Supplemental Online Content 1


Study Protocol

This supplemental material has been provided by the authors to give readers additional information about their work.
Title: A Double-blind, Randomized, Multicenter Study to Evaluate the Safety and Efficacy of AMG 145, Compared With Ezetimibe, in Hypercholesterolemic Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor Due to Muscle Related Side Effects

AMG 145
Amgen Protocol Number 20120332
EudraCT No. 2013-000935-29

GAUSS-3

Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects

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Date:
Original Protocol Date: 11 July 2013
Superceding Original Protocol Date: 06 September 2013
Amendment 1 Date: 27 September 2013
Amendment 2 Date: 15 January 2014

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If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number: US sites, 1-800-77-AMGEN, Canadian sites, 1-866-50-AMGEN; <<for all other countries, insert the local toll-free Medical Information number>> Amgen’s general number in the US (1-805-447-1000).
Investigator’s Agreement

I have read the attached protocol entitled A Double-blind, Randomized, Multicenter Study to Evaluate the Safety and Efficacy of AMG 145, Compared With Ezetimibe, in Hypercholesterolemic Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor Due to Muscle Related Side Effects, dated 15 January 2014, and agree to abide by all provisions set forth therein. I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines.

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

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

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

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

________________________________________
Signature

________________________________________
Name of Investigator

________________________________________
Date (DD Month YYYY)
Protocol Synopsis

Title: A Double-blind, Randomized, Multicenter Study to Evaluate the Safety and Efficacy of AMG 145, Compared With Ezetimibe, in Hypercholesterolemic Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor Due to Muscle Related Side Effects

Study Phase: 3

Indication: Primary hyperlipidemia and mixed dyslipidemia

Primary Objective: To evaluate the effect of 24 weeks of AMG 145 administered subcutaneously (SC) every month (QM) compared with ezetimibe (Part B), on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in hypercholesterolemic subjects who are unable to tolerate an effective dose of a statin due to muscle related side effects (MRSE) as confirmed by a lead-in, double-blind, placebo-controlled, cross-over statin rechallenge (Part A).

Secondary Objective(s):
- To evaluate the safety and tolerability of SC AMG 145 QM, compared with ezetimibe, in hypercholesterolemic subjects unable to tolerate an effective dose of a statin
- To assess the effect of 24 weeks of SC AMG 145 QM, compared with ezetimibe, on change from baseline in LDL-C, and percent change from baseline in total cholesterol, non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, ApoB/Apolipoprotein A1 (ApoA1) ratio, lipoprotein(a) [Lp(a)], triglycerides, HDL-C, and VLDL-C in hypercholesterolemic subjects unable to tolerate an effective dose of a statin
- To assess the effect of 24 weeks SC AMG 145 QM, compared with ezetimibe, on percent of subjects attaining LDL-C < 70 mg/dL (1.81 mmol/L) in hypercholesterolemic subjects unable to tolerate an effective dose of a statin

Exploratory objectives:
To evaluate the incidence of MRSE elicited by a double-blind, placebo-controlled, cross-over atorvastatin rechallenge

Hypothesis: The primary hypothesis is that AMG 145 SC 420 mg QM will be well tolerated and will result in greater reduction of LDL-C than ezetimibe, defined by the mean percent change from baseline at Weeks 22 and 24 of Part B and percent change from baseline at Week 24 of Part B, in hypercholesterolemic subjects unable to tolerate an effective dose of a statin.

Co-Primary Endpoints:
- Mean percent change from baseline in LDL-C at Weeks 22 and 24 of Part B
- Percent change from baseline in LDL-C at Week 24 of Part B

Co-Secondary Efficacy Endpoints:
Co-secondary endpoints of the means at Weeks 22 and 24 and at Week 24 of Part B for:
- Tier 1
  - Change from baseline in LDL-C
  - LDL-C response (LDL-C < 70 mg/dL [1.81 mmol/L])
  - Percent change from baseline in total cholesterol
  - Percent change from baseline in non-HDL-C
  - Percent change from baseline in ApoB
  - Percent change from baseline in the total cholesterol/HDL-C ratio
  - Percent change from baseline in ApoB/ApoA1 ratio
Study Design: This is a phase 3, multicenter, randomized, double-blind, ezetimibe-controlled, parallel group study of AMG 145 in hypercholesterolemic subjects unable to tolerate an effective dose of a statin. There are three parts to this study: Part A is a double-blind, placebo-controlled, cross-over statin rechallenge to confirm presence of statin-related MRSE and is approximately 24 weeks in duration; Part B is a double blind, active controlled comparison of AMG 145 to ezetimibe and is 24 weeks in duration; Part C is a two-year open-label extension to evaluate the long-term safety and efficacy of AMG 145 in statin-intolerant subjects. Randomization will occur at two separate time points, prior to Part A and prior to Part B. During screening, potential subjects taking low dose statins or ezetimibe will discontinue these medications and allow for a minimum of 4-week washout period. Potential subjects will be given placebo subcutaneous injections (SC) administered via 3 prefilled autoinjector/pens (prefilled AI/pen). Randomization should occur within 5 - 10 days of the screening LDL-C evaluation used to determine eligibility. Any subject with a documented history of CK elevation > 10 x ULN accompanied by muscle symptoms while on statin therapy and documented resolution of both CK elevation and muscle symptoms upon discontinuation of statin therapy, must bypass the statin rechallenge Part A and be randomized directly into Part B. Eligible subjects who meet all inclusion/exclusion criteria will be randomized to Part A with an allocation ratio of 1:1 to atorvastatin or placebo.

Part A consists of two 10-week periods (Period 1 and Period 2) for cross-over statin rechallenge of subjects. In Period 1, subjects will be assigned to 20 mg atorvastatin or matched placebo taken by mouth (PO) every day (QD). At the end of Period 1 and a 2-week washout, subjects will cross-over to the alternate therapy (either atorvastatin or placebo for Period 2), during which time subjects will be treated for an additional 10 weeks. During either treatment period the subject will complete the 10 week course or will discontinue oral IP due to intolerable MRSE or MRSE that develop and persist for 2 weeks which in the opinion of the investigator will lead to discontinuation of IP. Upon completion of both Periods 1 and 2 in Part A of the study, subjects who report MRSE on atorvastatin and fail to develop MRSE on placebo will enter into a 2-week washout and advance to Part B. Subjects who do not develop MRSE on atorvastatin or develop MRSE on placebo will be removed from the study. As IP will be blinded during Part A, sites will report presence of MRSE using IVRS/IWRS. Sites and subjects will be informed if they meet criteria to advance to Part B (ie, presence of MRSE on statin and absence of MRSE on placebo) upon completion of Part A. During Part A, a CK elevation > 10 x ULN accompanied by muscle symptoms levels will be considered the equivalent of intolerable MRSE (ie, if occurring in Period 1 subject will cross-over to Period 2 and if occurring in Period 2 subject will complete Part A).

In Part B, the subjects will be randomized with an allocation ratio 2:1 into one of 2 treatment groups:

1) 420 mg AMG 145 SC QM and placebo PO QD, or
2) Placebo SC QM and 10 mg ezetimibe PO QD

Randomization in Part B in will be stratified by screening LDL-C level (< 180 mg/dL [4.66 mmol/L] vs ≥ 180 mg/dL) at study baseline. The following describes procedures and restrictions of Part B: 1) blinded IP (AMG 145 or placebo) will be administered at the study site using a prefilled autoinjector/pen (AI/Pen); 2) central laboratory results of the lipid panel, ApoA1, ApoB, lipoprotein(a), and high sensitivity C-reactive protein (hsCRP) will be blinded for the duration of the study and will not be reported to the investigator (unless specified); 3) investigators are not to perform non-protocol testing of these analytes until at least 12 weeks after last blinded IP.
administration, as drawing non-protocol labs could unblind treatment assignment. Investigators will be informed if triglycerides are > 1000 mg/dL (11.3 mmol/L) so that appropriate subject follow-up can be initiated. The last dose of blinded SC IP will be given at Week 20 of Part B for all subjects. Subjects will be encouraged to complete all planned visits regardless of their adherence to IP administration. Subjects who complete Part B and do not discontinue SC IP for any reason, including an adverse event, will be eligible to proceed to Part C, a two-year, open-label, extension phase during which all subjects will receive AMG 145. All subjects will be invited to consent to pharmacogenetic analyses. The study includes collection of biomarker samples where approved by the independent ethics committee and/or institutional review board (IEC/IRB), applicable regulatory, and other authorities. The study includes adjudication of deaths and major cardiovascular (CV) events by an independent Clinical Events Committee (CEC) and formal review of the accumulating data by an independent Data Monitoring Committee (DMC).

Sample Size: The number of subjects in Part A will fulfill the planned sample size of 100 subjects in Part B. It is estimated that in a double-blind, placebo-controlled statin rechallenge study that the estimated MRSE rate in this study is 20%. Thus, the expected number of subjects to be enrolled in Part A is 500. However, enrollment in Part A will continue until Part B target sample size is met or an administrative decision is made to stop the study. All subjects that complete Part B are eligible to participate in Part C. Approximately 80% to 100% of subjects will continue to Part C.

Summary of Subject Eligibility Criteria: Males and females, ≥ 18 to ≤ 80 years of age are eligible for this study. Subject must be unable to tolerate at least 3 statins (one of which must be at the lowest approved dose per day or less) or unable to tolerate 2 statins (one of which must be atorvastatin at a dose of 10 mg per day or less). Subject must be unable to tolerate any dose or increase statin dose at 10 mg average daily dose of atorvastatin or the doses listed in Section 4.1 due to due to skeletal muscle related symptoms (eg., pain, aches, weakness or cramping). Subjects must bypass the statin rechallenge Part A and advance directly into Part B if they have a documented history of CK elevation > 10 x ULN accompanied by muscle symptoms while on statin therapy and documented resolution of both CK elevation and muscle symptoms upon discontinuation of statin therapy.

Depending on a subject’s risk category (based on National Cholesterol Education Program Adult Treatment Panel [NCEP ATP III] treatment goals) subjects must meet the following fasting LDL-C (by central laboratory) criteria at screening: ≥ 100 mg/dL (2.59 mmol/L) for subjects with diagnosed coronary heart disease (CHD) or CHD risk equivalent; ≥ 130 mg/dL (3.37 mmol/L) for subjects without diagnosed CHD or risk equivalent and 2 or more risk factors; ≥ 160 mg/dL (4.14 mmol/L) for subjects without diagnosed CHD or risk equivalent and with 1 risk factor; ≥190 mg/dL (4.92 mmol/L) for subjects without diagnosed CHD or risk equivalent and with no risk factors. Fasting triglycerides must be ≤ 400 mg/dL (4.52 mmol/L) as determined by the central laboratory analysis at screening.

Major exclusions are personal or family history of hereditary muscular disorders, moderate to severe heart failure, uncontrolled cardiac arrhythmia, symptomatic coronary artery disease within the last 3 months, recently diagnosed or poorly controlled diabetes, hypertension or hyper/hypothyroidism, known active infection or major hematologic, renal, hepatic, metabolic, gastrointestinal or endocrine dysfunction, systemic steroid use, pregnancy or lactation, previous exposure to AMG 145 or other PCSK9 inhibitor.

For a full list of eligibility criteria, please refer to Section 4.1 and Section 4.1.2

Investigational Product

Amgen Investigational Product Dosage and Administration: AMG 145 and matched placebo will be administered SC using a spring-based prefilled Al/Pen or a Personal Injector. Each prefilled Al/Pen contains 1.0 mL of deliverable volume. Each Personal Injector contains 3.5 mL of deliverable volume.
AMG 145 and placebo will be administered in 2 regimens:

Part B — AMG 145/placebo 420 mg SC QM (3 prefilled Al/Pen injections)
Part C – AMG 145 420 mg SC QM (3 prefilled Al/Pen injections or 1 Personal Injector injection) or 140 mg SC every 2 weeks (Q2W) (1 prefilled Al/Pen injection)

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.

Amgen Non-investigational Product Dosage and Administration: None
Non-Amgen Investigational Product Dosage and Administration: In Part A, over-encapsulated atorvastatin 20 mg (and placebo) will be provided by Amgen (or designee) and will be taken by the subject PO QD. In Part B, over-encapsulated ezetimibe 10 mg (and placebo) will be provided by Amgen (or designee) and will be taken by the subject PO QD.

Control Group: Placebo (Part A) and over-encapsulated ezetimibe (Part B).

Procedures: There are three parts to this study: Part A is a double-blind, placebo-controlled cross-over statin rechallenge; Part B is a double-blind comparison of AMG 145 to ezetimibe; Part C is a two-year open-label extension to evaluate long-term safety and efficacy. Subjects being considered for participation and who have signed informed consent, will be assessed for inclusion and exclusion criteria. Medical and medication history will be obtained. During screening, all subjects will undergo an ECG and central labs including fasting lipids will be collected. Subjects who do not meet the LDL-C inclusion criterion must be screen-failed and cannot be rescreened for this study. If all inclusion and exclusion criteria are met, subjects should return to the study site within 5 – 10 days of LDL-C screening for randomization and first dose of Part A IP. Part A consists of two 10-week periods (Period 1 and Period 2) for cross-over statin rechallenge of subjects. Clinic visits will occur at Screening, Day 1, Week 4, Week 8, and Week 10 (Period 1), Week 12, Week 16, Week 20, and Week 22 (Period 2). Each period of Part A consists of two treatment groups: PO QD 20mg atorvastatin and PO QD placebo. Treatment groups will be assigned by IVRS/IWRS. In Period 1, subjects will be assigned to either PO QD 20 mg atorvastatin or matched PO QD placebo for either 10 weeks or until MRSE develop and persists for 2 weeks or are deemed intolerable (whichever occurs first). At the end of Period 1 and a 2-week washout, subjects will cross-over to either PO QD atorvastatin or PO QD placebo for Period 2 and subjects will be treated for either 10 weeks or until MRSE develop and persists for 2 weeks or are deemed intolerable (whichever occurs first). Upon completion of both Periods 1 and 2 in Part A of the study, subjects who report MRSE on atorvastatin and fail to report MRSE on placebo will enter into a 2-week washout and advance to Part B. Subjects who do not develop MRSE on atorvastatin or develop MRSE on placebo will be removed from the study. During Part A, a CK elevation > 10 x ULN accompanied by muscle symptoms will be considered the equivalent of intolerable MRSE (ie, if occurring in Period 1 subject will cross-over to Period 2 and if occurring in Period 2 subject will complete Part A). In Part B, subjects will be randomized 2:1 by IVRS/IWRS into one of two groups: QD administration of oral ezetimibe and SC placebo QM or PO and SC AMG 145 QM. Clinic visits will occur once a month until Week 24 of Part B. Subjects who discontinue IP for any reason during Parts B or C of the study will be asked to remain in the trial and conduct all study procedures with the exception of IP administration. Subjects, who complete Part B without permanently discontinuing IP will be eligible to participate in Part C, a two-year AMG 145 open-label extension. During Part C, subjects will be given the option to select their preferred dosing regimen. The available dosing regimens, which are considered equivalent doses, are AMG 145 140 mg SC Q2W or AMG 145 420 mg SC QM. Subjects will be allowed to switch between these dosing regimens every 3 months.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments.
Statistical Considerations:

General Considerations

Unless otherwise specified, the baseline value of Part B or C is defined as the subject’s baseline value from the Part A of the study. The safety analysis during the Part A of the study will be performed on the rechallenge analysis set (RAS) including all randomized subjects in Part A who received at least one dose of oral IP.

Efficacy and safety analyses will be performed on the full analysis set (FAS), which includes all randomized subjects in Part B who have received at least 1 dose of IP in Part B. The superiority of AMG 145 420 mg QM to ezetimibe will be assessed for all efficacy endpoints. Multiplicity adjustments will be applied for primary analyses of co-primary and co-secondary endpoints to control the overall family wise error rate at 0.05 in strong sense. Methods of adjusting for multiplicity due to multiple endpoints are provided in protocol Section 10.5.1.

The long-term analysis set (LAS) includes all enrolled subjects in Part C of the study who received at least 1 dose of IP in Part C. The long-term efficacy and safety analysis on LAS will be descriptive.

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 CEC. Subject incidence of exploratory endpoint events will be summarized for each treatment group.

Analyses of Co-Primary Endpoints

To assess the co-primary endpoints of the mean percent change in LDL-C from baseline at Weeks 22 and 24 of Part B and the percent change from baseline at Week 24 of Part B, a repeated measures linear effects model will be used to compare the efficacy of AMG 145 with ezetimibe. The repeated measures model will include terms for treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit.

Analyses of Co-Secondary Efficacy Endpoints

The statistical model for the co-secondary efficacy endpoints will be similar to the co-primary endpoints. However, the co-secondary efficacy endpoints of LDL-C response will be analyzed using the Cochran-Mantel Haenszel (CMH) test adjusted by the stratification factors.

Safety Analyses

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

Measurements of laboratory parameters 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 independent DMC will formally review the accumulating unblinded data from this and other ongoing studies with AMG 145 to ensure there is no increased risk for harm to subjects and will advise Amgen on study conduct. Analyses for the DMC will be provided by a group which is external to Amgen.

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

Sponsor: Amgen

Data Element Standards Version(s)/Date(s): DES 3.0/ 31 JAN 2013
Study Design and Treatment Schema

GAUSS-3 Schema – High Level

Part A  Part B  Part C
Up to 6-Months  6-Months  2-Year OLE

Subjects with documented history of CK elevation > 10 x ULN and muscle symptoms

Double-blind cross-over rechallenge

Pass

Safety & Efficacy vs. Ezetimibe

Long-term Safety, Tolerability & Efficacy

Fail
(Do not advance to Part B)

GAUSS-3 Schema - Detail

Part A  Part B  Part C
Period 1  Period 2

N ~ 500

Atorvastatin 20mg

20mg

Placebo

AMG 145 SC + Placebo PO

N = 100

Atorvastatin 20mg

20mg

Placebo

AMG 145 SC + Ezetimibe PO

2-Year OLE

AMG 145

- Part A: All subjects in Period 1 will cross-over to alternate therapy in Period 2
- Subjects must have presence of MRSE on atorvastatin and absence of MRSE on PBO to advance to Part B
- Part B cross-over occurs 2 weeks after onset of MRSE or immediately if MRSE is deemed intolerable (ie., subjects are not obligated to take Part A IP for 20 weeks)
- Subjects who complete Part B are eligible to enroll in a 2-year open-label extension of AMG 145
<table>
<thead>
<tr>
<th>Abbreviation or Term</th>
<th>Definition/Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADE</td>
<td>Adverse device effect</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>Al/Pen</td>
<td>Autoinjector/pen</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 A1</td>
</tr>
<tr>
<td>ApoB</td>
<td>Apolipoprotein B</td>
</tr>
<tr>
<td>AST (SGOT)</td>
<td>Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>BPI-SF</td>
<td>Brief Pain Inventory – Short Form</td>
</tr>
<tr>
<td>CABG</td>
<td>Coronary artery bypass graft</td>
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<tr>
<td>CAS</td>
<td>Completer analysis set</td>
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<td>CBC</td>
<td>Complete blood count</td>
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<td>CEC</td>
<td>Clinical events committee</td>
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<tr>
<td>CETP</td>
<td>Cholesterylester transfer protein</td>
</tr>
<tr>
<td>CHD</td>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>CK</td>
<td>Creatine kinase</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximal concentration</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CTCAE</td>
<td>NCI Common Terminology Criteria for AEs</td>
</tr>
<tr>
<td>CV</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>Day 1</td>
<td>defined as the first day that protocol-specified investigational product is administered to the subject at the beginning of each study part</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td>DHA</td>
<td>Docosahexaenoic acid</td>
</tr>
<tr>
<td>DILI</td>
<td>Drug-induced liver injury</td>
</tr>
<tr>
<td>DMC</td>
<td>Data monitoring committee</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>ECG Triplicate Measurement</td>
<td>Electrocardiogram that is performed in triplicate.</td>
</tr>
<tr>
<td>Abbreviation or Term</td>
<td>Definition/Explanation</td>
</tr>
<tr>
<td>----------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>PR interval</td>
<td>PR interval is measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by ECG.</td>
</tr>
<tr>
<td>QRS interval</td>
<td>QRS interval is the interval between the Q wave and the S wave in the heart's electrical cycle as measured by ECG; represents the time it takes for the depolarization of the ventricles.</td>
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<tr>
<td>QT interval</td>
<td>QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by ECG.</td>
</tr>
<tr>
<td>QTc interval</td>
<td>QT interval corrected for heart rate using accepted methodology.</td>
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<tr>
<td>RR interval</td>
<td>The time elapsed between two consecutive R waves as measured by ECG.</td>
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<tr>
<td>eCRF</td>
<td>Electronic case report form.</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate; eGFR will be calculated by the central laboratory and provided to the investigator.</td>
</tr>
<tr>
<td>End of study</td>
<td>The end of the study is defined as the last day on which a randomized subject completes the study or the day the subjects terminates the study early.</td>
</tr>
<tr>
<td>End of study for individual subject</td>
<td>Defined as the last day that protocol-specified procedures are conducted for an individual subject or the day the subject withdraws from study early.</td>
</tr>
<tr>
<td>End of treatment</td>
<td>Defined as the day a subject receives the last treatment with investigational product before the subject completes the study or ends the treatment early.</td>
</tr>
<tr>
<td>Enrollment</td>
<td>A subject is considered enrolled upon randomization.</td>
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<td>EOS</td>
<td>End of study (for individual subject).</td>
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<tr>
<td>EPA</td>
<td>Eicosapentaenoic acid.</td>
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<td>EU</td>
<td>European Union.</td>
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<td>FAS</td>
<td>Full analysis set.</td>
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<td>FSH</td>
<td>Follicle-stimulating hormone.</td>
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<td>GCP</td>
<td>Good Clinical Practice.</td>
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<tr>
<td>HbA1c</td>
<td>Hemoglobin A1c.</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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<tr>
<td>HepG2 cells</td>
<td>Human hepatocellular carcinoma cell line.</td>
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<tr>
<td>HR</td>
<td>Heart Rate.</td>
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<tr>
<td>hsCRP</td>
<td>High sensitivity CRP.</td>
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<tr>
<td>Abbreviation or Term</td>
<td>Definition/Explanation</td>
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<tr>
<td>----------------------</td>
<td>------------------------</td>
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<tr>
<td>IBG</td>
<td>Independent Biostatistical Group</td>
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<tr>
<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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<tr>
<td>IEC/IRB</td>
<td>Independent Ethics Committee / Institutional Review Board</td>
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<tr>
<td>IFU</td>
<td>Instructions for use</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</td>
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<tr>
<td>IPIM</td>
<td>Investigational Product Instruction Manual</td>
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<tr>
<td>IVRS/IWRS</td>
<td>Interactive Voice Response System / Interactive Web Response System</td>
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<tr>
<td>IV</td>
<td>Intravenous</td>
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<tr>
<td>LAS</td>
<td>Long-term analysis set</td>
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<td>LDH</td>
<td>Lactate dehydrogenase</td>
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<td>LDL-C</td>
<td>Low-density lipoprotein cholesterol</td>
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<tr>
<td>LDLR</td>
<td>LDL receptor</td>
</tr>
<tr>
<td>LLN</td>
<td>Lower limit of normal</td>
</tr>
<tr>
<td>LLOQ</td>
<td>Lower limit of quantitation</td>
</tr>
<tr>
<td>LOCF</td>
<td>Last observation carried forward</td>
</tr>
<tr>
<td>LOF</td>
<td>Loss of function</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>Lipoprotein(a)</td>
</tr>
<tr>
<td>MAS</td>
<td>Monotherapy analysis set</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical dictionary for regulatory activities</td>
</tr>
<tr>
<td>MRSE</td>
<td>Muscle-related side effects</td>
</tr>
<tr>
<td>Muscle Symptoms</td>
<td>Muscle pain, aches, weakness, cramps</td>
</tr>
<tr>
<td>NASH</td>
<td>Nonalcoholic steatohepatitis</td>
</tr>
<tr>
<td>NCEP ATP III</td>
<td>National Cholesterol Education Program Adult Treatment Panel III (see Grundy et al, 2004)</td>
</tr>
<tr>
<td>NOAEL</td>
<td>No-observed-adverse-effect level</td>
</tr>
<tr>
<td>OLE</td>
<td>Open Label Extension</td>
</tr>
<tr>
<td>Part A</td>
<td>Rechallenge portion of study</td>
</tr>
<tr>
<td>Part B</td>
<td>Efficacy portion of study</td>
</tr>
<tr>
<td>Part C</td>
<td>Open Label Extension portion of study</td>
</tr>
<tr>
<td>PBO</td>
<td>Placebo</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>Abbreviation or Term</td>
<td>Definition/Explanation</td>
</tr>
<tr>
<td>----------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>PKPD</td>
<td>Pharmacokinetic / pharmacodynamic</td>
</tr>
<tr>
<td>PO</td>
<td>Oral administration</td>
</tr>
<tr>
<td>Q2W</td>
<td>Q2W is defined as every 2 weeks with a window of ± 3 days for each visit</td>
</tr>
<tr>
<td>Q4W</td>
<td>Every 4 weeks, (AMG 145 Background Section)</td>
</tr>
<tr>
<td>QD</td>
<td>Each day</td>
</tr>
<tr>
<td>QM</td>
<td>QM is defined as every 4 weeks with a window of ± 7 days for each visit</td>
</tr>
<tr>
<td>QW</td>
<td>Every week</td>
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<tr>
<td>Randomized Assignment to treatment group based on computer-generated randomization schedules prepared by Amgen before the start of the study</td>
<td></td>
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<tr>
<td>RAS</td>
<td>Rechallenge Analysis Set</td>
</tr>
<tr>
<td>RBC</td>
<td>Red blood cells</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>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short Form (36) Health Survey</td>
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<tr>
<td>Source Data</td>
<td>Information from an original record or certified a 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>TBL</td>
<td>Total bilirubin</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient ischemic attack</td>
</tr>
<tr>
<td>T_{\text{max}}</td>
<td>Time to maximum concentration</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 administered subcutaneously (SC) once every month (QM) compared with ezetimibe (Part B), on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in hypercholesterolemic subjects who are unable to tolerate an effective dose of a statin due to muscle related side effects (MRSE).

1.2 Secondary
- To evaluate the safety and tolerability of SC AMG 145 QM, compared with ezetimibe, in hypercholesterolemic subjects unable to tolerate an effective dose of a statin
- To assess the effect of 24 weeks of SC AMG 145 QM, compared with ezetimibe, on change from baseline in LDL-C, and percent change from baseline in total cholesterol, non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, ApoB/Apolipoprotein A1 (ApoA1) ratio, lipoprotein(a) [Lp(a)], triglycerides, HDL-C, and VLDL-C in hypercholesterolemic subjects unable to tolerate an effective dose of a statin
- To assess the effect of 24 weeks of SC AMG 145 QM, compared with ezetimibe, on percent of subjects attaining LDL-C < 70 mg/dL (1.81 mmol/L) in hypercholesterolemic subjects unable to tolerate an effective dose of a statin

1.3 Tertiary Objectives
Tertiary objectives are:
- To assess the effects of 24 weeks of SC AMG 145 QM, compared with ezetimibe, on percent change from baseline of ApoA1 in hypercholesterolemic subjects unable to tolerate an effective dose of a statin

1.4 Exploratory
Exploratory objectives are:
- To evaluate the incidence of MRSE elicited by a double-blind, cross-over atorvastatin rechallenge in Part A
- To describe the effects over time of SC AMG 145 QM, compared with ezetimibe, on change from baseline in proprotein convertase subtilisin/kexin type 9 (PCSK9) levels and on change from baseline and percent change from baseline of LDL-C, total cholesterol, non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/Apolipoprotein A1 ratio, triglycerides, VLDL-C, HDL-C, ApoA1, and Lp(a), and categorical change from baseline in high sensitivity C-reactive protein (hsCRP) in hypercholesterolemic subjects unable to tolerate an effective dose of a statin
- To investigate the relationship between novel and established biochemical cardiovascular and lipid biomarkers and effects of AMG 145
In subjects consenting to the optional pharmacogenetics analysis, to investigate potential correlations of study data including the subject response to AMG 145 with genetic variation in markers of PCSK9 signaling, low-density lipoprotein receptor (LDLR) turnover, cholesterol metabolism, inflammation, and plaque stability.

To estimate cardiovascular event rates in subjects treated with AMG 145, including aggregated exploratory analyses across the AMG 145 program.

2. BACKGROUND AND RATIONALE

2.1 Disease

2.1.1 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 facts below 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).

(i) In excess of one in three individuals in the US has some form of CVD. Coronary heart disease (CHD) affects almost 17 million Americans. Of those almost 8 million suffer from myocardial infarction; nearly 10 million from angina pectoris; nearly 6 million from heart failure; and 6 to 7 million from stroke. The aging of the population and the explosive increase in the prevalence of obesity and type 2 diabetes and their related complications (hypertension, hyperlipidemia, and atherosclerotic vascular disease) will only serve to increase the prevalence of CVD.

(ii) CVD claims more lives each year than cancer, chronic lower respiratory disease, and accidents combined. Over 2200 Americans die of CVD each day. Mortality data show that CVD accounted for more than one in three deaths (over 800,000) in the United States. Since 1900, CVD has been the number 1 killer in the United States every year, with the exception of 1 year only (1918).

(iii) CHD caused approximately 1 of every 6 deaths in the United States. CHD mortality was slightly more than 400,000. It is estimated that each year 785,000 and 470,000 Americans will have a new and recurrent acute coronary syndrome, respectively. An additional 195,000 silent first myocardial infarctions are estimated to occur each year.

The situation in the European Union (EU) is similar. CHD by itself remains the single most common cause of deaths in the EU (Allender et al, 2008). Each year CVD causes over 4.3 million deaths in Europe and over 2.0 million deaths in the 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.

Dyslipidemia is a major modifiable risk factor for the development of CVD. It is estimated that about 100 million Americans and about 34 million Americans have a total cholesterol in excess of 200 mg/dL (approximately 5.2 mmol/L) and 240 mg/dL (approximately 6.2 mmol/L), respectively. In Europe, up to 50% of the population aged 35-64 years has a total cholesterol > 250 mg/dL (6.5 mmol/L) (Tolonen et al, 2005). This high prevalence of dyslipidemia translates into a significant cardiovascular morbidity and mortality, as described above. Dyslipidemia is associated with more than 50% of the global cases of CHD and more than 4 million deaths per year worldwide.

To decrease the burden of CVD, over 50 million patients in the US, Europe, and Japan are currently treated with dyslipidemia therapies. The rationale for treatment of dyslipidemia, particularly elevated LDL-C, extends from extensive clinical trial data in both primary and secondary prevention that demonstrates the reduction in total cholesterol, non-HDL-C, and most importantly, LDL-C through pharmacological therapies, particularly statins, lowers the risk of CVD events (Kannel et al, 1974; Kannel, 1995; Kannel et al, 1979). The most recent Cholesterol Trialists Treatment Collaboration (CTTC) meta-analysis which included 21 randomized controlled trials of statin versus control involving nearly 170,000 patients showed that for every ~ 1 mmol/L there was a ~20% reduction in the risk of major vascular events (coronary death, non-fatal myocardial infarction, coronary revascularization, or stroke). Importantly, this meta-analysis, which also evaluated five trials that compared more versus less intensive statin therapy, did not find a LDL-C threshold; additional vascular risk reduction is possible in patients with low LDL-C.

Some individuals are intolerant to statin therapy due to muscle-related side effects (eg, Bruckert et al, 2005; Franc et al, 2003). In the literature, terminology used to describe muscle-related side effects can be confusing, therefore in this document the terms described by Pasternak in the ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins (Pasternak et al, 2002) have been adopted: Myopathy - a general term referring to any disease of muscles; Myalgia - muscle ache or weakness without creatine kinase (CK) elevation. Myositis - muscle symptoms with increased CK levels. Rhabdomyolysis - muscle symptoms with marked CK elevation (typically substantially
greater than 10 times the upper limit of normal [ULN]) and with creatinine elevation (usually with brown urine and urinary myoglobin).

The fact that statins are uncommonly associated with the development of myopathy is well accepted. The incidence of myopathy is increased under equally well-accepted conditions, such as when the statin is used in combination with drugs such as cyclosporine, fibrates, macrolide antibiotics, certain antifungal drugs, and niacin. Many of these associations relate to the use of drugs that antagonize metabolism through the cytochrome P-450 system, particularly the 3A4 isozyme. While myopathy is rare, a more common adverse event is the development of myalgia, described as non-specific muscle aches or perceptions of weakness that do not involve any increase in CK. In the placebo-controlled clinical trials with statins, the frequency of myalgia has been around 5% and has been very similar between drug and placebo. Nevertheless, many patients believe that their temporally associated myalgia is due to a statin, and it often returns on rechallenge. Other patients can have mild-to-moderate elevations of CK symptoms involving muscle complaints. Again, elevations may be non-specific, but a statin effect often cannot be ruled out.

The PRIMO Study was a French nationwide observational survey of the risk factors and management of muscular side effects in patients receiving high-dosage statin treatment in general practice in France (Bruckert et al, 2005). A total of 7,924 hyperlipidemic patients with age 18 - 75 years who were seen by their general practitioners (GPs) in regular outpatient visits were entered in the study. GPs were asked to include the first three consecutive patients who satisfied the survey inclusion criteria during a period of up to 2 months following initiation of the study. Patients were included if they had been prescribed high-dosage statin treatment (fluvastatin 80 mg; atorvastatin 40 or 80 mg; pravastatin 40 mg; or simvastatin 40 or 80 mg) for at least 3 months prior to the study. Patients were also included if their regimen had been adjusted (statin withdrawal or dose reduction) within the last 3 months due to muscular pain. The risk factor analysis in PRIMO was consistent with the results of a preliminary study (Franc et al, 2003), confirming that a personal or family history of muscular symptoms, cramps, hypothyroidism and elevated CK levels are major risk factors for muscular symptoms during high-dosage statin therapy. The presence of a family history almost doubled the risk of the adverse reaction. Thus, a genetic predisposition may be key in determining whether a patient will develop muscle pain while receiving statin therapy. The questionnaires in the PRIMO study did not specifically address diabetes or liver function,
and the study failed to detect any impact of impaired kidney function. Age, gender and BMI were not identified as risk factors by univariate analysis, although both lower body fat mass and regular physical activity were associated with a greater incidence of muscle pain. Symptomatic patients were generally more active than the population as a whole; this may be because active patients are more likely to sustain the type of low-level injury that is exacerbated by statins. Although CK levels were not measured, a history of elevated levels of CK emerged as a significant risk factor for muscular symptoms. This finding suggests that sub-clinical myopathy may predispose to statin-induced symptoms. The lower prevalence of lipid lowering therapy related muscular symptoms in patients treated for more than 3 months was explained by the fact that the majority of cases of lipid lowering therapy myotoxicity are clinically apparent within the first 3 months. In the PRIMO study population, 10.5% of patients on high-dosage statin therapy complained of muscle pain, a figure which is considerably higher than that reported previously for clinical trials but which is consistent with anecdotal experiences of practicing physicians. The experience in PRIMO may be more representative than data from large scale placebo controlled studies where patients may have been excluded on the basis of age, diabetes, renal or hepatic impairment or a history of muscular symptoms or CK elevations. Marked differences in the risk of muscular symptoms with individual statins were observed; fluvastatin XL treatment was associated with the lowest rate of muscular symptoms (5.1% of patients), while patients receiving high-dosage simvastatin showed the highest rate (18.2%). Comparisons between statins should be interpreted with caution due to the limitations of the study design.

Muscular symptoms were managed either by switching the patient to a different lipid-lowering agent (generally another statin), continuing the same statin at a lower dosage, or discontinuing statin therapy completely. Multivariate analysis demonstrated that a history of muscle pain with another lipid lowering therapy was the strongest predictor for muscular symptoms. Therefore switching to a different statin might not be expected to reduce muscular symptoms. Importantly, the results of the PRIMO study indicate that muscular symptoms associated with high dosage statin therapy may have a greater impact on the everyday life of patients than was previously thought. Muscular pain was continuous in 25% of patients, while 39% of patients reported using an analgesic for pain relief of their muscular symptoms. Moreover, 38% of patients reported that their muscular symptoms prevented even moderate exertion during everyday activities, while 4% of patients suffered major disruption to their everyday life (being confined to bed or unable to work) due to muscular pain. These findings are of
considerable importance, because patients who experience adverse events during statin treatment are more likely to discontinue therapy.

Given the extremely rare nature of clinical myositis or rhabdomyolysis, the most significant problem associated with statin intolerance may be the fact that these subjects are not able to be titrated to a target LDL-C that effectively reduces their risk of a cardiovascular event. Other treatment options either have limited efficacy (ezetimibe, resins, plant stanols), or are poorly tolerated (niacin).

In summary, there is an unmet medical need for an effective non-statin agent that will get a significant proportion of patients to LDL-C goal.

2.2 Amgen Investigational Product 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 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, 2013. AMG 145 binds to human, monkey, and hamster PCSK9 with high affinity ($K_d < 100 \text{ pM}$). 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, 2013), a program to develop AMG 145 as a treatment for dyslipidemia was initiated.

### 2.2.1 First-in-Human (FIH)/ Phase 1 Studies

Please consult the Investigator’s Brochure (2013) for study details.

### 2.2.2 Completed Phase 2, 12 Week LDL-C Lowering Studies

Please consult the Investigator’s Brochure (2013) for study results.

### 2.3 Non-Amgen Medicinal Product Background

Ezetimibe 10mg tablets and atorvastatin 20mg tablets will be provided during study participation. Both will be over-encapsulated to maintain blinding.

#### 2.3.1 Ezetimibe Background

This background information is based on the United States label information (ZETIA® [ezetimibe] package insert). Ezetimibe is in a class of lipid-lowering compounds that selectively inhibits the intestinal absorption of cholesterol and related phytosterols. Ezetimibe is approved for use as monotherapy as adjunctive therapy to diet for the reduction of elevated total cholesterol, LDL-C, and ApoB in patients with primary (heterozygous familial and non-familial) hyperlipidemia. It is approved for use in combination with statins as adjunctive therapy to diet for the reduction of elevated total cholesterol, LDL-C, and ApoB in patients with primary (heterozygous familial and non-familial) hyperlipidemia. It is approved for use in combination with fenofibrate as adjunctive therapy to diet for the reduction of elevated total cholesterol, LDL-C, ApoB, and non-HDL-C in adult patients with mixed hyperlipidemia. Ezetimibe is approved for use in combination with atorvastatin or simvastatin for the reduction of elevated total cholesterol and LDL-C levels in patients with homozygous familial hypercholesterolemia,
as an adjunct to other lipid-lowering treatments (eg, LDL aphaeresis) or if such treatments are unavailable.

**Response to Ezetimibe in Patients With Primary Hyperlipidemia**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>N</th>
<th>Total-C</th>
<th>LDL-C</th>
<th>ApoB</th>
<th>TG*</th>
<th>HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1‡ Placebo</td>
<td>205</td>
<td>+1</td>
<td>+1</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>622</td>
<td>-12</td>
<td>-18</td>
<td>-15</td>
<td>-7</td>
<td>+1</td>
</tr>
<tr>
<td>Study 2‡ Placebo</td>
<td>226</td>
<td>+1</td>
<td>+1</td>
<td>-1</td>
<td>+2</td>
<td>-2</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>666</td>
<td>-12</td>
<td>-18</td>
<td>-16</td>
<td>-9</td>
<td>+1</td>
</tr>
<tr>
<td>Pooled Data‡ (Studies 1 &amp; 2) Placebo</td>
<td>431</td>
<td>0</td>
<td>+1</td>
<td>-2</td>
<td>0</td>
<td>-2</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>1288</td>
<td>-13</td>
<td>-18</td>
<td>-16</td>
<td>-8</td>
<td>+1</td>
</tr>
</tbody>
</table>

* For triglycerides, median % change from baseline
† Baseline - on no lipid-lowering drug
‡ Ezetimibe significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to placebo.

In the ezetimibe controlled clinical trials database (placebo-controlled) of 2396 patients described in the label with a median treatment duration of 12 weeks (range 0 to 39 weeks), 3.3% of patients on ezetimibe and 2.9% of patients on placebo discontinued due to adverse reactions. The most common adverse reactions in the group of patients treated with ezetimibe that led to treatment discontinuation and occurred at a rate greater than placebo were arthralgia (0.3%), dizziness (0.2%) and increased Gamma-glutamyltransferase (0.2%). The most commonly reported adverse reactions (incidence ≥ 2% and greater than placebo) were upper respiratory tract infection (4.3%), diarrhea (4.1%), arthralgia (3.0%), sinusitis (2.8%), and pain in extremity (2.7%). The incidence of consecutive elevations (≥ 3 X the upper limit of normal [ULN]) in hepatic transaminase levels was similar between ezetimibe (0.5%) and placebo (0.3%). In controlled clinical combination studies of ezetimibe initiated concurrently with a statin, the incidence of consecutive elevations (≥ 3 X ULN) in hepatic transaminase levels was 1.3% for patients treated with ezetimibe administered with statins and 0.4% for patients treated with statins alone.

Ezetimibe is contraindicated in the following circumstances: in combination with a statin in patients with active liver disease or unexplained persistent elevations in hepatic transaminase levels, in women who are pregnant or may become pregnant, nursing mothers and in patients with a known hypersensitivity to ezetimibe.
The recommended dose of ezetimibe is 10 mg once daily, administered with or without food. No dosage adjustment is necessary in patients with mild hepatic or renal impairment. No dosage adjustment is necessary in geriatric patients.

2.3.2 Statin Background

The clinical benefits of statin treatment in primary prevention as well as secondary prevention have been documented in multiple trials (Weart and Hogan, 2011). A recent meta-analysis confirmed a beneficial effect on all-cause mortality as well as combined fatal and non-fatal cardiovascular endpoints in primary prevention (Taylor et al, 2011). Reported adverse events arising from statin therapy are infrequent and rarely severe (Weart and Hogan, 2011). Though some studies have suggested an association between lower LDL cholesterol levels and hemorrhagic stroke or intracranial hemorrhage (Iso et al, 1989; Collins et al (Heart Protection Collaborative Study Group), 2004; Amarenco et al, 2006), several contemporary studies utilizing high doses of potent statins as well as two large meta-analyses have not observed this association (Waters et al, 2006; CTTC, 2010; Hackam et al, 2011). Other meta-analyses have suggested that statin use can also affect the incidence of new onset diabetes (Sattar et al, 2010; Preiss et al, 2011). Combined, these analyses followed over 120,000 participants without a baseline diagnosis of diabetes for a mean duration of at least 4 years. Both studies found a small increased absolute risk for development of diabetes in patients treated with statins; however, this risk was outweighed by the overwhelming reduction in major adverse cardiovascular events resulting from statin use in patients at moderate to high cardiovascular risk. Regarding other safety profile data available for statins, a pooled analysis of 49 atorvastatin trials demonstrated that the overall safety profiles for the 10- and 80-mg/day doses are comparable, with the exception of a slightly increased rate of elevations in levels of the hepatic enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) for the higher dose (Newman et al, 2006). The most common adverse effects experienced by patients taking statins are those associated with the musculoskeletal system, and these effects occur with all statins. Symptoms are usually restricted to muscle pain, weakness and/or cramps. Myalgia, which according to various definitions may include some or all of these relatively minor symptoms, typically affects 5% to 10% of patients receiving statins (Weart and Hogan, 2011).

Refer to the regional manufacturer package insert for additional information.
2.4 Rationale
There is an established unmet medical need for patients with dyslipidemia who experience muscle-related side effects when using statins. Therefore, Amgen is investigating the use of AMG 145 alone or in combination with statin or other lipid-lowering therapies in patients with primary hyperlipidemia and mixed dyslipidemia who are statin-intolerant or unable to tolerate an effective dose of a statin.

This design supports advice from regulatory agencies requesting a scientifically rigorous study to identify statin-intolerant patients through active statin rechallenge. As such, a study design with self-reported statin intolerance or single-blind statin rechallenge is deemed insufficient. A cross-over, two-period rechallenge design with statin compared to placebo will be used to identify a subset of subjects who will proceed to a head to head comparison of AMG 145 to ezetimibe.

2.5 Clinical Hypotheses
The primary hypothesis is that AMG 145 SC 420 mg QM will be well tolerated and will result in greater reduction of LDL-C than ezetimibe, defined by the mean percent change from baseline at Weeks 22 and 24 and percent change from baseline at Week 24, in hypercholesterolemic subjects who are intolerant to statins or unable to tolerate an effective dose of a statin as confirmed by development of MRSE during a double-blind, cross-over statin rechallenge or documented evidence of CK elevation > 10 x ULN accompanied by muscle symptoms while on statin therapy levels and documented resolution of both CK elevation and muscle symptoms upon discontinuation of statin therapy.

3. EXPERIMENTAL PLAN
3.1 Study Design
This is a phase 3, multicenter, randomized, double-blind, ezetimibe-controlled, parallel group study of AMG 145 in hypercholesterolemic subjects unable to tolerate an effective dose of a statin. There are three parts to this study: Part A is a double-blind, placebo-controlled cross-over statin rechallenge to confirm presence of statin-related MRSE and is approximately 24 weeks in duration; Part B is a double-blind, active controlled comparing AMG 145 to ezetimibe and is 24 weeks in duration; Part C is a two-year open-label extension to evaluate the long-term safety and efficacy of AMG 145 in statin-intolerant subjects. Randomization will occur at two separate time points, prior to Part A and prior to Part B. Any subject with a documented history of CK elevation > 10 x ULN accompanied by muscle symptoms while on statin therapy
levels and documented resolution of both CK elevation and muscle symptoms upon discontinuation of statin therapy, must bypass the statin rechallenge Part A and advance directly into Part B. During screening, potential subjects taking low dose statins or ezetimibe will discontinue these medications and allow for a minimum of 4-week washout period. Potential subjects will be given placebo subcutaneous injections administered via 3 prefilled autoinjector/pens (prefilled Al/pen).

Randomization into Part A should occur within 5 – 10 days of the screening LDL-C evaluation used to determine eligibility. Eligible subjects who meet all inclusion/exclusion criteria will be randomized with an allocation ratio of 1:1 to atorvastatin or placebo. Part A consists of two 10-week periods (Period 1 and Period 2) for cross-over statin rechallenge of subjects. In Period 1, subjects will be assigned to 20 mg atorvastatin or matched placebo taken by mouth (PO) every day (QD). At the end of Period 1 and a 2-week washout, subjects will cross-over to the alternate therapy (either atorvastatin or placebo for Period 2), during which time subjects will be treated for an additional 10 weeks. During either treatment period the subject will complete the 10 week course or will discontinue oral IP due to intolerable MRSE or MRSE that develop and persist for 2 weeks which in the opinion of the investigator will lead to discontinuation of IP. Upon completion of both Periods 1 and 2 in Part A of the study, subjects who report MRSE on atorvastatin and absence of MRSE on placebo will enter into a 2-week washout and advance to Part B. Subjects who do not develop MRSE on atorvastatin or develop MRSE on placebo will be removed from the study. During Part A, a CK elevation > 10 x ULN accompanied by muscle symptoms will be considered the equivalent of intolerable MRSE (ie, if occurring in Period 1 subject will cross-over to Period 2 and if occurring in Period 2 subject will complete Part A). Investigators, who are blinded to IP, will determine if subjects are experiencing MRSE and will report their findings using the IVRS/IWRS system. Sites will administer the Brief Pain Inventory -Short Form (BPI-SF) and Short Form (36) Health Survey (SF-36) (Appendix D).

In Part B, the subjects will be randomized with an allocation ratio 2:1 into one of 2 treatment groups:

1. 420 mg AMG 145 SC QM and placebo PO QD, or
2. Placebo SC QM and 10 mg ezetimibe PO QD

Randomization in Part B in will be stratified by screening LDL-C level (< 180 mg/dL [4.66 mmol/L] vs. ≥ 180 mg/dL) at study baseline. The following describes procedures
and restrictions of Part B: 1) blinded Investigational Product (AMG 145 or placebo) will be administered at the study site using a prefilled autoinjector/pen (AI/Pen); 2) Central laboratory results of the lipid panel, ApoA1, ApoB, lipoprotein(a), and high sensitivity C-reactive protein (hsCRP) will be blinded for the duration of the study and will not be reported to the investigator (unless specified); 3) investigators are not to perform non-protocol testing of these analytes until at least 12 weeks after last blinded IP administration, as drawing non-protocol labs could unblind treatment assignment. The last dose of blinded SC IP will be given at Week 20 of Part B for all subjects. Subjects will be encouraged to complete all planned visits regardless of their adherence to investigational product (IP) administration. Subjects in Part B will continue to be assessed for MRSE, sites will continue to use BPI-SF and SF-36.

Subjects who complete Part B and do not discontinue SC IP for any reason including an adverse event will be eligible to proceed to Part C, a two-year, open-label, safety extension phase during which all subjects will receive AMG 145. All subjects will be invited to consent to pharmacogenetic analyses. The study includes collection of biomarker samples where approved by the independent ethics committee and/or institutional review board (IEC/IRB), applicable regulatory and other authorities. The study includes adjudication of deaths and major cardiovascular (CV) events by an independent Clinical Events Committee (CEC) and formal review of the accumulating data by an independent Data Monitoring Committee (DMC).

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

The study endpoints are defined in Section 10.1.

3.2 Number of Sites
Approximately 45 sites in US, Europe, Australia, Canada, and Asia will be selected to participate in this study. Additional regions, countries and/or centers may be added.

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”.

The number of subjects in Part A will fulfill the planned sample size of 100 subjects in Part B. Based on unpublished data from a double-blind, placebo-controlled statin rechallenge study, the estimated MRSE rate in this study is 20%. Thus, the expected number of subjects to be enrolled in Part A is 500. However, enrollment in Part A will
continue until Part B target sample size is met or an administrative decision is made to
stop the study. All subjects that complete Part B are eligible to participate in Part C.
Approximately 80% to 100% of subjects will continue to Part C.

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

3.5 Estimated Study Duration
3.5.1 Study Duration for Subjects
Subject participation is anticipated to continue for 36 months (excluding screening
period): 24 weeks for Part A; 24 weeks for Part B; 104 weeks for Part C. End of
Treatment will occur at Month 36.

3.5.2 End of Study
Primary Completion: defined as all the randomized subjects in Part B of the study have
either completed all the scheduled visits in Part B or have early terminated from the
study;

End of Trial: defined as all enrolled subjects in Part C of the study have either
completed all the scheduled visits in Part C or have early terminated from the study.

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. For a full list of eligibility criteria, please refer to Section 4.1
and Section 4.1.2

4.1 Inclusion and Exclusion Criteria
4.1.1 Inclusion Criteria
101 Subject who has provided informed consent/assent prior to initiation of any
study-specific activities/procedures
102 Male or female ≥ 18 to ≤ 80 years of age at signing of informed consent
103 Subject who is not at LDL-C goal as evidenced by their NCEP ATP III risk
category and the following LDL-C levels by central laboratory at
screening:
   a) Fasting LDL-C ≥ 100 mg/dL (2.59 mmol/L) for subjects with
diagnosed CHD or are CHD risk equivalent or
   b) Fasting LDL-C ≥ 130 mg/dL (3.37 mmol/L) for subjects without
diagnosed CHD or risk equivalent and 2 or more risk factors or
c) Fasting LDL-C ≥ 160 mg/dL (4.14 mmol/L) for subjects without diagnosed CHD or risk equivalent and with 1 or more risk factors or

d) Fasting LDL-C ≥ 190 mg/dL (4.9 mmol/L) for subjects without diagnosed CHD or risk equivalent and with no risk factors

104 Subject who has a history of statin intolerance as evidenced by the following:

a) Unable to tolerate atorvastatin at an average daily dose of 10 mg AND unable to tolerate any other statin at any dose due to skeletal muscle related symptoms (eg., pain, aches, weakness or cramping)

OR

b) Unable to tolerate at least three statins: one statin at the lowest starting average daily dose (defined below) AND any other two statins at any dose, due to skeletal muscle related symptoms (eg., pain, aches, weakness or cramping)

<table>
<thead>
<tr>
<th>Statin</th>
<th>Average Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>rosuvastatin</td>
<td>5 mg</td>
</tr>
<tr>
<td>simvastatin</td>
<td>10 mg</td>
</tr>
<tr>
<td>pravastatin</td>
<td>40 mg</td>
</tr>
<tr>
<td>lovastatin</td>
<td>20 mg</td>
</tr>
<tr>
<td>fluvastatin</td>
<td>40 mg</td>
</tr>
<tr>
<td>pitavastatin</td>
<td>2 mg</td>
</tr>
</tbody>
</table>

OR

c) A documented history of CK elevation > 10 x ULN accompanied by muscle symptoms while on statin therapy and documented resolution of both CK elevation and muscle symptoms upon discontinuation of statin therapy;

AND

Symptoms resolved or improved when statin dose was decreased or discontinued

105 Lipid lowering therapy has been stable prior to LDL-C screening for at least 4 weeks if currently on a bile-acid sequestering resin and/or stanol; if subject is on statin or ezetimibe at start of screening, statin or ezetimibe must be discontinued for ≥ 4 weeks before LDL-C screening

106 Fasting triglycerides ≤ 400 mg/dL (4.52 mmol/L) by central laboratory at screening

4.1.2 Exclusion Criteria

201 History of haemorrhagic stroke

202 Personal or family history of hereditary muscular disorders

203 NYHA III or IV heart failure, or last known left ventricular ejection fraction (LVEF) < 30%

204 Uncontrolled serious 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

205 Myocardial infarction, unstable angina, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) or stroke within 3 months prior to randomization

206 Planned cardiac surgery or revascularization

207 Type 1 diabetes, poorly controlled type 2 diabetes (HbA1c > 8.5%), newly diagnosed type 2 diabetes (within 6 months of randomization), or laboratory evidence of diabetes during screening (fasting serum glucose ≥ 126 mg/dL [7.0 mmol/L] or HbA1c ≥ 6.5%) without prior diagnosis of diabetes

208 Uncontrolled hypertension defined as sitting systolic blood pressure (SBP) > 160 mmHg or diastolic BP (DBP) > 100 mmHg

209 Subject who has taken in the last 4 weeks prior to LDL-C screening red yeast rice, > 200 mg/day niacin, or prescription lipid-regulating drugs (e.g., fibrates and derivatives, statins or ezetimibe) other than bile-acid sequestering resin, or stanols and stanol esters

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

211 Treatment in the last 3 months prior to LDL-C screening with any of the following drugs: systemic cyclosporine, systemic steroids (e.g., IV, intramuscular [IM], or PO) (Note: hormone replacement therapy is permitted), vitamin A derivatives and retinol derivatives for the treatment of dermatologic conditions (e.g., Accutane); (Note: vitamin A in a multivitamin preparation is permitted)

212 Uncontrolled hypothyroidism or hyperthyroidism as defined by thyroid stimulating hormone (TSH) < 1.0 time the lower limit of normal or >1.5 times the ULN, respectively, at screening. Potential subjects with TSH < 1.0 time the lower limit of normal due to thyroid replacement therapy is not considered an exclusion

213 Moderate to severe renal dysfunction, defined as an estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m2 at screening

214 Active liver disease or hepatic dysfunction, defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 times the ULN as determined by central laboratory analysis at screening

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

216 Diagnosis of deep vein thrombosis or pulmonary embolism within 3 months prior to randomization

217 Unreliability as a study participant based on the investigator's (or designee's) knowledge of the subject (e.g., alcohol or other drug abuse, inability or unwillingness to adhere to the protocol, or psychosis)
218 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)

219 Female subject who has either (1) not used at least 1 highly effective method of contraception for at least 1 month prior to screening or (2) is not willing to use such a method during treatment and for an additional 15 weeks after the end of treatment, unless the subject is sterilized or postmenopausal;

   a. 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

   b. highly effective methods of birth control include: not having intercourse or using birth control methods that work at least 99% of the time when used correctly and include: birth control pills, shots, implants, or patches, intrauterine devices (IUDs), tubal ligation/occlusion, sexual activity with a male partner who has had a vasectomy, condom or occlusive cap (diaphragm or cervical/vault caps) used with spermicide

220 Subject who is pregnant or breast feeding, or planning to become pregnant during treatment and/or within 15 weeks after the end of treatment

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

222 Subject who 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

223 Malignancy except non-melanoma skin cancers, cervical or breast ductal carcinoma in situ within the last 5 years

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

225 Subject who is likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (e.g., Patient Reported Outcomes [PROs]) to the best of the subject and investigator’s knowledge

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

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

A subject is considered enrolled upon randomization. The investigator is to document and date this decision in the subject’s medical record and on the enrollment eCRF.

Each subject who enters into the screening period for the study upon signing informed consent receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned through an 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. Subjects who do not meet LDL-C eligibility criteria cannot be rescreened.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened. This number will not necessarily be the same as the randomization number assigned for the study. Unique 11-digit subject identification numbers will be assigned in sequential order for each site in the format 332CCXXX### 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/IWRS (eg, 33212123001, 33212123002, etc.).

5.1 Randomization/Treatment Assignment

In Part A, subjects will be randomized 1:1 assignment to 2 treatment groups and will be based on a computer-generated randomization schedule prepared by Amgen before the start of the study. Randomization for Part B will be 2:1 and will be stratified by screening LDL-C concentration (< 180 mg/dL [4.66 mmol/L] vs. ≥ 180 mg/dL) at baseline.

The following are treatment groups for Part A:

- Atorvastatin 20mg PO QD
- Placebo 20mg PO QD
The following are treatment groups for Part B:

- AMG 145 SC, 420mg QM (3 Al/pen) and PO placebo 10mg QD
- Placebo SC 420mg QM (3 Al/pen) and PO ezetimibe 10mg QD

The following is the treatment for Part C:

- AMG 145 SC, 420 mg QM (3 Al/pen or one Personal Injector) or AMG 145 SC, 140 mg Q2W (1 Al/pen) - subjects can choose dosing regimen quarterly

Once eligibility into the study has been confirmed, a site representative will make the randomization call to the IVRS/IWRS to assign a randomization number to the subject. The randomization call to the IVRS/IWRS is accomplished by entering the pertinent information detailed in the IVRS/IWRS user manual. A confirmation fax will be sent to the site to verify that the correct information has been entered and to confirm the assignment of a randomization number. A subject will be considered randomized into either Part A or Part B of the study when a corresponding randomization number is assigned.

Please refer to Section 5.2 for details on when and how the randomization code may be broken. The treatment assignment date is to be documented in the subject’s medical record and on the enrollment CRF.

5.2 Site Personnel Access to Individual Treatment Assignments

A subject’s treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject on this study. Unblinding at the study site for any other reason will be considered a protocol deviation.

Refer to the IVRS/IWRS manual for instructions on unblinding.

The investigator is strongly encouraged to contact the Amgen Clinical Study Manager before unblinding any subject's treatment assignment, but must do so within 1 working day after the event.

6. TREATMENT PROCEDURES

AMG 145, placebo SC, atorvastatin PO, ezetimibe PO, and placebo PO 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 Classification of Product(s) and/or Medical Device(s)

The Amgen Investigational Product(s) and/or matched placebo (except if required by local regulation) used in this study include(s): SC AMG 145 and SC Placebo.

The Non-Amgen investigational product(s) used in this study include: PO Atorvastatin 20mg, PO Ezetimibe 10mg, and PO Placebo.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, and administration of AMG 145, matched placebo, over-encapsulated atorvastatin and over-encapsulated ezetimibe.

The medical device(s) used in this study include(s): Prefilled Al/pen and Personal Injector.

6.2 Investigational Product

6.2.1 Amgen Investigational Product AMG 145

AMG 145 and respective 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.

Placebo will be presented in a 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.

The 3.5 mL Personal Injector will only be made available for use in Part C of 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.
AMG 145 should be stored protected from light and according to the storage and expiration information (where required) provided on the label. AMG 145 should be handled per the instructions provided in the IPIM. AI/pens should be checked for cracks or damage that may occur during shipment or if not handled properly. Damaged product should not be administered. Further details are provided in the IPIM.

The box number of IP (active drug or placebo) is to be recorded on each subject’s Drug Administration electronic case report form (eCRF).

6.2.1.1 Dosage, Administration, and Schedule

IP will be administered SC (AMG 145 or matched placebo) at the investigator site by a qualified staff member in accordance with instructions in the IPIM. IP administration by SC injection at each visit must be done after vital signs, ECG, and blood draw procedures, if applicable. The date and time of AMG 145 or placebo will be recorded on the individual subject’s worksheet and/or eCRF. After IP administration at each dosing visit, subjects should be observed for at least 30 minutes before being discharged.

In Part B and Part C, 420 mg of AMG 145 will be administered subcutaneously once a month via three 1.0 mL prefilled AI/pens or a single 3.5 mL Personal Injector. The prefilled AI/pens injections should be administered in a consecutive fashion with all injections completed within 30 minutes.

In addition to the monthly regimen specified above, Part C includes an option for a regimen of 140 mg of AMG 145 administered subcutaneously every two weeks via one 1.0 mL prefilled AI/pen.

Details of preparing and administering IP are included in the IPIM provided by Amgen at the start of the study. The dosing schedule is described by a schema in the protocol synopsis.

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

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 IP, 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

Doses Except the Last Dose

Administration of IP should occur within the visit window for each scheduled visit. IP must never 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. These subjects will receive their next SC IP administration as previously scheduled.

Last Dose

Subjects, who are late in receiving the last dose of IP, should receive the dose as soon as possible, regardless of the relationship to visit window. If the last dose has not been received by the end of the visit window for the Week 24 visit, it should be omitted entirely.

Subjects who miss a Scheduled Dose of Investigational Product Completely

Doses Except the Last Dose

Subjects randomized to SC IP administration (placebo or AMG 145) who completely miss a scheduled visit or IP administration will continue in the study and receive scheduled study drug at the next scheduled visit.

Last Dose

Subjects randomized to SC IP administration (placebo or AMG 145) who completely miss the last scheduled IP administration will continue in the study and should return for an unscheduled visit as soon as possible to receive study drug. If the last dose has not been received by the end of the visit window for the Week 24 visit, it should be omitted entirely.

6.2.2 Non-Amgen Investigational Product(s)

Non-Amgen investigational product(s) including atorvastatin 20mg and ezetimibe 10mg will be used in this study.

6.2.2.1 Non-Amgen Investigational Product – Atorvastatin 20mg

6.2.2.1.1 Dosage, Administration, and Schedule

Atorvastatin 20 mg tablets will be administered orally, once daily, with or without food, at a time convenient to the subject. To enable blinding of the PO IP, atorvastatin will be supplied as over-encapsulated 20 mg tablets.

No other lipid-lowering treatment is required per protocol 20120332. All other drugs that are allowed per protocol and that are prescribed for the subject, must be commercially...
available and are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these drugs.

**6.2.2.1.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation**

**Subjects who Miss a Dose of Atorvastatin Therapy**

Subjects who miss a dose of atorvastatin 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.

**6.2.2.2 Non-Amgen Investigational Product - Ezetimibe**

**6.2.2.2.1 Dosage, Administration, and Schedule**

Ezetimibe 10 mg tablets will be administered orally, once daily, with or without food, at a time convenient to the subject. To enable blinding of the PO IP, ezetimibe will be supplied as over-encapsulated 10 mg tablets.

Ezetimibe 10mg is an approved drug for the treatment of patients with hyperlipidemia, either as monotherapy, or in combination with a statin or fenofibrate (ZETIA® [ezetimibe]).

Subjects who miss a dose of ezetimibe will be advised to take the missed dose as soon as they can however subjects should not take more than one dose of ezetimibe per day; subsequent doses will be taken at the usual time. However, if the next scheduled dose would be due in less than 12 hours, the subject will be advised to omit the missed dose entirely and to take the next dose at the normal time. Consult the IPIM for additional information on ezetimibe.

**6.2.2.3 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation**

No dosage adjustment is necessary in patients with mild hepatic or renal impairment. No dosage adjustment is necessary in geriatric patients. Additional details regarding ezetimibe are provided in the IPIM.

**6.2.3 Criteria for Withholding of Investigational Product**

Reports from the central laboratory after each visit must be reviewed before administration of IP at the next visit.
6.2.3.1 Elevation of Creatine Kinase (CK)

If CK is > 5x ULN, CK must be retested before IP is administered. The following rules apply:

<table>
<thead>
<tr>
<th>CK at prior visit</th>
<th>CK on retest</th>
<th>Investigational Product Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 5x ULN</td>
<td>&gt; 10x ULN</td>
<td>Discontinue IP.* Contact Amgen Medical Monitor</td>
</tr>
<tr>
<td>&gt; 5x to ≤ 10x ULN</td>
<td></td>
<td>Consider continuing IP if alternative explanation</td>
</tr>
<tr>
<td>≤ 5x ULN</td>
<td></td>
<td>Consider continuing IP</td>
</tr>
</tbody>
</table>

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

6.2.3.2 Elevation of Triglycerides

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

6.3 Hepatotoxicity Stopping and Rechallenge Rules

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

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

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

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

<table>
<thead>
<tr>
<th>Baseline AST or ALT value</th>
<th>AST or ALT elevation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; ULN</td>
<td>&gt; 3x ULN</td>
</tr>
</tbody>
</table>
AND no other cause for the combination of the above laboratory abnormalities is immediately apparent; important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (e.g., Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, toxoplasmosis, and Parvovirus)
- Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia.
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- Heritable disorders causing impaired glucuronidation (e.g., Gilbert’s Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (e.g., indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson’s disease and hemochromatosis
- Nonalcoholic Fatty Liver Disease including Steatohepatitis (NASH)
- Non-hepatic causes (e.g., rhabdomyolysis, hemolysis)

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

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

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

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

- OR: TBL > 3x ULN at any time

- OR: ALP > 8x ULN at any time
AMG 145 should be withheld pending investigation into alternative causes of DILI. If investigational product(s) is withheld, the subject is to be followed according to recommendations in Appendix A for possible DILI. Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (Section 6.3.3).

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

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

If signs or symptoms recur with rechallenge, then AMG 145 should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.3.1) should never be rechallenged.

6.4 Concomitant Therapy, Diet, and Exercise

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.7.

Subjects should maintain their current regimen of diet and 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 Medical Devices

IP will be administered per prefilled Al/Pen or Personal Injector, provided by Amgen. Additional details regarding the use of the Al/Pen or Personal Injector is provided in the IPIM and in the Instructions for Use (IFU) brochure. Medical devices (eg, syringes, sterile needles, alcohol prep pads), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

6.6 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of any investigational or non-investigational product(s) or device(s).

Concerns or irregularities about the packaging, appearance or usage of the prefilled Al/pen or Personal Injector 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 prefilled AI/pen or Personal Injector 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,
- subject or healthcare provider cannot appropriately use the product despite training (eg., due to malfunction of the prefilled AI/pen or Personal Injector),
- 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 amount of fluid in the prefilled AI/pen or Personal Injector, or
- evidence of tampering or stolen material.

If possible, please have the prefilled AI/pen or Personal Injector available for examination when making a product complaint. Maintain the prefilled AI/pen or Personal Injector 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 ICF 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.

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

6.7 Excluded Treatments and/or Procedures During Study Period

The following treatments are not permitted during the study:

- Prescription lipid regulating medications (eg, non-study ezetimibe, or fibrates and derivatives), other than bile-acid sequestering resin, or stanol and stanol esters
- Red yeast rice, niacin > 200 mg per day
Any other drug that significantly affects lipid metabolism (eg, systemic cyclosporine, systemic steroids [IV, IM, or PO] (Note: hormone replacement therapy is permitted, vitamin A derivatives and retinol derivatives for the treatment of dermatologic conditions [eg, Accutane]). Vitamin A as part of a multivitamin preparation is permitted.

Prescribed amphetamines, or amphetamine derivatives, and weight loss medications.

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

- For subjects receiving atorvastatin medications 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 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.

7. STUDY PROCEDURES

7.1 Schedule of Assessments
## Table 1. Schedule of Assessments

<table>
<thead>
<tr>
<th>Part A</th>
<th>Study Day / Timepoint</th>
<th>Screening</th>
<th>Visit D1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Visit W4</th>
<th>Visit W8</th>
<th>Visit W10</th>
<th>Visit W12</th>
<th>Visit W16</th>
<th>Visit W20</th>
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<td><strong>Central Laboratory</strong></td>
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</table>

Footnotes defined on next page
Table 1. Schedule of Assessments

<table>
<thead>
<tr>
<th>Study Day / Timepoint</th>
<th>Screening</th>
<th>Visit D1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Visit W4</th>
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<th>Visit W12</th>
<th>Visit W16</th>
<th>Visit W20</th>
<th>Visit W22</th>
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<tbody>
<tr>
<td><strong>Part A</strong></td>
<td></td>
<td>Period 1</td>
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<td></td>
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<td>Period 2</td>
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<tr>
<td><strong>Central Laboratory (continued)</strong></td>
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<td>TSH</td>
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<td>HCV antibodies</td>
<td>Xi</td>
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<td>HCV viral load</td>
<td>Xi</td>
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<td>Serum pregnancy; FSH</td>
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<td><strong>Investigational Product</strong></td>
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<td>Placebo injection</td>
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<td>X</td>
<td>X</td>
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</tr>
</tbody>
</table>

<sup>a</sup> D1 = day of first administration of IP; for visit windows see Section 7.1 of the protocol
<sup>b</sup> Vital signs collected for study purposes
<sup>c</sup> Only AEs possibly related to study procedures and SAEs are collected during the screening period
<sup>d</sup> Randomization should occur within 5 - 10 days of the screening LDL-C sample that determined eligibility
<sup>e</sup> PCSK9 samples must be taken prior to IP administration, if applicable
<sup>f</sup> Subjects with documented CK >10xULN (accompanied by muscle symptoms with statin use) and documented resolution of CK and muscle symptoms proceed directly to Part B.
<sup>g</sup> If measured CK >10xULN (accompanied by muscle symptoms) subjects are considered to have the equivalent of intolerable MRSE and period ends.
<sup>h</sup> If the subject consented to pharmacogenetics analyses, DNA will be extracted from some of the blood samples, eg, biomarker samples
<sup>i</sup> HCV antibodies only in high risk subjects (see Section 7) or if ALT or AST > 2x ULN at any time during screening; viral load only in subjects positive for HCV
<sup>j</sup> Pregnancy testing in females of childbearing potential, FSH only if applicable per exclusion
Table 1. Schedule of Assessments

Clinic visits will occur once a month except for an additional lab visit at Week 22

<table>
<thead>
<tr>
<th>Part B</th>
<th>Study Day / Timepoint</th>
<th>Visit D1</th>
<th>Visit W4</th>
<th>Visit W8</th>
<th>Visit W12</th>
<th>Visit W16</th>
<th>Visit W20</th>
<th>Visit W22</th>
<th>Visit W24</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>General Procedures</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Review for AEs/SAEs/CV events</td>
<td>X X X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Concomitant therapy</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Dietary instruction; medication compliance reminder</td>
<td>X X X X X X X X</td>
<td></td>
<td></td>
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<td>Randomization</td>
<td>Xa</td>
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<td></td>
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<tr>
<td></td>
<td>BPI-SF and SF-36 Questionnaireb</td>
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<td></td>
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<td></td>
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<tr>
<td></td>
<td>Central Laboratory</td>
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<td>Fasting lipids</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>ApoA1, ApoB, Lp(a)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Vitamin Ec</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>PCSK9 d</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td></td>
<td>Chemistry (incl. fasting glucose)</td>
<td>X X X X X</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>CK</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Hematology</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>HsCRP</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

a Randomization should occur within 5 - 10 days of the screening LDL-C sample that determined eligibility if subject is entering directly into Part B from screening based upon CK screening criteria
b PRO questionnaires must be completed before any other study procedures are performed on a given visit day
c Vitamin E samples will be drawn for all applicable visits, testing will be conducted by reflex when LDL-C is < 25 mg/dL
d PCSK9 samples must be taken prior to IP administration, if applicable
### Table 1. Schedule of Assessments

Clinic visits will occur once a month except for an additional lab visit at Week 22

<table>
<thead>
<tr>
<th>Study Day / Timepoint</th>
<th>Visit D1</th>
<th>Visit W4</th>
<th>Visit W8</th>
<th>Visit W12</th>
<th>Visit W16</th>
<th>Visit W20</th>
<th>Visit W22</th>
<th>Visit W24</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central Laboratory</strong></td>
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<tr>
<td>Biomarkers (blood)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Anti-AMG 145 antibodies</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td></td>
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<tr>
<td>HCV antibodiesb</td>
<td>X</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>HCV viral loadb</td>
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<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Urine pregnancyc</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Urinalysis</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td><strong>Investigational Product</strong></td>
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<tr>
<td>PO IP dispensation</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PO IP tablet count</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>SC IP administration, QM</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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</tr>
</tbody>
</table>

a If the subject did not participate in Part A and consented to pharmacogenetics analyses, DNA will be extracted from some of the blood samples, eg, biomarker samples

b HCV antibodies only in high risk subjects (see Section 7) or if ALT or AST > 2x ULN at any time during screening; viral load only in subjects positive for HCV

c Pregnancy testing in females of childbearing potential
Table 1. Schedule of Assessments

<table>
<thead>
<tr>
<th>Part C</th>
<th>Study Day / Timepoint</th>
<th>D1a</th>
<th>Q3M</th>
<th>EOS/Safety Followup Visit (W104)</th>
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<tr>
<td><strong>General Procedures</strong></td>
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<tr>
<td>Vital Signs (sitting BP, HR)</td>
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<tr>
<td>Review for AEs/SAEs/CV events</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Concomitant therapy</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dietary instruction</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td><strong>Central Laboratory</strong></td>
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<td></td>
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<tr>
<td>Fasting lipids</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ApoA1, ApoB, Lp(a), Vitamin Eb</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chemistry (incl fasting glucose)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>CK</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Hematology</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HbA1c</td>
<td>X (ANNUALLY ONLY)</td>
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<td>X</td>
</tr>
<tr>
<td>hsCRP</td>
<td>X (ANNUALLY ONLY)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Biomarkers (blood)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Anti-AMG 145 antibodies</td>
<td>X (ANNUALLY ONLY)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HCV viral loadc</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Urine pregnancy</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Investigational Product</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Al/Pen subject instruction for self-administration of AMG 145</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SC IP dispensation, QM or Q2Wd</td>
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<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SC IP count</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

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a Day 1 of Part C should occur on same day as or within 7 days of Part B Week 24 visit
b Vitamin E samples will be drawn for all applicable visits, testing will be conducted by reflex when LDL-C is < 25 mg/dL
c HCV viral load only in subjects positive for HCV
d Subjects will select preferred dosing regimen: Q2W or QM
7.2 General Study Procedures

There are three parts to this study:

- Part A is a double-blind, placebo-controlled cross over statin rechallenge;
- Part B is a comparison of AMG 145 to ezetimibe;
- Part C is a two-year open-label extension to evaluate long-term safety and efficacy.

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. 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, subjects will be invited to consent to pharmacogenetic analyses.

The procedures to be performed at visits are described below and are summarized in Table 1. If IP is administered during a study visit, administration should occur after completion of vital signs, ECG, and blood draw procedures, as applicable.

Subjects must be fasting for ≥ 9 hours before each study visit where fasting laboratory samples are obtained. If the subject is not fasting for any screening visit or the Day 1 visit, no laboratory samples should be collected and the subject must return as soon as possible in a fasting state for the visit. If the subject is not fasting for any visit with evaluation of lipids after study Day 1, 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, if possible within the window for the respective visit.

7.2.1 Placebo Run-in

In order to reduce the burden of unnecessary procedures on subjects on subjects who subsequently elect not to participate in the study or continue with study procedures, all subjects will enter a placebo run-in period to confirm tolerance of SC administration prior to randomization. This placebo run-in period can be started before or after venipuncture procedures for the study and will consist of SC administration of placebo consisting of 3 injections using 3 Al/Pens. This administration will follow the same procedures as injections of IP during the treatment period. Further details will be provided in the IPIM.

7.2.2 Rescreening

Subjects who screen fail due to the screening LDL-C concentration being out of range for eligibility cannot be rescreened for this study. Subjects who are ineligible at the initial
screening for other reasons may be re-consented and rescreened. With the exception of the placebo run-in, rescreened subjects will repeat all screening procedures. Rescreened subjects will maintain their originally assigned subject identification number and rescreening call registered in IVRS/IWRS.

7.3 Screen Fail
Subjects who are not eligible for participation must be registered as a screen failure in IVRS/IWRS.

7.3.1 Study Visit Definitions and Windows
Prior to study enrollment, subjects taking low dose statins or ezetimibe will discontinue these medications and allow for a minimum of 4-week washout period prior to LDL-C screening. Please see exclusion criterion 209 for complete list of drugs that should be washed out.

The screening period begins on the date that the ICF is signed (unless rescreening is required).

Randomization for Part A should occur within 5 - 10 days of the screening LDL-C evaluation used to determine eligibility.

The following visit windows will apply to all visits in each Part of the study:

- Part A: ± 7 days (except Day 1)
- Part B: ± 7 days
- Part C: ± 7 days

Study procedures for a specific visit may be completed on multiple days as long as all the procedures are completed within the visit window.
The Analyte Listing below outlines the specific analytes for serum chemistry, hematology, urinalysis, and other testing to be conducted.

**Analyte Listing**

<table>
<thead>
<tr>
<th>Chemistry</th>
<th>Urinalysis</th>
<th>Hematology</th>
<th>Other Labs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>Specific gravity</td>
<td>RBC</td>
<td>Fasting lipids</td>
</tr>
<tr>
<td>Potassium</td>
<td>pH</td>
<td>Hemoglobin</td>
<td>• Total cholesterol</td>
</tr>
<tr>
<td>Chloride</td>
<td>Blood</td>
<td>Hematocrit</td>
<td>• HDL-C</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>Protein</td>
<td>MCV</td>
<td>• LDL-C</td>
</tr>
<tr>
<td>Total protein</td>
<td>Glucose</td>
<td>MCH</td>
<td>• Triglycerides</td>
</tr>
<tr>
<td>Albumin</td>
<td>Bilirubin</td>
<td>MCHC</td>
<td>• VLDL-C</td>
</tr>
<tr>
<td>Calcium</td>
<td>WBC</td>
<td>RDW</td>
<td>• non-HDL-C</td>
</tr>
<tr>
<td>Magnesium</td>
<td>RBC</td>
<td>WBC</td>
<td>ApoA1</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>Epithelial cells</td>
<td>Platelets</td>
<td>ApoB</td>
</tr>
<tr>
<td>Fasting Glucose</td>
<td>Bacteria</td>
<td></td>
<td>hsCRP</td>
</tr>
<tr>
<td>BUN or Urea</td>
<td>Casts</td>
<td></td>
<td>LP (a)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Crystals</td>
<td></td>
<td>Anti-AMG 145</td>
</tr>
<tr>
<td>Uric acid</td>
<td></td>
<td></td>
<td>antibodies</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td></td>
<td></td>
<td>PCSK9</td>
</tr>
<tr>
<td>Direct bilirubin</td>
<td></td>
<td></td>
<td>HbA1c</td>
</tr>
<tr>
<td>CK</td>
<td></td>
<td></td>
<td>Vitamin E</td>
</tr>
<tr>
<td>Alk phos</td>
<td></td>
<td></td>
<td>Pregnancy test</td>
</tr>
<tr>
<td>LDH</td>
<td></td>
<td></td>
<td>(females of childbearing potential)</td>
</tr>
<tr>
<td>AST (SGOT)</td>
<td></td>
<td></td>
<td>FSH (if needed per exclusion 219)</td>
</tr>
<tr>
<td>ALT (SGPT)</td>
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<td></td>
<td>TSH</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 7.4.1. 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 blood/organs 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 HIV
• Have a known HCV-infected sexual partner

**Viral load will be tested at the time points indicated in Schedule of Assessments Section 7.1 only 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), Vitamin E and hsCRP 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 blinded IP administration. Investigators will be informed if triglycerides are > 1000 mg/dL (11.3 mmol/L) so that appropriate subject follow-up can be initiated.

### 7.4 Screening Enrollment and/or Randomization

The following procedures are to be completed during the screening period of subjects at time points designated in the Schedule of Assessments:

• Informed Consent Form signed
• Medical history
• Vital signs (eg, sitting blood pressure, heart rate, respiration rate, temperature)
• Review for Adverse Events and Serious Adverse Events (only AEs possibly related to study procedures and SAEs are collected during the screening period)
• Documentation of concomitant medications
• Dietary instruction: subject will be counseled on the importance of maintaining a “heart-healthy” diet throughout the course of the study; medication compliance reminder
• Physical exam
• Body height
• Body weight and waist circumference
• 12-lead ECG
• Statin Intolerance History Questionnaire
• Any subject with a documented history of CK elevation > 10 x ULN accompanied by muscle symptoms while on statin therapy and documented resolution of both CK elevation and muscle symptoms upon discontinuation of statin therapy, must bypass Part A and advance directly into Part B
Central Laboratory Assessments:

- Blood draw for fasting lipids (≥ 9 hour fasting sample), chemistry (including fasting glucose), CK, coagulation, hematology, hsCRP, HbA1c, TSH, and eGFR, (Note: eGFR will be calculated by the central laboratory and will be provided to the site for eligibility determination) Blood draws for hepatitis C virus (HCV) antibodies in subjects at high risk for, or with history of, HCV infection and in subjects with AST or ALT > 2x ULN at any time during screening, HCV viral load (only in subjects positive for HCV) Serum FSH (only if required to ensure menopause in a female subject by central laboratory)
- Serum pregnancy (females of childbearing potential only)
- Urine sample for urinalysis

- Placebo injection (does not need to be repeated for rescreening)

7.4.1 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. LDL-C should not be retested due to out-of-range LDL-C concentration at screening.

7.4.2 Treatment

7.4.2.1 Part A [Period 1: Visit Day 1 (Randomization)]: All Subjects

- Day 1 is the first day of Part A. The following procedures should be conducted for all subjects unless specified otherwise.
  - Review for Adverse Events and Serious Adverse Events
  - Documentation of concomitant medications
  - Dietary instruction: subject will be counseled on the importance of maintaining a "heart-healthy" diet throughout the course of the study; medication compliance reminder
  - Randomization treatment assignment via IVR/IWR system
  - BPI-SF and SF-36
  - Central Laboratory Assessments:
    - Blood draw for fasting lipids (≥ 9 hour fasting sample), Apo(A1), ApoB, Lp(a), PCSK9, chemistry (including fasting glucose), CK
    - Biomarkers
    - Urine sample for urinalysis
  - PO IP dispensing
7.4.2.2 Part A [Period 1: Visit/Week 4]: All Subjects

- The following procedures should be conducted for all subjects on Week 4 of Part A of study unless specified otherwise.

  - Review for Adverse Events and Serious Adverse Events
  - Documentation of concomitant medications
  - Provide dietary instruction: subject will be counseled on the importance of maintaining a “heart-healthy” diet throughout the course of the study; medication compliance reminder
  - BPI-SF and SF-36
  - Central Laboratory Assessments:
    - Blood draw for fasting lipids (≥ 9 hour fasting sample), chemistry (including fasting glucose), CK
    - Urine sample for urinalysis
  - PO IP dispensing
  - PO IP tablet count

7.4.2.3 Part A [Period 1: Visit/Week 8]: All Subjects

- The following procedures should be conducted on Week 8 of Part A of study for all subjects unless specified otherwise.

  - Review for Adverse Events and Serious Adverse Events
  - Documentation of concomitant medications
  - Provide dietary instruction: subject will be counseled on the importance of maintaining a “heart-healthy” diet throughout the course of the study; medication compliance reminder
  - BPI-SF and SF-36
  - Central Laboratory Assessments:
    - Blood draw for fasting lipids (≥ 9 hour fasting sample), chemistry (including fasting glucose), CK
    - Urine sample for urinalysis
  - PO IP tablet count

7.4.2.4 Part A [Period 1: Visit/Week 10]: All Subjects

- The following procedures should be conducted on Week 10 of Part A of study for all subjects unless specified otherwise.

  - Review for Adverse Events and Serious Adverse Events
  - Documentation of concomitant medications
  - Provide dietary instruction: subject will be counseled on the importance of maintaining a “heart-healthy” diet throughout the course of the study; medication compliance reminder
• BPI-SF and SF-36
• Central Laboratory Assessments:
  • Blood draw for fasting lipids (≥ 9 hour fasting sample), chemistry (including fasting glucose), CK
  • Biomarkers
  • Urine sample for urinalysis
• PO IP tablet count

7.4.2.5 Part A [Period 2: Visit/Week 12]: All Subjects
• The following procedures should be conducted on Week 12 of Part A of study for all subjects unless specified otherwise.
  • Vital signs (eg, sitting blood pressure, heart rate, respiration rate, temperature)
  • Review for Adverse Events and Serious Adverse Events
  • Documentation of concomitant medications
  • Provide dietary instruction: subject will be counseled on the importance of maintaining a “heart-healthy” diet throughout the course of the study; medication compliance reminder
• BPI-SF and SF-36
• Central Laboratory Assessments:
  • Blood draw for fasting lipids (≥ 9 hour fasting sample), chemistry (including fasting glucose), CK
  • Biomarkers
  • Urine sample for urinalysis
• PO IP dispensing
• PO IP tablet count

7.4.2.6 Part A [Period 2: Visit/Week 16]: All Subjects
• The following procedures should be conducted on Week 16 of Part A of study for all subjects unless specified otherwise.
  • Review for Adverse Events and Serious Adverse Events
  • Documentation of concomitant medications
  • Provide dietary instruction: subject will be counseled on the importance of maintaining a “heart-healthy” diet throughout the course of the study; medication compliance reminder
• Central Laboratory Assessments:
  • Blood draw for fasting lipids (≥ 9 hour fasting sample), chemistry (including fasting glucose), CK
  • Urine sample for urinalysis
• BPI-SF and SF-36
• PO IP dispensing
• PO IP tablet count

7.4.2.7 Part A [Period 2: Visit/Week 20]: All Subjects
• The following procedures should be conducted on Week 20 of Part A of study for all subjects unless specified otherwise.
  • Review for Adverse Events and Serious Adverse Events
  • Documentation of concomitant medications
  • Provide dietary instruction: subject will be counseled on the importance of maintaining a “heart-healthy” diet throughout the course of the study; medication compliance reminder
  • BPI-SF and SF-36
  • Central Laboratory Assessments:
    ▪ Blood draw for fasting lipids (≥ 9 hour fasting sample), chemistry (including fasting glucose), CK
    ▪ Urine sample for urinalysis
  • PO IP tablet count

7.4.2.8 Part A [Period 2: Visit/Week 22]: All Subjects
• The following procedures should be conducted on Week 22 of Part A of study for all subjects unless specified otherwise.
  • Vital signs (eg, sitting blood pressure, heart rate, respiration rate, temperature)
  • Review for Adverse Events and Serious Adverse Events
  • Documentation of concomitant medications
  • Provide dietary instruction: subject will be counseled on the importance of maintaining a “heart-healthy” diet throughout the course of the study; medication compliance reminder
  • BPI-SF and SF-36
  • Central Laboratory Assessments:
    ▪ Blood draw for fasting lipids (≥ 9 hour fasting sample), Apo(A1), ApoB, Lp(a), chemistry (including fasting glucose), hematology, CK
    ▪ Biomarkers
    ▪ Urine sample for urinalysis
  • PO IP tablet count
  • Collect unused IP
7.4.2.9 Part B: [Visit Day 1 (Randomization)]: All Subjects

- Part B Day 1 is the first day of Part B.
- The following procedures should be conducted at this visit for all subjects unless specified otherwise.
  - Vital signs (eg, sitting blood pressure, heart rate, respiration rate, temperature)
  - Physical Exam
  - Review for Adverse Events and Serious Adverse Events
  - Documentation of concomitant medications
  - Provide dietary instruction: subject will be counseled on the importance of maintaining a “heart-healthy” diet throughout the course of the study; medication compliance reminder
  - Randomization treatment assignment via IVR/IWR system
  - Urine pregnancy test (for women subjects of childbearing potential only)
  - PO IP dispensing
  - SC IP administration in clinic
  - BPI-SF and SF-36
  - Central Laboratory Assessments:
    - Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, Lp(a), PCSK9, chemistry (including fasting glucose), CK, hematology, hsCRP, biomarkers, anti-AMG 145 antibodies
    - Blood draws for hepatitis C virus (HCV) antibodies in subjects at high risk for, or with history of, HCV infection and in subjects with AST or ALT > 2x ULN at any time during screening. HCV viral load (only in subjects positive for HCV)
    - Urine sample for urinalysis
    - Anti-AMG 145 Antibodies

7.4.2.10 Part B: [Visit/Week 4]: All Subjects

The second visit in Part B, should occur 4 weeks after Day 1 of Part B. The following procedures should be conducted at this visit for all subjects unless specified otherwise.

- Review for Adverse Events and Serious Adverse Events
- Documentation of concomitant medications
- Provide dietary instruction: subject will be counseled on the importance of maintaining a “heart-healthy” diet throughout the course of the study; medication compliance reminder
- BPI-SF and SF-36
7.4.2.11 Part B: [Visit/Week 8]: All Subjects

- The third visit in Part B and should occur 8 weeks after Day 1 of Part B. The following procedures should be conducted at this visit for all subjects unless specified otherwise.
  - Review for Adverse Events and Serious Adverse Events
  - Documentation of concomitant medications
  - Provide dietary instruction: subject will be counseled on the importance of maintaining a “heart-healthy” diet throughout the course of the study; medication compliance reminder
  - BPI-SF and SF-36
  - Central Laboratory Assessments:
    - Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, Lp(a), PCSK9, chemistry (including fasting glucose), CK, hematology
    - Blood draws for hepatitis C virus (HCV) antibodies in subjects at high risk for, or with history of, HCV infection and in subjects with AST or ALT > 2x ULN at any time during screening, HCV viral load (only in subjects positive for HCV)
    - Urine sample for urinalysis and pregnancy test
  - PO IP dispensing
  - PO IP tablet count
  - SC IP administration in clinic

7.4.2.12 Part B: [Visit/Week 12]: All Subjects

- The fourth visit in Part B should occur 12 weeks after Day 1 of Part B. The following procedures will need to be conducted at this visit for all subjects unless specified otherwise.
  - Vital signs (eg, sitting blood pressure, heart rate, respiration rate, temperature)
  - Review for Adverse Events and Serious Adverse Events
  - Documentation of concomitant medications
• Provide dietary instruction: subject will be counseled on the importance of maintaining a “heart-healthy” diet throughout the course of the study; medication compliance reminder

• BPI-SF and SF-36

• Central Laboratory Assessments:
  ▪ Blood draw for fasting lipids (≥ 9 hour fasting sample), Apo(A1), ApoB, Lp(a), PCSK9, chemistry (including fasting glucose), CK, hematology, biomarkers
  ▪ Blood draws for hepatitis C virus (HCV) antibodies in subjects at high risk for, or with history of, HCV infection and in subjects with AST or ALT > 2x ULN at any time during screening, HCV viral load (only in subjects positive for HCV)
  ▪ Urine sample for urinalysis and pregnancy test

• PO IP dispensing

• PO IP tablet count

• SC IP administration in clinic

7.4.2.13 Part B: [Visit/Week 16]: All Subjects

• The fifth visit in Part B and should occur 16 weeks after Day 1 of Part B. The following procedures should be conducted at this visit for all subjects unless specified otherwise.

  • Review for Adverse Events and Serious Adverse Events
  • Documentation of concomitant medications
  • Provide dietary instruction: subject will be counseled on the importance of maintaining a “heart-healthy” diet throughout the course of the study; medication compliance reminder
  • BPI-SF and SF-36
  • Central Laboratory Assessments:
    ▪ Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, Lp(a), PCSK9, chemistry (including fasting glucose), CK, hematology
    ▪ Blood draws for hepatitis C virus (HCV) antibodies in subjects at high risk for, or with history of, HCV infection and in subjects with AST or ALT > 2x ULN at any time during screening, HCV viral load (only in subjects positive for HCV)
    ▪ Urine sample for urinalysis and pregnancy test
  • PO IP dispensing
  • PO IP tablet count
  • SC IP administration in clinic
7.4.2.14 Part B: [Visit/Week 20]: All Subjects

- The sixth visit in Part B and should occur 20 weeks after Day 1 of Part B. The following procedures will need to be conducted at this visit for all subjects unless specified otherwise.
  - Review for Adverse Events and Serious Adverse Events
  - Documentation of concomitant medications
  - Provide dietary instruction: subject will be counseled on the importance of maintaining a “heart-healthy” diet throughout the course of the study; medication compliance reminder
  - BPI-SF and SF-36
  - Central Laboratory Assessments:
    - Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, Lp(a), PCSK9, chemistry (including fasting glucose), CK, hematology
    - Blood draws for hepatitis C virus (HCV) antibodies in subjects at high risk for, or with history of, HCV infection and in subjects with AST or ALT > 2x ULN at any time during screening, HCV viral load (only in subjects positive for HCV)
    - Urine sample for urinalysis and pregnancy test
  - PO IP dispensing
  - PO IP tablet count
  - SC IP administration in clinic

7.4.2.15 Part B: [Visit/Week 22]: All Subjects

- The seventh visit in Part B and should occur 22 weeks after Day 1 of Part B. The following procedures will need to be conducted at this visit for all subjects unless specified otherwise.
  - Review for Adverse Events and Serious Adverse Events
  - Documentation of concomitant medications
  - Provide dietary instruction: subject will be counseled on the importance of maintaining a “heart-healthy” diet throughout the course of the study; medication compliance reminder
  - BPI-SF and SF-36
  - Central Laboratory Assessments:
    - Blood draw for fasting lipids (≥ 9 hour fasting sample), Apo(A1), ApoB, Lp(a), PCSK9

7.4.2.16 Part B: [Visit/Week 24]: All Subjects

- The final visit in Part B should occur 24 weeks after Day 1 of Part B. The following procedures will need to be conducted at this visit for all subjects unless specified otherwise. Subjects, who permanently discontinue IP, withdraw from or terminate study participation before EOS must have following procedures conducted.
  - Vital signs (eg, sitting blood pressure, heart rate, respiration rate, temperature)
  - Review for Adverse Events and Serious Adverse Events
- Documentation of concomitant medications
- Provide dietary instruction: subject will be counseled on the importance of maintaining a “heart-healthy” diet throughout the course of the study
- BPI-SF and SF-36
- Central Laboratory Assessments:
  - Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, Lp(a), Vitamin E (sample drawn, testing by reflex when LDL-C is < 25 mg/dL), PCSK9, chemistry (including fasting glucose), CK, hematology, hsCRP, biomarkers
  - Anti-AMG 145 Antibodies
  - Blood draws for hepatitis C virus (HCV) antibodies in subjects at high risk for, or with history of, HCV infection and in subjects with AST or ALT > 2x ULN at any time during screening, HCV viral load (only in subjects positive for HCV)
  - Urine sample for urinalysis and pregnancy test
- PO IP tablet count

7.4.2.17 Part C/D1: All Subjects who Complete Part B and Consent to Part C
- The following procedures should be conducted on Day 1 of Part C for all subjects unless specified otherwise. Day 1 of Part C should occur at the same visit or within 7 days of Week 24 visit of Part B
- Review for Adverse Events and Serious Adverse Events
- Documentation of concomitant medications
- Provide dietary instruction: subject will be counseled on the importance of maintaining a “heart-healthy” diet throughout the course of the study
- AI/Pen or Personal Injector subject instruction on self-administration of AMG 145
- Subjects will be allowed to select one of two dosing regimens: Q2W and QM
- Dispensation of SC IP

7.4.2.18 Part C/Q3M: All Subjects
- The following procedures will need to be conducted on a quarterly basis during Part C: of study for all subjects unless specified otherwise.
- Vital signs (eg, sitting blood pressure, heart rate, respiration rate, temperature)
- Review for Adverse Events and Serious Adverse Events
- Documentation of concomitant medications
- Provide dietary instruction: subject will be counseled on the importance of maintaining a “heart-healthy” diet throughout the course of the study
- Central Laboratory Assessments:
  - Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, Lp(a), Vitamin E (sample drawn, testing by reflex when LDL-C is < 25 mg/dL), chemistry (including fasting glucose), CK, hematology, HbA1c (annually only)
- HsCRP (annually only)
- Anti-AMG 145 Antibodies (annually only)
- Blood draws for hepatitis C virus (HCV) antibodies in subjects at high risk for, or with history of, HCV infection and in subjects with AST or ALT > 2x ULN at any time during screening, HCV viral load (only in subjects positive for HCV)
- Urine sample for urinalysis and pregnancy test

- Subjects will be allowed to switch between Q2W and QM regimens
- Dispensation of SC IP
- SC IP count

### 7.4.2.19 Safety Follow-up Visit(s)/End of Study Visit

- The following procedures will need to be conducted at End of Study (EOS) for all subjects unless specified otherwise.
  - Vital signs (eg, sitting blood pressure, heart rate, respiration rate, temperature)
  - Review for Adverse Events and Serious Adverse Events
  - Documentation of concomitant medications
  - Central Laboratory Assessments:
    - Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, Lp(a), Vitamin E (sample drawn, testing by reflex when LDL-C is < 25 mg/dL), chemistry (including fasting glucose), CK, hematology: HbA1c, hsCRP
    - Biomarkers
    - Anti-AMG 145 antibodies
    - Blood draws for hepatitis C virus (HCV) antibodies in subjects at high risk for, or with history of, HCV infection and in subjects with AST or ALT > 2x ULN at any time during screening, HCV viral load (only in subjects positive for HCV)
    - Urine sample for urinalysis and pregnancy test
  - SC IP count

### 7.4.3 Standardization of Study Procedures

#### 7.4.3.1 Measurement of Vital Signs

The following measurements must be performed: Systolic/Diastolic Blood Pressure, Heart Rate, Respirations, and Temperature.

Subject must be in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF.

Record all measurements on the vital signs CRF.
7.4.3.2 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.

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

ECGs should be performed in a standardized method, in triplicate, and approximately 30 seconds apart, prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals.

7.4.3.4 Lipid Measurements
Only the screening LDL-C concentration will be reported to the site for the eligibility decision. For subjects who are rescreened, data from the first screening period will not be used for the analysis. 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 from randomization until at least 12 weeks after the subject’s last blinded administration of IP. If a lipid panel is drawn, all reasonable steps must be undertaken to avoid informing the subject and study personnel of the results.
7.5 Antibody Testing Procedures

Blood samples will be collected from all subjects at Part B: [Day 1, and Week 24]; Part C: [Annually, and at End-of-Study] for the measurement of anti-AMG 145 binding antibodies. All subjects who have received at least one administration of AMG 145 will have samples assayed for binding 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. 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 12 weeks 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 4 weeks), 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.

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.

7.6 Biomarker Development

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

It is expected that further advances will occur 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. The samples collected will not be suitable for any DNA or other genetic testing and it is specifically stated that these specimens will not be used for this purpose.
Refer to the laboratory manual for detailed collection and handling procedures for all biomarker development samples.

**Blood Samples**

Blood samples are to be collected for biomarker development at the following time points:

For biomarker analysis, blood samples will be collected at Part A: Day 1, Week 10, Week 12, Week 22; Part B: Day 1, Week 12 and Week 24, and Part C: hsCRP (annually only) and HbA1c (annually only) and at End of Study so that analyses may be performed that will look at markers of PCSK9 signaling, LDL-R turnover, cholesterol metabolism, inflammation, and plaque stability. Examples of markers include certain glycosylated proteins, matrix metalloproteinases, markers of inflammation such as C-reactive protein, myeloperoxidase, bromo and nitro-tyrosine, and Tumor Necrosis Factor (TNF) cellular adhesion molecules.

### 7.7 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 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 primary hyperlipidemia and mixed dyslipidemia and/or to identify subjects who may have positive or negative response to AMG 145. For subjects who consent to this/these analysis/analyses, DNA may be extracted.

### 7.8 Sample Storage and Destruction

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 hyperlipidemia and mixed dyslipidemia, 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 will be the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the principal investigator or at the end of the storage period or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample).
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. If a commercial product is developed from this research project, the sponsor will own the commercial product. The subject will have no commercial rights to such product and will have no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 11.3 for subject confidentiality. Any blood (eg, biomarker) sample collected according to the Schedule of Assessments (Section 7.1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the PCSK9 inhibition, the dose response and/or prediction of response to AMG 145 or anti-AMG 145 antibodies, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

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

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

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

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY
8.1 Subjects’ Decision to Withdraw

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

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies, or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Section 7.1) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments (Section 7.1) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.
8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

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

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.1.

8.3 Reasons for Removal From

8.3.1 Reasons for Removal From Part A

Reasons for removal from Part A include any of the following:
- subject request
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, protocol-specified criteria (list criteria), pregnancy)
- decision by sponsor (other than subject request or safety concern)
- death
- lost to follow-up

8.3.2 Reasons for Removal From Treatment

Reasons for removal from protocol-required investigational product(s) or procedural assessments include any of the following:
- subject request
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, protocol-specified criteria, pregnancy)
- death
- lost to follow-up
- decision by Sponsor (other than subject request, safety concern, lost to follow-up)

8.3.3 Reasons for Removal From Study

- Reasons for removal of a subject from the study are:
  - decision by sponsor
  - withdrawal of consent from study
  - death
  - lost to follow-up
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 that 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.

Resolution of the adverse event will be captured in Safety CRF.

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

The investigator’s clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject’s legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

9.1.2 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, DILI (see Appendix A for drug-induced liver injury reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Reporting of Adverse Events

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

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after enrollment through the end of study are reported using the applicable CRF (eg, Adverse Event Summary).

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 SC IP (AMG 145 or placebo), PO IP (atorvastatin or placebo), PO IP (ezetimibe or placebo), medical device(s): prefilled Autoinjector/Pen (AI/Pen) or 3.5 mL Personal Injector and
- Action taken.

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE). The grading scale used in this study is described in Appendix A. The investigator must assess whether the adverse event is possibly related to SC IP (AMG 145 or placebo), PO IP (atorvastatin or placebo) or PO IP (ezetimibe 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 adverse event is possibly related to the prefilled AI/Pen or Personal Injector used to administer SC 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 is possibly related to any study-mandated activity [eg, administration of investigational product, protocol-required therapies, device(s)
and/or procedure (including any screening procedure(s)). This relationship is indicated by a “yes” or “no” response to the question: “Is there a reasonable possibility that the event may have been caused by a study activity [e.g., administration of investigational product, protocol-required therapies, device(s)], and/or 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) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

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

9.2.2 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 e.g., 30 days after the last day of the dosing interval of investigational product(s)/end of study/safety follow-up visit are recorded in the subject’s medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator’s knowledge of the event via the 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.

The serious adverse event must be submitted to Amgen within 24 hours following the investigator’s knowledge of the event via the applicable CRF. If the electronic data capture (EDC) system is unavailable to the site staff to report the Serious Adverse Event, the information is to be reported to Amgen via an electronic Serious Adverse
Event (eSAE) Contingency Report Form within 24 hours of the investigator’s knowledge of the event. See Appendix B for a sample of the electronic Serious Adverse Event Contingency Report Form. For EDC studies where 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 SC IP (AMG 145 or placebo), PO IP (atorvastatin or placebo) or PO IP (ezetimibe 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 SC 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 any study-mandated activity or procedure. This relationship is indicated by a “yes” or “no” response to the question: “Is there a reasonable possibility that the event may have been caused by a study activity/procedure”?

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

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. The investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the applicable CRF (eg, Adverse Event Summary CRF).

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

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

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

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

### 9.3 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 and for an additional 15 weeks after the end of treatment with IP, report the pregnancy to Amgen as specified below.

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 C). 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 the female subject is taking protocol-required therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through 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 event. Report a lactation case on the Lactation Notification Worksheet (Appendix C).
10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Co-Primary Endpoints

- Mean percent change from baseline in LDL-C at Weeks 22 and 24 of Part B
- Percent change from baseline in LDL-C at Week 24 of Part B

10.1.2 Co-Secondary Efficacy Endpoints

Co-secondary endpoints of the means at Weeks 22 and 24 of Part B and at Week 24 of Part B for:

Tier 1 endpoints

- Change from baseline in LDL-C
- LDL-C response (LDL-C < 70 mg/dL [1.81 mmol/L])
- Percent change from baseline in total cholesterol
- Percent change from baseline in non-HDL-C
- Percent change from baseline in ApoB
- Percent change from baseline in the total cholesterol/HDL-C ratio
- Percent change from baseline in ApoB/ApoA1 ratio

Tier 2 endpoints

- Percent change from baseline in Lp(a)
- Percent change from baseline in triglycerides
- Percent change from baseline in HDL-C
- Percent change from baseline in VLDL-C

10.1.3 Tertiary Efficacy Endpoints

- Mean percent change from baseline in ApoA1 at Weeks 22 and 24 of Part B
- Percent change from baseline in ApoA1 at Week 24 of Part B

10.1.4 Exploratory Endpoints

- Incidence of MRSE following a lead-in statin rechallenge (Part A)

- Subject incidence of adjudicated events:
  - death by any cause
  - cardiovascular death
  - myocardial infarction
  - hospitalization for unstable angina
  - coronary revascularization
stroke
- hospitalization for heart failure
- transient ischemic attack (TIA)
- Subject incidence of non-coronary revascularization

For both Part B and Part C of the study,

- 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
  - VLDL-C
  - HDL-C
  - ApoA1
  - Triglycerides
  - Lp(a)

For Part B of the study,

- hsCRP at each scheduled assessment
- PCSK9 change from baseline at each scheduled assessment
- SF-36 domain score: change from baseline at each scheduled assessment
- BPI items: change from baseline at each scheduled assessment

10.1.5 Safety Endpoints

- Subject incidence of adverse events

For both Part B and Part C of the study,

- Safety laboratory values at each scheduled visit
- Incidence of anti-AMG 145 antibody (binding and neutralizing) formation

10.1.6 Analysis Sets

Part A of the study

The rechallenge analysis set (RAS) will include all randomized subjects in Part A of the study who received at least 1 dose of oral IP. The safety analysis, especially the evaluation of incidence of MRSE in Part A will be conducted based on RAS.
Part B of the study

The full analysis set (FAS) will include all randomized subjects in Part B of the study who received at least 1 dose of Part B IP. This analysis set will be used in both efficacy and safety analyses for Part B of the study. In efficacy analyses for Part B of the study, subjects will be grouped according to their randomized treatment group assignment. In safety analyses for Part B of the study, 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.

The completer analysis set (CAS) includes subjects in the FAS who adhered to the scheduled IP regimen and have observed values for the co-primary endpoints.

Part C of the study

The long-term analysis set (LAS) will include all subjects enrolled in Part C of the study who received at least 1 dose of open label IP. This analysis set will be used in all analyses for Part C of the study.

10.1.7 Covariates and Subgroups

Baseline covariates include, but are not limited to:

- Stratification factor in Part B of the study:
  - Screening LDL-C: < 180 mg/dL [4.66 mmol/L] vs. ≥ 180 mg/dL

The following baseline covariates may be used for subgroup or covariate analyses with the subgroups as specified or in their original format:

- Age: < 65 years, ≥ 65 years
- Sex
- Race
- Study baseline LDL-C: < median, ≥ median
- Family history of premature coronary heart disease: yes, no
- PCSK9 level: < baseline median, ≥ baseline median

Subgroup levels may be combined as appropriate for subgroup analyses.

10.2 Sample Size Considerations

The planned total sample size for Part B of the study is 100 subjects at 2:1 ratio for AMG 145 arm and ezetimibe arm. The primary analysis will require the 2-sided tests of each co-primary endpoint to be significant at a level of 0.05. The planned sample size in
Part B should provide adequate power to determine the superiority of AMG 145 (QM) relative to ezetimibe as measured by the co-primary endpoints. From the global phase 2 study 20090159, the treatment effect of AMG 145 QM 420 mg compared to ezetimibe in the % change from baseline in LDL-C at week 12 is -35.9% (-44.1%, -27.8%) and from other phase 2 studies in AMG 145 program, the treatment effect measured as mean of week 10 and 12 were as large or larger than week 12 and highly correlated (> 85%) with ones at week 12. The assumed smallest treatment effect between the co-primary endpoints in AMG 145 QM 420 mg is 25%, with a common standard deviation (SD) of 20%. This SD assumption is based on AMG 145 phase 2 results and is consistent with literature review (FDA statistical reviews of ezetimibe and pitavastatin).

It is anticipated that the treatment effect will be attenuated due to the following assumptions:

- Approximately 15% of randomized subjects will end IP early but will remain on study. There will be no treatment effect difference between the AMG 145 and ezetimibe subjects after they end IP early.
- Approximately 5% of randomized subjects will end the study early. The treatment effect of AMG 145 over ezetimibe is a LDL-C reduction of approximately 12%.

After accounting for treatment attenuation and assuming 2% of randomized subjects do not receive any IP, the sample size will provide approximately 98% power for each of the co-primary endpoints in testing the superiority of AMG 145 QM 420 mg over ezetimibe. The sample size calculation is performed using a two-sided t-test with a 0.05 significance level, an attenuated treatment effect of 21% reduction in LDL-C and an attenuated common SD of 24%.

As the co-primary endpoints are correlated, there is at least 96%(98% x 98%) power to simultaneously detect significant treatment effects of the co-primary endpoints. The power calculation is derived using nQuery version 7.01.

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Individual subject treatment assignments for both Part A and Part B of the study will be maintained by the IVRS/IWRS. Members of the Amgen study team will not have access to unblinded data until the study is unblinded for the primary analysis. 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, and performing 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 Analyses

10.4.1 Data Monitoring Committee (DMC)

An external independent DMC has been established to formally review the accumulating data from this and other completed and ongoing studies with AMG 145 to ensure there is no avoidable increased risk for harm to subjects. The independent DMC is chaired by an external academic cardiologist who is an expert in lipids and clinical trials. 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 Primary Analysis

To evaluate efficacy and safety of 24 weeks of AMG 145 SC 420 mg QM compared with ezetimibe, the primary analysis will be performed when all randomized subjects in Part B have either completed all the scheduled study visits in Part B or have early terminated from the study. At that time, the database of the study will be cleaned, processed and a snapshot will be taken; the study will also be unblinded.

10.4.3 Final Analysis

The final analysis will be conducted when all enrolled subjects in Part C of the study have either completed all the scheduled study visits in Part C or have early terminated from the study. At that time, the database of the study will be cleaned, processed and a snapshot will be taken. The final analysis will be done to assess long-term safety and efficacy of AMG 145.

10.5 Planned Methods of Analysis

10.5.1 General Considerations

Based on the snapshot for the primary analysis, efficacy and safety analyses will be performed on FAS. Unless otherwise specified, the FAS will be the default analysis set in analyses for Part B of the study and data will be summarized by randomized treatment group.
Based on the snapshot for the final analysis, long-term efficacy and safety analyses will be performed on LAS and the analyses will be descriptive.

Subject disposition, demographics, baseline characteristics, exposure to IP and PRO (SF-36 and BPI) will be summarized. Unless otherwise specified, the baseline value of Part B or C is defined as the subject’s baseline value from the Part A of the study.

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. 95% confidence intervals will be calculated for select continuous and categorical endpoints.

Methods of handling missing data for efficacy endpoints will be described throughout this section. Missing data will not be imputed for safety endpoints.

**Multiplicity Adjustment Method**

Methods of adjusting for multiplicity due to multiple endpoints (co-primary and co-secondary efficacy endpoints) are described in the diagram below.
Testing of each co-endpoint pair will result in a single p-value, and for co-secondary endpoints these p-values will then be used in the Hochberg procedure. The following method will be used to preserve the familywise error rate at 0.05 for testing the co-primary and co-secondary efficacy endpoints:

1. If the treatment effect from the primary analysis of the co-primary endpoints are significant at a significance level of 0.05, statistical testing of the tier 1 co-secondary efficacy endpoints (as defined in Section 10.1.2) will follow the Hochberg procedure at a significance level of 0.005 (Hochberg, 1988).

2. If all tier 1 co-secondary efficacy endpoints are significant, the tier 2 co-secondary efficacy endpoints will be tested using the Hochberg procedure at a significance level of 0.05.

3. If not all tier 1 co-secondary efficacy endpoints are significant, the tier 2 co-secondary efficacy endpoints will be tested using the Hochberg procedure at a significance level of 0.045 (Wiens, 2003).

Unless specified otherwise, all other hypothesis testing will be 2-sided with a significance level of 0.05.

10.5.2 Co-Primary Efficacy Endpoints

Primary analyses

To assess the co-primary endpoints of the mean percent change from baseline in LDL-C at weeks 22 and 24 of Part B and the percent change in LDL-C from baseline at week 24 of Part B, a repeated measures linear effects model will be used to compare the efficacy of AMG 145 with ezetimibe. The repeated measures model will include terms for treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit. Missing values will not be imputed when the repeated measures linear effects model is used.

Sensitivity Analyses

To evaluate the robustness of the analysis results, sensitivity analyses will be performed as follows:

- The primary analysis will be repeated using the CAS.
- Non-parametric analyses (Quade test) will be performed.

Subgroup Analyses

If applicable, subgroup analyses on the co-primary endpoints will be conducted using the stratification factors and baseline covariates.
10.5.3 Co-Secondary Efficacy Endpoints
The statistical model and testing of the tier 1 co-secondary efficacy endpoints will be similar to the primary analysis of the co-primary endpoints. The co-secondary efficacy endpoints of LDL-C response will be analyzed using the Cochran-Mantel Haenszel (CMH) test adjusted by the stratification factor.

Analyses of the tier 2 co-secondary efficacy endpoints will use the same analysis model as the tier 1 endpoints, and the testing will use a union-intersection test.

Multiplicity adjustment procedures are defined in Section 10.5.1.

10.5.4 Tertiary Efficacy Endpoints
Analysis of the tertiary efficacy endpoints will be similar to the primary analysis of the co-primary endpoints. No multiplicity adjustment will be applied.

10.5.5 Safety Endpoints
Adverse Events
Adverse events will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Subject incidences 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 for each treatment group.

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 during the study.

Vital Signs
Vital signs will be summarized for each treatment group using descriptive statistics at each scheduled visit.

Concomitant Medications
Concomitant medications of interest 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.
11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Clinical Study Manager to the investigator. The written informed consent document is to 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 investigational product(s) is/are administered.

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

The acquisition of informed consent and the subject’s agreement or refusal of his/her notification of the primary care physician is to be documented in the subject’s medical records, and the informed consent form is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject.

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

11.2 Institutional Review Board/Independent Ethics Committee

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

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

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

11.3 Subject Confidentiality

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

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

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 IRB/IEC direct access to review the subject’s original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.
12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

If Amgen amends the protocol, agreement from the Investigator must be obtained. The IRB/IEC must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IRB/IEC to Amgen.

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

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

12.2 Study Documentation and Archive

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

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

In this study, the IVR/IWR system captures the following data points and these are considered source data: MRSE.

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

Elements to include:

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

• Non-investigational product(s) and or medical device(s) documentation, as applicable.

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

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

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

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

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

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

Data capture for this study is planned to be electronic:

• All source documentation supporting entries into the CRFs must be maintained and readily available.

• Updates to CRFs will be automatically documented through the software’s “audit trail”.


To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications are created in the EDC system database for site resolution and closed by Amgen reviewer.

The investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that investigator inspected or reviewed the data on the CRF, 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 Investigator Responsibilities for Data Collection**

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 1) the investigator can search publically available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

**12.5 Language**

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

**12.6 Publication Policy**

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

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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

12.7 Compensation

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


14. APPENDICES
Appendix A. Additional Safety Assessment Information

Adverse Event 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:


Drug-induced Liver Injury Reporting & Additional Assessments Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation according to the criteria specified in Section 6.2.3 require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate CRF (eg, Adverse Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Amgen.
- Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.2.2.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Sections 6.3.1 and 6.3.2 or who experience AST or ALT elevations >3 x ULN are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels. Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve
- Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic
- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL:
- Obtain complete blood count (CBC) with differential to assess for eosinophilia
- Obtain serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
- Obtain serum acetaminophen (paracetamol) levels
- Obtain a more detailed history of:
  - Prior and/or concurrent diseases or illness
  - Exposure to environmental and/or industrial chemical agents
  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - Prior and/or concurrent use of alcohol, recreational drugs and special diets
  - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Obtain viral serologies
- Obtain CPK, haptoglobin, LDH, and peripheral blood smear
- Perform appropriate liver imaging if clinically indicated
- Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in corresponding CRFs.
Appendix B. Sample Electronic Serious Adverse Event Contingency Reporting Form

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 (eg, 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/complete all that apply):
  - An event that applies to a specialty CRF page titled (eg, 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 (eg, 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 (eg, Rave) has ended
  - This is a new event report OR 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

[Table: Site Information, Subject Information, Serious Adverse Event]

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

3. SERIOUS ADVERSE EVENT
Provide the date the investigator became aware of this Serious Adverse Event Information: Day Month Year

<table>
<thead>
<tr>
<th>Date Started</th>
<th>Date Ended</th>
<th>Check box if event resolved before first dose of SP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day Month Year</td>
<td>Day Month Year</td>
<td></td>
</tr>
</tbody>
</table>

If you temporarily cannot access the EDC system (eg, Rave), sign below and submit ONLY this page to the number noted in the header above Section 1.

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

Version 3.0 Effective Date 04-FEB-2013
If access to the EDC system (eg, 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 □ Yes. If yes, please complete all of Section 4.

<table>
<thead>
<tr>
<th>Site Number</th>
<th>Subject ID Number</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Date Admitted</th>
<th>Date Discharged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>Month</td>
</tr>
</tbody>
</table>

5. Was IP administered prior to this event? □ No □ Yes. If yes, please complete all of Section 5.

<table>
<thead>
<tr>
<th>IMP:</th>
<th>Initial Start Date</th>
<th>Prior to, or at time of Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day</td>
<td>Month</td>
</tr>
<tr>
<td></td>
<td>Date of Dose</td>
<td>Route</td>
</tr>
<tr>
<td></td>
<td>01</td>
<td>Still being administered</td>
</tr>
</tbody>
</table>

6. RELEVANT CONCOMITANT MEDICATIONS (eg, chemotherapy)

<table>
<thead>
<tr>
<th>Medication Name(s)</th>
<th>Day</th>
<th>Month</th>
<th>Year</th>
<th>Start Date</th>
<th>Stop Date</th>
<th>Co-Suspected</th>
<th>Continuing</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

8. RELEVANT LABORATORY VALUES (include baseline values)

<table>
<thead>
<tr>
<th>Date</th>
<th>Unit</th>
<th>Day</th>
<th>Month</th>
<th>Year</th>
</tr>
</thead>
</table>

---

Not Approved
**Electronic Serious Adverse Event (eSAE) Contingency Reporting Form**

**For Restricted Use**

<table>
<thead>
<tr>
<th>Site Number</th>
<th>Subject ID Number</th>
</tr>
</thead>
</table>

9. OTHER RELEVANT TESTS (diagnostics and procedures)

<table>
<thead>
<tr>
<th>Date</th>
<th>Additional Tests</th>
<th>Results</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</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: ____________________________

---

**Not Approved**

---

FORM-055006

Page 3 of 3

Version 3.0 Effective Date: 04-FEB-2013
Appendix C. Pregnancy and Lactation Notification Worksheets

**AMGEN**

**Pregnancy Notification Worksheet**

*Fax Completed Form to the Country-respective Safety Fax Line*

**1. Case Administrative Information**

Protocol/Study Number: 

Study Design: ☐ Interventional ☐ Observational

☐ Observational ☐ Prospective ☐ Retrospective

**2. Contact Information**

Investigator Name:

Phone ( ) Fax ( )

Institution:

Address:

Site #

**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>
<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. Pregnancy Information**

Pregnant female’s LMP: mm_/ dd_/ yyyy ☐ Unknown

Estimated date of delivery: mm_/ dd_/ yyyy ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm_/ dd_/ yyyy

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

If Yes, provide date of delivery: mm_/ dd_/ yyyy

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

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

Form Completed by:

Print Name: __________________________ Title: __________________________

Signature: __________________________ Date: __________________________

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
### 1. Case Administrative Information

**Protocol/Study Number:**

**Study Design:**
- [ ] Interventional
- [ ] Observational (If Observational: [ ] Prospective [ ] Retrospective)

### 2. Contact Information

<table>
<thead>
<tr>
<th>Investigator Name</th>
<th>Site #</th>
</tr>
</thead>
</table>

| Phone ( ) | Fax ( ) | Email |

<table>
<thead>
<tr>
<th>Institution</th>
<th>Address</th>
</tr>
</thead>
</table>

### 3. Subject Information

| Subject ID # | Subject Date of Birth: mm__/dd__/yyyy |

### 4. Amgen Product Exposure

| Amgen Product | Dose of breast feeding | Frequency | Route | Start Date: mm__/dd__/yyyy |

- Was the Amgen product (or study drug) discontinued? [ ] Yes [ ] No
  - If yes, provide product (or study drug) stop date: mm__/dd__/yyyy
- Did the subject withdraw from the study? [ ] Yes [ ] No

### 5. Breast Feeding Information

- Currently breast feeding? [ ] Yes [ ] No
  - If No, provide 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:**

<table>
<thead>
<tr>
<th>Print Name:</th>
<th>TIME:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Signature:</th>
<th>Date:</th>
</tr>
</thead>
</table>

---

Amgen maintains a Lactation Surveillance Program that collects data about women who have been exposed to an 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 D. Sample Questionnaires

Statin Intolerance History Questionnaire

Name: ___________________________    Date:     

1. How many statins have you had to stop taking due to muscle-related side effects?
   a) 1
   b) 2
   c) >2

2. What was the main symptom that made you stop taking the statin?
   a) Muscle pain
   b) Muscle weakness
   c) Extreme tiredness
   d) Forgetfulness or memory problems

3. What part of your body was affected by the statin? (check all that apply)
   a) No part of body was affected
   b) Arms unilateral bilateral
   c) Legs unilateral bilateral
   d) Trunk

4. How long did the symptoms last?
   a) Several days
   b) Several weeks
   c) Several months
   d) Several years

5a. What did you do to make the symptoms get better (please mark the best answer)?
   a) Stopped taking statin
   b) Lowered the dose of the statin
   c) Took pain medication
   d) Performed less physical activity

5b. When you performed the above action, what happened to the symptoms?
   a) Muscle symptoms resolved completely
   b) Muscle symptoms improved but still ongoing
   c) Muscle symptoms unimproved and still ongoing

6. When did the problems with the statin begin?
   a) Within several days or weeks after starting the medication
   b) Increased dose of medication
   c) After several months of taking the medication
   d) After several years of taking the medication
7. What statin medications did you try (please check all that apply)?
   a) Lipitor (atorvastatin)
   b) Lescol (fluvasatin)
   c) Mevacor (lovastatin)
   d) Livalo (pitavastatin)
   e) Pravachol (pravastatin)
   f) Crestor (rosuvastatin)
   g) Zocor (simvastatin)
   h) Other statin

8. What was the maximum dose of statin medication that you were able to take without any symptoms (if known)?

9. How many times per week did you take the statin at that dose?
   a) Once per day
   b) Every other day
   c) Twice a week
   d) 3 times a week
   e) 4 times a week
   f) Once per week
   g) Once per month
   h) Other

10. On a scale of 1 – 10, with 1 being no aches at all and 10 being aches as bad as you can imagine, please describe your muscle aches and pains.
Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?
   1. Yes  2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.

3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.
   0  1  2  3  4  5  6  7  8  9  10  Pain as bad as you can imagine
   No Pain

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.
   0  1  2  3  4  5  6  7  8  9  10  Pain as bad as you can imagine
   No Pain

5. Please rate your pain by circling the one number that best describes your pain on the average.
   0  1  2  3  4  5  6  7  8  9  10  Pain as bad as you can imagine
   No Pain

6. Please rate your pain by circling the one number that tells how much pain you have right now.
   0  1  2  3  4  5  6  7  8  9  10  Pain as bad as you can imagine
   No Pain
7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

- 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

<table>
<thead>
<tr>
<th></th>
<th>General Activity</th>
<th>Mood</th>
<th>Walking Ability</th>
<th>Normal Work (includes both work outside the home and housework)</th>
<th>Relations with other people</th>
<th>Sleep</th>
<th>Enjoyment of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Does not interfere</td>
<td>Does not interfere</td>
<td>Does not interfere</td>
<td>Does not interfere</td>
<td>Does not interfere</td>
<td>Does not interfere</td>
<td>Does not interfere</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
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<tr>
<td>4</td>
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<td>5</td>
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<td>8</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Completely interferes</td>
<td></td>
<td>Completely interferes</td>
<td></td>
<td></td>
<td></td>
<td>Completely interferes</td>
</tr>
</tbody>
</table>

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Pain Research Group
All rights reserved

Not Approved
Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an ✗ in the one box that best describes your answer.

1. In general, would you say your health is:

<table>
<thead>
<tr>
<th>Excellent</th>
<th>Very good</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>✗</td>
<td>✗</td>
<td>❌</td>
<td>❌</td>
<td>❌</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

2. Compared to one year ago, how would you rate your health in general now?

<table>
<thead>
<tr>
<th>Much better now than one year ago</th>
<th>Somewhat better now than one year ago</th>
<th>About the same as one year ago</th>
<th>Somewhat worse now than one year ago</th>
<th>Much worse now than one year ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>❌</td>
<td>❌</td>
<td>❌</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

<table>
<thead>
<tr>
<th>Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports</th>
<th>▼ 1 ▼ 2 ▼ 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf</td>
<td>▼ 1 ▼ 2 ▼ 3</td>
</tr>
<tr>
<td>Lifting or carrying groceries</td>
<td>▼ 1 ▼ 2 ▼ 3</td>
</tr>
<tr>
<td>Climbing several flights of stairs</td>
<td>▼ 1 ▼ 2 ▼ 3</td>
</tr>
<tr>
<td>Climbing one flight of stairs</td>
<td>▼ 1 ▼ 2 ▼ 3</td>
</tr>
<tr>
<td>Bending, kneeling, or stooping</td>
<td>▼ 1 ▼ 2 ▼ 3</td>
</tr>
<tr>
<td>Walking more than a mile</td>
<td>▼ 1 ▼ 2 ▼ 3</td>
</tr>
<tr>
<td>Walking several hundred yards</td>
<td>▼ 1 ▼ 2 ▼ 3</td>
</tr>
<tr>
<td>Walking one hundred yards</td>
<td>▼ 1 ▼ 2 ▼ 3</td>
</tr>
<tr>
<td>Bathing or dressing yourself</td>
<td>▼ 1 ▼ 2 ▼ 3</td>
</tr>
</tbody>
</table>
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

a. Cut down on the amount of time you spent on work or other activities ........................................... □ 1 ......... □ 2 .......... □ 3 .......... □ 4 .......... □ 5

b. Accomplished less than you would like .......................................................... □ 1 .......... □ 2 .......... □ 3 .......... □ 4 .......... □ 5

c. Were limited in the kind of work or other activities ............................................... □ 1 .......... □ 2 .......... □ 3 .......... □ 4 .......... □ 5

d. Had difficulty performing the work or other activities (for example, it took extra effort) .......... □ 1 .......... □ 2 .......... □ 3 .......... □ 4 .......... □ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
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</tr>
</tbody>
</table>

a. Cut down on the amount of time you spent on work or other activities ........................................... □ 1 ......... □ 2 .......... □ 3 .......... □ 4 .......... □ 5

b. Accomplished less than you would like .......................................................... □ 1 .......... □ 2 .......... □ 3 .......... □ 4 .......... □ 5

c. Did work or other activities less carefully than usual ............................................... □ 1 .......... □ 2 .......... □ 3 .......... □ 4 .......... □ 5
6. **During the past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
</tbody>
</table>

7. How much **bodily** pain have you had during the **past 4 weeks**?

<table>
<thead>
<tr>
<th>None</th>
<th>Very mild</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
</tbody>
</table>

8. **During the past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little bit</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
</tbody>
</table>
9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks...

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>


b. Have you been very nervous? ........ □ 1 .......... □ 2 .......... □ 3 .......... □ 4 .......... □ 5

c. Have you felt so down in the dumps that nothing could cheer you up? ......................... □ 1 .......... □ 2 .......... □ 3 .......... □ 4 .......... □ 5


e. Did you have a lot of energy? ........ □ 1 .......... □ 2 .......... □ 3 .......... □ 4 .......... □ 5


g. Did you feel worn out? ........................ □ 1 .......... □ 2 .......... □ 3 .......... □ 4 .......... □ 5

h. Have you been happy? .................... □ 1 .......... □ 2 .......... □ 3 .......... □ 4 .......... □ 5


10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
</tbody>
</table>
11. How TRUE or FALSE is each of the following statements for you?

<table>
<thead>
<tr>
<th>Definitely true</th>
<th>Mostly true</th>
<th>Don’t know</th>
<th>Mostly false</th>
<th>Definitely false</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

a. I seem to get sick a little easier than other people ................... □ 1 ............ □ 2 ............ □ 3 ............ □ 4 ............ □ 5

b. I am as healthy as anybody I know ........................................ □ 1 ............ □ 2 ............ □ 3 ............ □ 4 ............ □ 5

c. I expect my health to get worse........................................... □ 1 ............ □ 2 ............ □ 3 ............ □ 4 ............ □ 5

d. My health is excellent...................................................... □ 1 ............ □ 2 ............ □ 3 ............ □ 4 ............ □ 5
Amendment 2

Title: A Double-blind, Randomized, Multicenter Study to Evaluate the Safety and Efficacy of AMG 145, Compared With Ezetimibe, in Hypercholesterolemic Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor Due to Muscle Related Side Effects

AMG 145
Amgen Protocol Number 20120332
EudraCT No. 2013-000935-29

GAUSS-3
Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects

Amendment Date: 15 January 2014

Rationale:
This document provides the rationale and detailed list of changes for Amendment 2, dated 15 January 2014, from amendment 1 of the study protocol, dated 27 September 2013. Amendment 2 is in response to comments issued in the Voluntary Harmonisation Procedure in the EU.

The purpose of the amendment is to:

- Address comments from the Voluntary Harmonisation Procedure in the EU
- Minor other updates, clarifications and corrections
Description of Changes:

Section: Title Page

Add:

Amendment 2 Date: 15 January 2014

Section: Protocol Synopsis, Study Design

Protocol Synopsis, Summary of Subject Eligibility Criteria

3.1 Study Design

7.4 Screening Enrollment and/or Randomization

Replace:

Any subject with a documented history of CK elevation > 10 x ULN accompanied by muscle symptoms while on statin therapy and documented resolution of both CK elevation and muscle symptoms upon discontinuation of statin therapy, may bypass the statin rechallenge Part A and be randomized directly into Part B.

With:

Any subject with a documented history of CK elevation > 10 x ULN accompanied by muscle symptoms while on statin therapy and documented resolution of both CK elevation and muscle symptoms upon discontinuation of statin therapy, must bypass the statin rechallenge Part A and be randomized directly into Part B.

Section: 3.1 Study Design

3.5.1 Study Duration for Subjects

Replace:

Part A is a double-blind, placebo controlled cross-over statin rechallenge to confirm presence of statin-related MRSE and is approximately 22 weeks in duration;

With:

Part A is a double-blind, placebo-controlled cross-over statin rechallenge to confirm presence of statin-related MRSE and is approximately 24 weeks in duration;
Section: 4.1.1 Inclusion Criteria

Add:

c) Fasting LDL-C ≥ 160 mg/dL (4.14 mmol/L) for subjects without diagnosed CHD or risk equivalent and with 1 or more risk factors or

Section: 4.1.1 Inclusion Criteria

Delete:

105 Lipid lowering therapy has been stable prior to LDL-C screening for at least 4 weeks if currently on a statin and/or bile-acid sequestering resin and/or stanol; if subject is on statin or ezetimibe at start of screening, statin or ezetimibe must be discontinued for ≥ 4 weeks before LDL-C screening.

Section: 4.1.2 Exclusion Criteria

Replace:

201 Subject who has taken in the last 4 weeks prior to LDL C screening red yeast rice, > 200 mg/day niacin, or prescription lipid-regulating drugs (eg, fibrates and derivatives) other than statins, ezetimibe, bile-acid sequestering resin, or stanols and stanol esters

With:

209 Subject who has taken in the last 4 weeks prior to LDL C screening red yeast rice, > 200 mg/day niacin, or prescription lipid-regulating drugs (eg, fibrates and derivatives, statins or ezetimibe) other than bile-acid sequestering resin, or stanols and stanol esters

Section: 6.2.1 Amgen Investigational Product AMG 145

Delete:

or in an identical Personal Injector containing a 3.5 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.
Section: 6.2.2.1.1 Dosage, Administration, and Schedule

Delete:

The subject’s lipid-lowering therapy (atorvastatin and ezetimibe, if applicable) should be stable for at least 4 weeks before the fasting LDL-C at screening.

Section: 7.3.1 Study Visit Definitions and Windows

Add:

Prior to study enrollment, subjects taking low dose statins or ezetimibe will discontinue these medications and allow for a minimum of 4-week washout period prior to LDL-C screening.

Section: 7.3.1 Study Visit Definitions and Windows

Replace:

Investigators should not perform non protocol testing of these analytes during a subject’s study participation from first administration of IP until at least 4 weeks after the subject’s end of study visit.

With:

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 blinded IP administration.

Section: 7.4.2.4 Part A [Period 1: Visit/Week 10]: All Subjects

Delete:

- PO IP dispensing

Section: 7.4.2.9 Part B: [Visit Day 1 (Randomization)]: All Subjects

Add:

HCV viral load (only in subjects positive for HCV)
Section: 7.7 Pharmacogenetic Studies

Delete:

Additional samples are collected for this part of the study.

Section: 9.2.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

Add:

or 3.5 mL Personal Injector

Section: 10.1.4 Exploratory Endpoints

Delete:

HbA1c at each scheduled assessment