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

Amgen Protocol Number: 20120138
EudraCTNumber: 2012-004357-83

OSLER 2

Open Label **S**tudy of **L**ong T**er**m Evaluation Against LDL-C Trial

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Confidentiality Notice

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for purposes of posting on clinicaltrials.gov

Investigator's Agreement

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 **03 April 2015**, and agree to abide by all provisions set forth therein.

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

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

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

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

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

_____
Signature

_____ _____
Name of Principal Investigator Date (DD Month YYYY)

Protocol Synopsis

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

Study Phase: 3

Indication: Primary hyperlipidemia and mixed dyslipidemia

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

Secondary Objectives:
To characterize efficacy of long-term administration of AMG 145 as assessed by low density lipoprotein cholesterol (LDL-C) in subjects with primary hyperlipidemia and subjects with mixed dyslipidemia.

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

Primary Endpoint: Subject incidence of adverse events.

Secondary Endpoints:
- Percent change from baseline in LDL-C at Week 48 and Week 104
- Change from baseline in LDL-C at Week 48 and Week 104

Study Design: This is a multicenter, randomized, controlled, open-label extension study designed to assess the long-term safety and efficacy of AMG 145. Subjects that successfully complete a qualifying protocol and sign informed consent will be randomized 2:1 to one of two groups: AMG 145 + standard of care (SOC) or SOC-alone. Subjects randomized to the treatment group will also be expected to take background lipid lowering therapy and will be able to choose from one of two dose regimens: AMG 145 (140mg) administered every 2 weeks (Q2W) + SOC, or AMG 145 (420mg) administered monthly (QM) + SOC. Subjects randomized to the control group will receive SOC alone for the first 48 weeks of the study. During the first 12 weeks of the study participation, LDL-C will remain blinded and subjects must remain on stable background lipid lowering therapy. Using clinical judgment, the primary investigator or qualified delegate should recommend background lipid lowering therapy the subject can be expected to tolerate: therapy either prescribed to them PRIOR to participation in parent study, or statin or ezetimibe therapy given during parent study. Investigators will be informed if triglycerides are > 1000 mg/dL (11.3 mmol/L) so that appropriate subject follow-up can be initiated if necessary (see Protocol Section 6.1.3.4). Randomization should occur within 30 days after the parent study's EOS visit. Subjects will be stratified by their parent study and frequency of SC dose (Q2W or QM) within the parent study. After Week 48 all subjects will receive open-label AMG 145 for up to 2 years (or until the investigator's recommendation for discontinuation, Amgen's recommendation for discontinuation, the subject's 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 4428 subjects are expected to participate in this study.

Summary of Subject Eligibility Criteria: Subjects who complete a qualifying AMG 145 protocol and do not discontinue IP in the parent study for any reason including an adverse event 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: AMG 145 will be administered via subcutaneous injection using a spring-based prefilled 1.0 mL auto-injector/pen (AI/Pen) or when available, a 3.5 mL Personal Injector.

AMG 145 will be administered via 1 of 2 regimens:

- AMG 145 140 mg SC Q2W (1 prefilled AI/Pen injection) or
- AMG 145 420 mg SC QM (3 prefilled AI/Pen injections or 1 Personal Injector, once made available)

The 3.5 mL Personal Injector will only be made available for use in this study once it has been determined that the intended user population for AMG 145 can safely and effectively use the device in clinical trials under guidance of study investigators.

Upon completion of the Week 12 Visit, subjects will have the opportunity to switch between Q2W and QM every 3 months, provided the appropriate supply of IP is available.

Non Amgen Investigational Product Dosage and Administration: None.

Control Group: The control group comprises of subjects randomized to SOC-alone during the first 48 weeks of study participation. Until laboratory results are unblinded at Week 12, the control group should remain on stable lipid lowering therapy (eg, therapy prescribed in parent study or the same therapy prescribed before parent study participation whichever the subject is likely to tolerate).After unblinding at Week 12, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care (Section 6.3).After 48 weeks of participation, these subjects will receive open-label AMG 145 in the regimen of their choice (Q2W or QM) and will no longer be considered part of a control group. These subjects may also switch between regimens every 12 weeks.

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 sign a new study Informed Consent Form and meet inclusion/exclusion criteria requirements. Subject identification numbers will be the same as those in their parent protocols.

Subjects that fall within a 30 day window of completing the final laboratory assessments for a qualifying parent study do not require laboratory procedures to be repeated.

Subject visit schedule will differ based upon 3 factors: randomization, selection of Q2W or QM regimen, and prior experience with self-injection of AMG 145. Subjects randomized to AMG 145 + SOC without previous experience with self-injection of AMG 145 will have additional IP training visits at time of study start. At Week 48, a similar training schedule will be utilized for subjects randomized to SOC-alone at Day 1 with no previous experience with self-injection of AMG 145.

Additional visits will occur quarterly. During site visits vital signs, adverse events (AEs)/Serious Adverse Events (SAEs), and concomitant therapy will be evaluated. Other assessments and procedures include fasting lipids, physical exam, measuring body weight, laboratory assessments, including: anti-AMG 145 antibodies, urine pregnancy testing (females of childbearing potential), and urinalysis. IP administration by SC injection will be done after all other procedures have been completed.

Statistical Considerations

General Considerations

Statistical analyses in this multicenter, open label study will be descriptive.

There will be interim analyses to support safety data reporting and assessments of efficacy endpoints. In particular, interim analyses of the randomized study period (up to Week 48) will be conducted after all subjects from sets of parent studies have completed the Week 48 visit or ended the study.

For all endpoints, results will be summarized by the treatment group to which subjects are randomized in this study, unless otherwise specified.

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, first and third quartiles, minimum, and maximum. For categorical variables, the frequency and percentage will be given. 95% confidence intervals will be calculated for select continuous and categorical endpoints.

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 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 phase 3 studies will be adjudicated by an independent Clinical Events Committee (CEC) to facilitate aggregated analyses across the program.

Analyses of the Primary Endpoint

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 will be tabulated by system organ class and preferred term.

Analysis of Secondary Endpoints

Point estimates of treatment group means and their 95% confidence intervals will be calculated.

Differences in group means for the secondary endpoints will be estimated between the AMG 145 + SOC group and the SOC-alone group.

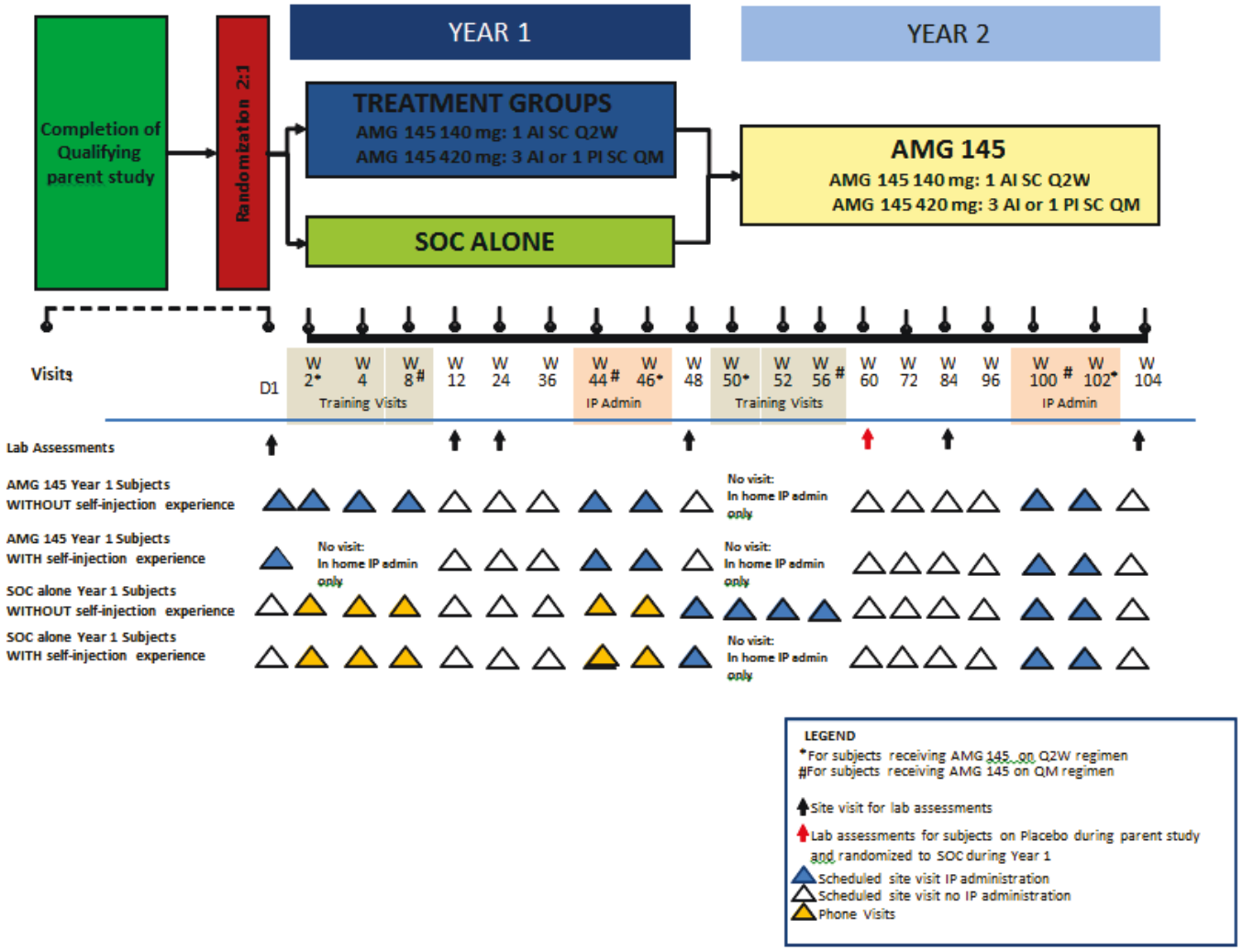
Other Safety Analyses

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. Summaries of vital signs will also be provided.

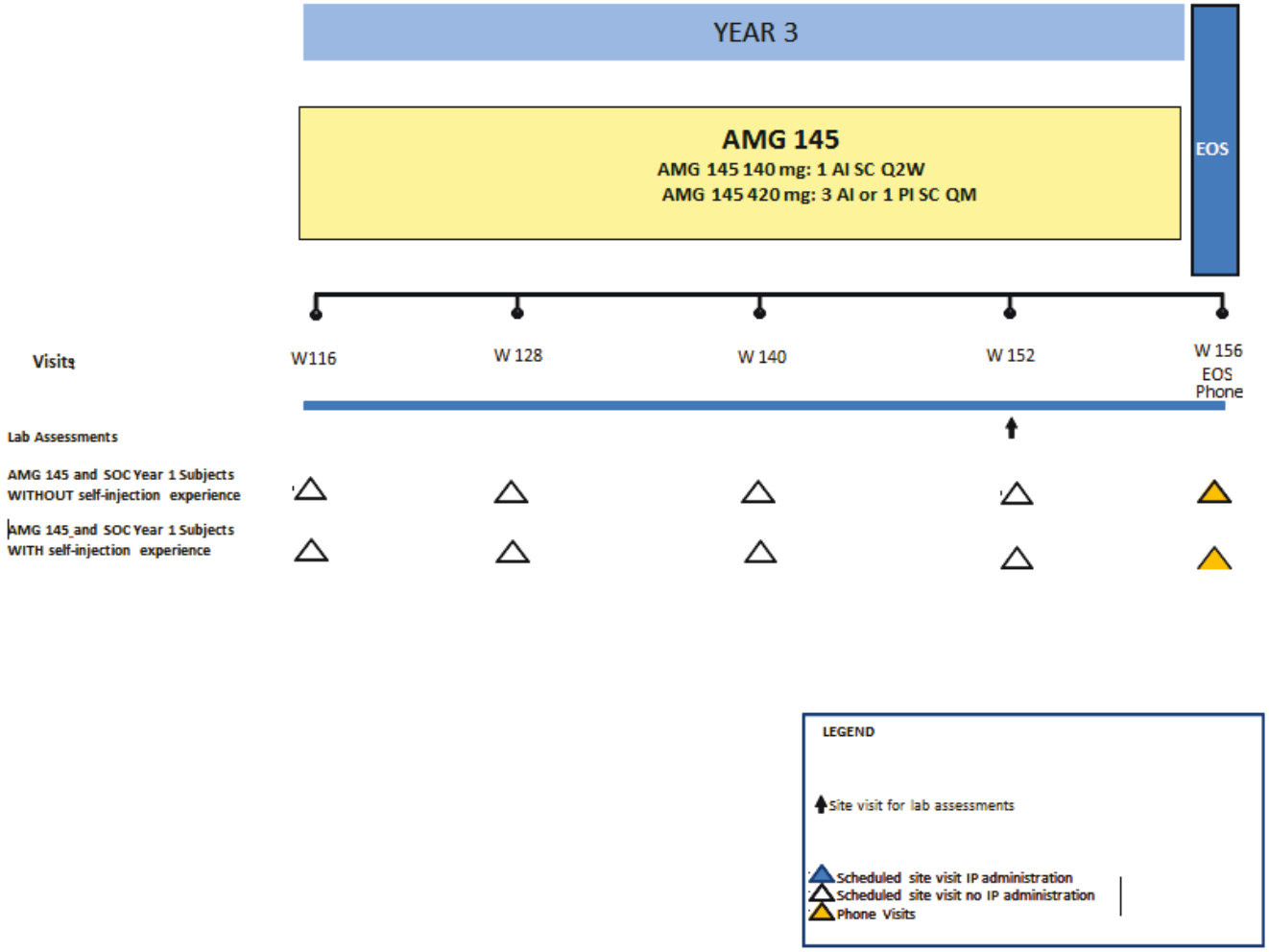
For a full description of statistical analysis methods, refer to Section 10.

Sponsor: Amgen Inc.

Study Design and Treatment Schema



Study Design and Treatment Schema



Study Glossary

Abbreviation or Term	Definition/Explanation
AE	Adverse event
AHA	American Heart Association
AI/pen	Prefilled Autoinjector/pen
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase (serum glutamic-pyruvic transaminase)
ApoA1	Apolipoprotein A-1
ApoB	Apolipoprotein B
AST (SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
BP	Blood pressure
CAD	Coronary artery disease
CBC	Complete blood count
CEC	Clinical Events Committee
CK	Creatine kinase
CHD	Coronary heart disease
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.
DILI	Drug-induced liver injury
eCRF	Electronic case report form
EDC	Electronic Data Capture
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
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HCV	Hepatitis C Virus
HDL-C	High density lipoprotein cholesterol
HepG2 cells	Human hepatocellular carcinoma cell line
HR	Heart Rate
hsCRP	High sensitivity CRP

Abbreviation or Term	Definition/Explanation
IBG	Independent Biostatistical Group
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC/IRB	Independent Ethics Committee / Institutional Review Board
IP	Investigational product
IMP	Investigational Medicinal Product
IPIM	Investigational Product Instruction Manual
LDL-C	Low-density lipoprotein cholesterol
LDLR	LDL receptor
LOF	Loss of function
Lp(a)	Lipoprotein(a)
Month	28 Days
MedDRA	Medical dictionary for regulatory activities
NASH	Nonalcoholic steatohepatitis
OLE	Open-Label Extension
PCSK9	Proprotein convertase subtilisin/kexin type 9
Q2W	Every 2 weeks
QM	Every month
SAE	Serious adverse event
SC	Subcutaneous
Source Data	Information from an original record or a certified copy of the original record containing subject 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
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 low density lipoprotein cholesterol (LDL-C) in subjects with primary hyperlipidemia and subjects with mixed dyslipidemia.

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%.

   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.

4. 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 Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays an important role in the recycling and regulation of LDLR (Horton et al, 2007; Brown and Goldstein, 2006). PCSK9 is a member of the subtilisin family of serine proteases and is expressed predominantly in the liver, kidney, and intestine (Zaid et al, 2008). Following secretion, it causes post-translational down regulation of hepatic cell surface LDLR by a mechanism that involves direct binding to the LDLR. Down regulation of hepatic LDLR in turn leads to increased levels of circulating LDL-C. Thus PCSK9 may represent a target for inhibition by novel therapeutics in the setting of dyslipidemia. The rationale for such an approach is available from studies in preclinical models, and from human genetic data that provide strong validation for the role of PCSK9 in modulating LDL-C levels and the incidence of CHD in man. These human studies have identified gain-of-function mutations in the PCSK9 gene that are associated with elevated serum LDL-C levels (> 300 mg/dL [approximately 7.8 mmol/L]) and premature CHD (Abifadel et al, 2003); and loss-of-function (LOF) mutations that are associated with low serum LDL-C levels (≤ 100 mg/dL [approximately 2.6 mmol/L]) (Cohen et al, 2005). Strikingly, subjects with

heterozygous LOF mutations exhibit lower serum PCSK9 levels and as much as 88% reduction in the incidence of CHD over a 15-year period compared with noncarriers of the mutations (Cohen et al, 2006). Moreover, despite complete loss of PCSK9 and associated very low serum LDL-C levels (< 20 mg/dL [approximately 0.5 mmol/L]), the 2 subjects who have been identified with compound heterozygote LOF mutations appear healthy (Hooper et al, 2007; Zhao et al, 2006).

AMG 145 is a fully human monoclonal immunoglobulin (Ig) G2 that binds specifically to human PCSK9 and prevents the interaction of PCSK9 with LDLR. Details of the biochemistry, nonclinical pharmacology, nonclinical pharmacokinetics (PK), and nonclinical toxicology with AMG 145 are contained in the Investigator's Brochure, 2013. AMG 145 binds to human, monkey, and hamster PCSK9 with high affinity (K_d < 100 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 cynomologus monkeys and in hamsters, in vivo administration of AMG 145 resulted in reduced serum lipoprotein cholesterol levels in a dose-dependent manner. Based on a comprehensive package of PK, pharmacodynamics (PD), and toxicology studies (Investigator's Brochure, 2013), a program to develop AMG 145 as a treatment for dyslipidemia was initiated.

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

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

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

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

2.3 Rationale

This study is being conducted to gather information on the long-term safety and efficacy of AMG 145 and to provide subjects who participated in Phase 3 studies with an opportunity to receive AMG 145 for approximately 3 years (or until the investigator's recommendation of discontinuation, Amgen's recommendation of discontinuation, the subject's decision to discontinue for any reason, or until an administrative decision is made to close the study). Many of the subjects in the parent Phase 3 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 primary hyperlipidemia and subjects with mixed dyslipidemia.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a multicenter, randomized, controlled, open-label extension study designed 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 450 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 4428.

3.3.1 Study Duration for Participants

Subjects will be enrolled into the study after completion of a qualifying AMG 145 study and signing the informed consent form (ICF) of this study. The study duration is anticipated to continue for 156 weeks (approximately 3 years). During that time subjects will visit the site multiple times.

3.3.2 End of Study

The study will continue for 156 weeks (approximately 3 years or until the investigator's recommendation of discontinuation, Amgen's recommendation of discontinuation, the subject's 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. The population will include

subjects whose primary hyperlipidemia or mixed dyslipidemia is treated with a variety of methods.

4.1 Inclusion Criteria

Subjects will be eligible for the study if they:

Complete a qualifying AMG 145 parent study protocol while still on assigned study medication.

4.2 Exclusion Criteria

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

1. Discontinued assigned study drug during the qualifying study for any reason including an adverse event or serious adverse event.
2. Female subject is not willing to use an acceptable method(s) of effective birth control during treatment with investigational product (IP) and for an additional 15 weeks after the end of treatment with IP. Female subjects, who have had a hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or who are postmenopausal, are not required to use contraception
    - Menopause is defined as 12 months of spontaneous and continuous amenorrhea in a female ≥ 55 years old; or age < 55 years but no spontaneous menses for at least 2 years; or age < 55 years and spontaneous menses within the past 1 year, but currently amenorrheic (eg, spontaneous or secondary to hysterectomy), and with postmenopausal gonadotropin levels (luteinizing hormone and follicle stimulating hormone levels > 40 IU/L) or postmenopausal estradiol levels (<5 ng/dL) or according to the definition of "postmenopausal range" for the laboratory involved.
    - **Acceptable methods of effective birth control include: sexual abstinence (when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception]), surgical contraceptive methods (vasectomy or bilateral tubal ligation), use of hormonal birth control methods (pills, shots, implants or patches), intrauterine devices (IUDs), or two (2) barrier methods (each partner must use one barrier method) with spermicide – males must use a condom with spermicide; females must choose either a diaphragm with spermicide, OR cervical cap with spermicide, OR contraceptive sponge with spermicide. Note: Additional medications given during treatment with evolocumab may alter the contraceptive requirements. These additional medications may require an increase in the number of contraceptive methods and/or length of time that contraception is to be utilized after the last dose of protocol-required therapies. The investigator is to discuss these contraceptive changes with the study subject.**

3. Female subject is pregnant or breast feeding, planning to become pregnant or planning to breastfeed during treatment with IP and/or within 15 weeks after the end of treatment with IP.
4. 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).
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, ICF, and all other subject information and/or recruitment material, if applicable (see Section 11.2). All subjects must personally sign and date the ICF before commencement of study specific procedures. A subject is considered enrolled once they have completed their end of study visit in the parent protocol and have signed the ICF.

All subjects who enter the study will keep the same subject identification number from the parent study. Each site participating in this study will be assigned a different site number from the parent study.

6. TREATMENT PROCEDURES

AMG 145 will be the investigational medicinal product (IMP) in this study.

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

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

6.1 AMG 145

AMG 145 will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical IP distribution procedures.

AMG145 will be presented as a sterile, preservative-free solution in a single use, disposable, handheld mechanical (spring-based) 1.0 mL prefilled auto-injector/pen (AI/Pen) or 3.5 mL Personal Injector (Personal Injector) for fixed dose, subcutaneous injection. The prefilled AI/Pen contains a 1.0 mL deliverable volume of 140 mg/mL AMG 145 in CCI mM proline, C mM acetate, CCI % (w/v) polysorbate 80, pH CC. The Personal Injector with prefilled cartridge assembly is a single-use, disposable, on-body electro-mechanical injection device that is co-packaged with a prefilled Crystal Zenith (CZ) cartridge assembly containing 3.5 mL deliverable volume of 120 mg/mL AMG 145 in CCI mM proline, C mM acetate, CCI % (w/v) polysorbate 80, pH CC.

The 3.5 mL Personal Injector will only be made available for use in this study once it has been determined that the intended user population for AMG 145 can safely and effectively use the device in clinical trials under the guidance of the study investigators.

AMG 145 should be stored protected from light and according to the storage and expiration information provided on the label. AMG 145 should be handled per the instructions provided in the IPIM and the Instructions for Use (IFU) for the prefilled AI/pen or Personal Injector. The prefilled AI/pen or Personal Injector should be checked for damage that may occur during shipment or if not handled properly. Damaged product should not be used. Further details are provided in the IPIM and IFU.

The lot number of investigational product should be recorded on each subject's Drug Administration Case Report Form.

6.1.1 Dosage, Administration, and Schedule

IP will be administered SC in accordance with instructions in the IPIM.

IP administration at each on-site visit must be done after vital signs and blood draw procedures, as applicable. The date, time, and amount (as designated by partial or full injection of AMG 145) will be recorded on the individual subject's worksheet and/or electronic Case Report Form (eCRF). After IP administration on Day 1 or Week 48 for subjects initially randomized to standard of care (SOC)-alone, subjects should be kept for observation for at least 30 minutes before being discharged.

On Day 1 of the study, subjects randomized to AMG 145 plus SOC will be trained on self-administration of study drug and will self-administer IP at the investigational site,

under the supervision of a healthcare provider. Subjects without prior experience of self-injection of AMG 145will subsequently visit the site to self-administer AMG 145 at Week 2 (Q2W regimen only), Week 4 (Q2W and QM regimens) and Week 8 (QM regimen only).After the Week 4 visit for subjects on Q2W regimen or Week 8 visit for subjects on QM regimen, IP can be administered at a location external to the study site, using the prefilled AI/Pen or Personal Injector provided. Thereafter, AMG 145 will be self-administered or administered by a caregiver at home.

The subject (or designee) must have demonstrated competency in administration of SC injections before self-injection will be permitted.For subjects that prefer not to self-administer IP, IP may be administered at the site.

Subjects will receive training on IP use prior to home administration; however IP may be administered at the site if subjects prefer not to self-inject AMG 145.

Subjects randomized to AMG 145 + SOC and selecting Q2W IP administration will receive a total volume of 1.0 mL via 1 prefilled AI/pen injection every 2 weeks.

Subjects randomized to AMG 145 + SOC and selecting QM IP administration will receive a total volume of 3.0 mL monthly via 3 separate prefilled AI/pen injections or a total volume of 3.5 mL via a single Personal Injector. Injection sites should be rotated throughout the study. For the AI/pen, the SC injections should be administered in a consecutive fashion with all injections completed within 30 minutes.

The dosing schedule is also described by a schema in the protocol synopsis.

For further details regarding IP administration procedures, the IPIM should be consulted.

6.1.2 Dosage Adjustments

Dose adjustments of background lipid lowering therapy during the study 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 background therapy 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

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

procedures should be conducted and administration of IP should occur as soon as possible at least 7 days after the previous administration. If 2 Q2W doses have been administered within 7 days of each other, any subsequent dose should occur at least 7 days after the most recent dose.

6.1.3 Criteria for Withholding of Investigational Product

Reports from the central laboratory after each visit must be reviewed on receipt. If abnormalities that would preclude further dosing are noted, subjects should be called at home and instructed to withhold further dosing and scheduled to return for an ad hoc visit.

6.1.3.1 Elevation of Creatine Kinase (CK)

If CK is > 5x upper limit of normal (ULN), CK must be retested before IP is administered. The following rules apply:

CK at prior visit	CK on retest	Investigational Product Administration
> 5x ULN	> 10x ULN	Discontinue IP[a] Contact Amgen Medical Monitor
	>5x to ≤ 10x ULN	Consider continuing IP if alternative explanation
	≤ 5x ULN	Consider continuing IP

[a] CK elevations >10x ULN that have been confirmed to be secondary to myocardial infarction do not require discontinuation of 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.

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

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

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

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

6.1.3.3 Criteria for Rechallenge of AMG 145 After Potential Hepatotoxicity

The decision to re-challenge the subject should be discussed and agreed upon unanimously by the subject, Principal Investigator, and Amgen.

If signs or symptoms recur with re-challenge, then AMG 145 should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation should never be re-challenged.

6.1.3.4 Elevation of Triglycerides

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

6.2 Product Complaints, Including Device Complaints

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

Any 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 are to be reported to Amgen within 24 hours of discovery or notification of the concern or irregularity. Should any such concerns or irregularities occur please do not use the prefilled AI/pen or Personal Injector until Amgen confirms that it is permissible to use.

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

- broken container or cracked container,
- subject or healthcare provider cannot appropriately use the product despite training (eg, due to malfunction of the prefilled AI/pen or Personal Injector),
- missing labels, illegible labels, incorrect labels, and/or suspect labels,
- change in IMP appearance, for example color change or visible presence of foreign material,
- unexpected quantity or volume, for example amount of fluid in the prefilled AI/pen or Personal Injector, or
- evidence of tampering or stolen material.

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

Injector at appropriate storage conditions until further instructions are received from Amgen.

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

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

6.3 Concomitant Therapy, Physical Exercise, and Diet

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.4. Background lipid lowering concomitant medications should be stable throughout study participation.

Subjects should maintain baseline level of exercise during the first year of study participation. Subjects will be required to refrain from unaccustomed intensive exercise (eg, heavy lifting or long runs) 48 hours prior to each visit.

6.4 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

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 administered in clinic should not be administered until all study procedures are completed at each visit.

Subject visit schedule will differ based upon 3 factors: randomization, selection of Q2W or QM regimen, and prior experience with self-injection of AMG 145. Subjects randomized to AMG 145 + SOC without previous experience with self-injection of AMG 145 will have additional IP training visits at time of study start. At Week 48, a similar training schedule will be utilized for subjects randomized to SOC-alone at Day 1

with no previous experience with self-injection of AMG 145. All visits also apply to subjects randomized to SOC-alone unless otherwise specified.

7.1 General Study Procedures

7.1.1 Enrollment (EOS Parent Study/Day 1 OLE)

All efforts should be made to minimize any time gaps between completion of the parent study end of study (EOS) laboratory visit and Day 1 of the OLE visit. It is recommended that the Day 1 OLE visit occurs within 30 days of completion of the parent EOS laboratory visit. If the Day 1 OLE visit does not occur within 30 days of completion of the parent EOS laboratory visit, then all of the procedures detailed below will need to be repeated at the Day 1 OLE visit.

- Parent Study EOS lab visit procedures:
  - Medical History
  - Vital signs: sitting blood pressure (BP), heart rate (HR)
  - Review adverse events/ serious adverse events (AEs/SAEs)
  - Review concomitant medications
  - Body weight
  - Physical exam
  - Urine pregnancy (females of childbearing potential only)
  - Serum Follicle-stimulating hormone (FSH)(females deemed sterile or post-menopausal as defined above)
  - Urinalysis
  - Urine microalbumin
  - Hepatitis C virus (HCV) antibodies (Only in high risk subjects or if ALT or AST>2X ULN)
  - HCV viral load (in subjects positive for HCV)
  - Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, chemistry, hematology, high sensitive C-reactive protein (hsCRP), Lp(a), HbA1c,and anti-AMG 145 antibodies; TSH

On Day 1 OLE, potential subjects will have the risks and benefits of participating in this study explained to them. Subjects will need to sign a new OLE ICF and will be evaluated against inclusion/exclusion criteria.

The following procedures will be performed during the Day 1 OLE visit:

- Medical History
- Cardiac History (If > 30 days from end of parent study)
- Vital Signs

- Weight
- Review AEs/SAEs
- Review concomitant medications
- Repeat parent EOS laboratory visit procedures if Day 1 OLE > 30 days from parent study EOS laboratory visit procedures (see above)
- Coagulation (PT/INR)
- Train subject on self-injection of AMG 145 if randomized to AMG 145 + SOC
- Observe subject self-inject AMG 145 at study site if randomized to AMG 145 + SOC (AMG 145 administration, must occur after completion of vital signs, if applicable, and blood draw procedures).
- Dispense IP for at-home injections (only for subjects who have previous experience of self-injecting AMG 145)

7.1.1.1 Week 2 (± 7 Days)–If Subject with no Previous Experience of Self-injection is Randomized to AMG 145 + SOC and Selects Q2W Regimen

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- Review AEs/SAEs
- Review concomitant medications
- Train subject on self-injection of AMG 145
- Observe subject self-inject AMG 145 at study site (AMG 145 administration must occur after other procedures)

7.1.1.2 Week 2 (± 7 Days)–Phone Visit for SOC-alone Subjects

- Review AEs/SAEs
- Review concomitant medications

7.1.1.3 Week 4 (± 7 Days)–If Subject with no Previous Experience of Self-injection is Randomized to AMG 145+ SOC

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- Review AEs/SAEs
- Review concomitant medications
- Train subject on self-injection of AMG 145
- Observe subject self- inject AMG 145 at study site (AMG 145 administration must occur after other procedures). Dispense IP quantity for at-home injections for subjects on Q2W dosing only

7.1.1.4 Week 4 (± 7 Days) – Phone Visit for SOC-alone Subjects

- Review AEs/SAEs
- Review concomitant medications

7.1.1.5 Week 8 (± 7 Days)–If Subject with no Previous Experience of Self-injection is Randomized to AMG 145 + SOC and Selects QM Regimen

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- Review AEs/SAEs
- Review concomitant medications
- Train subject on self-injection of AMG 145
- Observe subject self- inject AMG 145 at study site (AMG 145 administration must occur after other procedures)

7.1.1.6 Week 8 (± 7 Days)–Phone Visit for SOC-alone Subjects

- Review AEs/SAEs
- Review concomitant medications

7.1.1.7 Week 12 (± 7 Days)

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- Review AEs/SAEs
- Review concomitant medications
- Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, Lp(a), Vitamin E (sample drawn, testing by reflex when LDL-C is < 25 mg/dL),and chemistry, hematology, HbA1c, Anti-AMG 145 antibodies
- HCV viral load (in subjects positive for HCV)
- Urine pregnancy
- Urinalysis
- Urine microalbumin
- Dispense IP quantity for at-home injections for subjects on AMG 145 + SOC
- IP reconciliation

7.1.1.8 Week 24 Visit (± 7 Days)

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- Review AEs/SAEs
- Review concomitant medications
- Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, Lp(a), Vitamin E (sample drawn, testing by reflex when LDL-C is < 25 mg/dL),chemistry, hematology, HbA1c, Anti-AMG 145 antibodies
- HCV viral load (in subjects positive for HCV)
- Urine pregnancy
- Urinalysis
- Dispense IP quantity for at-home injections for subjects on AMG 145 + SOC
- IP reconciliation

7.1.1.9 Week 36 Visit (± 7 Days)

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- Review AEs/SAEs
- Review concomitant medications
- Dispense IP quantity for at-home injections for subjects on AMG 145 + SOC
- IP reconciliation

7.1.1.10 Week 44 (± 7 days)–for Subjects on QM Regimen Only

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- Review AEs/SAEs
- Review concomitant medications
- In-office IP administration (either self-injection or HCP administered)
- IP reconciliation

7.1.1.11 Week 44 (± 7 Days)–Phone Visit for SOC-alone Subjects

- Review AEs/SAEs
- Review concomitant medications

7.1.1.12 Week 46 (± 7 days)–for Subjects on Q2W Regimen Only

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- Review AEs/SAEs
- Review concomitant medications
- In-office IP administration (either self-injection or HCP administered)
- IP reconciliation

7.1.1.13 Week 46 (± 7 Days)–Phone Visit for SOC-alone Subjects

- Review AEs/SAEs
- Review concomitant medications

7.1.1.14 Week 48 Visit (± 7 Days)

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- Review AEs/SAEs
- Review concomitant medications
- Body weight
- Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, Lp(a),Vitamin E (sample drawn, testing by reflex when LDL-C is < 25 mg/dL), hsCRP, chemistry, hematology, HbA1c, Anti-AMG 145 antibodies, coagulation
- HCV viral load (in subjects positive for HCV)
- Urine pregnancy
- Urinalysis

- Urine microalbumin
- Train subject on self-injection of AMG 145 (for subjects randomized to SOC-alone in Year 1)
- Observe subject self- inject AMG 145 at study site for subjects randomized to SOC-alone in Year 1 (AMG 145 administration must occur after other procedures).
- Dispense IP quantity for at-home injections to subjects with previous experience of self-injection with AMG 145

7.1.1.15 Week 50 (± 7 Days)–Additional Procedures for Subjects Randomized to SOC–alone in Year 1 with no Previous Experience of Self-injection and Selects Q2W Regimen

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- Review AEs/SAEs
- Review concomitant medications
- Train subject on self-injection of AMG 145
- Observe subject self- inject AMG 145 at study site (AMG 145 administration must occur after other procedures)

7.1.1.16 Week 52 (±7 Days)–Additional Procedures for Subjects Randomized to SOC–alone in Year 1 with no Previous Experience of Self-injection

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- Review AEs/SAEs
- Review concomitant medications
- Train subject on self-injection of AMG 145
- Observe subject self- inject AMG 145 at study site (AMG 145 administration must occur after other procedures)
- Dispense IP quantity for at-home injections for subjects on Q2W dosing only

7.1.1.17 Week 56 (± 7 Days)–Additional Procedures for Subjects Randomized to SOC–alone in Year 1 with no Previous Experience of Self-injection and Selects QM Regimen

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- Review AEs/SAEs
- Review concomitant medications
- Train subject on self-injection of AMG 145
- Observe subject self- inject AMG 145 at study site (AMG 145 administration must occur after other procedures)

7.1.1.18 Week 60 (± 7 Days)

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

- Dispense IP quantity for at-home injections
- IP reconciliation

7.1.1.19 Week 60 (± 7 Days)–Additional Procedures for Subjects Randomized to Placebo or SOC in Parent Study and Randomized to SOC-alone in Year 1

- Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, Lp(a), Vitamin E (sample drawn, testing by reflex when LDL-C is < 25 mg/dL), chemistry, and hematology
- HCV viral load (in subjects positive for HCV)
- Urine pregnancy test
- Urinalysis
- Urine microalbumin

7.1.1.20 Week 72 (± 7 Days)

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- Review AEs/SAEs
- Review concomitant medications
- Dispense IP quantity for at-home injections
- IP reconciliation

7.1.1.21 Week 84 (± 7 Days)

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- Review AEs/SAEs
- Review concomitant medications
- Urine pregnancy test
- Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, Lp(a), Vitamin E (sample drawn, testing by reflex when LDL-C is < 25 mg/dL), chemistry, hematology, and anti-AMG 145 antibodies
- HCV viral load (in subjects positive for HCV)
- Urinalysis
- Urine Microalbumin
- Dispense IP quantity for at-home injections
- IP reconciliation

7.1.1.22 Week 96 (± 7 Days)

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- Review AEs/SAEs
- Review concomitant medications
- Dispense IP quantity for at-home injections

- IP reconciliation

7.1.1.23 Week 100 (± 7 Days)–for Subjects on QM Regimen Only

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- Review AEs/SAEs
- Review concomitant medications
- In-office IP administration (either self-injection or HCP administered)
- IP reconciliation

7.1.1.24 Week 102 (± 7 Days)–for Subjects on Q2W Regimen Only

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- Review AEs/SAEs
- Review concomitant medications
- In-office IP administration (either self-injection or HCP administered)
- IP reconciliation

7.1.1.25 Week 104 (± 7 Days)

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- Review AEs/SAEs
- Review concomitant medications
- Urine pregnancy test
- Body weight
- Physical exam
- Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, Lp(a), Vitamin E (sample drawn, testing by reflex when LDL-C is < 25 mg/dL), chemistry, hematology, hsCRP, anti-AMG 145 antibodies, HbA1c, coagulation
- HCV Viral load (in subjects positive for HCV)
- Urinalysis
- Urine microalbumin
- Dispense IP quantity for at-home injections

7.1.1.26 Weeks 116, 128, or 140 (± 7 Days)

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- Review AEs/SAEs
- Review concomitant medications
- Dispense IP quantity for at-home injections
- IP reconciliation

7.1.1.27 Week 152 (± 7 Days)

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- Physical exam
- Body weight
- Review AEs/SAEs
- Review concomitant medications
- Blood draw for fasting lipids (≥ 9 hour fasting sample), chemistry, hematology, anti-AMG 145 antibodies, HbA1c, coagulation
- Urine pregnancy test
- HCV Viral load (in subjects positive for HCV)
- IP reconciliation

7.1.1.28 End of Study–Wk156 (± 7 Days) – Phone visit

- Review AEs/SAEs
- Review concomitant medications

Completion of the study is defined as the last day that protocol-specified procedures are conducted for an individual subject. If a subject withdraws from the study early, all efforts should be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. If possible, the procedures of Week 104 should be completed at the time of withdrawal if withdrawal occurs prior to W104.

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 primary hyperlipidemia and mixed dyslipidemia 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

In order to protect the blinding of the parent study, the following rules related to lipid results obtained at any time during the first 12 weeks will be followed. Fasting lipids, ApoA1, ApoB, Lp(a), or hsCRP measurements prior to the week 12 visit, for example at baseline due to a delay between the parent EOS visit and Day 1, will be blinded to investigators, site staff, and subjects. The study team will remain blind to these measurements until the subject's parent study is unblinded. 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. 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. Background lipid lowering concomitant medications should be stabilized as soon as possible after obtaining Week 12 data.

Vitamin E samples will be drawn for all applicable visits, testing will be conducted by reflex when LDL-C is < 25 mg/dL.

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 anti-AMG 145 antibody assessments and the central laboratory will ship the samples to Amgen or a specialty laboratory for assay (depending on the assessment).

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

Table 1 below outlines the specific analytes for serum chemistry, hematology, urinalysis, and other testing to be conducted.

Table 1. Analyte Listing

Chemistry	Coagulation	Urinalysis	Hematology	Other Labs
Sodium	PT/INR (per Appendix B)	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		ApoB/ApoA1 ratio
BUN or Urea		Casts		Total Cholesterol/HDL-C ratio
Creatinine		Crystals		hsCRP
Uric acid		Microalbumin		Lp(a)
Total bilirubin				Vitamin E
Direct bilirubin				Anti-AMG 145 antibodies
CK				HbA1c
ALP				Urine Pregnancy test
LDH				HCV antibodies
AST (SGOT)				HCV viral load
ALT (SGPT)				FSH (if applicable)

High risk subjects for HCV for this protocol are those who meet any of the following conditions:

- Ever injected illegal drugs
- Received clotting factors made before 1987
- Received blood/organs before July 1992 or were exposed to blood known to be infected with HCV
- Were ever on chronic hemodialysis
- Are known the be infected with HIV
- Have a known HCV infected sexual partner

7.2 Device Questionnaire

In order for the Sponsor to better understand the subject perspective on device use and rationale for switching devices, subjects experiencing a change in the device used to deliver AMG 145 may be asked to complete a short questionnaire at the next quarterly visit following their switch. This questionnaire will only be given to a subject once. The Sponsor may choose to discontinue the use of the questionnaire following a

non-specified number of subject responses. Clinical sites will be chosen by the Sponsor to administer the questionnaire.

If an Adverse Event or Product Complaint is identified from the questionnaire, it should be investigated and reported within the appropriate timeframe (eg, within 24 hours if serious).

Not all sites or countries involved in the conduct of this study will be provided the questionnaire.

7.3 Antibody Testing Procedures

Blood samples will be collected from all subjects at Day 1, Week 12, Week 24, Week 48, Week 84, Week 104 and Week 152 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 (± 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.

7.3.1 Sample Storage and Destruction

Samples and any other components from the cells may be stored for up to 20 years from the end of the study to research scientific questions related to hyperlipidemia and mixed dyslipidemia, metabolic disorders, and/or AMG 145. The subject retains the right to request that the sample material be destroyed at any time by contacting the principal investigator. The sponsor will be the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the principal investigator or at the

end of the storage period or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). Following the request from the subject, the principal investigator will provide the sponsor with the required study and subject numbers so that any remaining plasma and blood samples and any other components from the cells can be located and destroyed. If a commercial product is developed from this research project, the sponsor will own the commercial product. The subject will have no commercial rights to such product and will have no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 11.3 for subject confidentiality.

8. REMOVAL AND REPLACEMENT OF SUBJECTS

8.1 Removal of Subjects

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

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

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

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

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

- withdrawal of full consent
- subject request to end investigational product administration
- administrative decision by Amgen
- decision by the primary investigator / physician
- pregnancy in a female subject (report on Pregnancy Notification Worksheet; see Appendix D)
- adverse event (eg, serious adverse event related to study drug or procedures)

Reasons for removal of a subject from the study are:

- 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 the pre-existing medical condition (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study is not considered an adverse event.

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

9.1.2 Reporting Procedures for Adverse Events

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

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
- Assessment of relatedness to IMP: AMG 145
- Assessment of relatedness to the device (prefilled Autoinjector/Pen (AI/Pen) or 3.5 mL Personal Injector), or other protocol-required therapies
- Action taken

The adverse event grading scale used will be the NCI Common Terminology Criteria for AEs (CTCAE) grading scale. 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 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 prefilled AI/pen or 3.5 mL Personal Injector device used to administer IMP: 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 other study-mandated activity or procedure. This relationship is indicated by a “yes” or “no” response to the question: “Is there a reasonable possibility that the event may have been caused by a study activity/procedure”?

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

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

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

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.

If adverse events correspond to grade 4 "life threatening" CTCAE (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. However, the Investigator may report an SAE, irrespective of relatedness, to Amgen after the protocol-reporting timeframe has ended.

Serious adverse events must be submitted to Amgen within 24 hours following the Investigator's knowledge of the event via the applicable CRF. See Appendix C for a sample of the Serious Adverse Event Report Form.

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

The investigator must assess whether the serious adverse event is possibly related to the investigational medicinal product: 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 investigational medicinal product: AMG 145 and/or other protocol required therapies?

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

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

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

If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen within 24 hours.

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

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

The investigator should 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 through 15 weeks after the end of treatment with evolocumab.

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

If a lactation case occurs while a 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 through 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).

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

- Percent change from baseline in LDL-C at Week 48 and Week 104
- Change from baseline in LDL-C at Week 48 and Week 104

10.1.3 Exploratory Endpoints

- Achieving an LDL-C < 70 mg/dL(1.8 mmol/L) at Week 48 and Week 104
- Change and percent change from baseline at each scheduled visit in each of the following lipid parameters:
  - LDL-C
  - Non-HDL-C
  - ApoB
  - Total cholesterol/HDL-C ratio
  - Total cholesterol
  - ApoB/ApoA1
  - Lp(a)
  - Triglycerides
  - HDL-C
  - VLDL-C

- ApoA1
- High sensitivity C-reactive protein (hsCRP)

10.1.4 Other Safety Endpoints

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

10.1.5 Analysis Sets

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.

10.1.6 Baseline Covariates

The stratification factors are the parent study and the randomized treatment dose frequency in the parent study (Q2W or QM).

Baseline covariates for subgroup analyses include, but are not limited to:

- Age
- Sex
- Race
- LDL-C
- Family history of premature coronary heart disease

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. At the time of this protocol amendment, 3478 subjects have enrolled from closed parent studies. Based on the observed rollover rate and the planned sample sizes for additional parent studies that are not closed, approximately 950 additional subjects are expected to enroll. This gives a total expected sample size of 4428 subjects.

Additional parent studies may be identified in the future further increasing the sample size.

The anticipated exact 95% confidence interval for a 5% incidence rate for a particular adverse event for the SOC-alone treatment group is (4.0%, 6.3%) and for the AMG 145 + SOC treatment group is (4.3%, 5.9%). The estimates are derived using R version 3.0.3 ignoring stratification.

10.3 Interim Analysis and Early Stopping Guidelines

There will be interim analyses to support safety data reporting and assessments of efficacy endpoints. In particular, interim analyses of the randomized study period (up to Week 48) will be conducted after all subjects from sets of parent studies have completed the Week 48 visit or ended the study.

The study is not anticipated to stop early unless a major unexpected safety signal is detected.

10.4 Planned Methods of Analysis

10.4.1 General Approach/Considerations

Statistical analyses in this open-label extension study will be descriptive. 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, first and third quartiles, minimum, and maximum. For categorical variables, the frequency and percentage will be given. 95% confidence intervals will be calculated for select continuous and categorical endpoints.

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 phase 3 studies will be adjudicated by an independent Clinical Events Committee (CEC) to facilitate aggregated analyses across the program. These events adjudicated by the CEC include:

- death by any cause
- cardiovascular death
- myocardial infarction
- hospitalization for unstable angina
- coronary revascularization
- stroke
- hospitalization for heart failure
- transient ischemic attack (TIA)

The CEC will adhere to a charter which details the adjudication process.

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 will be tabulated by system organ class and preferred term for each treatment group.

Subgroup analyses on the primary endpoint will be conducted by parent study.

10.4.2.2 Secondary Endpoint Analyses

Point estimates of treatment group means and their 95% confidence intervals will be calculated using a mixed effects model containing the stratification factors, treatment group, visit, and treatment group by visit. Differences in group means for the secondary and exploratory endpoints will be estimated between the AMG 145 + SOC group and the SOC-alone group.

Subgroup analyses for secondary endpoints may be conducted on baseline covariates specified in Section 10.1.6.

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. For achieving LDL-C < 70 mg/dL, subjects missing LDL-C for a particular planned visit will be considered as not achieving LDL-C < 70 mg/dL. For continuous exploratory endpoints, the same model as for the secondary endpoint analyses may be used for estimating treatment group means and differences at weeks 48 and 104.

Subgroup analyses for exploratory endpoints may be conducted on baseline covariates specified in Section 10.1.6.

10.4.2.4 Safety Endpoint Analyses

Safety Laboratory Parameters

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

Vital Signs

Vital signs will be summarized for each treatment group 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 anytime will be tabulated.

Concomitant Medications

Concomitant medications of interest will be summarized for each treatment group.

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 subject population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational 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 on the demographics CRF.
- For Serious Adverse Events reported to Amgen, subjects should be identified by 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/ International Conference on Harmonization (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 pre-study 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).

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14. APPENDICES

Appendix A. Schedule of Assessments

Applies to both AMG 145 and SOC-alone groups unless specified otherwise																				
Timepoint/Frequency	**D1[a]**	**W2[b]**	**W4[b/c]**	**W8[c]**	**W12**	**W24**	**W36**	**W44[f]**	**W46[g]**	**W48**	**W50[i]**	**W52[i/j]**	**W56[j]**	**W60**	**W72**	**W84**	**W96**	**W100[f]**	**W102[g]**	**W104**
General Procedures																				
Informed consent	X																			
Medical history	X																			
Vital Signs (sitting BP, HR)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review for AEs/SAEs	X	X[e]	X[e]	X[e]	X	X	X	X[e]	X[e]	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X[e]	X[e]	X[e]	X	X	X	X[e]	X[e]	X	X	X	X	X	X	X	X	X	X	X
Physical exam	X[d]																			X
Body weight	X									X										X
Randomization	X																			
Central Laboratory																				
Fasting lipids	X[d]				X	X				X				X[k]		X				X
ApoA1, ApoB, Lp(a)	X[d]				X	X				X				X[k]		X				X
Vitamin E[h]					X	X				X				X[k]		X				X
hsCRP	X[d]									X										X

Footnotes defined on last page of this table

Appendix A. Schedule of Assessments

Applies to both AMG 145 and SOC-alone groups unless specified otherwise																				
Timepoint/Frequency	**D1[a]**	**W2[b]**	**W4[b/c]**	**W8[c]**	**W12**	**W24**	**W36**	**W44[f]**	**W46[g]**	**W48**	**W50[i]**	**W52[i/j]**	**W56[j]**	**W60**	**W72**	**W84**	**W96**	**W100[f]**	**W102[g]**	**W104**
Central Laboratory																				
Chemistry, fasting glucose	X[d]				X	X				X				X[k]		X				X
Coagulation (PT/INR)	X									X										X
Hematology	X[d]				X	X				X				X[k]		X				X
TSH	X[d]																			
HbA1c	X[d]				X	X				X										X
Anti-AMG 145 antibodies	X[d]				X	X				X						X				X
HCV antibodies[l]	X[d]																			
HCV viral load[l]	X[d]				X	X				X				X[k]		X				X
Urine pregnancy, FSH[m]	X[d]				X	X				X				X[k]		X				X
Urinalysis	X[d]				X	X				X				X[k]		X				X
Urine microalbumin	X[d]				X	X				X				X[k]		X				X
Investigational Product																				
Subject **without** previous in home use experience: IP in-office administration	X[f/g]	X[b]	X[b/c]	X[c]				X	X	X[i/j]	X[i]	X[i/j]	X[j]					X	X	
Subject **with** previous in-home use experience: IP in-office administration	X[f/g]							X	X	X[i/j]								X	X	
IP dispense	X		X[b]		X	X	X			X		X[i]		X	X	X	X			X
IP reconciliation					X	X	X	X	X					X	X	X	X	X	X	

Footnotes defined on last page of this table

Appendix A. Schedule of Assessments

Applies to both AMG 145 and SOC-alone groups unless specified otherwise					
Timepoint/Frequency	**W116**	**W128**	**W140**	**W152**	**EOS Phone visit W156**
General Procedures					
Vital Signs (sitting BP, HR)	X	X	X	X	
Review for AEs/SAEs	X	X	X	X	X
Concomitant therapy	X	X	X	X	X
Physical Exam				X	
Body Weight				X	
Laboratory					
Fasting lipids				X	
Chemistry, fasting glucose				X	
Hematology				X	
Coagulation (PT/INR)				X	
HbA1c				X	
Anti-AMG 145 antibodies				X	
HCV viral load[l]				X	
Urine pregnancy				X	
Investigational Product					
IP Dispense	X	X	X		
IP Reconcile	X	X	X	X	

[a] D1 = day of first administration of IP. This visit should also coincide with EOS visit for parent study; for visit windows see Section 7 of the protocol. Procedures NOT conducted as part of EOS visit for parent study should be completed at this visit.
[b b] Training visit applies to subjects who are randomized to AMG 145 and select the Q2W regimen
[c] Training visit applies to subjects who are randomized to AMG 145 and select QM regimen
[d] Only if enrollment into 138 exceeds last laboratory visit from parent study by 30 days. Cardiac History Form will also need to be completed.
[e] Telephone visit for subjects randomized to SOC-alone
[f] Only for subjects receiving AMG 145 who have selected the QM regimen
[g] Only for subjects receiving AMG 145 who have selected the Q2W regimen
[h] Vitamin E samples will be drawn for all applicable visits, testing will be conducted by reflex when LDL-C is < 25 mg/dL
[i i] Training visit applies to subjects who are randomized SOC-alone in year 1 and select the Q2W regimen in year 2
[j] Training visit applies to subjects who are randomized SOC-alone in year 1 and select the QM regimen in year 2
[k] Only for subjects randomized to placebo or SOC in parent study AND randomized to SOC-alone in Year 1
[l] HCV antibodies only in high risk subjects (see Section 7.1.2.4) or if ALT or AST > 2x ULN; viral load only in subjects positive for HCV
[m] FSH in applicable subjects for study entry only – see exclusion criteria; urine pregnancy in females of childbearing potential
[n] Dispense IP for at-home injections (only for subjects who have previous experience of self-injecting AMG 145)

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.

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 or INR>1.5 ULN) 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 Form (DO NOT USE)

AMGEN evolocumab (AMG 145) 20120138	**Clinical Trial Serious Adverse Event Report (3–IMP)** *Notify Amgen Within 24 Hours of knowledge of the event*	❑New ❑Follow-up

SELECT OR TYPE IN A FAX NUMBER

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	Race
		❑F ❑M	

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

Provide the date the Investigator became aware of this Serious Adverse Event Information: Day____ Month___ Year____

Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event *List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.*	Date Started (Day Month Year)	Date Ended (Day Month Year)	Potential Endpoint? No✓	Potential Endpoint? Yes✓	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 — evolocumab (AMG 145) No✓	evolocumab (AMG 145) Yes✓	Pre-filled autoinjector /pen (AI/pen) No✓	Pre-filled autoinjector /pen (AI/pen) Yes✓	3.5 mL personal injector No✓	3.5 mL personal injector Yes✓	Outcome of Event (01 Resolved 02 Resolving 03 Not resolved 04 Fatal)	Check only if event is related to study procedure eg, biopsy

Serious Criteria: **01** Fatal; **02** Immediately life-threatening; **03** Required hospitalization; **04** Prolonged hospitalization; **05** Persistent or significant disability /incapacity; **06** Congenital anomaly / birth defect; **07** Other significant medical hazard

4. HOSPITALIZATION

	Date Admitted (Day Month Year)	Date Discharged (Day Month Year)
Was subject hospitalized? ❑No ❑Yes, If yes, please complete date(s):		

5. INVESTIGATIONAL PRODUCT (IP)

	Initial Start Date (Day Month Year)	Prior to, or at time of Event: Date of Dose (Day Month Year)	Dose	Route	Frequency	Action Taken with Product (01 Still being Administered 02 Permanently discontinued 03 Withheld)
evolocumab (AMG 145) ☑ Open Label						
Pre-filled autoinjector/pen (AI/pen) ☑ Open Label						
3.5 mL personal injector ☑ Open Label						

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

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

FORM-065033 Clinical Trial SAE Report (3–IMP) V5.0 Effective date: 20-August-2014 (This is a variant of parent FORM-015482)
SAER Created: 21-AUG-2014 Page 1 of 2

AMGEN evolocumab (AMG 145) 20120138	**Clinical Trial Serious Adverse Event Report (3–IMP)** *Notify Amgen Within 24 Hours of knowledge of the event*	☐New ☐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 (Day Month Year)	Test										
	Unit										

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

Date (Day Month Year)	Additional Tests	Results	Units

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

FORM-065033 Clinical Trial SAE Report (3–IMP) V5.0 Effective date: 20-August-2014 (This is a variant of parent FORM-015482)
SAER Created: 21-AUG-2014 Page 2 of 2

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

Effective Date: March 27, 2011 Page 1 of 1

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

Amendment 6

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

Amgen Protocol Number: 20120138
EudraCT Number: 2012-004357-83

OSLER 2

Open Label **S**tudy of **L**ong T**er**m Evaluation Against LDL-C Trial

Amendment 1 Date : 12 February 2013
Amendment 2 Date: 30 April 2013
Superseding Amendment 2 Date: 23 May 2013
Amendment 3 Date: 15 November 2013
Superseding Amendment 3 Date: 15 February 2014
Superseding Amendment 3 Date: 24 February 2014
Amendment 4 Date: 15 April 2014
Amendment 5 Date: 19 December 2014
Amendment 6 Date: 03 April 2015

Rationale:

This document provides the rationale and detailed list of changes for Amendment 6, dated 03 April 2015, from Amendment 5 of the study protocol, dated 19 December 2014.

The purpose of the amendment is to:

- Update exclusion criteria to include methods of effective birth control in the protocol language

Description of Changes:

Section: Header

Replace:

19 December 2014

With:

03 April 2015

Section: Coverpage

Add:

Amendment 6 Date: 03 April 2015

Section: 4.2 Exclusion Criteria

Second Criterion, Bullet point 2

Replace:

- Acceptable methods of effective contraception are defined in the ICF. Where required by local laws, regulations and/or guidelines, additional country-specific requirements are outlined in a country-specific protocol supplement.

With:

- **Acceptable methods of effective birth control include: sexual abstinence (when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception]), surgical contraceptive methods (vasectomy or bilateral tubal ligation), use of hormonal birth control methods (pills, shots, implants or patches), intrauterine devices (IUDs), or two (2) barrier methods (each partner must use one barrier method) with spermicide – males must use a condom with spermicide; females must choose either a diaphragm with spermicide, OR cervical cap with spermicide, OR contraceptive sponge with spermicide. Note: Additional medications given during treatment with evolocumab may alter the contraceptive requirements. These additional medications may require an increase in the number of contraceptive methods and/or length of time that contraception is to be utilized after the last dose of protocol-required therapies. The investigator is to discuss these contraceptive changes with the study subject.**

Amendment 5

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

Amgen Protocol Number: 20120138
EudraCT Number: **2012-004357-83**

OSLER 2

Open Label **S**tudy of **L**ong T**er**m Evaluation Against LDL-C Trial

Amendment 5 Date: 19 December 2014

Rationale:

This document provides the rationale and detailed list of changes for Amendment 5, dated 19 December 2014, from amendment 4 of the study protocol, dated 15 April 2014.

The purpose of the amendment is to:

- Extend the treatment duration of the study by an additional 1 year to further characterize the safety and tolerability of evolocumab(AMG 145) over 3 years of exposure consistent with the primary objective for this study.
- Update the expected sample size to account for additional studies that are scheduled to complete to permit the timely analysis and disclosure of results. Rather than extend the duration of other studies allowing patients into this open label extension study will contribute to the evidence for safety and tolerability of up to 3 years of exposure of evolocumab
- Update the schedule of assessments and schema for clarification and ease of use
- Update exclusion criteria regarding effective methods of birth control to align with current Amgen standards, it is noted that this change is not a consequence of a change in the safety profile of evolocumab.
- Clarify definition of Investigational Product (IP) as combination product of evolocumab (AMG 145) and device with term Investigational Medicinal Product (IMP) used to refer to evolocumab (AMG 145) to align with standards provided by CMC Safety
- Clarify reporting process for adverse events and serious adverse events
- Update process for Pregnancy and Lactation Reporting
- 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.

- Minor other updates, clarifications and corrections

Amendment 4

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

Amgen Protocol Number:20120138
EudraCT Number: **2012-004357-83**

OSLER 2

Open Label **S**tudy of **L**ong T**er**m Evaluation Against LDL-C Trial

Amendment 4 Date: 15 April 2014

Rationale:

This document provides the rationale and detailed list of changes for Amendment 4, dated 15 April 2014, from superseding amendment 3 of the study protocol, dated 24 February 2014.

The purpose of the amendment is to:

- Update the schedule of assessments schema for clarification and ease of use
- Add a patient questionnaire for patients experiencing a change in the device used to deliver AMG 145
- Minor other updates, clarifications and corrections

Amendment 3

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

Amgen Protocol Number: 20120138
EudraCT Number: **2012-004357-83**

OSLER 2

Open Label **S**tudy of **L**ong T**er**m Evaluation Against LDL-C Trial

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

Amendment Date: 15 November 2013
Superseding Amendment Date: 15 February 2014
Superseding Amendment Date: 24 February 2014

Rationale:

This document provides the rationale and detailed list of changes for Amendment 3, dated 24 February 2014, from superseding amendment 2 of the study protocol, dated 23 May 2013.

The purpose of the amendment is to:

- Add Vitamin E reflex testing to the protocol in cases where LDL-C is < 25 mg/dL.
- Add language for the use of the 3.5 mL personal injector. The 3.5 mL Personal Injector will only be made available for use in this study once it has been determined that the intended user population for AMG 145 can safely and effectively use the device in clinical trials under guidance of study investigators.
- The schedule of assessments and schema were clarified and changed in format to be easier to use
- The body of the protocol and schedule of assessments were updated and made consistent
- The visit schedule was clarified to list the exact timing of the visit, replacing reference to quarterly visits
- The protocol now references the latest IB (2013)
- The protocol now includes “Investigator Responsibilties for Data Collection”
- Non-coronary revascularizations will no longer be collected (update to be consistent with DMC charter)
- Minor other updates, clarifications and corrections

Amendment 2 - Superseding Amendment

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** ***20120138***

Amendment Date: 23 May *2013*

Rationale:

This protocol is being amended to support feedback received from VHP to include a minor administrative change to Protocol Amendment 2.

Description of Changes:

Section: Study Schema

Changes:

- Addition of one blue triangle on Day 1 indicating in-clinic administration of IP.

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** ***20120138***

Amendment Date: 12 *February 2013*

Rationale:

This protocol is being amended to support feedback received from FDA and our Data Monitoring Committee (DMC) to include a standard of care (SOC) group for the first year. Doing so increases the scientific rigor of the study and reduces undue relatedness and causality of adverse events in subjects receiving AMG 145.

Additional major changes include:

- Reduction to 2 years duration – to facilitate cost containment as 2+ year data will be captured through other OLE/Outcomes studies.
- Inclusion of Q2W dose regimen – for consistency with other Phase 3 studies and opportunity to allow subjects to experience different dosing regimens
- Alignment of assessments with other approved longer term AMG 145 studies, eg, 118 - for consistency with other Phase 3 studies and pooling of data
- Addition of extra visits for AMG 145 naïve subjects requiring training on use of prefilled AI/pen – to improve opportunity for successful in-home use administration of AMG 145