or ALT > 2x ULN at any time during screening*
  • The subject will be instructed in the NCEP ATP III/TLC-type diet and lifestyle regimen (example, http://www.nhlbi.nih.gov/public/heart/index.htm#chol). The subject will also be counseled on the importance of maintaining good compliance with current lipid lowering medications
  • Subjects will receive a placebo administration with three 1.0 ml SC injections with the prefilled AI pen to confirm tolerance of SC administration prior to randomization. In order to reduce the burden of unnecessary procedures on subjects who subsequently elect not to participate in the study or continue with study procedures. During this time the subject will receive instruction/training on AI/Pen use

*Please note that subjects with ALT or AST > 2x ULN must be screen failed unless the elevation is transient as confirmed by retesting per Section 7.1.1.2. High risk subjects are defined in Section 7.1.3.6

**Section: 7.1.1.1 Enrollment and Lipid Stabilization Period**

Replace:

Subjects who complete the screening and placebo run-in procedures and who meet the inclusion/exclusion criteria will be enrolled and enter the lipid stabilization period (if applicable). During this period investigators will assign subjects to 20 mg, 40 mg or 80 mg of atorvastatin background therapy. Subjects must be titrated to an optimal dose within one month and with a maximum of one upitation step, which will occur at week 2 (if necessary). Subjects on a stable (ie, at least 4 weeks), optimal dose of atorvastatin and at their LDL-C goal at the **time of** initial screening visit can forgo the lipid stabilization period. Ensuring stable individualized LDL-C levels will be required as physicians will be blinded to LDL-C values after randomization and no changes to lipid medications will be allowed during the trial.

At the end of each 2 week stabilization period, the following data will be obtained and procedures performed during screening:

• Review for AEs/SAEs
• Blood draw for fasting lipids, chemistry and serum pregnancy (females of childbearing potential only) by central laboratory
Local laboratory LDL-C will be evaluated for eligibility and if applicable, for titration of background therapy.

Subjects who do not tolerate atorvastatin during the lipid stabilization period must not be randomized. **Rather, they should be early-terminated and perform the above end of lipid stabilization procedures.** If a fasting sample for a laboratory qualification LDL-C could not be obtained after the lipid stabilization period and the other screening laboratory assessments confirm eligibility for the study, an additional fasting lipid sample to determine eligibility must be obtained before the planned day 1 (randomization) visit. It is recommended to schedule collection of this fasting lipid sample as quickly as possible.

With:

Subjects who complete the screening procedures and who meet the inclusion/exclusion criteria will be enrolled and enter the lipid stabilization period (if applicable). **At a minimum, subjects must receive an effective statin dose of at least atorvastatin 20 mg daily or equivalent (see Appendix E) titrated to achieve target LDL-C (change or goal) as defined by regional guidelines.** Where locally approved, highly effective statin therapy, defined as at least atorvastatin 40 mg daily or equivalent (see Appendix E), is recommended. For subjects with LDL-C > 100 mg/dL (2.6 mmol/L) and not receiving highly effective statin therapy (atorvastatin ≥ 40 mg daily or equivalent), the investigator must attest that higher dose statin therapy is not appropriate for this subject (eg, dose not tolerated, dose not available in that country, other significant concern). Subjects who, in the investigator’s opinion, are already at LDL-C goal at initial screening and are on stable (≥ 4 weeks) and acceptable lipid lowering therapy (per Appendix E) during screening, with no changes planned or expected for the duration of the study will be enrolled directly, skip the lipid stabilization period, and, if eligible, randomized. Subjects requiring any change to their lipid therapy will be enrolled and then enter a two to four week lipid stabilization period. During this period subjects must be titrated to an optimal statin dose within one month and with a maximum of one uptitration step, which will occur at week 2 (if necessary). Ensuring stable individualized LDL-C levels will be required as physicians will be blinded to LDL-C values at randomization and no changes to lipid medications will be allowed during the trial except for clinically-compelling reasons.

At the end of each 2 week lipid stabilization period, the following data will be obtained and procedures performed during screening:

- Review for AEs/SAEs
- Blood draw for fasting lipids, chemistry (CK, AST and ALT) and serum pregnancy (females of childbearing potential only). **The central laboratory may be used if a local laboratory is not available.**
  
  LDL-C will be evaluated for eligibility and if applicable, for titration of background therapy.

Subjects who do not tolerate a statin or **do not qualify for any other reason** during the lipid stabilization period must not be randomized, **unless they meet statin intolerant inclusion criteria 4.1.5 and 4.1.6.** Rather, they should be early-terminated and labs for pregnancy, CK and LFT should be collected. If a fasting sample for a laboratory qualification LDL-C could not be obtained after the lipid stabilization period and the other screening laboratory assessments confirm eligibility for the study, an additional fasting
lipid sample to determine eligibility must be obtained before the planned day 1 (randomization) visit. It is recommended to schedule collection of this fasting lipid sample as quickly as possible.

Section: 7.1.2 Treatment Period

Replace:

Subjects must be fasting for ≥ 9 hours before each study visit. If the subject is not fasting for the scheduled study randomization visit, no visit procedures are performed. The subject must return as soon as possible in a fasting state for study randomization visit procedures. If the subject is not fasting for any visit after randomization, all visit procedures, including investigational product administration, should be completed except for the fasting lipid blood sample. Please make sure to schedule an extra visit for the fasting sample collection as soon as possible and if possible, within the window for the respective visit.

Final IVUS assessment and angiography will be performed at Week 78.

It is critical that the follow-up IVUS be obtained in subjects, regardless of whether or not they discontinued study drug prematurely.

Any subjects who require cardiac catheterization for clinically indicated reasons at Week 52 or later must have IVUS examination of the target vessel performed at that time. The Week 78 IVUS will not be required for these subjects. Those subjects will be considered to have completed the study and will have all end of study assessments performed at that time.

If PCI to either the target or non-target vessel is indicated prior to Week 52, the IVUS should not be performed for these subjects. An IVUS performed prior to week 52 will not be accepted as the final study IVUS. Subjects should remain on study drug and complete all required visits.

With:

Subjects must be fasting for ≥ 9 hours before each study visit. If the subject is not fasting for the scheduled study randomization visit, no visit procedures are performed. The subject must return as soon as possible in a fasting state for study randomization visit procedures. If the subject is not fasting for any visit after randomization, all visit procedures, including investigational product administration, should be completed except for the fasting lipid blood sample. Please make sure to schedule an extra visit for the fasting sample collection as soon as possible and if possible, within the window for the respective visit.

Final IVUS assessment and angiography will be performed at Week 78.

It is critical that the follow-up IVUS be obtained in subjects, regardless of whether or not they discontinued study drug prematurely.

Any subjects who require cardiac catheterization for clinically indicated reasons at Week 52 or later must have IVUS examination of the target vessel performed at that time. The Week 78 IVUS will not be required for these subjects. **If PCI of a non-target vessel is required, subjects will undergo the final IVUS after PCI is completed. If PCI of the target vessel is required, the final IVUS should be completed prior to PCI if clinically appropriate.** These subjects will continue IP and all study visits with the exception of the Week 78 IVUS.

For subjects requiring coronary angiography prior to Week 52, the final IVUS examination should not be performed in these subjects at this time. An IVUS performed prior to week 52 will not be accepted as the final study IVUS. Subjects will remain on study drug and complete all required visits, including the second
IVUS examination at week 78. However, subjects requiring PCI to the IVUS target vessel prior to Week 52 will not undergo a final IVUS examination. These subjects will continue IP and all study visits with the exception of the Week 78 IVUS. If PCI to the a non-target vessel is indicated prior to Week 52, the follow up IVUS should not be performed at this time. These subjects will remain on study drug and complete all required visits, including the second IVUS examination at week 78.

Section: 7.1.2.1 Day 1 Visit (Randomization)

Replace:

Subjects that tolerate the placebo injection, complete the screening procedures successfully, and who satisfy the inclusion/exclusion criteria will visit the study site for randomization, and initiate their first dose of IP. The first administration of IP should be on the day of randomization, if not, it should be no later than within 5 calendar days after randomization.

The following data will be obtained and procedures performed for the day 1 visit:

- Vital signs (sitting BP, HR)
- Review of concomitant therapy.
- Review for AEs/SAEs/ CV events
- Body height
- Body weight
- Waist circumference
- 12-lead ECG in triplicate using centralized ECG services equipment
- Encourage subject to maintain a stable diet
- Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, chemistry, HbA1c, hematology, PK (AMG 145) PCSK9, hsCRP, Lp(a), biomarkers, anti-AMG 145 antibodies, fasting Vitamin E and glucose, viral load in subjects positive for HCV, and pharmacogenetic studies\(^a\) (if subject consented to pharmacogenetic analyses)
- Urine sample for urinalysis
- Retraining on AI/Pen use
- Administer IP to all subjects (must be after completion of vital signs, ECG, and blood draw procedures)

With:

Subjects that tolerate the placebo injection, complete the screening procedures successfully, satisfy the inclusion/exclusion criteria, have a negative pregnancy test (if applicable), do not have active liver disease or hepatic dysfunction (defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) < 3 times the ULN), and have a CK ≤ 3 times ULN at the end of the lipid stabilization period, will visit the study site for randomization, and initiate their first dose of IP. The first administration of IP should be on the day of randomization, if not, it should be no later than within 5 calendar days after randomization.

The following data will be obtained and procedures performed for the day 1 visit:

- Vital signs (sitting BP, HR)
• Review of concomitant therapy.
• Review for AEs/SAEs/ CV events
• Body height
• Body weight
• Waist circumference
• 12-lead ECG in triplicate using centralized ECG services equipment
• Encourage subject to maintain a stable diet
• Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, chemistry, HbA1c, hematology, PK (AMG 145) PCSK9, hsCRP, Lp(a), biomarkers, anti-AMG 145 antibodies, fasting Vitamin E and glucose, viral load in subjects positive for HCV, and pharmacogenetic studies (if subject consented to pharmacogenetic analyses)
• Urine sample for urinalysis
• Retraining on AI/Pen or Personal Injector use
• Administer IP to all subjects (must be after completion of vital signs, ECG, and blood draw procedures)

Section: 7.1.2.2 – 7.1.2.7
Add:
Or Personal Injector after AI/Pens
Section: 7.1.2.2 – 7.1.2.7
Add:
Angiogram
Section: 7.1.3.4 Lipid Measurement
Add:
Either central or
Section: 9.1.2 Reporting Procedures for Adverse Events
Replace:
All adverse events (see Section 9.2) are reported after signing of the informed consent. The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after signing of the inform consent through the EOS are reported using the applicable eCRF (eg, Adverse Event Summary eCRF), including events that are also reported to the CEC for adjudication.

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,
• Severity [and/or toxicity per protocol],
• Assessment of relatedness to IP
• Assessment of relatedness to the device (prefilled Al/Pen), and

• Assessment of relatedness to study procedure

• Action taken.

The adverse event toxicity grading scale used will be the NCI Common Terminology Criteria for AEs (CTCAE) grading score. The toxicity grading scale used in this study is described in Appendix B.

The investigator must assess whether the adverse event is possibly related to IP and/or other study drugs. 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 IP and/or other study drugs? The investigator must assess whether the adverse event is possibly related to the prefilled Al/Pen used to administer IP. The 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 device?

The investigator must assess whether the adverse event, if reported during screening (serious adverse events or study-related adverse events only), is possibly related to any study-mandated screening procedure. This relationship is indicated by a “yes” or “no” response to the question: “Is there a reasonable possibility that the event may be related to screening procedures?”

The investigator must assess whether the adverse event is possibly related to any other 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 must assess whether the adverse event is possibly related to the device (auto-injector) used to administer IP. The 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 device?

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) should not 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) should be recorded as the adverse event.

The investigator’s clinical judgment is used to determine whether a subject is to be removed from treatment or from the study due to an adverse event. A subject, or subject’s parent/legal guardian, can also voluntarily withdraw from treatment due to an adverse event. If the subject withdraws full consent, the subject is encouraged to undergo, at a minimum, an end of study assessment.

Adverse events considered related to IP or any Amgen-provided protocol-required product or device will be followed until resolved, improved to baseline, or stabilized.

With:

All adverse events (see Section 9.2) are reported after signing of the informed consent. The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent
through the EOS are reported using the applicable eCRF (eg, Adverse Event Summary eCRF), including events that are also reported to the CEC for adjudication.

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 (AMG 145 or placebo)
- Assessment of relatedness to other protocol-required therapies
- Assessment of relatedness to the device (prefilled Al/Pen or Personal Injector), and
- Assessment of relatedness to study procedure, and
- Action taken.

The adverse event toxicity grading scale used will be the NCI Common Terminology Criteria for AEs (CTCAE) grading score. The toxicity grading scale used in this study is described in Appendix B

The investigator must assess whether the adverse event is possibly related to IP (AMG 145 or placebo) and/or other protocol-required therapies (eg. study-mandated statin background therapy). 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 IP and/or other protocol-required therapies?

The investigator must assess whether the adverse event is possibly related to the prefilled Al/Pen or Personal Injector device used to administer IP (AMG 145 or placebo). The 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 device?

The investigator must assess whether the adverse event is possibly related to any other 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 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) should not 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) should be recorded as the adverse event.

The investigator’s clinical judgment is used to determine whether a subject is to be removed from treatment or from the study due to an adverse event. A subject, or subject’s parent/legal guardian, can also voluntarily withdraw from treatment due to an adverse event. If the subject withdraws full consent, the subject is encouraged to undergo, at a minimum, an end of study assessment. Refer to section 8.1 for
additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

The investigator is expected to follow reported adverse events, any Amgen-provided protocol-required product or device until resolved, improved to baseline, or stabilized.

Section: 9.2.2 Reporting Procedures for Serious Adverse Events

Add:

After the protocol-required reporting period defined above, the investigator does not need to actively monitor subjects for serious adverse events. However, if the investigator becomes aware of a serious adverse event after this protocol-required reporting period, the investigator will report the event 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.

The investigator must assess whether the serious adverse event is possibly related to IP (AMG 145 or placebo). 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 IP?

The investigator must assess whether the serious adverse event is possibly related to the prefilled Al/Pen or Personal Injector used to administer IP. The 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 device?

The investigator must assess whether the serious adverse event is possibly related to study-mandated statin background therapy. 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 study-mandated statin background therapy”?

The investigator must assess whether the serious adverse event is possibly related to any other 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 resolved, improved to baseline, or stabilized.

Section: 9.3 Pregnancy and Lactation Reporting

Replace:

The pregnancy, contraception and breastfeeding instructions provided in this protocol and in its informed consent form apply only to the Amgen product(s) administered for this study. It is the responsibility of the Investigator to provide pregnancy, contraception and breastfeeding guidance for any non-Amgen medicinal product(s) associated with this study, based on the respective product label(s).

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 monitor for pregnancies that occur after the last dose of protocol-required therapies through an additional 15 weeks.

The pregnancy should be reported to Amgen’s global Pregnancy Surveillance Program within 7 business days of the site receiving notification of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix D). The Pregnancy Surveillance Program (PSP) will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

If a lactation case occurs while a 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 monitor for lactation cases that occur after the last dose of protocol-required therapies through an additional 15 weeks.

Any lactation case should be reported to Amgen’s global Lactation Surveillance Program (LSP) within 7 business days of the site receiving notification on the Lactation Notification Worksheet (Appendix D).

With:

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 monitor for pregnancies that occur after the last dose of protocol-required therapies through 15 weeks after the end of treatment with IP.

The pregnancy should be reported to Amgen’s global Pregnancy Surveillance Program within 24 hours of the investigator’s knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix D). The Pregnancy Surveillance Program (PSP) will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

If a lactation case occurs while a female subject is taking protocol-required therapies, and for an additional 15 weeks after the end of treatment with IP, report the lactation case to Amgen as specified below.

Any lactation case should be reported to Amgen’s global Lactation Surveillance Program (LSP) within 24 hours of the investigator’s knowledge of the event. Report a lactation case on the Lactation Notification Worksheet (Appendix D).

Section: 10.1.2 Secondary Efficacy Endpoints

Replace:

The secondary endpoints are listed in the following sequential order to reflect the multiplicity adjustment method stated in Section 10.5.1

- Percentage of subjects demonstrating regression (any reduction from baseline) in PAV
- Nominal change in normalized TAV from baseline to 78 weeks
- Percentage of subjects demonstrating regression (any reduction from baseline) in TAV
With:

The secondary endpoints are listed in the following sequential order to reflect the multiplicity adjustment method stated in Section 10.5.1

- Nominal change in total atheroma volume (TAV) from baseline to week 78
- Regression (any reduction from baseline) in PAV
- Regression (any reduction from baseline) in TAV

Section: 10.2 Sample Size Considerations

Replace:

The planned total sample size is 950 subjects (475 randomized to AMG 145 420 mg Q4W and 475 randomized to placebo Q4W). This sample size will provide sufficient power to determine whether there is a treatment effect of AMG 145 relative to placebo in the primary endpoint.

The assumptions in the sample size calculation are based on a latest published IVUS study (reference: NEJM 2011, The study of coronary atheroma by intravascular ultrasound: Effect of rosuvastatin versus atorvastatin (SATURN)). The SATURN study indicates that every 1 mg/dL reduction in LDL-C is estimated to be associated with change of 0.03026 in PAV at week 104. For this study, the assumed treatment effect is change of at least change of 0.706 in PAV at week 78, which is approximated from an expected treatment effect of > 31 mg/dL reduction in LDL-C from baseline to week 78. The assumed common standard deviation (SD) is 2.9.

With:

The planned total sample size is 950 subjects (475 randomized to AMG 145 420 mg QM and 475 randomized to placebo QM). This sample size will provide sufficient power to determine whether there is a treatment effect of AMG 145 relative to placebo in the primary endpoint.

The assumptions in the sample size calculation are based on the study of coronary atheroma by intravascular ultrasound: effect of rosuvastatin versus atorvastatin (SATURN) (Nicholls, 2011). The SATURN study indicates that every 1 mg/dL reduction in LDL-C is estimated to be associated with change of 0.03026 in PAV at week 104. For this study, the assumed treatment effect is change of at least change of 0.706 in PAV at week 78, which is approximated from an expected treatment effect of > 31 mg/dL reduction in LDL-C from baseline to week 78. The assumed common standard deviation (SD) is 2.9.

Section: 10.5.2 Analysis of Primary Efficacy Endpoint

Add: QM

References

Add:


Appendix A: SOA

Replace:

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Footnotes defined on next page
a At the end of the 2 week lipid stabilization period the subject will be assessed for early termination, up titration or randomization. Subjects with qualifying LDL-C levels who are on stable doses of atorvastatin per the investigators discretion will not be required to undergo lipid stabilization

b D1 = day of first administration of IP

c AEs/SAEs collected from the time of informed consent

d Concomitant therapy collected in all subjects entering lipid stabilization period

e IVUS imaging needs to be approved by the Core Lab before a subject can be randomized

f PK samples must be taken prior to IP administration, if applicable. Screening samples will be analyzed only for PCSK9 and not for AMG 145 (PK). Samples from subjects receiving placebo will be analyzed for PCSK9 but will not be assayed for AMG 145 (PK).

g At the end of each 2 week lipid stabilization period a blood draw for LDL-C, chemistry and serum pregnancy (females of childbearing potential only) is required. These laboratory results apply to relevant exclusion criteria

h If the subject consented to pharmacogenetics analyses, DNA will be extracted from some of the blood samples, eg, biomarker samples

i HCV antibodies only in high risk subjects (see Section 7.1.3.6) or if ALT or AST > 2x ULN at any time during screening; viral load only in subjects positive for HCV

j FSH = in applicable subjects for study entry only – see exclusion criteria

k Last IP will be given at week 76. IP must be administered after vital signs, ECG, and blood sampling procedures

l Local labs may be used for fasting lipids, chemistry, hematology, fasting glucose/HbA1c, TSH, and assessing eGFR during screening. In addition, at the end of the lipid stabilization period, local labs may be used to assess both fasting lipids and chemistry. Starting on Day 1 all labs will be analyzed via the central laboratory only.

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**Investigational Product**

- **Placebo run-in**: X
- **Observe IP administration at clinic**: X

Footnotes defined on next page
At the end of the initial 2 week lipid stabilization period the subject will be assessed for early termination, up titration or randomization. Subjects with qualifying LDL-C levels (a local LDL-C level drawn within 4 weeks of screening visit may be used for the initial screening value) who are on stable doses of a statin per the investigators discretion will not be required to undergo lipid stabilization.

\[D1 = \text{day of first administration of IP}\]

AEs/SAEs collected from the time of informed consent

Concomitant therapy collected in all subjects entering lipid stabilization period

IVUS imaging needs to be approved by the Core Lab before a subject can be randomized

At the end of each 2 week lipid stabilization period a blood draw for LDL-C, chemistry (CK, AST and ALT only) and serum pregnancy (females of childbearing potential only) is required. These laboratory results apply to relevant exclusion criteria.

If the subject consented to pharmacogenetics analyses, DNA will be extracted from some of the blood samples, eg, biomarker samples

HCV antibodies only in high risk subjects (see Section 7.1.3.6) or if ALT or AST > 2x ULN at any time during screening; viral load only in subjects positive for HCV

FSH = in applicable subjects for study entry only – see exclusion criteria

Last IP will be given at week 76. IP must be administered after vital signs, ECG, and blood sampling procedures

Local labs may be used for fasting lipids, chemistry, hematology, fasting glucose/HbA1c, TSH, and assessing eGFR during screening. In addition, at the end of the lipid stabilization period, local labs may be used to assess both fasting lipids and chemistry. Starting on Day 1 all labs will be analyzed via the central laboratory only.
Add Appendices E, F and G:

**Appendix E: Acceptable Statin Lipid Lowering Background Therapy**

Background lipid lowering therapy should be optimized for the individual subject consistent with local professional society guidelines. At randomization, all subjects that tolerate statins must receive at least an effective statin dose, i.e., at least atorvastatin 20 mg daily or equivalent. Where locally approved, highly effective statin therapy, defined as at least atorvastatin 40 mg daily or equivalent, is recommended. For subjects with LDL-C > 100 mg/dL (> 2.6 mmol/L) and not receiving highly effective statin therapy (atorvastatin ≥ 40 mg daily or equivalent), the investigator must attest that higher dose statin therapy is not appropriate for this subject (e.g., dose not tolerated, dose not available in that country, other significant concern).

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For subjects enrolled with LDL-C > 100 mg/dL, confirmation is required that the selected dose of statin therapy was optimized and is appropriate for the duration of the study. Highly effective therapy includes atorvastatin 40 mg or 80 mg, rosuvastatin 10 mg, 20 mg or 40 mg, and simvastatin 80 mg monotherapy.

Use of simvastatin 80 mg was associated with myopathy and is not commonly recommended for use. Simvastatin 80 mg is not available in all countries participating in this study. Approval of simvastatin 80 mg by the local regulatory authority is required for patients using simvastatin 80 mg in this study.

No other lipid therapy is required for the GLAGOV trial. Statins other than atorvastatin, are not provided or reimbursed by Amgen (except if required by local regulation). Background statin therapy received at randomization and other approved lipid lowering background therapies (niacin and/or ezetimibe, if applicable) should remain unchanged throughout the entire duration of the study (up to approximately 18 months).
Appendix F: Drugs With Known Major Interactions with Statin Background Therapy

Atorvastatin:

- strong Cyp3A4 inhibitors (eg, Itraconazole, ketoconazole, and other antifungal azoles, erythromycin, clarithromycin, telithromycin, HIV or HCV protease inhibitors, systemic cyclosporine nefazodone and grapefruit juice in large quantities [> 1 quart or approximately 1 Liter daily])
- colchicine

Simvastatin:

- strong Cyp3A4 inhibitors (eg, Itraconazole, ketoconazole, and other antifungal azoles, erythromycin, clarithromycin, telithromycin, HIV or HCV protease inhibitors, systemic cyclosporine nefazodone and grapefruit juice in large quantities [> 1 quart or approximately 1 Liter daily])
- verapamil
- diltiazem
- danazol
- colchicine
- if simvastatin dose > 20 mg
  - amlodipine
  - amiodarone
  - ranolazine

Rosuvastatin:

- systemic cyclosporine
- and if rosuvastatin > 10 mg, HIV or HCV protease inhibitors

Pravastatin:

- colchicine
- if pravastatin dose > 40 mg:
  - clarithromycin
- if pravastatin dose > 20 mg:
  - systemic cyclosporine

Lovastatin:
- strong Cyp3A4 inhibitors (e.g., Itraconazole, ketoconazole, and other antifungal azoles, erythromycin, clarithromycin, telithromycin, HIV or HCV protease inhibitors, systemic cyclosporine, nefazodone and grapefruit juice in large quantities (> 1 quart or approximately 1 Liter daily))
- colchicine
- ranolazine
- if lovastatin dose > 40 mg:
  - amiodarone
- if lovastatin dose > 20 mg:
  - verapamil
  - diltiazem
  - danazol

Pitavastatin:
- systemic cyclosporine
- combination protease inhibitor therapy with lopinavir and ritonavir
- erythromycin
- rifampin
Appendix G: Statin Intolerance Criteria

4.1.5 Subjects who are intolerant to statins (limited to no more than approximately 10% of total planned enrollment) as evidenced by both of the following (per subject or physician report):

i. Tried at least 2 statins and was unable to tolerate any dose or increase statin dose above the total weekly maximum doses listed below due to intolerable myopathy, ie, myalgia (muscle pain, ache, or weakness without CK elevation), myositis (muscle symptoms with increased CK levels), or rhabdomyolysis (muscle symptoms with marked CK elevation)

ii. Symptoms resolved or improved when statin dose was decreased or discontinued

The following maximum total prescribed weekly dosages for statins are:

i. atorvastatin - 70 mg or less
ii. simvastatin - 140 mg or less
iii. pravastatin - 140 mg or less
iv. rosuvastatin - 35 mg or less
v. pitavastatin – 7 mg or less
vi. lovastatin - 140 mg or less
vii. fluvastatin - 280 mg or less