

Title: A Multicenter, Controlled, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of Evolocumab (AMG 145)

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OSLER

Open Label Study of Long Term Evaluation Against LDL-C Trial

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I have read the attached protocol entitled "A Multicenter, Controlled, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of Evolocumab (AMG 145)", dated **12 November 2015**, and agree to abide by all provisions set forth therein.

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Signature

Name of Principal Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: A Multicenter, Controlled, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of Evolocumab (AMG 145)

Study Phase: 2

Indication: Hypercholesterolemia

Primary Objective: To characterize the safety and tolerability of long-term administration of AMG 145

Secondary Objectives:

- To characterize the efficacy of long-term administration of AMG 145 as assessed by low density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, and ApoB/Apolipoprotein A-1 (ApoA1) ratio in subjects with hypercholesterolemia

Hypotheses: The primary clinical hypothesis is that long-term exposure of AMG 145 will be safe and well tolerated in subjects with hypercholesterolemia.

Primary Endpoint:

- Subject incidence of adverse events

Secondary Endpoints:

- LDL-C at week 24 and week 52
- Non-HDL-C at week 24 and week 52
- ApoB at week 24 and week 52
- Total cholesterol/HDL-C ratio at week 24 and week 52
- ApoB/ApoA1 ratio at week 24 and week 52

Study Design: This is a multicenter, controlled, open-label extension study designed to assess the long-term safety and efficacy of AMG 145. Subjects that complete a qualifying protocol will be randomized 2:1 to two treatment groups: Monthly AMG 145 (420mg QM) + standard of care (SOC) or SOC alone for the first year of the study. During the first 12 weeks of the study (blinded post-randomization stabilization period), LDL-C will remain blinded and subjects must remain on the background lipid lowering therapy from the parent study. After 12 weeks, LDL-C will be unblinded and subjects may receive additional lipid-lowering therapy based on local standards of care. Subjects in the SOC only arm will not receive AMG 145 or a placebo injection for the first year of the study. Randomization should occur at the end of the parent study's end of study (EOS) visit or within 3 days after the parent study's EOS visit and will be stratified by the treatment arm the subject was randomized to in the parent study. Investigators, site staff, subjects, and the study team will be blinded to on-study lipid levels until the Week 12 (1st quarterly) visit of this study. At the end of the first year (week 52), starting at week 56 (week 4/year 2) all subjects will receive open-label AMG 145 for **up to 4 years** (or until the investigator's recommendation of discontinuation, Amgen's recommendation of discontinuation, the subjects' decision to discontinue for any reason, or until an administrative decision is made to close the study).

Sample Size: The number of subjects entering this study will depend on the number of subjects completing their respective AMG 145 parent studies and willingness to enroll. Approximately 1600 subjects are expected to participate in this study.

Summary of Subject Eligibility Criteria: Subjects who complete a qualifying AMG 145 protocol and do not experience a treatment related serious adverse event that led to IP discontinuation in the parent study will be eligible for this study. For a full list of eligibility criteria, please refer to [Section 4.1](#) and [Section 4.2](#).

Amgen Investigational Product Dosage and Administration: During the first year, for subjects randomized to evolocumab (AMG 145), sites will administer investigational product (IP = AMG 145, 420 mg) to subjects subcutaneously QM. The total volume of AMG 145 70 mg/ml will be 6 mL. Doses can be split into multiple injections (eg, 3 injections at 2 mL each) with the condition that the full 6 mL is provided at each respective study visit. Once available, AMG 145 will be administered using 3 spring-based prefilled 1.0 mL autoinjector/pens (prefilled AI/Pen) or a 3.5 mL Personal Injector. All subjects will receive appropriate lipid-lowering therapy based on local standards of care. Nonetheless, until laboratory results are unblinded at week 12, subjects must remain on the same background lipid lowering therapy from the parent study, unless there is a clinically compelling reason for change. The investigator must contact the Amgen medical monitor to discuss such cases on an individual basis. After unblinding at week 12, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care ([Section 6.4](#)). After the end of the first year, sites will administer investigational product to all subjects.

Non Amgen Investigational Product Dosage and Administration: None.

Control Group: The control group comprises those subjects randomized to standard of care alone during the first year of study participation. Until laboratory results are unblinded at week 12, the control group must also remain on the same background lipid lowering therapy from the parent study, unless there is a clinically compelling reason for change. The investigator must contact the Amgen medical monitor to discuss such cases on an individual basis. After unblinding at week 12, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care ([Section 6.4](#)). After 1 year of participation, these subjects will receive open-label AMG 145 and will no longer be part of the control group.

Procedures: Prior to enrolling in this study, subjects will need to undergo end of study (EOS) procedures for their qualifying parent study. In addition, subjects will need to meet inclusion/exclusion criteria requirements. Before randomization subjects will need to sign a new study informed consent form. Subject numbers will be the same as those in their parent protocols. Randomization will be stratified by the treatment arm the subject was randomized to in their parent study.

During the first year, subjects randomized to AMG 145 + SOC will need to visit the site every 4 weeks. During these visits vital signs will be obtained and adverse events (AEs), **adverse device effects (ADEs)**, serious adverse events (SAEs), and concomitant medications will be recorded. Subjects randomized to SOC only, will not visit the site every 4 weeks (except at specified visits); rather the site will call these subjects at the scheduled visits to review concomitant medication changes, AEs, **ADEs**, and SAEs. During quarterly (every 12 weeks) visits, central laboratory tests will be performed for all subjects. For a full list of study procedures, including the timing of each procedure, please refer to [Section 7.1](#) and [Appendix A](#).

Statistical Considerations

General Considerations

Statistical analyses in this open-label extension study will be descriptive in nature.

Analysis may be performed periodically throughout the study after parent studies are closed and individual subjects are unblinded to their lipid values.

For all endpoints, results will be summarized by the treatment group to which subjects are randomized in this study, unless otherwise specified. Subjects will be further categorized according to whether they were randomized to AMG 145 or not in their parent study. For the randomized period, this combined treatment group will have 4 levels (parent study treatment group/year 1 treatment group): "AMG 145/AMG 145 + SOC"; "AMG 145/SOC only"; "Not AMG 145/AMG 145+SOC", and "Not AMG 145/SOC only". For the final analysis (end of the 5 years), this combined treatment group will also have 4 levels (parent study treatment group/year 1 treatment group/year 2-5 open-label AMG 145): "AMG 145/AMG 145 +

SOC/AMG 145”; “AMG 145/ SOC only/AMG 145”; “Not AMG 145/AMG 145 + SOC/AMG 145”, and “Not AMG 145/SOC only/AMG 145”.

Unless otherwise specified, the baseline value is defined as the subject’s baseline value from the parent study.

The full analysis set (FAS) will include all subjects randomized in this study. All analyses of the randomized controlled period of the study will be performed using the FAS. Analyses of the period after the randomized controlled period may be limited to those receiving investigational product. There will be no imputation for missing data.

Deaths and major cardiovascular events from this and other studies with evolocumab will be adjudicated by an independent Clinical Events Committee (CEC) to facilitate aggregated analyses across the program. Subject incidence of adjudicated events will be summarized for each treatment group.

Analyses of Primary Endpoint

AEs will be coded using the latest version of MedDRA. Subject incidence of adverse events, serious adverse events, and adverse events leading to withdrawal from IP will be tabulated by system organ class and preferred term.

Analyses of Secondary Endpoints

Secondary endpoints will be summarized at each scheduled visit by both randomized treatment group in this study and the combined treatment group (4 levels). For the 1-year interim analysis, point estimates of group means and their 95% confidence intervals will be presented.

Differences in group means for the secondary endpoints will be estimated at each scheduled visit between

- the AMG 145 + SOC group and the SOC only group in this study, regardless of the treatment arm the subject was randomized to in their parent study
- the AMG 145 + SOC group and the SOC only group in this study, by whether the subject was randomized to AMG 145 or not in their parent study

Other Safety Analyses

Measurements of laboratory parameters and vital signs will be summarized at each scheduled visit. 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.

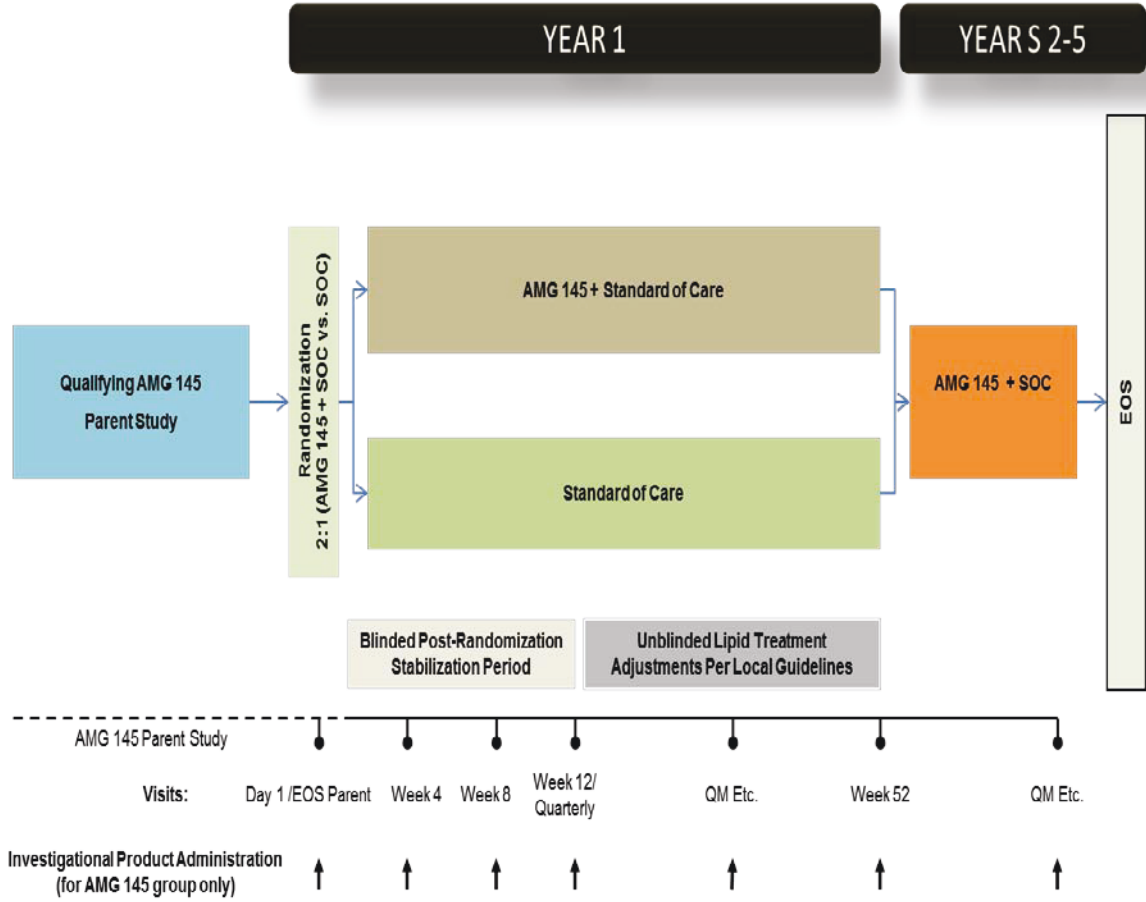
Safety Monitoring

Amgen Global Patient Safety will perform ongoing monitoring and assessment of safety data to determine potential impact on study subject safety and protocol conduct.

For a full description of statistical analysis methods, refer to [Section 10](#).

Sponsor: Amgen

Study Design and Treatment Schema



Study Glossary

Abbreviation or Term	Definition/Explanation
AE	Adverse event
ADE	Adverse Device Effect
AHA	American Heart Association
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase (serum glutamic-pyruvic transaminase)
AMG 145	Evolocumab
ApoA1	Apolipoprotein A-1
ApoB	Apolipoprotein B
ACTH	Adrenocorticotrophic hormone
AST (SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
AUC	Area under the curve
BP	Blood pressure
CAD	Coronary artery disease
CBC	Complete blood count
CEC	Clinical Events Committee
CK	Creatine kinase
CHD	Coronary heart disease
C _{max}	Mean maximum measured concentration
CRP	C-reactive protein
CVD	Cardiovascular disease
CTCAE	NCI Common Terminology Criteria for AEs
Day 1	Defined as the first day that protocol-specified investigational product is administered to the subject. Day 1 for subjects randomized to SOC will occur upon randomization
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
End of treatment	Defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
EOS	End-of-study for individual subject
EU	European Union
FAS	Full analysis set
FH	Familial hypercholesterolemia
FSH	Follicle-stimulating hormone

Abbreviation or Term	Definition/Explanation
GCP	Good Clinical Practice
HDL-C	High density lipoprotein cholesterol
HepG2 cells	Human hepatocellular carcinoma cell line
HR	Heart Rate
hsCRP	High sensitivity CRP
IBG	Independent Biostatistical Group
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC/IRB	Independent Ethics Committee / Institutional Review Board
IFU	Instructions for use
IP	Investigational product
IPIM	Investigational Product Instruction Manual
IVRS	Interactive Voice Response System
IV	Intravenous
LDL-C	Low-density lipoprotein cholesterol
LDLR	LDL receptor
LH	Luteinizing hormone
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LOF	Loss of function
Lp(a)	Lipoprotein(a)
LSP	Lactation Surveillance Program
MedDRA	Medical dictionary for regulatory activities
NASH	Nonalcoholic steatohepatitis
NCEP	National Cholesterol Education Program
NCEP ATP II	NCEP Adult Treatment Panel II (see References)
NCI	National Cancer Institute
OLE	Open-Label Extension
PCSK9	Proprotein convertase subtilisin/kexin type 9
PKPD	Pharmacokinetic / pharmacodynamic
Q4W	Every 4 weeks, (AMG 145 Background Section)
QM	QM is defined as every 4 weeks with a window of ± 7 days for each visit
SAE	Serious adverse event
SC	Subcutaneous
SOC	Standard of care

Abbreviation or Term	Definition/Explanation
Source Data	Information from an original record or a certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline (E6)). Examples of source data include Subject ID, Randomization ID, and Stratification Value.
TBL	Total bilirubin
T _{max}	Time to maximum concentration
TNF	Tumor necrosis factor
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol

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1. OBJECTIVES

1.1 Primary

To characterize the safety and tolerability of long-term administration of AMG 145

1.2 Secondary

- To characterize the efficacy of long-term administration of AMG 145 as assessed by LDL-C and non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, and ApoB/Apolipoprotein A-1 (ApoA1) ratio in subjects with hypercholesterolemia

1.3 Exploratory

- To assess the percent change in fasting plasma lipids (non-HDL-C, apolipoprotein B, total-cholesterol/HDL-C ratio, total cholesterol), and ApoB/ApoA1 ratio, triglycerides, Lp(a), and high sensitivity C-reactive protein (hsCRP)
- To investigate potential biomarker development by biochemical analysis of blood samples
- To characterize pharmacokinetics of AMG 145 and proprotein convertase subtilisin/kexin type 9 (PCSK9) levels
- To estimate cardiovascular event rates in subjects treated with AMG 145 in aggregated exploratory analyses across the AMG 145 program

2. BACKGROUND AND RATIONALE

2.1 Cardiovascular Disease

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

1. The 2005 overall death rate from CVD in the US was 278.9 per 100,000. Nearly 2400 Americans die of CVD each day - an average of 1 death every 37 seconds. More than 150,000 Americans killed by CVD in 2005 were less than 65 years of age. In 2005, 32% of deaths from CVD occurred before the age of 75 years, which is well before the average life expectancy of 77.9 years. Preliminary mortality data from 2006 show that CVD accounted for 34.2% (829,072) of all 2,425,900 deaths in 2006, or 1 of every 2.9 deaths in the United States.
2. Coronary heart disease (CHD) caused 1 of every 5 deaths in the United States in 2005. Coronary heart disease mortality was 445,687. In 2009, an estimated 785,000 Americans will have a new coronary attack, and about 470,000 will have a recurrent attack. It is estimated that an additional 195,000 silent first myocardial infarctions occur each year. About every 25 seconds, an American will have a coronary event, and about every minute someone will die from one.

3. Each year, about 795,000 people experience a new or recurrent stroke. About 610,000 of these are first attacks, and 185,000 are recurrent attacks. Preliminary data from 2006 indicate that stroke accounted for about 1 of every 18 deaths in the United States. On average, every 40 seconds someone in the United States has a stroke. From 1995 to 2005, the stroke death rate fell 29.7%, and the actual number of stroke deaths declined 13.5%.
4. Coronary artery disease (CAD) affects almost 17 million Americans. Of those 7,900,000 suffer from myocardial infarction; 9,800,000 from angina pectoris; 5,700,000 from congestive heart failure; and 6.5 million from stroke. One in three individuals in the US has some form of cardiovascular disease. The aging of the population will undoubtedly result in an increased incidence of coronary artery disease, heart failure, and stroke. There has been an explosive increase in the prevalence of obesity and type 2 diabetes and their related complications (hypertension, hyperlipidemia, and atherosclerotic vascular disease) will also increase. An alarming increase in unattended risk factors in the younger generations will continue to fuel the cardiovascular epidemic for years to come.
5. Cardiovascular disease claims more lives each year than the next 5 leading causes of death combined. Cardiovascular disease claimed 35.3% of all deaths in the United States in 2005. Since 1900, cardiovascular disease has been the No. 1 killer in the United States every year but 1918.

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

Each year CVD causes over 4.3 million deaths in Europe and over 2.0 million deaths in the European Union (EU). CVD causes nearly half of all deaths in Europe (48%) and in the EU (42%). CVD is the main cause of death in women in all countries of Europe and is the main cause of death in men in all countries except France, the Netherlands and Spain. CVD is the main cause of the disease burden (illness and death) in Europe (23% of the entire disease burden) and the second main cause of the disease burden in those EU countries with very low child and adult mortality (17%). CVD mortality, incidence and case fatality are falling in most Northern, Southern and Western European

Countries but either not falling as fast or rising in Central and Eastern European countries.

Clearly, more effective primary and secondary CHD prevention measures are required. CHD prevention in the future will be the result of the ground breaking research that has been conducted over the past 25 years. For example, in the 1970s, data from the Framingham Epidemiological Study demonstrated that increases in serum cholesterol levels in the general population were associated with an increased risk of death from CHD (Kannel et al, 1974; Kannel et al, 1979; Kannel, 1995). In 1988, the National Cholesterol Education Program (NCEP) identified elevated low-density lipoprotein cholesterol (LDL-C) as a primary risk factor for CHD (NCEP, 1988). In the 1993 NCEP Adult Treatment Panel II Report, this conclusion was further strengthened by the addition of aggressive dietary and drug therapy recommendations for subjects with known CHD (NCEP, 1993). In 1995, Gould and associates reported meta-analysis data on 35 randomized clinical trials that lasted more than two years and were designed to reduce serum cholesterol levels (Gould et al, 1995). They concluded that for every 10 percentage points of cholesterol lowering, CHD mortality was reduced by 13% ($p < 0.002$) and total mortality by 10% ($p < 0.03$). According to the most recently reported United States National Health and Nutrition Examination Survey (NHANES III), an estimated 5.5 million Americans with CHD should be treated with lipid-lowering medications under the NCEP guidelines (Sempos et al, 1993). Presently, less than one-third of those CHD subjects who require lipid-lowering medications actually receive treatment, and only a small proportion of those who do receive treatment achieve NCEP target levels (Eisenberg, 1998).

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

2.2 AMG 145 Background

Recycling of the hepatic cell surface LDL receptor (LDLR) plays a critical role in the maintenance of cellular and whole body cholesterol balance by regulating plasma LDL-C levels. Recently it has been shown that 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, 2012. AMG 145 binds to human, monkey, and hamster PCSK9 with high affinity ($K_d < 100$ pM). AMG 145 caused a dose-dependent inhibition of PCSK9 binding to the LDLR and of PCSK9-mediated reduction in low-density lipoprotein (LDL) uptake in HepG2 cells (human hepatocellular carcinoma cell line) in culture. In cynomolgus monkeys and in hamsters, in vivo administration of AMG 145 resulted in reduced serum lipoprotein cholesterol levels in a dose-dependent manner. Based on a comprehensive package of PK, pharmacodynamics (PD), and toxicology studies (Investigator's Brochure, 2012), a program to develop AMG 145 as a treatment for dyslipidemia was initiated.

2.2.1 First-in-Human (FIH) Study 20080397

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

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

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

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

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

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

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

2.2.2 Multiple-dose Phase 1b Study 20080398

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

also included subjects with heterozygous familial hypercholesterolemia who received 3 doses of AMG 145 at 140 mg SC Q2W.

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

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

For further details on study 20080398, please consult the Investigator's Brochure (2013).

2.2.3 Phase 2, 12-week, Lipid-lowering Parent Studies Included in Aggregate Interim Analysis for Dose Selection

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

2.2.3.1 Phase 2 Aggregate Interim Analysis Results

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

Table 1. Summary of Study Design of Four Parent Studies and Extension Study

	20101154	20101155	20090158	20090159	20110110
Trial Name	MENDEL	LAPLACE-TIMI 57	RUTHERFORD	GAUSS	OSLER
Sample Size	405	600	150	150	>500
Patient Population	Subjects not on statins	Subjects on statins + ezetimibe	Subjects with HeFH	Subjects with statin intolerance	Subjects from studies 20101154, 20101155, 20090158, 20090159
Fasting LDL-C	≥ 100 mg/dL and < 190 mg/dL	≥ 85 mg/dL (≥ 85 to < 100 mg/dL limited to 20%)	≥ 100 mg/dL	≥ 100 mg/dL; Not at LDL-C goal (NCEP ATP III)	≥ 75 mg/dL
Randomization Ratio	9 arms, equal allocation	8 arms, equal allocation	3 arms, equal allocation	5 arms, equal allocation	2:1
Treatment Duration	12 weeks	12 weeks	12 weeks	12 weeks	52 weeks

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Table 1. Summary of Study Design of Four Parent Studies and Extension Study

	20101154	20101155	20090158	20090159	20110110
Treatment Groups	70mg Q2W	70mg Q2W			
	105mg Q2W	105mg Q2W			
	140mg Q2W	140mg Q2W			
	Placebo Q2W	Placebo Q2W			
	280mg Q4W	280mg Q4W		280mg Q4W	
	350mg Q4W	350mg Q4W	350mg Q4W	350mg Q4W	
	420mg Q4W	420mg Q4W	420mg Q4W	420mg Q4W	420mg Q4W + SOC
	Placebo Q4W	Placebo Q4W	Placebo Q4W		SOC only
	Ezetimibe QD			Placebo Q4W + Ezetimibe QD 420mg Q4W + Ezetimibe QD	

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

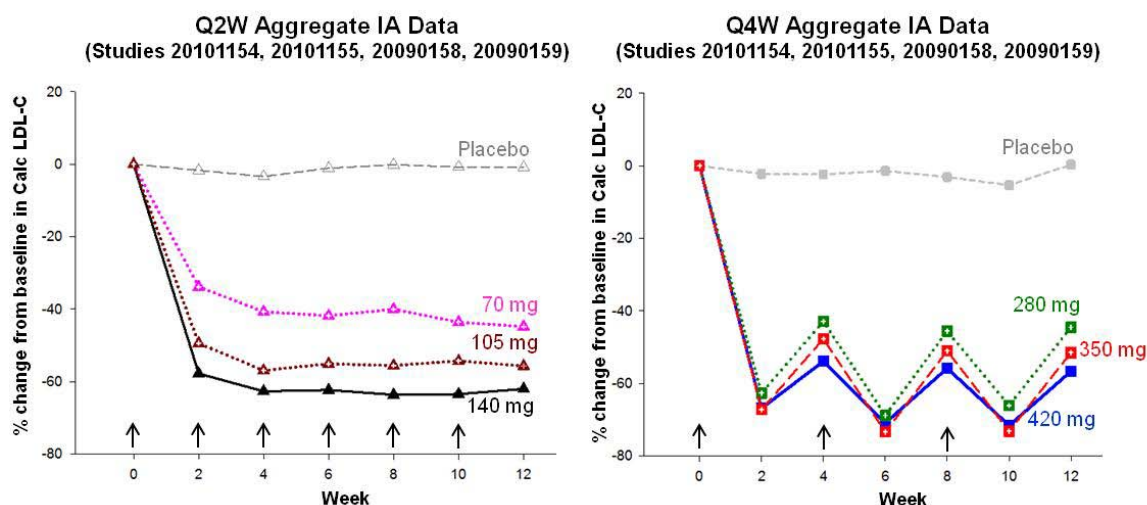
As of the snapshot dates, 606 subjects from the 4 phase 2 parent studies had rolled over into the long-term extension study (20110110). The mean time on study for subjects in study 20110110 was 1.4 months plus an additional three months from the parent study. This translates into approximately 31% and 10% of subjects being on study (ie, parent and extension studies) for ≥ 5 and ≥ 6 months, respectively.

In order to maintain blinding in the ongoing phase 2 studies, data presented herein were aggregated by dose and dosing regimen across the 4 parent studies.

2.2.3.2 Phase 2 Aggregate Interim Analysis Efficacy Results

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

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



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

Integrated analyses of mean percent change from baseline to week 12 in other lipid parameters are presented in [Table 2](#). Statistically significant decreases from baseline for all 6 AMG 145 treatment groups were observed for total cholesterol (p < 0.001), ApoB (p < 0.001), non-HDL-C (p < 0.001), VLDL-C (p < 0.03), Lp(a) (p < 0.001). Mean reductions from baseline to week 12 relative to placebo in total cholesterol (range: 25% to 37%), ApoB (range: 33% to 51%), non-HDL-C (range: 36% to 53%) were strictly dose-dependent within each dosing frequency (ie, Q2W or Q4W). Mean reductions from

baseline to week 12 relative to placebo in VLDL-C (14% to 44%) and Lp(a) (15% to 31%) concentrations were generally dose dependent, although a single deviation for each parameter was observed. Favorable trends in the mean reductions from baseline to week 12 relative to placebo for triglycerides (range: 7% to 25%) were also observed. Statistically significant increases in HDL-C and ApoA1 were seen in all AMG 145 dose groups except for the 280 mg Q4W cohort, and the 70 mg Q2W and 280 mg Q4W cohorts, respectively. AMG 145 treatment resulted in dose-dependent elevations in HDL-C (3% to 10%) and ApoA1 (2% to 5%) in all dose groups.

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

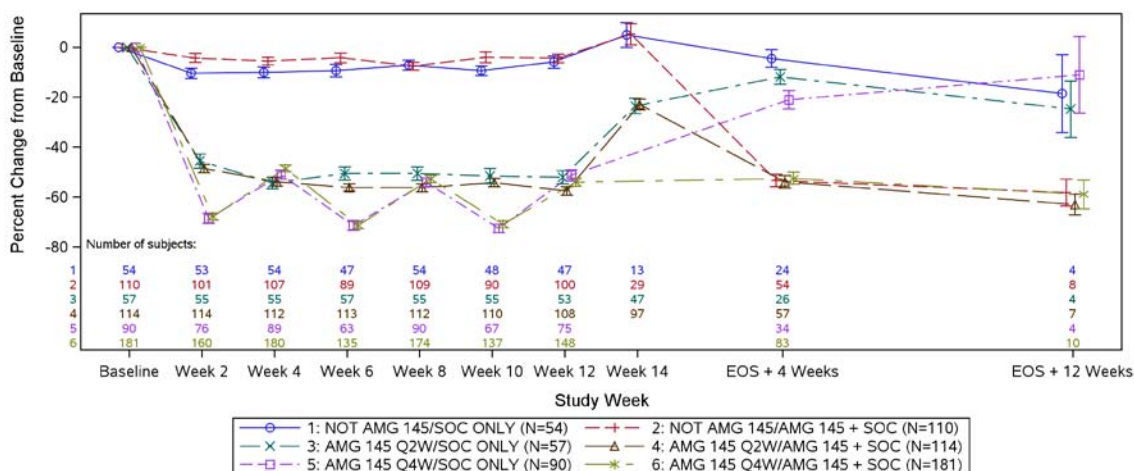
Lipid parameter	Treatment Difference (Estimate) Relative to Placebo ^{a,b}					
	AMG 145 Q2W vs Placebo Q2W			AMG 145 Q4W vs Placebo Q4W		
	AMG 145 70 mg (N = 43)	AMG 145 105 mg (N = 43)	AMG 145 140 mg (N = 42)	AMG 145 280 mg (N = 41)	AMG 145 350 mg (N = 41)	AMG 145 420 mg (N = 42)
Calc LDL-C	-40.96	-50.53	-59.54	-44.25	-51.14	-55.99
95% CI	(-46.82, -35.10)	(-56.41, -44.65)	(-65.45, -53.62)	(-50.26, -38.24)	(-56.95, -45.33)	(-61.84, -50.13)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Total Chol	-25.27	-30.75	-36.80	-28.12	-32.31	-34.78
95% CI	(-29.47, -21.06)	(-34.97, -26.54)	(-41.04, -32.55)	(-32.17, -24.06)	(-36.23, -28.39)	(-38.74, -30.83)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
ApoB	-33.04	-41.70	-50.83	-33.24	-38.87	-42.22
95% CI	(-38.05, -28.03)	(-46.73, -36.68)	(-55.89, -45.77)	(-38.41, -28.08)	(-43.86, -33.88)	(-47.25, -37.19)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
non-HDL-C	-35.96	-43.60	-53.45	-38.02	-44.30	-47.79
95% CI	(-41.25, -30.67)	(-48.91, -38.29)	(-58.80, -48.10)	(-43.18, -32.85)	(-49.29, -39.31)	(-52.82, -42.76)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
VLDL	-27.73	-22.53	-43.74	-14.40	-18.03	-22.77
95% CI	(-43.71, -11.74)	(-38.79, 6.27)	(-60.06, 27.42)	(-27.39, 1.40)	(-30.69, 5.37)	(-35.57, 9.96)
p-value	<0.001	0.007	<0.001	0.030	0.005	<0.001
Lp(a)	-15.21	-24.12	-30.69	-21.96	-27.58	-27.23
95% CI	(-24.18, -6.24)	(-33.12, -15.12)	(-39.85, -21.53)	(-29.59, 14.33)	(-34.90, 20.26)	(-34.69, 19.76)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Triglycerides	-14.89	-12.18	-25.27	-7.28	-12.11	-9.14
95% CI	(-28.37, -1.41)	(-25.71, 1.34)	(-38.89, 11.65)	(-18.07, 3.50)	(-22.53, 1.69)	(-19.64, 1.37)
p-value	0.031	0.077	<0.001	0.180	0.023	0.088
HDL-C	5.72	7.13	9.84	2.79	4.82	5.52
95% CI	(0.82, 10.61)	(2.22, 12.04)	(4.89, 14.78)	(-1.43, 7.00)	(0.74, 8.90)	(1.41, 9.63)
p-value	0.022	0.005	<0.001	0.190	0.021	0.009
ApoA1	2.98	4.09	5.22	2.42	4.18	5.28
95% CI	(-1.01, 6.96)	(0.10, 8.09)	(1.19, 9.24)	(-0.73, 5.56)	(1.14, 7.22)	(2.22, 8.34)
p-value	0.140	0.045	0.011	0.130	0.007	<0.001

Source: Modified from integrated analysis Tables 14-4.14.1, 14-4.15.6, 14-4.9.1, 14-4.8.1, 14-4.18.6, 14-4.24.6, 14-4.17.6, 14-4.16.6, and 14-4.20.6.

2.2.3.3 Phase 2 Interim Efficacy Analysis Results for the Randomized, Controlled, Open-label Extension

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

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



2.2.3.4 Phase 2 Aggregate Interim Analysis Safety Results

Treatment emergent adverse events were reported in 51% in the AMG 145 Q2W group, 49% in the AMG 145 Q4W group, and 43% subjects in the combined placebo groups (Table 3). The incidence of treatment emergent adverse events considered related to treatment by the investigator was 9% in the AMG 145 Q2W group, 10% in the AMG 145 Q4W group, and 6% in the placebo group. No trend in the incidence or severity (\geq grade 2 to 4) of treatment emergent adverse events or treatment-related adverse events was observed.

A total of 18 (1.3%) subjects experienced serious adverse events across the 4 studies. Serious adverse events were reported in a similar proportion of AMG 145 Q2W (6 [1.6%]), AMG 145 Q4W (8 [1.4%]), and placebo (4 [1.3%]) subjects.

A total of 8 (0.6%) adverse events led to discontinuation of investigational product. The incidence of adverse events leading to discontinuation was similar in the AMG 145 (0.5%) and placebo (0.3%) treatment groups.

One fatal adverse event was reported across the 4 studies; the event was considered unrelated to investigational product by the investigator.

Table 3. Overall Summary of Treatment Emergent Adverse Events by Investigational Product -Studies 20101154 20101155 20090158 20090159 (Integrated Interim Observed Analysis Set)

	Placebo Total (N=298)	AMG 145 Q2W Total (N=372)	AMG 145 Q4W Total (N=566)	AMG 145 Total (N=938)	All Study Groups (N=1340)
All treatment emergent AEs, n (%)	127 (42.6)	191 (51.3)	278 (49.1)	469 (50.0)	645 (48.1)
Treatment-related AEs, n (%)	19 (6.4)	34 (9.1)	55 (9.7)	89 (9.5)	118 (8.8)
Serious adverse events, n (%)	4 (1.3)	6 (1.6)	8 (1.4)	14 (1.5)	18 (1.3)
Leading to discontinuation of IP, n (%)	1 (0.3)	2 (0.5)	3 (0.5)	5 (0.5)	8 (0.6)
Serious	0 (0)	1 (0.3)	0 (0)	1 (0.1)	1 (0.1)
Non-Serious	1 (0.3)	1 (0.3)	3 (0.5)	4 (0.4)	7 (0.5)

Source: Integrated Interim Analysis Table 14-6.1.2

The incidence of treatment emergent adverse events that occurred in $\geq 2\%$ of subjects in the combined AMG 145 treatment arms and with an incidence greater than placebo is summarized in [Table 4](#). The overall incidence of treatment emergent adverse events was slightly higher in the AMG 145 group (50%) than in the placebo group (43%); however, there was no notable increase in any particular adverse event. The adverse events that occurred in $\geq 2\%$ of subjects in the combined AMG 145 treatment arm and whose incidence was greater than in the placebo group were nasopharyngitis (7% AMG 145; 5% placebo), upper respiratory tract infection (3% AMG 145; 4% placebo), back pain (3% AMG 145; 2% placebo), myalgia (2% AMG 145; 1% placebo), and cough (2% each). All other adverse events occurred in $< 2\%$ of subjects overall.

Table 4. Summary of Treatment Emergent Adverse Events Occurring in \geq 2% Subjects in AMG 145 Groups (Combined) and Greater Than Placebo by Preferred Term in Descending Order of Frequency and by Investigational Product Studies 20101154, 20101155, 20090158, and 20090159 (Integrated Interim Observed Analysis Set)

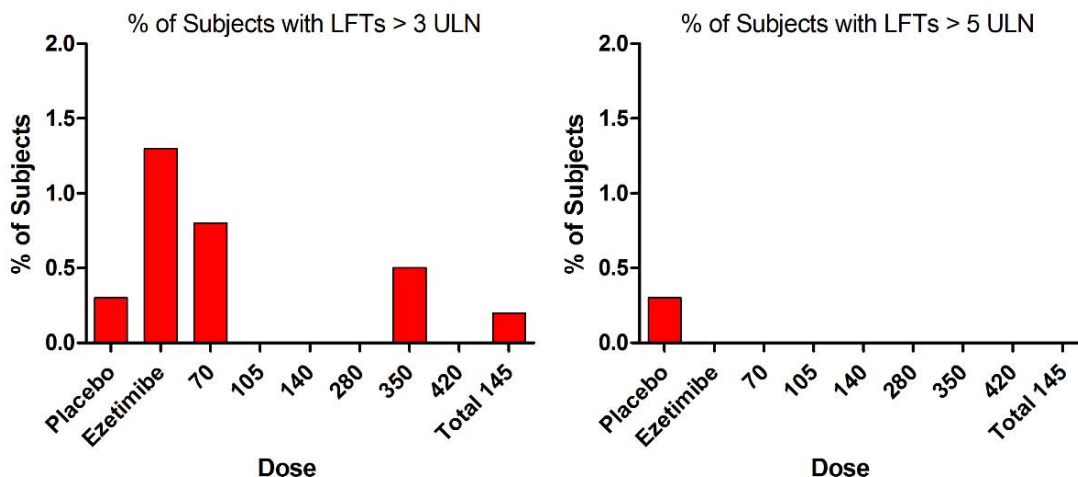
PREFERRED TERM	Placebo Total (N = 298) n (%)	AMG 145 Q2W (N = 372) n (%)	AMG 145 Q4W (N = 566) n (%)	AMG 145 Total (N = 938) n (%)	All Study Groups (N = 1340) n (%)
Subjects with Treatment Emergent Adverse Events	127 (42.6)	191 (51.3)	278 (49.1)	469 (50.0)	645 (48.1)
NASOPHARYNGITIS	16 (5.4)	26 (7.0)	41 (7.2)	67 (7.1)	88 (6.6)
UPPER RESPIRATORY TRACT INFECTION	11 (3.7)	14 (3.8)	16 (2.8)	30 (3.2)	47 (3.5)
BACK PAIN	7 (2.3)	8 (2.2)	17 (3.0)	25 (2.7)	33 (2.5)
MYALGIA	2 (0.7)	9 (2.4)	13 (2.3)	22 (2.3)	29 (2.2)
COUGH	6 (2.0)	7 (1.9)	13 (2.3)	20 (2.1)	28 (2.1)
NAUSEA	3 (1.0)	5 (1.3)	16 (2.8)	21 (2.2)	24 (1.8)

Source: Modified from Integrated Interim Analysis Table 14-6.13.2

Elevated liver function tests (AST, ALT, total bilirubin) were uncommon in the 4 parent phase 2 studies and had a similar incidence rate across treatment groups (Figure 3). A total of 4 subjects had post-baseline liver function tests $> 3 \times$ ULN with an incidence of 0.3% for placebo (n = 1), 1.3% for ezetimibe (n = 1), 0.8% for AMG 145 70 mg Q2W (n = 1), 0% for AMG 145 105 mg Q2W and 140 mg Q2W, 0% for AMG 145 280 mg Q4W, 0.5% for AMG 145 350 mg Q4W (n = 1), and 0% for AMG 145 420 mg Q4W. One subject who received placebo and no subjects who received AMG 145 had liver function tests $> 5 \times$ ULN.

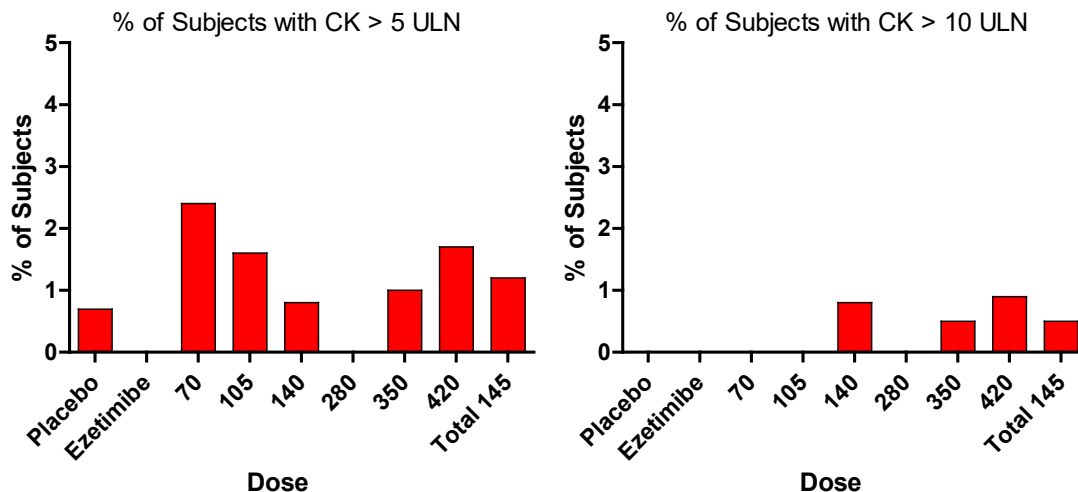
In addition to these 4 subjects, 3 additional subjects had elevated liver function tests. One of these subjects (AMG 145 350 mg Q4W) had elevated ALT at baseline ($> 3 \times$ ULN, but $< 5 \times$ ULN) that returned to $< 3 \times$ ULN by the next assessment. The other 2 subjects (1 AMG 145 105 mg Q2W and 1 AMG 145 420 mg Q4W) had elevations in bilirubin $> 2 \times$ ULN in the absence of liver enzyme abnormalities during the study; these subjects were diagnosed as probable Gilbert's Syndrome and not included in the summary of elevated LFTs due to the lack of clinical relevance. There were no serious adverse events reported in subjects who experienced LFT elevations.

Figure 3. Incidence of Liver Function Tests Greater than 3- or 5-fold ULN by Investigational Product Studies 20101154, 20101155, 20090158, and 20090159 (Integrated Interim Observed Analysis Set)



Post-baseline elevations in creatine kinase in the 4 parent studies were uncommon and transient (Figure 4). A total of 14 subjects had post-baseline creatine kinase > 5 x ULN with an incidence of 0.7% for placebo (n = 2), 0% for ezetimibe, 2.4% for AMG 145 70 mg Q2W (n = 3), 1.6% for AMG 145 105 mg Q2W (n = 2), 0.8% for AMG 145 140 mg Q2W (n = 1), 0% for AMG 145 280 mg Q4W, 1.0% for AMG 145 350 mg Q4W (n = 2), and 1.7% for AMG 145 420 mg Q4W (n = 4). Four of 967 (0.4%) AMG 145-treated subjects and no placebo subjects in these studies experienced post-baseline CK elevations > 10 x ULN. Two additional subjects (1 in AMG 145 105 mg Q2W and 1 in AMG 420 mg Q4W) had baseline creatine kinase elevations > 5 x ULN. There was no relationship between the dose of AMG 145 and the incidence of CK elevations. In almost all cases, elevations in CK were associated with obvious precipitating events in the form of unaccustomed exercise; in all subjects, except 1 (additional data unknown), creatine kinase returned to < 5 x ULN by the next visit. In general, elevations of CK did not lead to discontinuation. Two of the 14 subjects with elevated post-baseline creatine kinase discontinued investigational product; 1 subject (AMG 145 350 mg Q4W) discontinued after experiencing a temporally-associated grade 2 adverse event of myositis, and 1 subject (AMG 145 140 mg Q2W) discontinued after an unrelated car accident. No serious-related adverse events occurred in subjects with creatine kinase elevations.

Figure 4. Incidence of Creatine Kinase > 5- or 10-fold ULN by Investigational Product Studies 20101154, 20101155, 20090158, and 20090159 (Integrated Interim Observed Analysis Set)



Analyses of treatment emergent adverse events were carried out for the subgroups of subjects whose lowest post-dose LDL-C concentration was ≤ 40 mg/dL (N=519) and for subjects whose lowest post-dose LDL-C concentration was > 40 mg/dL (N=770). The overall incidence of treatment emergent adverse events in these 2 subgroups was similar (52% and 47%, respectively). Similar analysis was carried out for subjects whose lowest post-dose LDL-C concentration was ≤ 25 mg/dL (N=290) and for subjects whose lowest post-dose LDL-C concentration was > 25 mg/dL (N=999). The overall incidence of treatment-emergent adverse events was similar for the 2 subgroups (52% and 48%, respectively). It should be noted that no placebo subjects had a post-dose LDL-C concentration ≤ 25 mg/dL, so comparisons could not be made.

Samples from 1146 subjects from the 4 parent studies were tested in the immunoassay for anti-AMG 145 binding antibodies. One AMG 145-treated subject and 1 placebo subject tested positive for anti-AMG 145 binding antibodies out of 478 AMG 145 treated subjects and 198 placebo treated subjects who had at least one post baseline result. Both subjects tested negative for neutralizing antibodies. This represents a 0.2% and 0.5% incidence of binding antibody development for the AMG 145 and placebo groups, respectively.

2.3 Rationale

This study is being conducted to gather information on the long-term safety and efficacy of AMG 145. Many of the subjects in the parent Phase 2 studies are in a high unmet

medical need group such as heterozygous familial hypercholesterolemia, or statin intolerance, or have failed to reach goal with available therapies. For these populations, participation in this open-label extension will provide close medical supervision via healthcare professionals while on current standard of care therapies and an opportunity to receive an additional therapeutic option for LDL-C lowering.

2.4 Clinical Hypotheses

The primary clinical hypothesis is that long-term exposure of AMG 145 will be safe and well tolerated in subjects with hypercholesterolemia.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a multicenter, controlled, open-label extension study to assess the long-term safety and efficacy of AMG 145.

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 Centers

It is anticipated that approximately 240 centers will participate in the study. The number of sites may vary depending on the number of subjects from the parent study.

3.3 Number of Subjects

The number of subjects entering this study will depend on the number of subjects completing their respective AMG 145 parent studies and willingness to enroll. The number of subjects expected to participate in this study is approximately 1600.

3.3.1 Study Duration for Participants

Subjects will be enrolled into the study after completion of a qualifying AMG 145 study. During this study subjects will visit the site multiple times. During the first year, visits will occur every 4 weeks for all subjects. Quarterly visits will be data-rich and interval visits (every 4 weeks) will be data-sparse. During the first year those randomized to SOC-only will have their interval visits conducted via phone after week 4. Nonetheless SOC only subjects will still need to visit the site for their quarterly visits. **After the first year, quarterly visits will continue up to Week 260** (approximately 5 years).

3.3.2 End of Study

The study will **complete when the last subject has completed assessments for Week 260** (approximately year 5) or until the investigator's recommendation of

discontinuation, Amgen's recommendation of discontinuation, the subjects' decision to discontinue for any reason, or until an administrative decision is made to close the study.

4. SUBJECT ELIGIBILITY

The study population will consist of male and female subjects who have completed a qualifying AMG 145 protocol. Subjects who complete any future qualifying AMG 145 studies may be allowed to enroll if they meet the inclusion/exclusion criteria and the sponsor agrees to open the study to additional subjects.

4.1 Inclusion Criteria

Subjects will be eligible for the study if they:

1. Complete a qualifying AMG 145 parent study protocol.

4.2 Exclusion Criteria

Subjects will be ineligible for the study if they fulfill any of the following criteria:

1. Female subject is not willing to use at least one highly effective method of birth control during treatment and for an additional 15 weeks after the end of treatment unless subject is sterilized or postmenopausal;
 - Menopause is defined as 12 months of spontaneous and continuous amenorrhea in a female \geq 55 years old or 12 months of spontaneous and continuous amenorrhea with a follicle-stimulating hormone level $>$ 40 IU/L (or according to the definition of "postmenopausal range" for the laboratory involved) in a female $<$ 55 years old unless the subject has undergone bilateral oophorectomy.
 - Highly effective methods of birth control include abstinence, birth control pills, shots, implants, or patches, intrauterine devices (IUDs), sexual activity with a male partner who has had a vasectomy, condom or occlusive cap (diaphragm or cervical/vault caps) used with spermicide.
2. Subject is pregnant or breast feeding, or might become pregnant during treatment and/ or within 15 weeks after the end of treatment
3. Unreliability as a study participant based on the investigator's (or designee's) knowledge of the subject (eg, inability or unwillingness to adhere to the protocol)
4. Experienced a treatment-related serious adverse event that led to IP discontinuation in the parent study
5. Disorder that would interfere with understanding and giving informed consent or compliance with protocol requirements
6. Have an unstable medical condition, in the judgment of the investigator
7. Subject's medical condition requires lipid measurement and/or adjustment of background lipid-regulating therapy during the first 12 weeks of study participation

8. Known sensitivity to any of the products to be administered during dosing
9. Currently enrolled in another investigational device or drug study (excluding AMG 145 parent study), or less than 30 days since ending another investigational device or drug study(s), or receiving other investigational agent(s)

5. SUBJECT ENROLLMENT

Before subjects may be entered into the study, Amgen requires a copy of the site's written independent ethics committee and/or institutional review board (IEC/IRB) approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable (see [Section 11.2](#)). All subjects must personally sign and date the informed consent form before commencement of study specific procedures. A subject is considered enrolled once they have completed their end of study visit in the parent protocol and have been randomized.

All subjects who enter the study will keep the same subject identification number from the parent study.

5.1 Randomization

During the first year subjects will be randomized to one of two treatment arms. After completion of the first year, all subjects will be given open-label AMG 145. Assignment to the 2 treatment arms will be based on a computer-generated randomization schedule prepared by Amgen before the start of the study.

The following are the treatment arms:

- AMG 145, 420 mg, 6 mL QM SC + SOC
- SOC only

Randomization to these arms will be 2 (AMG 145 + SOC): 1 (SOC only).

Randomization will be stratified by the treatment arm a subject was randomized to in the parent study, which has the following 3 levels:

- Randomized to AMG 145 Q2W
- Randomized to AMG 145 QM
- Not randomized to AMG 145

A subject may only receive one randomization number for this OLE study and each randomization number will only be assigned to 1 subject. Once eligibility into the study has been confirmed, a site representative will make the randomization call to the Interactive Voice Response System (IVRS) to assign a new OLE randomization number

to the subject. The randomization call to the IVRS is accomplished by entering the pertinent information detailed in the IVRS user manual. A confirmation fax will be sent to the site to verify that the correct information has been entered.

6. TREATMENT PROCEDURES

AMG 145 will be the investigational product (IP) in this study. **In several countries, IP is referred to as investigational medicinal product (IMP). In this document, IMP will be referred to as IP.** During the first year subjects will be randomized to AMG 145 +SOC or SOC only. After completion of the first year, all subjects will be given open-label AMG 145.

The investigational medical devices used in this study are the prefilled autoinjector/pen (AI/Pen) and the 3.5 mL Personal Injector.

An Investigational Product Instruction Manual (IPIM), **a document external to this protocol**, contains detailed information regarding the storage, preparation, **destruction**, and administration of the investigational product **and this document** will be provided separately.

6.1 AMG 145

Investigational product will be administered by SC injections in this study. AMG 145 in its original formulation is currently used in this study, which requires larger total volumes of administration and use of vials and syringes. A new (more concentrated) formulation of AMG 145 has recently become available, which reduces the volume of a 420 mg injection and allows for administration by 3 prefilled autoinjector/pen devices or one 3.5 mL personal injector device. As reduced injection volume and the added convenience of using a device to administer the injection will benefit study subjects, the new formulation and prefilled autoinjector/pen device or 3.5 mL personal injector will be introduced to study subjects when they are available for dispensation to study sites.

Initial Formulation:

AMG 145 will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical IP distribution procedures. AMG 145 will be presented as a sterile, clear, colorless frozen liquid. Each sterile vial is filled with a 1 mL deliverable volume of 70 mg/mL AMG 145 formulated with **C** mM sodium acetate, **C**% (w/v) sucrose, **CC**% (w/v) polysorbate 20, pH **CC**. Each vial is for single use only.

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

thawed per the instructions provided in the IPIM. Vials should be checked for cracks or damage that may occur if the thawing process is not performed properly. Damaged product should not be administered. Further details are provided in the IPIM.

New Formulation:

AMG 145 will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical IP distribution procedures. When available in each country, AMG 145 will be presented as a sterile, preservative-free solution in a single use, disposable, handheld mechanical (spring-based) prefilled autoinjector/pen (AI/Pen) for fixed dose, subcutaneous injection. The prefilled AI/Pen contains a 1-mL deliverable volume of 140 mg/mL AMG 145 in [CCI] mM proline, [C] mM acetate, [CCI] % (w/v) polysorbate 80, pH [CC].

The 3.5 mL 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 [CCI] mM proline, [C] mM acetate, [CCI] % (w/v) polysorbate 80, pH [CC].

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

The prefilled AI/Pen or 3.5 mL personal injector should be inspected for IP quality, expiry, and damage before using. Damaged, expired, or degraded product should not be used and any issues with the prefilled AI/Pen or 3.5 mL personal injector should be reported to Amgen. Further details are provided in the IPIM and IFU.

The box number of investigational product should be recorded on each subject's Drug Administration case report form.

6.1.1 Dosage, Administration, and Schedule

All initial formulation investigational product (IP) will be administered via vial and syringe at the investigator site by a qualified staff member. Once the AI/Pen and personal injector are available, IP should be self-administered at home or other locations by subjects (or designee, which may include a qualified health care professional) in accordance with instructions in the IPIM. Subjects who prefer not to self-administer IP may return to the study site for administration by qualified site personnel. Subjects

should self-administer IP during visits to the investigator site under supervision of site personnel. The date, time, and volume of AMG 145 will be recorded on the individual subject's eCRF.

IP will be administered either at 6 mL via vials and syringes via study site staff or depending on device availability preferably by subjects (while under direct observation) at sites; at 3ml via 3 prefilled autoinjectors/pens or at 3.5 ml via 1 personal injector. The 6 mL dose can be split (eg, 3 injections at 2 mL each) and administered into different injection sites. The SC injections should be administered in a consecutive fashion with all injections completed within 30 minutes. For further details regarding the injection procedures, the IPIM should be consulted.

After completion of IP administration at each dosing visit up to year 2, subjects should be kept for observation for at least 30 minutes before being discharged. The observation period is optional after the Week 4 visit in year 2 visit, if in the opinion of the investigator, the subject has not manifested an allergy or hypersensitivity to the IP to date.

The effects of overdose of AMG 145 are not known. All overdose occurrences must be documented, and corresponding AEs recorded on the appropriate electronic case report form (eCRF) page and in source documents.

The dosing schedule is described by a [schema](#) in the protocol synopsis.

6.1.2 Dosage Adjustments

Dose adjustments during the study (including discontinuation of IP) are discouraged, but will be permitted for subjects that experience intolerable adverse events. If an investigator wants to make a dose adjustment they must contact the medical monitor prior to doing so. All dose adjustments must be clearly documented and recorded on the appropriate eCRF page and in the source documents.

Subjects who are Late for a Scheduled Dose of Investigational Product

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.

Subjects who Miss a Scheduled Dose of Investigational Product Completely

Subjects that completely miss a scheduled visit or IP administration will continue in the study and receive scheduled study drug at the next scheduled visit. However, this must be clearly documented both in the source documents and the case report forms.

6.1.3 Criteria for Withholding of Investigational Product

Reports from the central laboratory after each clinic visit must be reviewed as soon as possible after receipt and before the next administration of IP (AMG 145). If any of the criteria below are met for withholding IP, statin, or other applicable background lipid therapy, the subject must be instructed to stop the applicable treatment and an additional visit must be scheduled for the required laboratory evaluations. If a subject is experiencing elevations of laboratory values and is receiving other lipid therapies that may result in such elevations, eg, ezetimibe, fenofibrate, or niacin, the additional therapies should also be evaluated for a potential role in these elevations and considered for discontinuation. Fenofibrate, ezetimibe, or niacin can result in elevation of CK or liver function tests. If a subject experiences elevations in triglycerides > 500 mg/dL (5.65 mmol/L) and is concomitantly receiving a bile acid binding resin, the bile acid binding resin should be evaluated for discontinuation

6.1.3.1 Elevation of Creatine Kinase (CK)

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

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

CK at scheduled or unscheduled visit	CK on retest	Investigational Product and/or Statin and/or other lipid lowering therapies Administration
> 5x ULN	> 10x ULN	Discontinue both statin, other lipid lowering therapies, and IP ^a . Collect urine sample for urinalysis. Contact Amgen Medical Monitor.
	> 5x to ≤ 10x ULN	Discontinue statin, other lipid lowering therapies, and retest CK before administration. Consider continuing IP if alternative explanation.
	≤ 5x ULN	Consider continuing statin, other lipid lowering therapies and IP

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

6.1.3.2 Elevation of Liver Function Tests

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

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

- TBL > 2x upper limit of normal (ULN) or INR > 1.5

AND

- AST or ALT > 3x ULN

AND

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

- Progression of malignancy involving the liver (note that metastatic disease to the liver, by itself, should not be used as an explanation for significant AST/ALT elevations)
- Hypoxic or ischemic hepatopathy or congestive hepatopathy in association with significant right sided heart failure
- Concomitant administration of other hepatotoxins, including drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir, irinotecan) or herbal or dietary supplements
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome); alpha-one antitrypsin deficiency
- Autoimmune hepatitis
- Nonalcoholic steatohepatitis (NASH) or other fatty liver disease

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

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

If IP, statin and other applicable lipid background therapy is withheld due to any of the conditions above, the subject should be followed according to recommendations in [Appendix B](#) for possible DILI.

6.1.3.3 Criteria for Rechallenge After Withholding or Discontinuation of IP (AMG 145), Statin and Other Applicable Lipid Background Therapy

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

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

6.2 Medical Devices

IP will be administered per prefilled AI/Pen and 3.5 mL Personal Injector, provided by Amgen (Section 6.1). Additional details regarding the use of the AI/Pen and the 3.5 mL Personal Injector are provided in the IPIM and in the Instructions for Use (IFU) brochure.

Medical supplies (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.

6.3 Product Complaints, Including Device Complaints

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

Any product complaints 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.

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

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

- broken container or cracked container
- misuse of the AI/pen **or the 3.5 mL personal injector** due to misunderstanding of the IFU or error on the part of the user, or other inability to appropriately use the product (eg, due to malfunction of the AI/Pen or 3.5 mL 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 number of tablets or amount of fluid in the prefilled AI/Pen or 3.5 mL personal injector cartridge
- evidence of tampering or stolen material

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

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

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

6.4 Concomitant Therapy, Physical Exercise, and Diet

Prior to week 12 lipid-regulating concomitant medications cannot be altered, unless there is a clinically compelling reason for change. The investigator must contact the Amgen medical monitor to discuss such cases on an individual basis. After the post-randomization stabilization period (Week 12 visit), laboratory results ([Section 7.1.2.3](#)) will be unblinded and investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in [Section 6.5](#). However, during year 1, investigators must refrain from down-titrating background therapy (eg, discontinuation or reduction of statin therapy) due to unblinded LDL-C values. After year 1, investigators may down-titrate background therapy if deemed necessary.

All subjects should maintain their current regimen of diet and exercise for at least the first 12 weeks of the study, but should also be encouraged to continue to do so through the remainder of the study. Subjects will be required to refrain from unaccustomed intensive exercise (eg, heavy lifting or long runs) 48 hours prior to each visit.

6.5 Excluded Treatments During Study Period

The use of magnesium or aluminum hydroxide-containing antacids is not recommended within the period of two hours before and two hours after dosing with statins given the potential for interference with absorption.

7. STUDY PROCEDURES

This will be a multicenter, controlled, open-label extension study to assess the long-term safety and efficacy of AMG 145. During the first year, subjects receiving AMG 145 will have site visits every 4 weeks. For SOC only subjects, after week 4 all 4-week interim (non-quarterly) visits will be conducted via phone and all quarterly visits will occur at the site. For the purpose of this study, a month is defined as 4 weeks and a quarter is defined as 12 weeks.

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 procedures to be performed at each clinic visit are described below and are summarized in [Appendix A](#). IP should not be administered until all study procedures are completed at each visit.

7.1 General Study Procedures

7.1.1 Enrollment (EOS Parent/Day 1 OLE)

Day 1 for OLE study and the end of study (EOS) visit for the parent study should occur on the same day. All efforts should be made to minimize any time gaps between the parent study EOS and Day 1 in the OLE study. The Day 1 OLE visit will need to occur within 3 days of the parent EOS or all procedures (except ECG) will need to be repeated. The following procedures will be performed during the end of study visit in the parent study:

- Medical History
- Vital signs: sitting blood pressure (BP), heart rate (HR)
- AEs/ADEs/SAEs
- Concomitant medications
- Body weight
- Physical exam
- 12-lead electrocardiogram (ECG)
- Blood draw for serum pregnancy (females of childbearing potential only) and FSH (for applicable subjects)
- Urinalysis
- Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, chemistry, hematology, PK (AMG 145), PCSK9, coagulation, hsCRP, Lp(a), HbA1c, biomarkers, fasting Vitamin E, and anti-AMG 145 antibodies
- Administer IP (AMG 145 QM) to AMG 145 subjects (must be after completion of vital signs, ECG, and blood draw procedures)

For subjects on a Q2W schedule during the parent study, some of the above procedures will occur during the week 12 visit and not at week 14 (eg weight, HbA1c, hsCRP, Lp(a), biomarkers, etc).

Randomization - subjects will have the risks and benefits of participating in this study explained to them. Subjects that meet inclusion/exclusion criteria will need to sign a new OLE informed consent form, if they already have not done so, before randomization. During this visit subjects randomized to AMG 145 study drug (QM) will have their first injection administered at the site (must be after completion of vital signs, ECG, and blood draw procedures). Subsequent injections with vials and syringes will also occur at the site. After year 1, once the AI/Pen and 3.5 mL personal injector are available, IP should be self-administered at home or other appropriate non-study site settings/locations by subjects (or designee, which may include a qualified health care professional) between study visits. For subjects randomized to AMG 145 + SOC, Day 1 is defined as the first day that protocol-specified investigational product is administered. For subjects randomized to SOC only, Day 1 is defined as the day of randomization.

The following visits are for Year 1 only:

7.1.1.1 Week 4 (\pm 7 Days)

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- AEs/**ADEs**/SAEs
- Concomitant medications
- Blood draw for serum pregnancy
- Blood draw for fasting lipids (\geq 9 hour fasting sample), ApoA1, ApoB, chemistry, hematology, PK (AMG 145), PCSK9, coagulation, hsCRP, Lp(a), HbA1c, and anti-AMG 145 antibodies
- Blood draw for biomarkers
- Administer IP (AMG 145 QM) to AMG 145 subjects (must be after completion of vital signs, and blood draw procedures)

7.1.1.2 Interval Visits (Every 4 Weeks \pm 7 Days)

- SOC visit will occur via phone
- Vital signs (only for AMG 145 subjects): sitting blood pressure (BP), heart rate (HR)
- AEs/**ADEs**/SAEs
- Concomitant medications
- Observe IP Administration (AMG 145 QM) unless subject elects not to self-inject (must be after completion of vital signs)

7.1.1.3 Quarterly Visits (Every 12 Weeks \pm 7 Days)

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- AEs/ADEs/SAEs
- Concomitant medications
- Blood draw for serum pregnancy (performed at week 24 for females of childbearing potential only)
- Blood draw for fasting lipids (\geq 9 hour fasting sample), ApoA1, ApoB, chemistry, hematology, PK (AMG 145), PCSK9, coagulation, hsCRP, Lp(a), HbA1c, and anti-AMG 145 antibodies
- Blood draw for biomarkers at week 12 only
- Fasting Vitamin E at weeks 12 and 24 only
- Observe IP Administration (AMG 145 QM) unless subject elects not to self-inject (must be after completion of vital signs, and blood draw procedures)

7.1.1.4 Week 52 - End of Year 1 Visit (\pm 7 Days)

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- AEs/ADEs/SAEs
- Concomitant medications
- Body Weight
- Physical exam
- Blood draw for serum pregnancy (for females of childbearing potential only)
- Blood draw for fasting lipids (\geq 9 hour fasting sample), ApoA1, ApoB, chemistry, hematology, PK (AMG 145, PCSK9), coagulation, hsCRP, Lp(a), HbA1c, fasting Vitamin E, and anti-AMG 145 antibodies
- Urinalysis
- Observe IP Administration (AMG 145 QM) unless subject elects not to self-inject (must be after completion of vital signs, and blood draw procedures)

The following visits are for Years 2 through 5:

7.1.1.5 Week 4/Year 2 (4 Weeks \pm 7 Days)

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- AEs/ADEs/SAEs
- **Concomitant** medications
- Observe IP Administration (AMG 145 QM) unless subject elects not to self-inject (must be after completion of vital signs).

7.1.1.6 Quarterly Visits (Every 12 Weeks \pm 7 Days)

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- AEs/ADEs/SAEs
- Concomitant medications

- Blood draw for serum pregnancy (performed every 6 months for females of childbearing potential only)
- Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, chemistry, hematology, PK (AMG 145), PCSK9, coagulation, hsCRP, Lp(a), HbA1c, and anti-AMG 145 antibodies (at the end of each year only)
- Fasting Vitamin E at weeks 76 and 100 only
- Observe IP Administration (AMG 145 QM) unless subject elects not to self-inject (must be after completion of vital signs, and blood draw procedures).

7.1.1.7 End of Study/Early Term OLE Visit

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- AEs/ADEs/SAEs
- Concomitant medications
- Body weight
- Physical exam
- Blood draw for serum pregnancy (for females of childbearing potential only)
- Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, chemistry, hematology, PK (AMG 145), PCSK9, coagulation, hsCRP, Lp(a), HbA1c, and anti-AMG 145 antibodies
- Urinalysis

Completion of the study is defined as the last day that protocol-specified procedures are conducted for an individual subject. At the end of the study, vital status must be obtained for all subjects within the limits of local law. It is preferable that all end of study procedures are carried out. Subjects who are not deceased, have not withdrawn consent, or are not lost to follow-up, should have at minimum an End of Study assessment for Vital Status (alive or deceased), Adverse Events and Potential Endpoints. Sites should interrogate public databases, if necessary to obtain this information. If deceased, the date and reported cause of death should be obtained.

7.1.2 Standardization of Study Procedures

7.1.2.1 Measurement of Vital Signs

Blood pressure (BP) and heart rate (HR) should be measured at each visit. BP should continue to be measured in the same arm as in the parent study unless a concomitant condition favors the use of a different arm. The appropriate size cuff should be used. The diastolic blood pressure (DBP) will be recorded as the pressure noted when sound disappears (Korotkoff Phase V). Blood pressure and heart rate measurements should be determined after the subject has been seated for at least 5 minutes. The subject's

pulse should be measured for 30 seconds and the number should be multiplied by 2 to obtain heart rate.

7.1.2.2 Blood Sample Use

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

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

7.1.2.3 Lipid Measurements

Central laboratory results of the lipid panel, as well as ApoA1, ApoB, Lp(a), and high sensitivity C-reactive protein (hsCRP) will be blinded to investigators, subjects, and the study team until the week 12 visit is completed. Investigators and staff involved with this trial and all medical staff involved in the subject's medical care should refrain from obtaining lipid panels between parent EOS and week 12. Consequently, lipid lowering concomitant medications may not be adjusted based upon such results, unless there is a clinically compelling reason for change. The investigator must contact the Amgen medical monitor to discuss such cases on an individual basis. After the week 12 visit occurs, central laboratory results will be available to sites and lipid lowering concomitant medications may be adjusted as necessary. However, investigators must refrain from down-titrating standard of care therapy during the first year. If a lipid panel is drawn prior to week 12, all reasonable steps must be undertaken to avoid informing the subject and study personnel of the results.

7.1.2.4 Laboratory Assessments

All on-study laboratory samples will be processed and sent to the central laboratory. Amgen or designee will be responsible for PK (AMG 145), PCSK9 serum levels, anti-AMG 145 antibody, and biomarker development assessments and the central laboratory will ship the samples to Amgen or a specialty laboratory for assay (depending

on the assessment). PK (AMG 145), PCSK9 serum levels, anti-AMG 145 antibody, and biomarker will be blinded to the investigator, site and subjects.

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

Table 5 below outlines the specific analytes for serum chemistry, hematology, urinalysis, and other testing to be conducted.

Table 5. Analyte Listing

<u>Chemistry</u>	<u>Coagulation</u>	<u>Urinalysis</u>	<u>Hematology</u>	<u>Other Labs</u>
Sodium	PT/INR	Specific gravity	Hemoglobin	Fasting lipids
Potassium		pH	Hematocrit	• Total cholesterol
Chloride		Blood	MCV	• HDL-C
Bicarbonate		Protein	MCH	• LDL-C
Total protein		Glucose	MCHC	• Triglycerides
Albumin		Bilirubin	RDW	• VLDL-C
Calcium		WBC	Platelets	• Non-HDL-C
Magnesium		RBC	RBC	ApoA1
Phosphorus		Epithelial cells	WBC	ApoB
Glucose		Bacteria	Differential	ApoB/ApoA1 ratio
BUN or Urea		Casts	• Neutrophils	Total Cholesterol/HDL-C ratio
Creatinine		Crystals	• Bands	hsCRP
Uric acid			• Eosinophils	Lp(a)
Total bilirubin			• Basophils	Anti-AMG 145 antibodies
Direct bilirubin			• Lymphocytes	AMG 145 (PK)
CK			• Monocytes	PCSK9
ALP				HbA1c
LDH				FSH
AST (SGOT)				Fasting Vitamin E
ALT (SGPT)				Steroids
				• ACTH
				• FSH
				• LH
				• Cortisol
				• Testosterone
				• Estradiol
				Pregnancy test

Because Amgen wishes to examine LDL-C responses in subjects who previously received AMG 145 in a parent study and are subsequently randomized to SOC-alone in the extension study, investigators may not adjust lipid lowering background therapy until

the week 12 (Quarter 1) visit is conducted ([Section 6.4](#)). Furthermore, central laboratory results of the lipid panel, ApoA1, ApoB, Lp(a), and hsCRP will not be reported to the investigator prior to week 12 since some laboratory results may inadvertently unblind investigators to treatment assignment in the parent study. PK (AMG 145), PCSK9 serum levels, anti-AMG 145 antibody, biomarker, vitamin E and steroids substudy samples will be blinded to the investigator, site and subjects throughout the study. Finally, Investigators should not perform local testing of these analytes.

7.2 Antibody Testing Procedures

Blood samples will be collected quarterly from all subjects for the measurement of anti-AMG 145 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 (\pm 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.

7.3 Pharmacokinetic Sampling

7.3.1 All Subjects

Blood samples will be collected as shown in the Schedule of Assessments ([Appendix A](#)) to determine pre-dose AMG 145 and fasting PCSK9 serum concentration.

Approximately 5 mL blood will be collected at each time point. Serum will be prepared as instructed and will be frozen within 1 hour of collection in 2 aliquots for PCSK9 and 2 aliquots for AMG 145 at $CC^{\circ}C$ ($CC^{\circ}C$ if a $CC^{\circ}C$ freezer is not available). The site will be expected to complete a shipping log or requisition that will include subject identification information and the time and date of collection for each sample shipped. Missing samples must be clearly documented on the shipping log or requisition. Please

refer to the laboratory manual for detailed instructions on sample collection, processing, and shipping of PK samples.

7.3.2 Steroid Substudy

Subjects in the substudy will be required to consent to additional blood samples to be taken or for the potential use of the biomarker samples (in some cases collected previously) for steroid testing at Day 1, and at weeks 12, 24, and 52. These samples will be used for the following tests: ACTH, FSH, LH, cortisol, testosterone, estradiol. The substudy schedule is provided in [Appendix A](#).

7.4 Biomarkers Development Studies

7.4.1 Biomarker Sample Collection

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

It is expected that further advances will occur in investigational techniques that look at markers of PCSK9 signaling, LDLR turnover, cholesterol metabolism, inflammation, and plaque stability. It is not possible at this stage to anticipate what these advances will be; however, considerable benefit could accrue to future sufferers of coronary artery disease if these markers can be correlated with the data from the study. It is also important to clarify any potential drug interactions in this population of subjects who will be on a number of other drugs. For biomarker analysis, blood samples will be collected at the end of the parent study, week 4, and at week 12 so that analyses may be performed that will look at markers of PCSK9 signaling, LDL-R turnover, cholesterol metabolism, inflammation, and plaque stability such as 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.

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.

7.4.2 Sample Storage and Destruction

The biomarker 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

hypercholesterolemia, 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.

8. REMOVAL AND REPLACEMENT OF SUBJECTS

8.1 Removal of Subjects

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

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

Subjects may decline to continue receiving IP or other protocol-required therapies or procedures at any time during the study. If this occurs, the investigator will discuss with the subject appropriate procedures for discontinuation from IP or other protocol-required therapies or procedures and should encourage the subject to continue with collection of data, including endpoints and adverse events. These subjects, as well as those who

have stopped receiving IP or other protocol-required therapies or procedures for other reasons (eg, investigator or sponsor concern) should continue the schedule of study observations. If the subject is unable or unwilling to continue the schedule of observation, the investigators should clarify what type of follow-up the subject is agreeable to: in person, by phone/mail, through family/friends, in correspondence/communication with other physicians, and/or from review of the medical records. For these subjects, the EOS procedures should be used as a guide for the depth of information obtained for any subject that elects to continue via follow-up.

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

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

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

Reasons for removal from study:

- **decision by Amgen (sponsor)**
- **withdrawal of full consent from study**
- **death**
- **lost to follow-up**

8.2 Replacement of Subjects

There will be no replacement of subjects.

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment.

The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition **or underlying disease** (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration **more than would be expected**, and/or has an association with a significantly worse outcome **than expected**. A pre-existing condition that has not worsened **more than anticipated (ie, more than usual fluctuation of disease)** during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study is not considered an adverse event.

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

9.1.2 Reporting Procedures for Adverse Events 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 randomization through the EOS are reported using the applicable eCRF (eg, Adverse Event Summary eCRF) except for potential endpoints that are submitted to the CEC for adjudication. Potential endpoints must NOT be reported on the AE eCRF UNLESS notified by Amgen (or delegates).

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 the device (prefilled AI/Pen or 3.5 mL Personal Injector),
- Assessment of relatedness to investigational product (AMG 145) or **any study mandated activity or procedure** or other protocol-required therapies, and
- Action taken.

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

The investigator must assess whether the adverse event is possibly related to IP (AMG 145) and/or other protocol-required therapies. 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 AMG 145 and/or other protocol-required therapies?

The investigator must assess whether the adverse event is possibly related to the device: Prefilled AI/Pen or 3.5 mL Personal Injector used to administer IP (AMG 145). 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 or procedure. This relationship is indicated by a “yes” or “no” response to the question: “Is there a reasonable possibility that the event may have been caused by a study activity/procedure”?

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject’s baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator’s judgment) should not be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) should be recorded as the adverse event.

The investigator’s clinical judgment will be used to determine whether a subject should be removed from treatment or from the study due to an adverse event. A subject, or subject’s parent/legal guardian, may also voluntarily withdraw from treatment due to an adverse event, refer to [section 8.1](#) for additional instructions on the procedures recommended for safe withdrawal from treatment or the study. If the subject withdraws full consent, the subject should be encouraged to undergo, at a minimum, an end-of-study assessment.

The investigator is expected to follow any reported adverse events until resolved, improved to baseline, or stabilized.

9.2 Serious Adverse Events

9.2.1 Definition of Serious Adverse Events

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

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

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

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

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

9.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 days after the last dose of investigational product or EOS, whichever is later, are recorded in the subject’s medical records and are submitted to Amgen. All serious adverse events, except as specified below, must be submitted to Amgen within 24 hours following the investigator’s knowledge of the event, using the Serious Adverse Event Report (SAER) Form. The endpoint column on the SAER form must also be populated by indicating “no” or “yes”.

For all events submitted to the CEC that also meet serious criteria according to the definition above ([Section 9.2.1](#)), an SAER Form must be completed and submitted to Amgen Global Patient Safety within 24 hours of discovery of the potential endpoint event. However, a corresponding AE eCRF will only be completed if notified by Amgen (or delegate). These events include the following:

- Death
- Cardiac ischemic events (myocardial infarction, hospitalization for unstable angina, coronary revascularization)
- Hospitalization for heart failure
- Cerebrovascular events (transient ischemic attack, stroke)

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 Serious Adverse Event Report Form. See [Appendix C](#) for a sample of the Serious Adverse Event Report Form.

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

The investigator must assess whether the serious adverse event is possibly related to the device: Prefilled AI/Pen or 3.5 mL Personal Injector used to administer IP (AMG 145). 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 other study-mandated activity or procedure. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity/procedure"?

The investigator is expected to follow reported serious adverse events until resolved, improved to baseline, or stabilized.

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

If a subject is permanently withdrawn from the study because of a serious adverse event, this information must be submitted to Amgen within 24 hours. For all Amgen products expectedness will be determined based on the current Investigator's Brochure. Expectedness assessments will be made for all investigational products (Amgen and non-Amgen) using the appropriate reference safety information per local regulatory reporting requirements. Suspected unexpected serious adverse reactions reported for subjects receiving a non-Amgen investigational product will be expedited according to local requirements.

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

The investigator is to notify the appropriate IRB/EC 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 **evolocumab** 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 **evolocumab** through an additional 15 weeks after the end of treatment with **evolocumab**.

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

If a lactation case occurs while the female subject is taking **evolocumab**, 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 **evolocumab** through an additional 15 weeks after the end of treatment with **evolocumab**.

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

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Subsets, and Covariates

10.1.1 Primary Endpoint

Subject incidence of adverse events

10.1.2 Secondary Endpoints

- LDL-C at week 24 and week 52
- Non-HDL-C at week 24 and week 52
- ApoB at week 24 and week 52
- Total cholesterol/HDL-C ratio at week 24 and week 52
- ApoB/ApoA1 ratio at week 24 and week 52

10.1.3 Exploratory Endpoints

- Subject incidence of adjudicated events
 - Death (all cause, cardiovascular)
 - Cardiac ischemic events (myocardial infarction, hospitalization for unstable angina, coronary revascularization)
 - Hospitalization for heart failure
 - Cerebrovascular events (transient ischemic attack, stroke)
- Subject incidence of non-coronary revascularization
- Change and percent change from baseline at each scheduled visit in each of the following lipid parameters:
 - Total cholesterol
 - non-HDL-C
 - LDL-C
 - ApoB
 - total cholesterol/HDL-C ratio
 - ApoB/ApoA1 ratio

- Triglycerides
- HDL-C
- VLDL-C
- ApoA1
- Lp(a)
- hsCRP
- PCSK9 at each scheduled visit

10.1.4 Safety Endpoints

- Changes from baseline in safety laboratory values (including clinical chemistry and hematology) and vital signs at each scheduled visit
- Subject incidence of anti-AMG 145 antibodies

10.1.5 Pharmacokinetics Endpoints

Serum concentration of AMG 145 at selected time points

10.1.6 Analysis Set

The full analysis set (FAS) will include all subjects randomized in this study. All analyses of the randomized controlled period of the study will be performed using the FAS.

Analyses of the period after the randomized controlled period may be limited to those receiving investigational product. The steroid analysis set (SAS) includes all subjects who participate in the steroid substudy.

10.1.7 Baseline Covariates

Baseline covariates include, but are not limited to:

- Age
- Gender
- Ethnicity or race
- LDL-C
- PCSK9
- Lipid modifying background therapy (eg statin, ezetimibe)

10.2 Sample Size Considerations

The number of subjects entering this study will depend on the number of subjects completing their respective AMG 145 parent studies and willingness to enroll.

Approximately 2000 (1970) subjects will be randomized in the qualifying parent studies.

Assuming 80% of these subjects enroll in this extension study, the sample size will be approximately 1600 (1576) subjects.

The exact 95% confidence intervals for a 5% incidence rate under various enrollment assumptions using the binomial distribution for particular adverse events are provided in the table below. The estimates are derived using SAS version 9.2.

Percent of Subjects Enrolling	Total Number of Subjects Reporting Adverse Event	Estimated Adverse Event Incidence Rate	
		Incidence Rate	95% Confidence Interval
60	59/1182	5%	(0.04, 0.06)
70	69/1379	5%	(0.04, 0.06)
80	79/1576	5%	(0.04, 0.06)
90	89/1773	5%	(0.04, 0.06)

10.3 Interim Analysis and Early Stopping Guidelines

An administrative interim analysis, which included pharmacokinetic / pharmacodynamic (PKPD) modeling and was based on accumulated efficacy and safety data from this and other concurrently conducted studies with AMG 145, was performed by an internal unblinded group to guide future clinical development plans. Members in the designated internal unblinded group did not have direct roles or responsibilities in conducting any study included in this administrative interim analysis. There was an additional 1-year interim analysis to summarize the data collected in the randomized study period (up to week 52) after all subjects had completed the week 52 visits. There were no plans to modify or discontinue this study based on the results of the interim analysis. Also, additional analysis may be performed periodically throughout the study after parent studies are closed and individual subjects are unblinded to their lipid values.

10.4 Planned Methods of Analysis

10.4.1 General Approach/Considerations

Statistical analyses in this open-label extension study will be descriptive in nature. No statistical inference is planned.

Subject disposition, demographics and baseline characteristics will be summarized.

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.

One year interim and final analyses will be based on data collected from this study. Descriptions of any integrated analyses with the parent studies are out of scope for this study.

For all endpoints, results will be summarized by the treatment group to which subjects are randomized to in this study, unless otherwise specified. Subjects will be further categorized according to whether they were randomized to AMG 145 or not in their parent study. For the randomized period, this combined treatment group will have 4 levels (parent study treatment group/year 1 treatment group): “AMG 145/AMG 145 + SOC”; “AMG 145/ SOC only”; “Not AMG 145/AMG 145 + SOC”, and “Not AMG 145/SOC only”. For the final analysis (end of the 5 years), this combined treatment group will also have 4 levels (parent study treatment group/ year 1 treatment group/year 2-5 open-label AMG 145): “AMG 145/AMG 145 + SOC/AMG 145”; “AMG 145/ SOC only/AMG 145”; “Not AMG 145/AMG 145 + SOC/AMG 145”, and “Not AMG 145/SOC only/AMG 145”.

Unless specified otherwise, the baseline value is defined as the subject’s baseline value from the parent study.

There will be no imputation for missing data.

Deaths and major cardiovascular events from this and other studies with evolocumab will be adjudicated by an independent Clinical Events Committee (CEC) to facilitate aggregated analyses across the program.

10.4.2 Analysis of Key Study Endpoints

10.4.2.1 Primary Endpoint Analyses

Adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Subject incidences of adverse events, serious adverse events, and adverse events leading to withdrawal from IP will be tabulated by system organ class and preferred term.

Subgroup analyses on the primary endpoint will be conducted on each baseline covariate specified in [Section 10.1.7](#).

10.4.2.2 Secondary Endpoint Analyses

The secondary endpoints will be summarized at each scheduled visit by randomized treatment group in this study and also the combined treatment group (4 levels). For the 1-year interim analysis, point estimates of group means and their 95% confidence intervals will be presented. Differences in the group means, along with the 95%

confidence intervals, of the secondary endpoints will be estimated at each scheduled visit between

- the AMG 145 + SOC group and the SOC only group in this study, regardless of the treatment arm the subject was randomized to in their parent study, and
- the AMG 145 + SOC group and SOC only group in this study, by whether the subject was randomized to AMG 145 or not in their parent study.

A repeated measures linear model will be fit for each secondary endpoint for the 1-year interim analysis. The model will include at least terms for the treatment group (AMG 145 plus SOC, SOC only), the stratification factor, scheduled visit and the interaction of the treatment group with scheduled visit. Contrasts between treatment levels will be provided to estimate AMG 145 treatment effects at week 24 and week 52, continuing long term effect or discontinuing effect after 12 weeks of AMG 145 exposure. Details of these contrasts will be provided in the Statistical Analysis Plan.

10.4.2.3 Exploratory Endpoint Analyses

The percent change and change from baseline in laboratory based exploratory endpoints at each scheduled visit will be summarized.

Adjudicated Cardiovascular Events

Major cardiovascular events from this and other studies with evolocumab will be adjudicated by an independent Clinical Events Committee (CEC) to facilitate aggregated safety analyses across the program. These events may include death (cardiovascular, cerebrovascular and non-vascular), MI, stroke, coronary revascularization, urgent admissions for unstable angina and urgent admission for congestive heart failure. Subject incidence of adjudicated adverse events will be summarized.

10.4.2.4 Safety Endpoint Analyses

Safety Laboratory Parameters

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

Vital Signs

Vital signs will be summarized using descriptive statistics at each scheduled visit.

Anti-AMG 145 antibodies

The incidence and percentages of subjects who develop anti-AMG 145 antibodies (binding and neutralizing) at any time will be tabulated.

Concomitant Medications

Concomitant medications of interest will be summarized.

Steroid substudy

Analytes for the steroid substudy listed in [Section 7.3.2](#) will be summarized for each treatment group using descriptive statistics at each measurement time point.

10.4.2.5 Pharmacokinetics Endpoint Analyses

Summary statistics of PK concentration will be provided.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial generic informed consent template form is provided for the investigator to use to customize accordingly to his or her site's requirements. Updates to the template will be communicated by letter from the Amgen study manager to the investigator. The written informed consent document should be prepared in the language(s) of the potential patient population.

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

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

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, 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.

11.2 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

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

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

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

11.3 Subject Confidentiality

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

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

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

11.4 Investigator Signatory Obligations

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

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

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

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

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

12.2 Study Documentation and Archive

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

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

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for

inspection at any time by representatives from Amgen and/or applicable regulatory authorities. Elements should include:

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

In addition, all original source documents supporting entries in the 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 and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

The Amgen 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 monitor should 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 monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

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

Data capture for this study is planned to be electronic:

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

- Updates to electronic CRFs (eCRF) will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review will be performed on subject data received at Amgen. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications will be created in the EDC system database for site resolution and closed by Amgen reviewer.
- The principal investigator signs only the Investigator Verification Form for this electronic data capture study. This signature will indicate that the principal investigator inspected or reviewed the data on the 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 to comply 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 ([Appendix A](#)), 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

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

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood. Consult the country-specific requirements for language requirements.

12.6 Publication Policy

To coordinate dissemination of data from this study, Amgen encourages the formation of a publication committee consisting of several principal 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 should 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 corporate review. The Clinical Study Agreement among the institution, principal 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. Depending on the type of study, and if permitted under applicable regional laws or regulatory guidelines, subjects may be compensated for other inconveniences not associated with study-related injuries (eg, travel costs).

13. REFERENCES

Abifadel M, Varret M, Rabes J-P, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nature Genetics*. 2003;34:154-156.

Allender S, Scarborough P, Peto V, et al. European Cardiovascular Disease Statistics 2008 Edition.

Brown MS, Goldstein JL. Biomedicine. Lowering LDL--not only how low, but how long? *Science*. 2006;311:1721-1723.

Cohen J, Pertsemlidis A, Kotowski IK, et al. Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. *Nature Genetics*. 2005;37:161-165.

Cohen JC, Boerwinkle E, Mosley TH, Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med*. 2006;354:1264-1272.

Eisenberg, DA. Cholesterol lowering in the management of coronary artery disease: the clinical implications of recent trials. *Am J Med*. 1998;104(2A):2S-5S.

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Summary of the second report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II). *JAMA*. 1993 ;269:3015-3023.

Gould AL, Rossouw JE, Santanella NC, Heyse JF, Furberg CD. Cholesterol reduction yields clinical benefit. A new look at old data. *Circulation*. 1995;91 2274-2282.

Hooper AJ, Marais AD, Tanyanyiwa DM, Burnett JR. The C679X mutation in PCSK9 is present and lowers blood cholesterol in a Southern African population. *Atherosclerosis*. 2007;193:445-448.

Horton JD, Cohen JC, Hobbs HH. Molecular biology of PCSK9: its role in LDL metabolism. *Trends Biochem Sci*. 2007;32:71-77.

Kannel WB, et al. The Framingham Study: An epidemiological investigation of cardiovascular disease, Section 30. Some characteristics related to the incidence of cardiovascular disease and death: The Framingham Study. 18-year follow-up. Washington, D.C., Dept. of Health, Education, and Welfare, Publication No. (NIH) 74 599, 1974.

Kannel WB, Castelli WP, Gordon T. Lipoprotein cholesterol in the prediction of atherosclerotic disease: New perspectives based on the Framingham Study. *Ann Int Med*. 1979;90:85-91.

Kannel WB. Range of serum cholesterol values in the population developing coronary artery disease. *Am J Cardiol*. 1995;76:69C-77C.

Roger VL, et al. Heart Disease and Stroke Statistics – 2011 Update. *Circulation*. 2011;123:e18-e209.

Sempos CT, Cleeman CT, Carroll MD, et al. Prevalence of high blood cholesterol among US adults. An update based on guidelines from the second report of the National Cholesterol Education Program Adult Treatment Panel. *JAMA*. 1993;269:3009-3014.

Zaid A, Roubtsova A, Essalmani R, et al. Proprotein convertase subtilisin/kexin type 9 (PCSK9): hepatocyte-specific low-density lipoprotein receptor degradation and critical role in mouse liver regeneration. *Hepatology*. 2008;48:646-654.

Zhao Z, Tuakli-Wosornu Y, Lagace TA, et al. Molecular characterization of loss-of-function mutations in PCSK9 and identification of a compound heterozygote. *Am J Hum Genet.* 2006;79:514-523.

14. APPENDICES

Appendix A. Schedule of Assessments

Study Day / Timepoint	Year 1 (AMG 145 +SOC vs SOC alone)					Years 2-5 (AMG 145 +SOC)			
	EOS Parent Day 1 OLE ^a	Week 4	Interval Visits (4 Weeks) Weeks 8, 16, 20, 28, 32, 40, and 44		Quarterly Visits (12 weeks) Weeks 12,24,36 and 48	Week 52	Week 4/ Yr2*	Quarterly Visits 12 weeks	EOS/ET OLE**
<i>General Procedures</i>			AMG	SOC					
Medical History	X								
Informed consent	X								
Vital Signs (HR, BP)	X	X	X		X	X	X	X	X
AEs/ADEs/SAEs	X	X	X	X ^b	X	X	X	X	X
Concomitant medication	X	X	X	X ^b	X	X	X	X	X
Body Weight	X					X			X
Physical exam	X					X			X
12 Lead ECG ^c	X								
<i>Central Laboratory</i>									
Fasting plasma lipids, ApoA1,ApoB	X ^d	X			X	X		X	X
PK samples (AMG 145 PCSK9)	X	X			X	X		X	X
Chemistry	X	X			X	X		X	X
Hematology	X	X			X	X		X	X
HbA1c	X	X			X	X		X	X
Coagulation	X	X			X	X		X	X
hsCRP, Lp(a)	X	X			X	X		X	X
Fasting Vitamin E	X ^e				X ^e	X ^e		X ^e	X ^e
Biomarkers (blood)	X	X ^f			X ^f				
Anti-AMG 145 antibodies	X	X			X	X		X ^g	X
Serum pregnancy (females of childbearing potential) and FSH	X ^h	X ⁱ			X ⁱ	X ⁱ		X ⁱ	X
Urinalysis	X					X			X
Randomization	X								
<i>Investigational Product</i>									
IP administration, QM	X	X	X		X	X ^j	X	X	

Footnotes defined on next page.

^a D1 = day of first administration of investigational product for the open-label extension; subjects will undergo EOS procedures for their parent study and sign a new OLE consent before being randomized. -Subjects randomized to study drug (AMG 145 + SOC QM) will have their first injection. Visit will need to occur within 3 days of the parent EOS or all procedures (except ECG) will need to be repeated.

^b Subjects not receiving IP every 4 weeks will receive a phone call every 4 weeks to document any changes in concomitant medications or new AE/SAEs.

^c ECGs for subjects randomized to Q2W in the parent study will occur at week 12

^d Day 1 - measurement will only occur during parent EOS for Q2W subjects and QM subjects that miss their 3 day EOS window.

^e Vitamin E will only be collected at EOS Parent/Day 1 and at weeks 12, 24, 52 (year 1), 76, and 100. Vitamin E will remain blinded throughout the study to the investigator, site and subject. If a subject early terms before week 100 a Vitamin E sample should be collected.

^f Biomarkers will be collected only at week 4 and week 12.

^g After year 1 antibody samples will only be collected at the end of each year.

^h FSH = in applicable subjects for study entry only – see [exclusion criteria](#)

ⁱ Serum pregnancy testing will occur at week 4, week 24, week 52, and every 6 months thereafter.

^j SOC subjects will obtain their first dose of AMG 145 at week 56

* Once the AI Pen and personal injector are available, IP should be self-administered at home or other locations both between and during quarterly visits after week 4/Year 2. Subjects who prefer not to self-administer IP may return to the study site for administration (see [section 6.1.1](#)).

** The EOS procedures should be used as a guide for the depth of information obtained for any subject that elects to continue via follow-up (see [section 8](#)).

STEROID SUBSTUDY

Additional Procedures for subjects enrolled in the steroid substudy.

Test	Day 1	Week 12	Week 24	Week 52
Substudy informed consent	X			
ACTH	X	X	X	X
FSH	X	X	X	X
LH	X	X	X	X
Cortisol	X	X	X	X
Testosterone	X	X	X	X
Estradiol	X	X	X	X

Appendix B. Additional Safety Assessment Information

Adverse Event Toxicity Grading Scale

Refer to the NCI Common Terminology Criteria for AEs (CTCAE) Version 4.0 for AE grading and information. The CTCAE is available at the following link:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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

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

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST/ALT and TBL elevation according to the criteria specified in [Section 6.1.3.2](#) (3x ULN for AST/ALT and 2x ULN for TBL) require the following:

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

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

Additional Clinical Assessments and Observation

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

- Repeat liver chemistries within 24-48 hours (ALT, AST, ALP, TBL); in cases of TBL >2x ULN or AST/ALT much greater than 3x ULN, retesting should be performed within 24 hours
 - Subjects should be monitored at least twice weekly; testing frequency may decrease to once per week or less if laboratory abnormalities stabilize or the IP has been discontinued AND the subject is asymptomatic
- Obtain PT/INR, fractionated bilirubin and any other potentially relevant laboratory evaluations of liver function or disease
- Obtain complete blood count (CBC) with differential to assess for eosinophilia
- Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Obtain a more detailed history of:
 - Prior and/or concurrent diseases or illness
 - Exposure to environmental and/or industrial chemical agents
 - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
 - Prior and/or concurrent use of alcohol, recreational drugs and special diets
 - Concomitant medications (including non-prescription medicines & herbal and dietary supplements)
- Initiate full viral and autoimmune hepatitis evaluation (serologies for hepatitis A,B,C, D, E, Epstein-Barr Virus, Herpes Simplex Virus, etc); evaluate for other potential causes of DILI including but not limited to: NASH, hypoxic/ischemic hepatopathy, and biliary tract disease
- Obtain gastroenterology or hepatology consult
- Perform appropriate liver imaging or biopsy if clinically indicated; strongly consider these tests in cases of concurrent transaminase and TBL elevation as specified in [Section 6.1.3.2](#).
- Follow the subject until all laboratory abnormalities return to baseline or normal. The “close observation period” should continue for a minimum of 4 weeks after drug discontinuation.

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

Appendix C. Sample Serious Adverse Event Report (SAER) Form

AMGEN evolocumab (AMG 145) 20110110	Clinical Trial Serious Adverse Event Report (3-IMP) <i>Notify Amgen Within 24 Hours of knowledge of the event</i>	<input type="checkbox"/> New <input type="checkbox"/> Follow-up
--	---	--

US: +1 888 814 8653											
1. SITE INFORMATION											
Site Number			Investigator						Country		
Reporter				Phone Number () () ()				Fax Number () () ()			
2. SUBJECT INFORMATION											
Subject ID Number			Date of Birth Day Month Year			Sex <input type="checkbox"/> F <input type="checkbox"/> M		Race			
3. SERIOUS ADVERSE EVENT - Information in this section must also be entered on the Serious Adverse Event Summary CRF											
Provide the date the investigator became aware of this Serious Adverse Event information: Day Month Year											
Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event <i>List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.</i>	Date Started Day Month Year	Date Ended Day Month Year	Potential Endpoint?	Check only if event occurred before first dose of IP	Enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the event may have been caused by if yes see section 10				Outcome of Event	Check only if event is related to study procedure eg biopsy
						evolocumab (AMG 145)	Pre-filled autoinjector /pen (AI/pen)	3.5 mL personal injector			
Serious Criteria: 01 Fatal 02 Immediately life-threatening 03 Required hospitalization 04 Prolonged hospitalization 05 Persistent or significant disability /incapacity 06 Congenital anomaly / birth defect 07 Other significant medical hazard											
4. HOSPITALIZATION											
						Date Admitted Day Month Year			Date Discharged Day Month Year		
Was subject hospitalized? <input type="checkbox"/> No <input type="checkbox"/> Yes, If yes, please complete date(s):											
5. INVESTIGATIONAL PRODUCT (IP)											
Initial Start Date Day Month Year			Date of Dose Day Month Year			Dose Route Frequency			Action Taken with Product		
evolocumab (AMG 145) <input checked="" type="checkbox"/> Open Label									01 Still being Administered 02 Permanently discontinued 03 Withheld		
Pre-filled autoinjector/pen (AI/pen) <input checked="" type="checkbox"/> Open Label											
3.5 mL personal injector <input checked="" type="checkbox"/> Open Label											
6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Concomitant Medications? <input type="checkbox"/> No <input type="checkbox"/> Yes, If yes, please complete:											
Medication Name(s)		Start Date Day Month Year		Stop Date Day Month Year		Co-suspect Nb/ Yes/		Continuing Nb/ Yes/		Dose Route Freq. Treatment Med Nb/ Yes/	

 evolocumab (AMG 145) 20110110	Clinical Trial Serious Adverse Event Report (3-IMP) <i>Notify Amgen Within 24 Hours of knowledge of the event</i>	<input type="checkbox"/> New <input type="checkbox"/> Follow-up
---	---	--

	Site Number	Subject ID Number	
--	-------------	-------------------	--

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

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

Date	Test	Unit									
	Day	Month	Year								

9. OTHER RELEVANT TESTS (diagnostics and procedures) Any Other Relevant tests? No Yes, if yes, please complete:

Date	Additional Tests	Results	Units
Day	Month	Year	

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

Signature of Investigator or Designee	Title	Date
---------------------------------------	-------	------

Appendix D. Pregnancy and Lactation Notification Worksheets

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information
 Protocol/Study Number: _____
 Study Design: Interventional Observational (If Observational: Prospective Retrospective)

2. Contact Information
 Investigator Name _____ Site # _____
 Phone (____) _____ Fax (____) _____ Email _____
 Institution _____
 Address _____


3. Subject Information
 Subject ID # _____ Subject Gender: Female Male Subject DOB: mm ____ / dd ____ / yyyy ____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm ____ / dd ____ / yyyy ____

Was the Amgen product (or study drug) discontinued? Yes No
 If yes, provide product (or study drug) stop date: mm ____ / dd ____ / yyyy ____
 Did the subject withdraw from the study? Yes No

5. Pregnancy Information
 Pregnant female's LMP mm ____ / dd ____ / yyyy ____ Unknown
 Estimated date of delivery mm ____ / dd ____ / yyyy ____ Unknown N/A
 If N/A, date of termination (actual or planned) mm ____ / dd ____ / yyyy ____
 Has the pregnant female already delivered? Yes No Unknown N/A
 If yes, provide date of delivery: mm ____ / dd ____ / yyyy ____
 Was the infant healthy? Yes No Unknown N/A
 If any Adverse Event was experienced by the infant, provide brief details: _____

Form Completed by:
 Print Name: _____ Title: _____
 Signature:  _____ Date: _____

AMGEN™ Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: _____

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

2. Contact Information

Investigator Name _____ Site # _____

Phone (____) _____ Fax (____) _____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Date of Birth: mm ____ / dd ____ / yyyy ____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm ____ / dd ____ / yyyy ____

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

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

Did the subject withdraw from the study? Yes No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? Yes No

If No, provide stop date: mm ____ / dd ____ / yyyy ____

Infant date of birth: mm ____ / dd ____ / yyyy ____

Infant gender: Female Male

Is the infant healthy? Yes No Unknown N/A

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

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Amendment 7

Protocol Title: A Multicenter, Controlled, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of Evolocumab (AMG 145)

Amgen Protocol Number (evolocumab) 20110110
EudraCT 2011-001915-29

Date:	24 May 2011
Amendment 1 Date:	15 April 2015
Superseding Amendment 1 Date	26 August 2011
Amendment 2 Date	08 September 2011
Amendment 3 Date	24 April 2012
Amendment 4 Date	20 June 2012
Amendment 5 Date	26 February 2014
Amendment 6 Date	09 March 2015
Amendment 7 Date	12 November 2015

Rationale:

The protocol is being amended to:

- Update Safety language
- Update End of Study Language
- Make minor editorial changes

Description of Changes

Section: Global

Change: Version dates updated throughout document from 09 March 2015 to 12 November 2015.

Section: Title Page

Replace:

PPD

1 Sanderson Road (Uxbridge Business Park)
Uxbridge UB8 1DH
United Kingdom

PPD

With:

PPD

1 Sanderson Road (Uxbridge Business Park)
Uxbridge UB8 1DH
United Kingdom

PPD

Section: Title Page

Replace:

Date:	24 May 2011
Amendment 1 Date:	15 August 2011
Superseding Amendment 1 Date:	26 August 2011
Amendment 2 Date:	08 September 2011
Amendment 3 Date:	24 April 2012
Amendment 4 Date:	20 June 2012
Amendment 5 Date:	26 February 2014
Amendment 6 Date:	09 March 2015

With:

Date:	24 May 2011
Amendment 1 Date:	15 August 2011
Superseding Amendment 1 Date	26 August 2011
Amendment 2 Date	08 September 2011
Amendment 3 Date	24 April 2012
Amendment 4 Date	20 June 2012
Amendment 5 Date	26 February 2014
Amendment 6 Date	09 March 2015
Amendment 7 Date	12 November 2015

Section: Protocol Synopsis, Study Design

Replace:

At the end of the first year (week 52), starting at week 56 (week 4/year 2) all subjects will receive open-label AMG 145 for approximately 4 years (or until the investigator's recommendation of discontinuation, Amgen's recommendation of discontinuation, the subjects' decision to discontinue for any reason, or until an administrative decision is made to close the study).

With:

At the end of the first year (week 52), starting at week 56 (week 4/year 2) all subjects will receive open-label AMG 145 for **up to** 4 years (or until the investigator's recommendation of discontinuation, Amgen's recommendation of discontinuation, the subjects' decision to discontinue for any reason, or until an administrative decision is made to close the study).

Section: Protocol Synopsis, During the First Year

Add:

During the first year, subjects randomized to AMG 145 + SOC will need to visit the site every 4 weeks. During these visits vital signs will be obtained and adverse events (AEs), **adverse device effects (ADEs)**, serious adverse events (SAEs), and concomitant medications will be recorded. Subjects randomized to SOC only, will not visit the site every 4 weeks (except at specified visits); rather the site will call these subjects at the scheduled visits to review concomitant medication changes, AEs, **ADEs**, and SAEs. During quarterly (every 12 weeks) visits, central laboratory tests will be

performed for all subjects. For a full list of study procedures, including the timing of each procedure, please refer to Section 7.1 and Appendix A.

Section: Study Glossary

Add:

ADE	Adverse Device Effect
NCI	National Cancer Institute

Section: 3.3.1 Study Duration for Participants

Replace:

Subjects will be enrolled into the study after completion of a qualifying AMG 145 study. During this study subjects will visit the site multiple times. During the first year, visits will occur every 4 weeks for all subjects. Quarterly visits will be data-rich and interval visits (every 4 weeks) will be data-sparse. During the first year those randomized to SOC-only will have their interval visits conducted via phone after week 4. Nonetheless SOC only subjects will still need to visit the site for their quarterly visits. The study will continue for approximately 5 years (or until the investigator's recommendation of discontinuation, Amgen's recommendation of discontinuation, the subjects' decision to discontinue for any reason, or until an administrative decision is made to close the study).

With:

Subjects will be enrolled into the study after completion of a qualifying AMG 145 study. During this study subjects will visit the site multiple times. During the first year, visits will occur every 4 weeks for all subjects. Quarterly visits will be data-rich and interval visits (every 4 weeks) will be data-sparse. During the first year those randomized to SOC-only will have their interval visits conducted via phone after week 4. Nonetheless SOC only subjects will still need to visit the site for their quarterly visits. **After the first year, quarterly visits** will continue **up to Week 260** (approximately 5 years).

Section: 3.3.2 End of Study

Replace:

The study will continue for approximately 5 years (or until the investigator's recommendation of discontinuation, Amgen's recommendation of discontinuation, the subjects' decision to discontinue for any reason, or until an administrative decision is made to close the study).

With:

The study will **complete when the last subject has completed assessments for Week 260** (approximately year 5) or until the investigator's recommendation of discontinuation, Amgen's recommendation of discontinuation, the subjects' decision to discontinue for any reason, or until an administrative decision is made to close the study.

Section: 6 Treatment Procedures

Replace:

AMG 145 will be the investigational product (IP) in this study. During the first year subjects will be randomized to AMG 145 +SOC or SOC only. After completion of the first year, all subjects will be given open-label AMG 145.

An Investigational Product Instruction Manual (IPIM) containing detailed information regarding the storage, preparation, and administration of the investigational product will be provided separately.

With:

AMG 145 will be the investigational product (IP) in this study. **In several countries, IP is referred to as investigational medicinal product (IMP). In this document, IMP will be referred to as IP.** During the first year subjects will be randomized to AMG 145 +SOC or SOC only. After completion of the first year, all subjects will be given open-label AMG 145.

The investigational medical devices used in this study are the prefilled autoinjector/pen (AI/Pen) and the 3.5 mL Personal Injector.

An Investigational Product Instruction Manual (IPIM), **a document external to this protocol**, contains detailed information regarding the storage, preparation, **destruction**, and administration of the investigational product **and this document** will be provided separately.

Section: 6.2 Medical Devices

Add:

IP will be administered per prefilled AI/Pen and 3.5 mL Personal Injector, provided by Amgen ([Section 6.1](#)).

Section: 6.3 Product Complaints, Including Device Complaints

Replace:

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

Any product complaints 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.

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

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

- broken container or cracked container
- misuse of the AI/pen due to misunderstanding of the IFU or error on the part of the user, or other inability to appropriately use the product (eg, due to malfunction of the AI/Pen or 3.5 mL personal injector)

With:

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

Any product complaints 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.

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

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

- broken container or cracked container
- misuse of the AI/pen **or the 3.5 mL personal injector** due to misunderstanding of the IFU or error on the part of the user, or other inability to appropriately use the product (eg, due to malfunction of the AI/Pen or 3.5 mL personal injector)

Section: 7.1.1 Enrollment (EOS Parent/Day 1 OLE), 3rd bullet

Add:

- AEs/**ADEs**/SAEs

Section: 7.1.1.1 Week 4 (\pm 7 Days), 2nd bullet

Add:

- AEs/**ADEs**/SAEs

Section: 7.1.1.2 Interval Visits (Every 4 Weeks \pm 7 Days), 3rd bullet

Add:

- AEs/**ADEs**/SAEs

Section: 7.1.1.3 Quarterly Visits (Every 12 Weeks \pm 7 Days), 2nd bullet

Add:

- AEs/**ADEs**/SAEs

Section: 7.1.1.4 Week 52 - End of Year 1 Visit (\pm 7 Days), 2nd bullet

Add:

- AEs/**ADEs**/SAEs

Section: 7.1.1.5 Week 4/Year 2 (4 Weeks \pm 7 Days), 2nd bullet

Add:

- AEs/**ADEs**/SAEs

Section: 7.1.1.6 Quarterly Visits (Every 12 Weeks \pm 7 Days)

Add:

- AEs/ADEs/SAEs

Section: 7.1.1.7 End of Study/Early Term OLE Visit

Add:

- AEs/ADEs/SAEs

Section: 7.1.2.3 Lipid Measurements

Delete:

~~Adverse event data for all subjects who experience 2 consecutive UC LDL-C values below 25 mg/dL during the trial will be reviewed in aggregate by an independent non-program related Amgen safety physician to evaluate any potential safety risks.~~

Section: 8.1 Removal of Subjects

Add:

Reasons for removal from study:

- decision by Amgen (sponsor)
- withdrawal of full consent from study
- death
- lost to follow-up

Section: 9.1.1 Definition of Adverse Events

Add:

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition **or underlying disease** (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration **more than would be expected**, and/or has an association with a significantly worse outcome **than expected**. A pre-existing condition that has not worsened **more than anticipated (ie, more than usual fluctuation of disease)** during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study is not considered an adverse event.

Section: 9.1.2 Reporting Procedures for Adverse Events

Add:

9.1.2 Reporting Procedures for Adverse Events That Do Not Meet Serious Criteria

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 the device (prefilled AI/Pen or 3.5 mL Personal Injector),
- Assessment of relatedness to investigational product (AMG 145) or **any study mandated activity or procedure** or other protocol-required therapies, and
- Action taken.

Section: 9.3 Pregnancy and Lactation Reporting

Replace:

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

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of protocol-required therapies through an additional 15 weeks after the end of treatment with IP (AMG 145).

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

If a lactation case occurs while 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 (AMG 145).

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

With:

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking **evolocumab** 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 **evolocumab** through an additional 15 weeks after the end of treatment with **evolocumab**.

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

If a lactation case occurs while the female subject is taking **evolocumab**, 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 **evolocumab** through an additional 15 weeks after the end of treatment with **evolocumab**.

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

Section: Appendix A, 5th row

Add:

AEs/ADEs/SAEs	X	X	X	X ^b	X	X	X	X	X
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Section: Appendix D. Pregnancy and Lactation Notification Worksheets

Replace:

AMGEN Pregnancy Notification Worksheet
Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX#

1. Case Administrative Information														
Protocol/Study Number: _____														
Study Design: <input type="checkbox"/> Interventional <input type="checkbox"/> Observational (If Observational: <input type="checkbox"/> Prospective <input type="checkbox"/> Retrospective)														
2. Contact Information														
Investigator Name _____		Site # _____												
Phone (____) _____		Fax (____) _____		Email _____										
Institution _____														
Address _____														
3. Subject Information														
Subject ID # _____ Subject Gender: <input type="checkbox"/> Female <input type="checkbox"/> Male Subject DOB: mm ____ / dd ____ / yyyy ____														
4. Amgen Product Exposure														
<table border="1"><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>					Amgen Product	Dose at time of conception	Frequency	Route	Start Date					mm ____ / dd ____ / yyyy ____
Amgen Product	Dose at time of conception	Frequency	Route	Start Date										
				mm ____ / dd ____ / yyyy ____										
Was the Amgen product (or study drug) discontinued? <input type="checkbox"/> Yes <input type="checkbox"/> No														
If yes, provide product (or study drug) stop date: mm ____ / dd ____ / yyyy ____														
Did the subject withdraw from the study? <input type="checkbox"/> Yes <input type="checkbox"/> No														
5. Pregnancy Information														
Pregnant female's LMP mm ____ / dd ____ / yyyy ____ <input type="checkbox"/> Unknown														
Estimated date of delivery mm ____ / dd ____ / yyyy ____ <input type="checkbox"/> Unknown <input type="checkbox"/> N/A														
If N/A, date of termination (actual or planned) mm ____ / dd ____ / yyyy ____														
Has the pregnant female already delivered? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> N/A														
If yes, provide date of delivery: mm ____ / dd ____ / yyyy ____														
Was the infant healthy? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> 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.

AMGEN Lactation Notification Worksheet

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

1. Case Administrative Information

Protocol/Study Number: _____
Study Design: Interventional Observational (If Observational: Prospective Retrospective)

2. Contact Information

Investigator Name _____ Site # _____
Phone (____) _____ Fax (____) _____ Email _____
Institution _____
Address _____

3. Subject Information

Subject ID # _____ Subject Date of Birth: mm____/dd____/yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? Yes No
If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____
Did the subject withdraw from the study? Yes No

5. Breast Feeding Information

Currently breast feeding? Yes No
If No, provide stop date: mm____/dd____/yyyy____
Infant date of birth: mm____/dd____/yyyy____
Infant gender: Female Male
Is the infant healthy? Yes No Unknown N/A

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

Form Completed by:
Print Name: _____ Title: _____
Signature: _____ Date: _____

Amgen maintains a Lactation Surveillance Program that collects data about women who have been exposed to 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: _____ Page 1 of 1

With:

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: _____

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

2. Contact Information

Investigator Name _____ Site # _____

Phone (____) _____ Fax (____) _____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Gender: Female Male Subject DOB: mm ____ / dd ____ / yyyy ____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm ____ / dd ____ / yyyy ____

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

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

Did the subject withdraw from the study? Yes No

5. Pregnancy Information

Pregnant female's LMP mm ____ / dd ____ / yyyy ____ Unknown

Estimated date of delivery mm ____ / dd ____ / yyyy ____ Unknown N/A

If N/A, date of termination (actual or planned) mm ____ / dd ____ / yyyy ____

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

If yes, provide date of delivery: mm ____ / dd ____ / yyyy ____

Was the infant healthy? Yes No Unknown N/A

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

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

AMGEN Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: _____
Study Design: Interventional Observational (If Observational: Prospective Retrospective)

2. Contact Information

Investigator Name _____ Site # _____
Phone (____) _____ Fax (____) _____ Email _____
Institution _____
Address _____

3. Subject Information

Subject ID # _____ Subject Date of Birth: mm ____ / dd ____ / yyyy ____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm ____ / dd ____ / yyyy ____

Was the Amgen product (or study drug) discontinued? Yes No
If yes, provide product (or study drug) stop date: mm ____ / dd ____ / yyyy ____
Did the subject withdraw from the study? Yes No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? Yes No
If No, provide stop date: mm ____ / dd ____ / yyyy ____
Infant date of birth: mm ____ / dd ____ / yyyy ____
Infant gender: Female Male
Is the infant healthy? Yes No Unknown N/A

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

Form Completed by:
Print Name: _____ Title: _____
Signature: _____ Date: _____

Amendment 6

Protocol Title: A Multicenter, Controlled, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of Evolocumab (AMG 145)

Amgen Protocol Number AMG 145 20110110

Amendment Date: 09 March 2015

Rationale:

This document provides the rationale and detailed list of changes for Amendment 6, dated 09 March 2015, from amendment 5 of the study protocol, dated 26 February 2014.

The purpose of the amendment is to:

- Remove the external data monitoring committee (DMC) following the DMC's expressed preference to not review open-label, uncontrolled safety data. Safety monitoring will continue to be performed by AMGEN. Even though review of this specific study would no longer fall under direct DMC review, the DMC will continue to consider the totality of data from all studies. Any emerging safety considerations identified by AMGEN would be discussed with the DMC and the committee would incorporate that data when making its recommendations to AMGEN.
- Remove non-coronary revascularizations from adjudication. Collection and review of such events is achieved by specific eCRF and safety review by Amgen Global Patient Safety.
- Minor other updates, clarifications and corrections.

Amendment 5

Protocol Title: A Multicenter, Controlled, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of AMG 145

Amgen Protocol Number: 20110110
EudraCT Number: 2011-001915-29

OSLER Open Label Study of Long Term Evaluation Against LDL-C Trial

Amendment Date: 26 February 2014

Rationale:

This document provides the rationale and detailed list of changes for Amendment 5, dated 26 February 2014, from the amendment 4 protocol, dated 20 June 2012.

The purpose of the amendment is to:

- Update safety reporting language
- Add new AMG 145 formulation and autoinjector language
- Introduce the simplified terminology of monthly dosing
- Implement minor clarifications and error corrections
- Clarify blinding requirements

Amendment 4

Protocol Title: A Multicenter, Controlled, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of AMG 145

Amgen Protocol Number: 20110110
EudraCT Number: 2011-001915-29

OSLER

Open Label Study of Long Term Evaluation Against LDL-C Trial

Amendment Date: 20 June 2012

Rationale:

This document provides the rationale and detailed list of changes for Amendment 4, dated 20 June 2012, from the amendment 3 protocol, dated 24 April 2012.

The purpose of the amendment is to:

- Change the study duration language per global regulatory feedback
- Highlight that week 4 will be required for all subjects
- Add a steroid substudy rather than requiring all subjects to undergo steroid sampling
- Clarify pregnancy and lactation reporting requirements
- Decrease the frequency of Anti-AMG 145 antibody collection after year 1

Description of Changes

Section: Title page

Add:

Amendment 4 Date: 20 June 2012

Section: Investigator's Agreement

Replace:

I have read the attached protocol entitled "A Multicenter, Controlled, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of AMG 145", dated **24 April 2012**, and agree to abide by all provisions set forth therein.

With:

I have read the attached protocol entitled "A Multicenter, Controlled, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of AMG 145", dated **20 June 2012**, and agree to abide by all provisions set forth therein.

Amendment 3

Protocol Title: A Multicenter, Controlled, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of AMG 145

Amgen Protocol Number: 20110110
EudraCT Number: 2011-001915-29

OSLER

Open Label Study of Long Term Evaluation Against LDL-C Trial

Amendment Date: 24 April 2012

Rationale:

This document provides the rationale and detailed list of changes for Amendment 3, dated 24 April 2012, from the amendment 2 protocol, dated 08 September 2012.

The purpose of the amendment is to:

- Update the AMG 145 background section with the most currently available data
- Incorporate new AE/SAE language
- Increase the sample size from approximately 375 to approximately 1600
- Increased the site number from 200 to 240
- Increase the study duration from 1 year to 5 years or until AMG 145 becomes commercially available
- Align the parent EOS/OLE Day 1 assessments for Q2W subjects from parent studies 154 (monotherapy) and 155 (combination therapy).
- Add additional language to help highlight the importance of maintaining the blind during the first 12 weeks of the study
- Add steroid testing (ACTH, FSH, LH, Cortisol, Testosterone, Estradiol) measurements to the protocol
- Remove the term “absolute” from all endpoints

Amendment 2

Protocol Title: A Multicenter, Controlled, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of AMG 145

Amgen Protocol Number AMG 145 20110110

Amendment Date: 08 September 2011

Rationale:

This document provides the rationale and detailed list of changes for Amendment 2, dated **08** September 2011, from the superseding amended protocol, dated 26 August 2011.

The purpose of the amendment is to:

- Clarify measurement methods for LDL-C by a preparative ultracentrifugation and by calculation
- Add fasting Vitamin E measurements to the protocol
- Removed the term “treatment emergent”

Description of Changes

Section: Title page

Add:

Amendment 2 Date: 08 September 2011

Section: Investigator’s Agreement

Replace:

I have read the attached protocol entitled “A Multicenter Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of AMG 145”, dated 24 May 2011, and agree to abide by all provisions set forth therein.

With:

I have read the attached protocol entitled “A Multicenter, Controlled, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of AMG 145”, dated **08 Sept 2011**, and agree to abide by all provisions set forth therein.

Section: Protocol Synopsis

Delete: “treatment emergent”

Amendment 1

Protocol Title: A Multicenter, Controlled, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of AMG 145

Amgen Protocol Number AMG 145 20110110

Amendment Date: 26 August 2011

Rationale:

This document provides the rationale and detailed list of changes for **superseding** Amendment 1, dated **26** August 2011, from the original study protocol, dated 24 May 2011.

The purpose of the amendment is to:

- Add "OSLER" study name
- Add a standard of care control arm
- Clarify that subjects should remain in follow-up after discontinuation of investigational product (IP) and update the list of possible reasons for withdrawal from IP
- Add an exploratory objective of estimation of cardiovascular event rates
- Add international units for lipid concentrations for informational purpose
- Open up inclusion criteria to all qualifying AMG 145 parent protocols
- Clarify measurement methods for LDL-C by a preparative ultracentrifugation and by calculation
- Revise section 8.1 (Removal of Subjects) in accordance with current regulatory guidelines
- Clarify that death and certain cardiovascular events that are submitted for adjudication are not submitted as adverse event/serious adverse event until the site is notified that the event was a death that is not expected in this patient population or an event that was adjudicated negatively (did not qualify as adjudicated endpoint)
- Add adjudicated events as exploratory endpoints
- Add a week 4 study visit
- Decrease the study duration to 1 year
- Add section 5.1 Randomization
- Update the statistics section to reflect the control arm

New superseding amendment changes - Sections 9.1.2 and 9.2.2 were revised to clarify that events reported to the Clinical Events Classification Committee (CEC) for adjudication as potential endpoints are not reported as serious adverse events. Such events are only reported as SAEs if they are found by the CEC not to meet pre-defined criteria for a positively adjudicated endpoint.