Title: A Multicenter, Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of AMG 145 on LDL-C in Subjects With Severe Familial Hypercholesterolemia

Evolocumab (AMG 145)

Amgen Protocol Number 20110271
EudraCT Number: 2011-005400-15

TAUSSIG

Trial **A**ssessing long term **US**e of PCSK9 Inhibition in **S**ubjects w**I**th **G**enetic LDL Disorders

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Investigator's Agreement

I have read the attached protocol entitled "A Multicenter, Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of AMG 145 on LDL-C in Subjects With Severe Familial Hypercholesterolemia", dated **02 December** 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, Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of AMG 145 on LDL-C in Subjects With Severe Familial Hypercholesterolemia

Study Phase: 2/3

Indication: Hypercholesterolemia

Primary Objective: To characterize the safety and tolerability of long-term administration of AMG 145 among subjects with severe familial hypercholesterolemia

Secondary Objectives: To characterize the efficacy of long-term administration of AMG 145 as assessed by low density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C), **lipoprotein(a) [**Lp(a)**]**, apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, ApoB/Apolipoprotein A-1 (ApoA1) ratio, and response of LDL-C reduction (15% or greater) in subjects with severe familial hypercholesterolemia

Hypotheses: Long-term exposure of AMG 145 will be safe and well tolerated in subjects with severe familial hypercholesterolemia.

Primary Endpoint

- Subject incidence of treatment emergent adverse events

Secondary Endpoints

- Percent change in LDL-C from baseline at each scheduled visit
- Percent change in non-HDL-C from baseline at each scheduled visit
- Percent change in Lp(a) from baseline at each scheduled visit
- Percent change in ApoB from baseline at each scheduled visit
- Percent change in total cholesterol/HDL-C ratio from baseline at each scheduled visit
- Percent change in ApoB/ApoA1 ratio from baseline at each scheduled visit
- Response rate of subjects with 15% or greater reduction in LDL-C by scheduled visit.

Study Design: A multicenter, open-label study designed to assess the long-term safety, tolerability, and efficacy of AMG 145. The study will continue **until the date when the last subject has completed the assessments for week 260 (approximately 5 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**. Central laboratory results of the lipid panel, ApoA1, ApoB, Lp(a), and hsCRP will not be reported to the investigator prior to week 8 for subjects coming from a blinded (or blinded portion) of an AMG 145 parent protocol, since some laboratory results may inadvertently unblind investigators to treatment assignment in the parent study. **Proprotein convertase subtilisin/kexin type 9 (**PCSK9**)** levels will be blinded until week 4. Vitamin E samples will be blinded to sites for the first 96 weeks of the study. Investigators should not perform local testing of these analytes. Study participation may be stopped for subjects that do not demonstrate minimal benefit (ie, subjects that have less than 5% LDL-C reduction from baseline while on therapy). Additional detail can be found in Section 6.1.1.

Sample Size: The approximate total number of subjects expected to participate in this study is 310.

Summary of Subject Eligibility Criteria

1. Subjects that participated in a qualifying AMG 145 parent protocol must have a diagnosis of familial hypercholesterolemia. Subjects must not have experienced an **investigational product (**IP**)** treatment related serious adverse event that led to IP discontinuation during their participation in the qualifying AMG 145 parent study.

2. Subjects with homozygous familial hypercholesterolemia who meet the inclusion and exclusion criteria of study 20110233 may enroll after study 20110233 is closed.
3. Subjects that have not participated in a qualifying AMG 145 parent protocol must:
   A. Have a diagnosis of familial hypercholesterolemia.
   B. Bodyweight must be 40 kg or greater at screening for subjects age < 18 years.
   C. Receive stable low-fat diet and pre-existing, background lipid-lowering therapy (eg statins, cholesterol-absorption inhibitors, bile-acid sequestrants, nicotinic acid, omega 3 fatty acids or combinations thereof) for at least 4 weeks prior to final screening.
   D. Demonstrate a fasting central lab triglyceride concentration ≤ 400 mg/dL (4.5 mmol/L) and either LDL cholesterol concentration ≥ 100 mg/dL (2.6 mmol/L) for subjects with CHD or CHD risk equivalent by NCEP ATP III criteria or ≥ 130 mg/dL (3.4 mmol/L) for subjects that do not have CHD or CHD risk equivalent by NCEP ATP III criteria. Subjects that are receiving apheresis are not required to demonstrate a minimum LDL-C level at baseline due to the fluctuations caused by apheresis therapy.
   E. Male or female ≥ 12 to ≤ 80 years of age

Major exclusions are: use of Mipomersen or Lomitapide within 5 months of screening or a cholesterylester transfer protein (CETP) inhibitor in the last 12 months; New York Heart Failure Association (NYHA) class III or IV or last known left ventricular ejection fraction < 30%; cardiac arrhythmia within past 3 months that is not controlled by medication; systolic blood pressure (SBP) > 180 mmHg or diastolic BP (DBP) > 110 mmHg; requiring statin up-titration within 4 weeks of screening; estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m^2; persistent aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3x **upper limit of normal (**ULN**)**, creatine kinase (CK) > 5x ULN without a known cause; known major active infection, or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction; deep vein thrombosis or pulmonary embolism within 3 months prior to enrollment; history of malignancy in the last 5 years; subject previously received a non-AMG 145 investigational therapy to inhibit PCSK9; currently enrolled in a non-AMG 145 investigational device or drug study, or less than 30 days since ending a non-AMG 145 investigational device or drug study(s), or receiving other investigational agent(s).

Female subjects cannot be pregnant or breast-feeding or planning to become pregnant or breastfeed and premenopausal females of childbearing potential must be willing to use an acceptable method(s) of birth control during treatment **with AMG 145 (IP)** and for an additional 15 weeks after the **last dose of** AMG 145 (IP).

Amgen Investigational Product Dosage and Administration

AMG 145 will be administered at 1 of 2 regimens: 420 mg SC QM or 420 mg SC Q2W.

AMG 145 will be available in 1 of 3 presentations based on regional availability;

1) six 1.0 mL vials (70 mg/dL) with doses that can be split into multiple injections (eg, 3 injections at 2 mL each for 420 mg) with the condition that the full dose is provided at each respective study visit,
2) three 1.0 mL auto injectors (140 mg/dL),
3) one 3.5 mL Personal Injector (PI) (120 mg/dL), based on device availability.

Parent Study 20110233 Subjects:

Subjects coming from parent study 20110233 will initiate this study with **AMG 145** 420 mg SC monthly (QM) dosing. After 12 weeks of 420 mg SC QM, if observed LDL-C reduction is ≥ 5% and PCSK9 levels have been shown to be maximally suppressed (ie, < 100 ng/mL), subjects may

continue QM dosing for the duration of the study. In subjects with PCSK9 levels ≥ 100 ng/mL assessed at the end of a 420 mg SC QM dosing interval (eg, assessed at weeks 4 and/or 8), dosing may be changed to 420 mg SC Q2W at the week 12 visit. If the observed LDL-C reduction from baseline is < 5% and PCSK9 levels have been shown to be maximally suppressed (ie, < 100 ng/mL) the subject may be withdrawn from the study at week 12. Depending on the subject response to 420 mg SC Q2W dosing, these subjects may continue Q2W dosing, return to QM dosing, or be withdrawn from the study at the week 24 visit.

Apheresis Subjects:

Subjects on apheresis should initiate treatment with **AMG 145** 420 mg SC Q2W in this study to correspond with their apheresis schedule. For apheresis subjects initiating this study on 420 mg Q2W dosing, the dosing schedule may be continued or downtitrated to 420 mg QM at the week 12 visit provided there is evidence of sufficient efficacy (LDL-C reduction of ≥ 5% is considered sufficient efficacy for these subjects). Subjects downtitrating to 420 mg QM dosing at week 12 may revert to 420 mg Q2W dosing 12 weeks after the initiation of 420 mg QM dosing (eg, week 24) if clinically indicated. Dosing changes that do not occur on week 12 or 24 are permitted in cases where apheresis therapy is discontinued by patients. Dose adjustments after week 24 are discouraged.

Other Subjects:

Subjects that are not receiving apheresis will be provided with AMG 145 420 mg SC QM. Similar to subjects coming from study 20110233, an option of 420 mg SC Q2W will also be available to other subjects pending observed LDL-C levels and insufficient suppression of PCSK9 (≥ 100 ng/mL) at the end of a dosing interval (eg, assessed at week 4, 8, etc). Dosing changes should occur at week 12 or 24 if clinically indicated. Dosing changes after week 24 are discouraged.

Any other dosing changes must be discussed with the medical monitor. Finally, subjects who have known insufficient efficacy (recommended to be considered as LDL-C reduction < 5% after an adequate trial of AMG 145 dosing) may be removed at either the week 12 or 24 study visit pending a final risk/benefit discussion with Amgen's medical monitor.

Further details about dosing can be found in both the study schema and in Section 6.1.1.

Adolescent Subjects:

Subjects are considered adolescent if their 18th birthday occurs after the date of enrollment in the parent study (for parent study rollover subjects) or after the date of enrollment in Study 20110271 (for all other subjects). Other subjects are considered adults, including those whose 18th birthday coincides with the date of enrollment in the parent study or present study, as applicable.

At Home Dosing:

Self-administration, defined as SC administration of AMG 145 by the subject, designee, or a qualified health care professional will be permitted in a non-site setting (eg, at home or at a location where a qualified health care professional is available). Prior to week 24, subjects that are treated with AMG 145 420 mg administered SC Q2W may self-administer study drug between visits. Starting at the week 24 visit, all subjects will have the option of AMG 145 self-administration. The subject or designee (if not a qualified healthcare professional) must have demonstrated competency at administration of SC injections before self-administration is permitted: the first self-administered dose by the subject (or designee, if not a healthcare professional) must be administered at the site under the supervision of a healthcare provider. For subjects that prefer not to self-administer AMG 145 or for subjects that will receive AMG 145 during lipid apheresis, AMG 145 may be administered at the site. The dosing schedule is described by a schema in the protocol synopsis.

Non Amgen Investigational Product Dosage and Administration: Only AMG 145 will be provided for this study.

Control Group: No control group will be used in this open-label study.

Procedures

This will be a multicenter, open-label study to assess the long-term safety, tolerability, and efficacy of AMG 145**.** For the purpose of this study, a month is defined as 4 weeks and a quarter is defined as 12 weeks.

Subjects that fall within a 1 month window of completing a qualifying parent study do not require screening procedures; they may be enrolled into the study directly, as outlined in Section 7.1.2. All other subjects must go through the study screening procedures as outlines in Section 7.1.1.

Vital signs, **adverse events (**AEs**)/adverse device effects (ADEs)/serious adverse events (**SAEs**)**, and concomitant therapy will be evaluated and dietary instruction provided at every study visit, including screening. Other assessments and procedures include fasting lipids, physical exam, measuring body height and weight, assessment of growth and pubertal development (Tanner staging) for adolescent subjects only, 12-lead ECGs, other laboratory assessments, including assessment for anti-AMG 145 antibodies, biomarker sample collection, serum pregnancy testing (females of childbearing potential), urinalysis, and SC IP administration. If the subject consented to pharmacogenetics analyses, deoxyribonucleic acid (DNA) will be extracted from some of their existing blood samples. IP administration by SC injection will be done after all other procedures have been completed. This study includes adjudication of deaths and specific cardiovascular (CV) events by an independent Clinical Events Committee (CEC).

Statistical Considerations

Statistical analyses in this open label, multicenter single arm study will be descriptive in nature. No statistical inference is planned.

Subject disposition, demographics and baseline characteristics will be summarized.

Summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation or standard error, minimum, and maximum. For categorical variables, the frequency and percentage will be given.

Subjects will be summarized according to whether subject rolled over from a parent study and their treatment allocation from a parent study when applicable.

For efficacy analyses, the baseline value is defined as:

- Subjects from a qualifying parent study with baseline parent study data: the baseline is defined as the baseline of the parent study
- Subjects not enrolling from a parent study or without baseline parent study data: the baseline is defined as the baseline obtained in this study (study 20110271)

For non-efficacy analyses, baseline values for all subjects are defined as the baseline values obtained in this study, 20110271.

There will be no imputation for missing data.

Analysis of Primary Endpoint

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

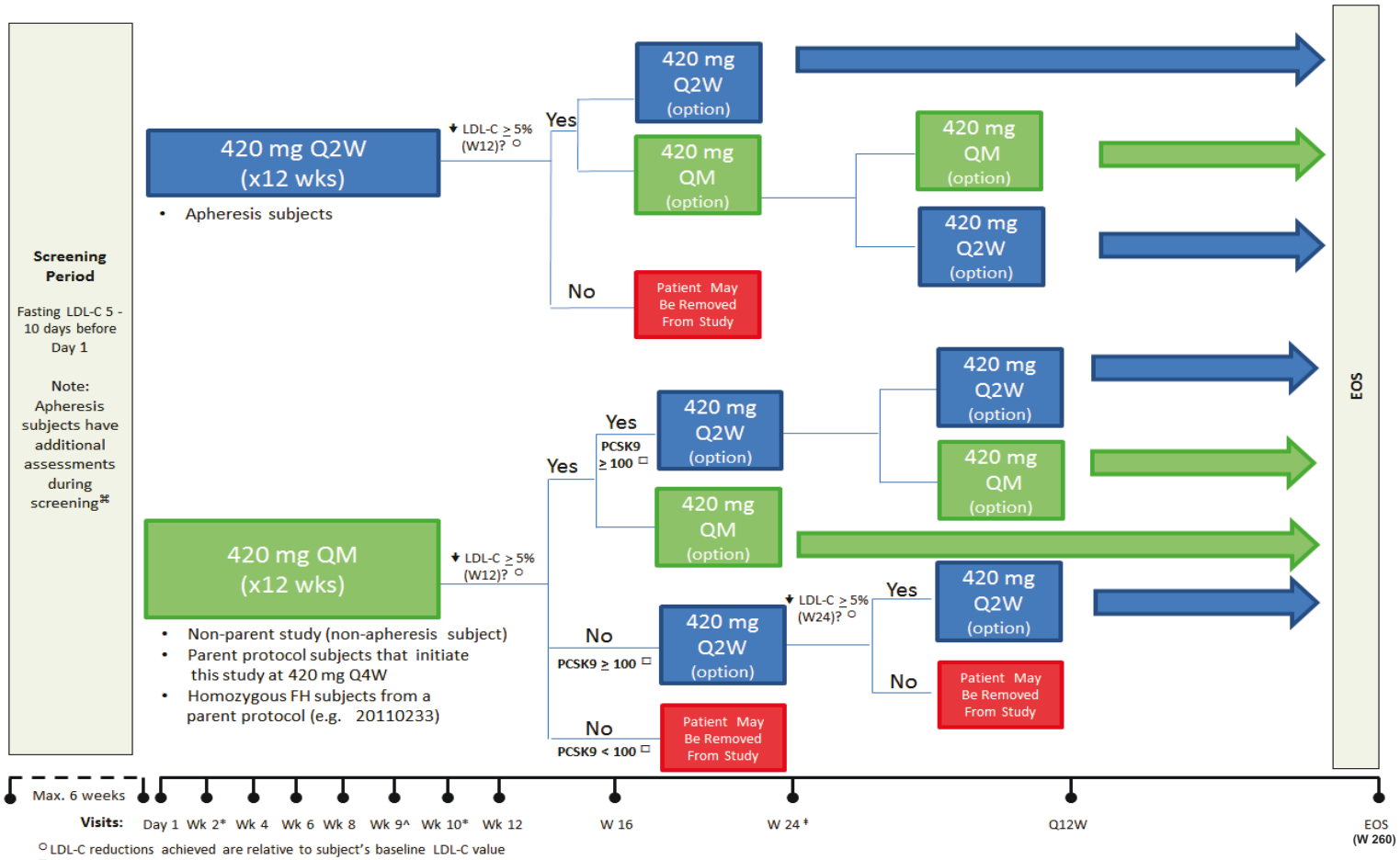
Analysis of Secondary Endpoints

Secondary endpoints will be summarized at each scheduled visit. Descriptive statistics will be presented.

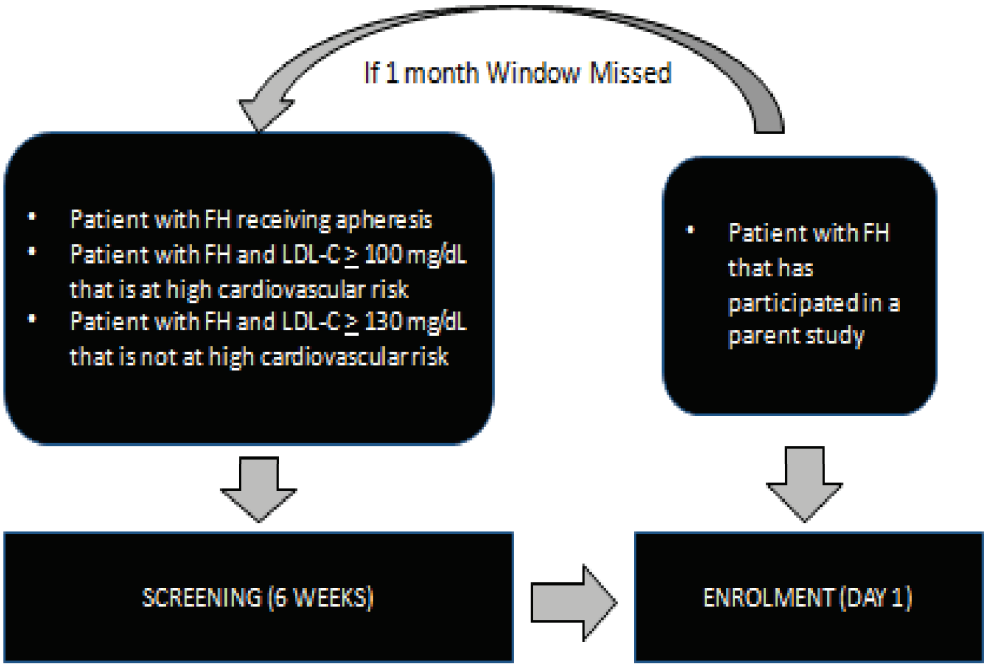
For a full description of statistical analysis methods, refer to Section 10**.**

Sponsor: Amgen

Study Design and Treatment Schema



○ LDL-C reductions achieved are relative to subject's baseline LDL-C value
□ PCSK9 levels are measured at the end of the 4 week dosing interval for subjects that have received 420 mg QM
*Week 2 and week 10 assessments and visits are not compulsory for non-parent/nonapheresis subjects only, should not be performed for parent study subjects and are mandatory for apheresis subjects
^Week 9 and screening weeks -2 and -1 are for apheresis subjects only
⌘Week -2 and -1 assessments are performed for all apheresis subjects.
ǂ Dose changes after Week 24 are discouraged, dose changes must be discussed with the medical monitor
FH = familal hypercholesterolemia


If 1 month Window Missed
Patient with FH receiving apheresis
Patient with FH and LDL-C ≥ 100 mg/dL that is at high cardiovascular risk
Patient with FH and LDL-C ≥ 130 mg/dL that is not at high cardiovascular risk
Patient with FH that has participated in a parent study
SCREENING (6 WEEKS)
ENROLMENT (DAY 1)

Study Glossary

Abbreviation or Term	Definition/Explanation
ADE	**Adverse device effect**
Adolescent	Subjects are considered adolescent if their 18th birthday occurs after the date of enrollment in the parent study (for parent study rollover subjects) or after the date of enrollment in Study 20110271 (for all other subjects). Other subjects are considered adults, including those whose 18th birthday coincides with the date of enrollment in the parent study or present study, as applicable
AE	Adverse event
AHA	American Heart Association
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)
AUC	Area under the curve
BP	Blood pressure
CBC	Complete blood count
CEC	Clinical Events Committee
CK	Creatine kinase
CHD	Coronary heart disease
Cmax	Maximal concentration
CRP	C-reactive protein
CTTC	Cholesterol Trialists Treatment Collaboration
CVD	Cardiovascular disease
Day 1	defined as the first day that protocol-specified investigational product is administered to the subject
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR (by MDRD equation)	Estimated glomerular filtration rate (by Modification of Diet in Renal Disease equation to calculate eGFR [Levey et al, 1999]). Calculation will be done by central laboratory and eGFR provided to the investigator.

Abbreviation or Term	Definition/Explanation
End of treatment	Defined as the last **dose** for the protocol-specified treatment phase of the study for an individual subject
EOS	End of study
ET OL	**Early termination open label**
EU	European Union
EAS	Evaluable analysis set
FH	Familial hypercholesterolemia
GCP	Good Clinical Practice
HDL-C	High density lipoprotein cholesterol
HepG2 cells	Human hepatocellular carcinoma cell line
HR	Heart Rate
hsCRP	High sensitivity CRP
IBG	Independent Biostatistical Group
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC/IRB	Independent Ethics Committee / Institutional Review Board
IFU	Instructions for use
IP	Investigational product
IPIM	Investigational Product Instruction Manual
IVRS	Interactive Voice Response System
IV	Intravenous
LDL-C	Low-density lipoprotein cholesterol
LDLR	LDL receptor
LLN	Lower limit of normal
LOCF	Last observation carried forward
LOF	Loss of function
Lp(a)	Lipoprotein(a)
MedDRA	Medical dictionary for regulatory activities
NASH	Nonalcoholic steatohepatitis
NCEP ATP III	NCEP Adult Treatment Panel III (see References)
NCI-CTCAE	N**ational** C**ancer** I**nstitute** Common Terminology Criteria for A**dverse** E**vent**s
OL	Open Label
PCSK9	Proprotein convertase subtilisin/kexin type 9
PKPD	Pharmacokinetic / pharmacodynamic

Abbreviation or Term	Definition/Explanation
QM	QM is defined as every 4 weeks with a window of ± 7 days for each visit, thus dosing intervals are allowed to be up to 35 days for the QM regimen.
Q2W	Q2W is defined as every 2 weeks with a window of ± 7 days for each visit, thus dosing intervals are allowed to be up to 21 days for the Q2W regimen.
SAE	Serious adverse event
SC	Subcutaneous
SMR	Sexual maturity rating
Source Data	Information from an original record or a certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline (E6)). Examples of source data include Subject ID, Randomization ID, and Stratification Value.
TIA	Transient ischemic attack
TBL	Total bilirubin
Tmax	Time to maximum concentration
TNF	Tumor necrosis factor
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol

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1. OBJECTIVES

1.1 Primary

To characterize the safety and tolerability of long-term administration of AMG 145 among subjects with severe familial hypercholesterolemia

1.2 Secondary

- To characterize the efficacy of long-term administration of AMG 145 as assessed by low density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C), **lipoprotein(a) [**Lp(a)**]**, apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, ApoB/Apolipoprotein A-1 (ApoA1) ratio, and response of LDL-C reduction (15% or greater) in subjects with severe familial hypercholesterolemia

1.3 Exploratory

- To investigate potential biomarker development by biochemical analysis of blood samples
- To characterize pharmacokinetics of AMG 145 and proprotein convertase subtilisin/kexin type 9 (PCSK9) levels

2. BACKGROUND AND RATIONALE

2.1 Familial Hypercholesterolemia and Cardiovascular Disease

Individuals with monogenic causes of hypercholesterolemia comprise a small and unvarying portion of the collective dyslipidemia population. The vast majority of culprit mutations (approximately 95%) exist within the LDL receptor and manifest with the clinical diagnosis of familial hypercholesterolemia (FH). Well over 1,000 LDL receptor mutations have been described, with most resulting in impaired LDL receptor function in the range of 2-25% (Rader et al, 2003). Because LDL receptor-mediated endocytosis is the principal mode of hepatic LDL-C clearance, compromised LDL receptor function often manifests with an increase in circulating LDL-C levels. This renders affected individuals extremely vulnerable to the attendant consequences of severe atherosclerotic disease, such as myocardial infarction and stroke. The prevalence of people heterozygous for LDL receptor mutation based FH is approximately 1:500, and despite aggressive use of statin therapy, there is still a 2-fold excess of coronary heart disease related deaths relative to age-matched controls in this population (Neil et al, 2008). By comparison, the prevalence of homozygous LDL receptor mutation based FH (most commonly referred to as HoFH) is approximately 1:1,000,000 individuals. Many in fact represent compound heterozygotes possessing different mutations on each of the LDL receptor alleles (Goldstein et al, 2001). In large part owing to the extensive longitudinal study of families affected by this condition, and

the founder effect, the geographical prevalence of the specific LDL receptor mutations among homozygous subjects are often well known (Leitersdorf et al, 1989; Leitersdorf et al, 1990). The incidence of major cardiovascular illness among homozygous individuals is even higher than that of affected FH heterozygotes, with events such as myocardial infarction happening by the second decade of life (Goldstein et al, 2001). Due to the rapid and aggressive nature of atherosclerosis in HoFH, it is commonly studied and treated as a disease beginning in childhood and manifesting with untoward morbidity and mortality in affected adults. This also applies to other, even more rare genetic causes of dyslipidemia that fall under the umbrella diagnosis of familial hypercholesterolemia. These conditions include mutations in PCSK9 (dominant-gain of function), Apo B (dominant-loss of function) and ARH (recessive-loss of function).

High-dose statin therapy (and at times even using twice the maximum recommended dose of statin) has reduced both LDL cholesterol (in the range of 10-25%) as well as cardiovascular event rates among subjects with homozygous familial hypercholesterolemia (Raal et al, 1997; Neil et al, 2008). However, the response to therapy has been limited in part by the biology underlying this disease, and possibly by the concomitant elevation of PCSK9 levels that result from statin treatment (Lakoski et al, 2009). In addition to maximal medical therapy, some subjects have been placed on a biweekly to weekly schedule of lipid apheresis, a process similar to hemodialysis where LDL cholesterol is physically removed from their circulation. Though a helpful tool in the treatment of HoFH, this procedure is cumbersome, expensive, and generally difficult to access. Furthermore, the reduction in LDL-C seen with apheresis is transient, as LDL cholesterol begins to reaccumulate after each session.

Because, the majority of LDL receptor mutations in HoFH subjects result in impaired LDL receptor function (as opposed to the receptor null phenotype), therapies which further support LDL cholesterol clearance through LDL-receptor mediated endocytosis can be expected to reduce LDL cholesterol beyond levels seen with existing pharmacologic therapies. Thus therapeutics like AMG 145 may provide a significant survival and quality of life advantage to this population of subjects. The large unmet medical need remaining in the HoFH population may in part be addressed by augmenting existing lipid lowering therapies with AMG 145. Similarly, there is also a high likelihood that the other rare causes of FH will benefit from therapies AMG 145.

This is especially true for subjects with PCSK9 gain of function mutations, as AMG 145 is an antibody designed to block the function of PCSK9.

2.2 AMG 145 Background

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

AMG 145 is a fully human monoclonal immunoglobulin (Ig) G2 that binds specifically to human PCSK9 and prevents the interaction of PCSK9 with LDLR. Details of the biochemistry, nonclinical pharmacology, nonclinical pharmacokinetics (PK), and nonclinical toxicology with AMG 145 are contained in the **Evolocumab (AMG 145)** 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

cynomolgus monkeys and in hamsters, in vivo administration of AMG 145 resulted in reduced serum lipoprotein cholesterol levels in a dose-dependent manner. Based on a comprehensive package of PK, pharmacodynamics (PD), and toxicology studies (Investigator's Brochure, 2013), a program to develop AMG 145 as a treatment for dyslipidemia was initiated.

2.2.1 First-in-Human (FIH) Study 20080397

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

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

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

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

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

and the dose of AMG 145, or between the subject incidence of adverse events and the route of administration of AMG 145 (SC versus IV).

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

For further details on study 20080397, please consult the Investigator's Brochure (2013).

2.2.2 Multiple-dose Phase 1b Study 20080398

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

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

Treatment-emergent adverse events were reported by 28 of 43 subjects (65%) receiving AMG 145 and 9 of 14 subjects (64%) receiving placebo. No adverse events were reported as serious, and no subjects discontinued the study due to an adverse event. There were no deaths on study. No relationship was apparent between the subject incidence of treatment-emergent adverse events and the dose of AMG 145 or between

the subject incidence of treatment-related adverse events and the dose of AMG 145. There were no trends indicative of clinically important effects of AMG 145 on hepatic function tests, ECGs, or vital signs. One subject who received 140 mg AMG 145 Q2W for 6 weeks with a high-dose statin tested positive for AMG 145-binding antibodies at day 29, but was negative for neutralizing antibodies.

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

2.2.3 Completed Phase 2, 12 Week, Lipid Lowering Studies

The following four 12-week LDL-C lowering study studies have been completed:

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

2.2.4 Ongoing Phase 2, Longer-term, or Special Population Studies

- Study 20110109 (planned N = 905; enrollment complete) which is a randomized, double-blind, placebo-controlled study evaluating safety, tolerability, and efficacy of AMG 145 compared with placebo for 52 weeks in hypercholesterolemic subjects
- Study 20110110 (planned N ~ 1325; enrollment complete) which is a multicenter, controlled, open-label extension (OLE) study to assess the long-term safety and efficacy of AMG 145 that includes subjects from the aforementioned phase 2 studies.
- Study 20110231 (N = 310; enrollment complete), which is a double-blind, randomized, placebo-controlled, multicenter study to evaluate tolerability and efficacy of AMG 145 on LDL-C in combination with stable statin therapy in Japanese subjects with hypercholesterolemia and high cardiovascular risk
- Study 20110233 (planned N = 59; enrollment ongoing) which is a 2-Part, Phase 2/3 study to assess the safety, tolerability and efficacy of AMG 145 in subjects with homozygous familial hypercholesterolemia

2.2.4.1 Phase 2 Aggregate Interim Analysis Results

On 15 March 2012, a protocol-specified interim analysis was performed to facilitate phase 3 dose selection via an assessment of the safety, tolerability, and efficacy of 6 AMG-145-dosing regimens from the ongoing phase 2 program. This interim analysis included safety, tolerability, and efficacy data from 5 studies (Table 1). The results of the interim analysis were corroborated in the final analysis of phase 2 data. Further result details for these studies can be found in the AMG 145 Investigator's Brochure. Primary analysis results of 2 of the studies (20101154, 20101155) have been published (Koren et al, 2012; Giugliano et al, 2012).

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

	20101154	20101155	20090158	20090159	20110110
Trial Name	MENDEL	LAPLACE-TIMI 57	RUTHERFORD	GAUSS	OSLER
Sample Size	405	600	150	150	>375
Patient Population	Subjects not on statins	Subjects on statins ± ezetimibe	Subjects with HeFH	Subjects with statin intolerance	Subjects from studies 20101154, 20101155, 20090158, 20090159
Fasting LDL-C	≥ 100 mg/dL and < 190 mg/dL	≥ 85 mg/dL	≥ 100 mg/dL	≥ 100 mg/dL; Not at LDL-C goal (NCEP ATP III)	≥ 75 mg/dL
Randomization Ratio	9 arms, equal allocation	8 arms, equal allocation	3 arms, equal allocation	5 arms, equal allocation	2:1
Treatment Duration	12 weeks	12 weeks	12 weeks	12 weeks	5 years
Treatment Groups	70mg Q2W	70mg Q2W			
	105mg Q2W	105mg Q2W			
	140mg Q2W	140mg Q2W			
	Placebo Q2W	Placebo Q2W			
	280mg Q4W	280mg Q4W		280mg Q4W	
	350mg Q4W	350mg Q4W	350mg Q4W	350mg Q4W	
	420mg Q4W	420mg Q4W	420mg Q4W	420mg Q4W	420mg Q4W + SOC
	Placebo Q4W	Placebo Q4W	Placebo Q4W		SOC Only
	Ezetimibe QD			Placebo Q4W + Ezetimibe QD	
				420mg Q4W + Ezetimibe QD	

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

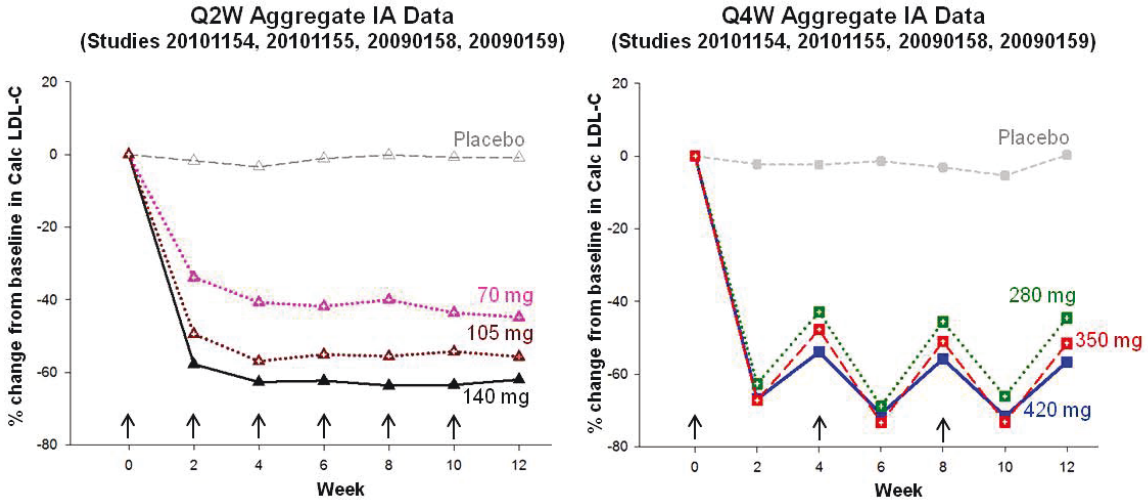
As of the snapshot dates, 606 subjects from the 4 phase 2 parent studies had rolled over into the long-term extension study (20110110). The mean time on study for subjects in study 20110110 was 1.4 months plus an additional three months from the parent study. This translates into approximately 31% and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

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

2.2.4.2 Phase 2 Aggregate Interim Analysis Efficacy Results

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

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



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

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

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

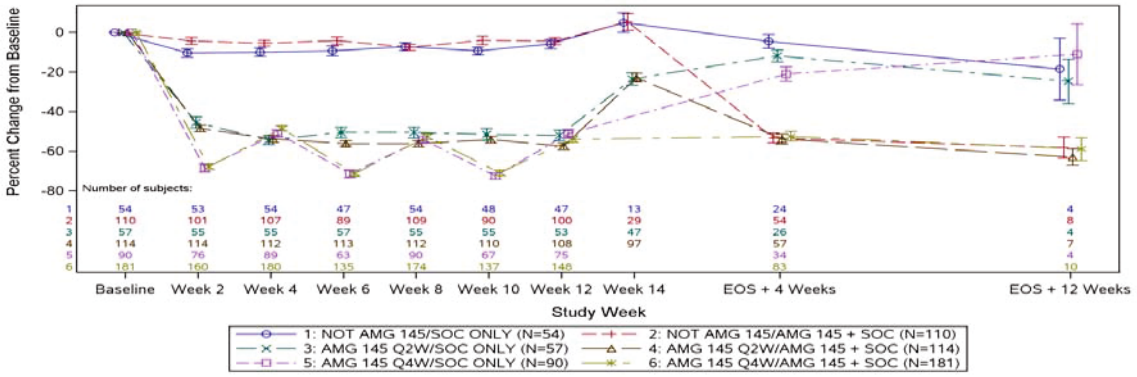
	Treatment Difference (Estimate) Relative to Placebo[a, b]					
	AMG 145 Q2W vs Placebo Q2W			AMG 145 Q4W vs Placebo Q4W		
Lipid parameter	AMG 145 70 mg (N = 43)	AMG 145 105 mg (N = 43)	AMG 145 140 mg (N = 42)	AMG 145 280 mg (N = 41)	AMG 145 350 mg (N = 41)	AMG 145 420 mg (N = 42)
Calc LDL-C	-40.96	-50.53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

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

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

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

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



2.2.4.4 Aggregate Safety Data From Completed Phase 2 Studies

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

- In completed phase 2 studies, subjects treated with AMG 145 (n = 961) experienced a higher overall incidence of treatment emergent adverse events compared with placebo (n = 301) (57% and 48%, respectively); however, there was no relationship between the dose or dosing frequency of AMG 145 and the incidence of treatment emergent adverse events.
- In completed phase 2 studies, adverse events with a subject incidence of at least 2% in the AMG 145 group and exceeding the placebo incidence by at least 1% were as follows (AMG 145, placebo): nasopharyngitis (8.2%, 6.6%), myalgia (2.7%, 1.0%), and nausea (2.7%, 1.7%).
- In completed phase 2 studies, the overall incidence of serious adverse events was similar between the AMG 145 and placebo groups (2.1% and 1.3%, respectively). No individual serious adverse event was reported in more than 2 (0.2%) subjects treated with AMG 145 in these studies.

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

2.3 Rationale

This study is being conducted to gather information on the long-term safety of AMG 145 and to provide subjects that participated in 20110233 or another Amgen qualifying study with an opportunity to receive treatment **with** AMG 145 **for up to approximately 5 years**. In addition, subjects with severe familial hypercholesterolemia will also be included (see Section 4.1 inclusion criteria). Subjects enrolled in this study will have a high unmet medical need and almost all have failed to reach goal LDL-C levels with current available therapies. For these underserved individuals, the opportunity to receive open label AMG 145 will provide the subject with an additional therapeutic option for LDL-C lowering. Study participation will be stopped for subjects that do not demonstrate minimal benefit while receiving optimal dosing of AMG 145. Additional detail can be found in Section 6.1.1. Treatment of subjects with severe familial hypercholesterolemia will then be evaluated on an individual basis, using achieved LDL-C reduction as a basis for continuing the study.

2.4 Clinical Hypotheses

Long-term exposure of AMG 145 will be safe and well tolerated in subjects with severe familial hypercholesterolemia.

3. EXPERIMENTAL PLAN

3.1 Study Design

A multicenter, open-label study designed to assess the long-term safety, tolerability, and efficacy of AMG 145. The study will continue **until the date when the last subject has completed the assessments for week 260 (approximately 5 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**. Central laboratory results of the lipid panel, ApoA1, ApoB, Lp(a), and hsCRP will not be reported to the investigator prior to week 8 for subjects coming from a blinded (or blinded portion) of a parent study, since some laboratory results may inadvertently unblind investigators to treatment assignment in the parent study, until results from the parent study are made publically available.

PCSK9 levels will be blinded until week 4. Vitamin E samples will only be blinded to investigators and subjects in the first 96 weeks of the study. Study participation may be stopped for subjects that do not demonstrate minimal benefit (ie, subjects that have less than 5% LDL-C reduction from baseline while on therapy). The study includes adjudication of deaths and specific cardiovascular events potential endpoints (PEPs) by an independent Clinical Events Committee (CEC).

Investigators should not perform local testing of these analytes.

The study endpoints are defined in Section 10.1.

3.2 Number of Centers

It is anticipated that approximately 50 centers will participate in the study.

3.3 Number of Subjects

The approximate total number of subjects expected to participate in this study is 310.

3.4 Study Duration for Participants

The study will continue for **260 weeks (approximately** 5 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**.

3.5 End of Study

The study will **continue until the date when the last subject has completed the assessments for week 260 (approximately 5 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 diagnosed with severe familial hypercholesterolemia.

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. Subjects with homozygous familial hypercholesterolemia who meet the inclusion and exclusion criteria of study 20110233 may enroll after study 20110233 is closed.

Before any study specific procedures informed consent must be obtained.

4.1 Inclusion Criteria

4.1.1 Participated in a qualifying AMG 145 parent protocol and have a diagnosis of familial hypercholesterolemia. Subjects must not have experienced an IP treatment related serious adverse event that led to IP discontinuation during their participation in the qualifying AMG 145 parent study, or

Subjects that have not participated in a qualifying AMG 145 parent protocol must also meet all of the following inclusion criteria:

4.1.2 Are male or female ≥ 12 to ≤ 80 years of age

4.1.3 Have a diagnosis of familial hypercholesterolemia

4.1.4 Are on a stable low-fat diet and taking pre-existing lipid-lowering therapies (such as statins, cholesterol-absorption inhibitors, bile-acid sequestrants or nicotinic acid, or combinations thereof) for at least 4 weeks, with fasting central lab LDL cholesterol concentration and meet the following LDL-C values based on risk factor status (NCEP ATPIII risk categories Grundy et al, 2004):

- ≥ 100 mg/dL (2.6 mmol/L) for subjects with diagnosed CHD or CHD risk equivalent (includes clinical manifestations of noncoronary forms of atherosclerotic disease [peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease], diabetes, and 2+ risk factors with 10-year risk for hard CHD >20%). Risk factors include cigarette smoking, hypertension (**blood pressure [**BP**]** ≥ 140/90 mmHg or on antihypertensive medication), low HDL cholesterol (< 40 mg/dL), family history of premature CHD (CHD in male first-degree relative < 55 years of age; CHD in female first-degree relative < 65 years of age), and age (men ≥ 45 years; women ≥ 55 years) or
- ≥ 130 mg/dL (3.4 mmol/L) for subjects without diagnosed CHD or CHD risk equivalent or
- There is **n**o LDL-C entry requirement for apheresis subjects - because their LDL-C values fluctuate and may not be representative of their overall LDL-C burden.

4.1.5 Fasting triglycerides ≤ 400 mg/dL (4.5 mmol/L) by central laboratory at screening

4.1.6 Bodyweight must be 40 kg or greater at screening for subjects less than 18 years of age

4.2 Exclusion Criteria

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

4.2.1 Female subject who has either (1) not used an acceptable method(s) of birth control for at least 1 month prior to screening or (2) is not willing to use such a method during treatment with AMG 145 (IP) and for an additional 15 weeks after the end of treatment with AMG 145 (IP) unless subject is sterilized or postmenopausal;

- Menopause is defined as 12 months of spontaneous and continuous amenorrhea in a female ≥ 55 years old or 12 months of spontaneous and continuous amenorrhea with a follicle-stimulating hormone level > 40 IU/L (or according to the definition of "postmenopausal range" for the laboratory involved) in a female < 55 years old unless the subject has undergone bilateral oophorectomy
- Acceptable methods of preventing pregnancy include sexual abstinence, surgical contraceptive methods (vasectomy or bilateral tubal ligation), use of hormonal birth control methods (pills, shots, implants or patches), intrauterine devices (IUDs), or two (2) barrier methods (each partner must use one barrier method) with spermicide – males must use a condom with spermicide; females must choose either a Diaphragm with spermicide, OR or Cervical cap with spermicide, OR Contraceptive sponge with spermicide.

4.2.2 Subject is pregnant or breastfeeding, or planning to become pregnant or breastfeed during treatment with AMG 145 **(IP)** and for an additional 15 weeks after the end of treatment with AMG 145 (IP)

4.2.3 Unreliability as a study participant based on the investigator's (or designee's) knowledge of the subject (eg, inability or unwillingness to adhere to the protocol)

4.2.4 Experienced a treatment related serious adverse event that led to IP discontinuation in the AMG 145 parent protocol

4.2.5 Disorder that would interfere with understanding and giving informed consent or compliance with protocol requirements

4.2.6 Have an unstable medical condition, in the judgment of the investigator.

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

In addition, all subjects that undergo screening procedures will be ineligible for the study if they fulfill any of the following criteria:

4.2.8 Use of Mipomersen or Lomitapide within 5 months of screening

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

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

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

4.2.12 Uncontrolled hypertension defined as sitting systolic **BP** (SBP) > 180 mmHg or diastolic BP (DBP) > 110 mmHg, confirmed with repeat measurement

4.2.13 Subject requires uptitration of their current statin dose within 4 weeks of screening (these subjects can be uptitrated and rescreened one month later)

4.2.14 Moderate to severe renal dysfunction, defined as an estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m^2 at screening

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

4.2.16 Unexplained CK > 5 times the ULN at screening, confirmed by a repeat measurement at least 1 week apart

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

4.2.18 Diagnosis of deep vein thrombosis or pulmonary embolism within 3 months prior to screening

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

4.2.20 Subject has previously received a non-AMG 145 investigational therapy to inhibit PCSK9

4.2.21 Currently enrolled in a non-AMG 145 investigational device or drug study, or less than 30 days since ending a non-AMG 145 investigational device or drug study(s), or receiving other investigational agent(s)

4.2.22 Known sensitivity to any of the products to be administered during dosing

5. SUBJECT ENROLLMENT

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

All subjects that have not participated in an AMG 145 parent protocol who enter this study will be assigned a unique subject identification number. All subjects who enter the study after finishing a parent study will be assigned the same unique subject identification number from the parent study, except subjects that participated in phase 1 studies.

6. TREATMENT PROCEDURES

AMG 145 will be the investigational product in this study.

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

6.1 AMG 145

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

Initial Formulation:

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

AMG 145 should be stored protected from light and according to the storage and expiration information (where required) provided on the label. AMG 145 should be thawed per the instructions provided in the IPIM. Vials should be checked for cracks or damage that may occur if the thawing process is not performed properly. Damaged product should not be administered. Further details are provided in the IPIM.

New Formulation:

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

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, CCI mM acetate, CCI % (w/v) polysorbate 80, pH CCI.

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

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

The lot number of IP is to be recorded on each subject's Drug Administration eCRF.

6.1.1 Dosage, Administration, and Schedule

All investigational product (IP) will be administered at the investigator site by a qualified staff member during site visits or at home or other location by subjects (or designee, which may include a qualified health care professional) between on-site visits. The date, time, and volume of AMG 145 will be collected and recorded on the individual subject's eCRF for doses administered at the study site. IP administration by SC injection at each on-site visit must be done after vital signs, ECG, and blood draw procedures, if applicable.

IP will be administered either at 6 mL via vials and syringes or, depending on device availability at sites; at 3ml via 3 prefilled autoinjectors/pens or at 3.5 ml via 1 personal injector. The 6 mL dose can be split (eg, 3 injections at 2 mL each) and administered into different injection sites. The SC injections should be administered in a consecutive

fashion with all injections completed within 30 minutes. For further details regarding the injection procedures, the IPIM should be consulted.

Parent Study 20110233 Subjects:

Subjects coming from parent study 20110233 will initiate this study with 420 mg SC monthly (QM) dosing. After 12 weeks of 420 mg SC QM, if observed LDL-C reduction is > 5% and PCSK9 levels have been shown to be maximally suppressed (ie, < 100 ng/mL), subjects may continue QM dosing for the duration of the study. In subjects with PCSK9 levels > 100 ng/mL assessed at the end of a 420 mg SC QM dosing interval (eg, assessed at weeks 4 and/or 8), dosing may be changed to 420 mg SC Q2W at the week 12 visit. If the observed LDL-C reduction from baseline is < 5% and PCSK9 levels have been shown to be maximally suppressed (ie, < 100 ng/mL) the subject may be withdrawn from the study at week 12. Depending on the subject response to 420 mg SC Q2W dosing, these subjects may continue Q2W dosing, return to QM dosing, or be withdrawn from the study at the week 24 visit.

Apheresis Subjects:

Subjects on apheresis should initiate treatment with 420 mg SC Q2W in this study to correspond with their apheresis schedule. For apheresis subjects initiating this study on 420 mg Q2W dosing, the dosing schedule may be continued or downtitrated to 420 mg QM at the week 12 visit provided there is evidence of sufficient efficacy (LDL-C reduction of > 5% is considered sufficient efficacy for these subjects). Subjects downtitrating to 420 mg QM dosing at week 12 may revert to 420 mg Q2W dosing 12 weeks after the initiation of 420 mg QM or dosing (eg, week 24) if clinically indicated. Dosing changes that do not occur on week 12 or 24 are permitted in cases where apheresis therapy is discontinued by patients. Dose adjustments after week 24 are discouraged.

Other Subjects:

Subjects that are not receiving apheresis will be provided with AMG 145 420 mg SC QM. Similar to subjects coming from Study 20110233, an option of 420 mg SC Q2W will also be available to other subjects pending observed LDL-C levels and insufficient suppression of PCSK9 (> 100 ng/mL) at the end of a dosing interval (eg, assessed at week 4, 8, etc). Dosing changes should occur at week 12 or 24 if clinically indicated. Dosing changes after week 24 are discouraged.

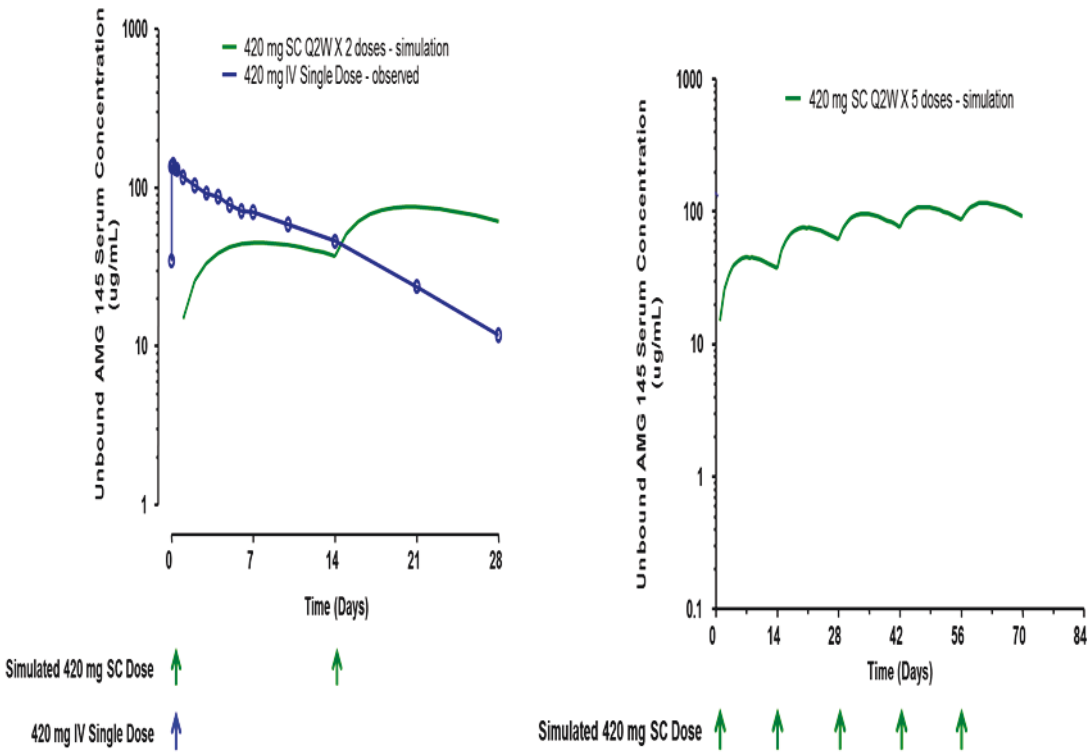
Any other dosing changes must be discussed with the medical monitor. Finally, subjects who have known insufficient efficacy (recommended to be considered as LDL-C reduction < 5% after an adequate trial of AMG 145 dosing) may be removed at either the

week 12 or 24 study visit pending a final risk/benefit discussion with Amgen's medical monitor.

Support for Q2W Dosing with 420 mg:

In a repeat dose (QW, SC) 6 month toxicology study conducted in the cynomolgus monkey, no evidence of toxicity was observed up to the highest dose tested, 300 mg/kg. Based on AUC, this dose level provides a 156-fold exposure margin relative to a 420 mg Q2W clinical dose, respectively.

Study 20080397 also included testing of single dose AMG 145 420 mg IV. Based on the almost 2-fold greater exposure for IV dosing (compared to SC), we anticipate that the C_{max} and AUC over the dosing interval at steady-state to be similar between the two dosing regimens (shown in the left panel of the figure below).



In addition, AMG 145 concentrations are not predicted to exceed the current projection at steady-state over an extended period of 420 mg Q2W dosing (right panel).

The 420 mg dose was selected because of the LDL-C response to this dose observed in other studies, as well as the resulting PCSK9 levels. Additionally, pharmacologic LDL-C reduction in severe familial hypercholesterolemia is known to be extraordinarily difficult to manage due in large part to the fundamental biology underlying the illness, and

current data suggests that subjects with homozygous familial hypercholesterolemia will require more frequent dosing to adequately suppress PCSK9 levels. Thus it is likely that daily doses of AMG 145 greater than those previously administered will provide a substantive therapeutic benefit in this patient population. Details of preparing and administering AMG 145 are included in the IPIM provided by Amgen prior to the start of the study.

After IP administration at each dosing site visit, subjects should be kept for observation for at least 30 minutes before being discharged. The effects of overdose of AMG 145 are not known. All overdose occurrences must be documented, and corresponding AEs recorded on the appropriate eCRF page and in source documents.

Self-administration, defined as SC administration of AMG 145 by the subject, designee or a qualified health care professional will be permitted in a non-site setting (eg, at home or at a location where a qualified health care professional is available). Prior to week 24, subjects that are treated with AMG 145 420 mg administered SC Q2W may self-administer study drug between visits. Starting at the week 24 visit, all subjects will have the option of AMG 145 self-administration. The subject (or designee, if not a qualified healthcare professional) must have demonstrated competency at administration of SC injections before self-administration is permitted: the first self-administered dose by the subject (or designee, if not a healthcare professional) must be administered at the site under the supervision of a healthcare provider. For subjects that prefer not to self-administer AMG 145 or for subjects that will receive AMG 145 during lipid apheresis, AMG 145 may be administered at the site. The dosing schedule is described by a schema in the protocol synopsis.

6.1.2 Dosage Adjustments

As stated in Section 6.1.1 above, doses may be either uptitrated or downtitrated depending on the starting dose on Day 1. If an investigator wants to make a dose adjustment they must contact the medical monitor and obtain approval prior to doing so. All dose adjustments must be clearly documented and recorded on the appropriate eCRF page and in source documents.

Subjects who are Late for a Scheduled Dose of Investigational Product

Doses Except the Last Dose

Administration of IP should occur within the visit window for each scheduled visit. IP should not be administered within less than 7 days of a previous dose. If a subject arrives for a visit outside the above IP window the dose should not be administered, but all other study procedures should be conducted. These subjects will receive their next SC IP administration as previously scheduled.

Last Dose

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

Subjects who Miss a Scheduled Dose of Investigational Product Completely

Doses Except the Last Dose

Subjects who completely miss a scheduled visit or IP administration will continue in the study and receive scheduled study drug at the next scheduled visit. If a dose is missed between quarterly visits, the dose should not be administered within 7 days of the previous dose or within 7 days of the next scheduled dose.

Last Dose

Subjects who completely miss the last scheduled IP administration will continue in the study and should return for an unscheduled visit as soon as possible to receive study drug. If the last dose has not been received by the EOS visit, it should be omitted entirely.

6.1.3 Criteria for Withholding of Investigational Product

Reports from the central laboratory after each visit must be reviewed as soon as possible after receipt and before the next administration of IP. If any of the criteria below are met for withholding IP, statin, or other applicable background lipid therapy, the subject must be instructed to stop the applicable treatment and an additional visit must be scheduled for the required laboratory evaluations. If a subject is experiencing elevations of laboratory values below (Sections 6.1.3.1 and 6.1.3.2) and is receiving other lipid therapies that may result in such elevations, eg, ezetimibe, fenofibrate, or niacin, the additional therapies should also be evaluated for a potential role in these

elevations and considered for discontinuation. Fenofibrate, ezetimibe, or niacin can result in elevation of CK or liver function tests. If a subject experiences elevations in triglycerides > 500 mg/dL (5.65 mmol/L) and is concomitantly receiving a bile acid binding resin, the bile acid binding resin should be evaluated for discontinuation.

6.1.3.1 Elevation of Creatine Kinase (CK)

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

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

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

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

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

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 signs/symptoms of hepatitis may meet the criteria for withholding of IP, statin, and other applicable lipid background therapy. If the subject

experiences an ALT or AST > 3**x** ULN, then they must be followed as detailed under section on close observation in Appendix B.

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

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

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

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

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

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

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

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

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**(s)** or device**(s)** after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. **This includes drug(s) or device(s) provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.**

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

Medical supplies (eg, syringes, sterile needles, alcohol prep pads), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The Investigator will be responsible for obtaining supplies of these devices.

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

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

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

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

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

6.3 Concomitant Therapy

Prior to week 12, lipid-regulating concomitant medications should not be altered, unless there is a clinically compelling reason for change. The investigator must contact the Amgen medical monitor to discuss such cases on an individual basis. After week 12, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.4. If needed, apheresis will be permitted at any time during the study.

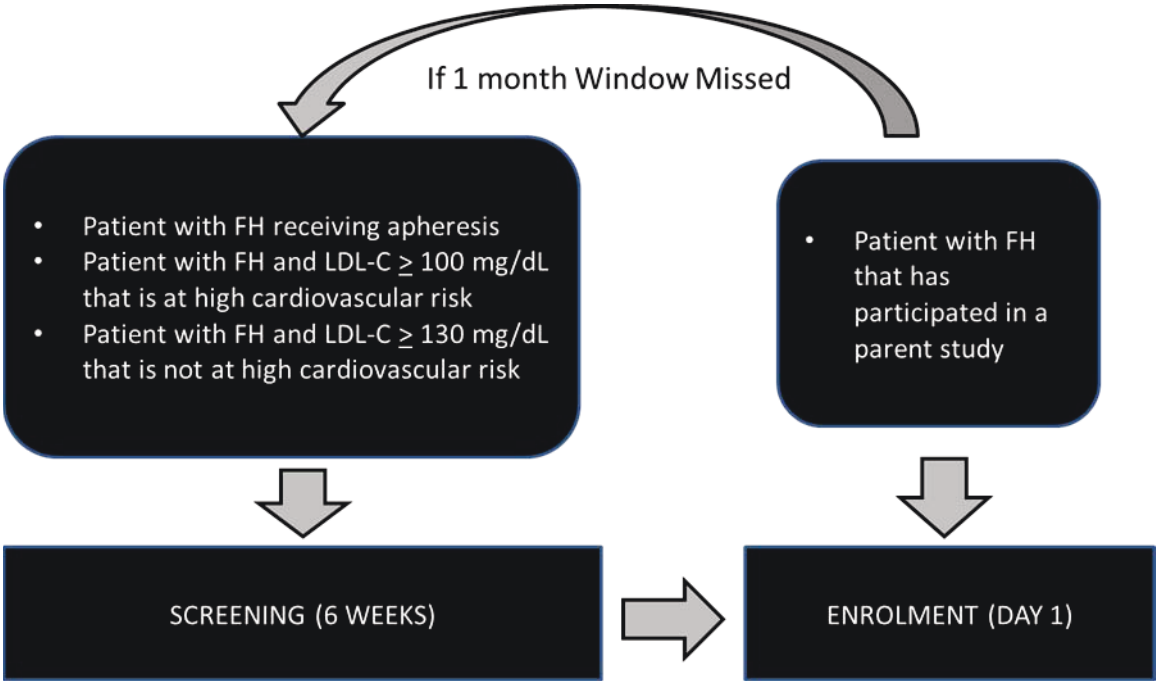
6.4 Excluded Treatments During Study Period

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

7. STUDY PROCEDURES

This will be a multicenter, open-label study to assess the long-term safety, tolerability, and efficacy of AMG 145. For the purpose of this study, a month is defined as 4 weeks and a quarter is defined as 12 weeks.

Subjects that fall within a 1 month window of completing a qualifying parent study do not require screening procedures to be performed; they may be enrolled into the study directly, as outlined in Section 7.1.2. All other subjects must go through the study screening procedures as outlines in Section 7.1.1.



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. Subjects must be fasting for ≥ 9 hours before each study visit where labs are collected. IP should not be administered until all study procedures are completed at each visit. Blood draws for subjects on apheresis (main study and sub-study) will need to occur both before and after apheresis

7.1 General Study Procedures

7.1.1 Screening (for all Non-parent Study Subjects and for Parent Study Rollover Subjects That Have not Completed a Parent Study (EOS/Day 1 Visit) Within the 1 Month Allowable Window)

Subjects who are considered for entry into the study and have the risk and benefits of participating in the study explained will enter screening by signing and dating the informed consent form for this study.

Screening should be completed and the subject randomized or screen failed within 6 weeks of signing the informed consent. The following data will be obtained and procedures performed during screening:

- Written informed consent
- Medical history
- Vital signs (see Section 7.1.3.1): sitting BP, heart rate (HR)
- Body weight
- Physical exam
- Review for AEs/**adverse device effects (ADEs)/**SAEs (AEs possibly related to study procedures and SAEs are collected during screening)
- Concomitant medication
- 12-lead ECG in triplicate using centralized ECG services equipment
- Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, Lp(a), chemistry, coagulation, hematology, PK (PCSK9 only), HbA1c, serum pregnancy (females of childbearing potential only) urinalysis, and FSH (only if required to ensure menopause in a female subject [see exclusion criterion 4.2.18]) by central laboratory *(Note: eGFR will be calculated by the central laboratory and will be provided to the site for eligibility determination)*

In addition, apheresis subjects will have 2 mandatory screening visits (week -2 and week -1). Week -2 will need to occur on an apheresis day in order to obtain baseline lab values (lipids and PCSK9) prior to study entry. Assessments for week -2 can be found above in Section 7.1.1. Serum pregnancy testing and FSH need not be performed for apheresis subjects at week -2. Assessments for week -1 can be found below in Section 7.1.2.3. All other screening procedures may occur at any time during the 6 week screening window.

If a fasting sample could not be obtained at the initial screening visit and the other screening laboratory assessments confirm eligibility for the study, a fasting lipid sample to determine eligibility must be obtained before the planned day 1 visit.

7.1.1.1 Retesting

If, in the investigator's judgment, lab abnormalities are likely to be transient (ie, subject participated in vigorous exercise and CK is elevated immediately afterwards), laboratory tests can be retested. Triglycerides, CK, liver function**,** and other laboratory values can be retested during screening as long as the subject can be evaluated for eligibility and randomized within the allowed screening period. Care should be taken to avoid potential inadvertent unblinding of subjects that have completed a blinded (or blinded portion) parent AMG 145 study. In such cases certain laboratory results such as the lipid panel, hs-CRP**,** and vitamin E may need to be avoided. Further clarification is provided in Sections 7.1.3.3 and 7.1.3.4.

7.1.1.2 Rescreening

Subjects who, in the opinion of the investigator, require major medication changes (ie, statin up-titration, uptitration of blood pressure medications) can be put on a higher dose of medication and rescreened after at least 1 month.

Suitable subjects who are ineligible at the initial screening for other reasons can be re-consented and rescreened at a later time unless they withdraw from screening. There will be a maximum of 2 rescreens per subject.

Rescreened subjects who are re-consented will repeat all screening procedures. Rescreened subjects will maintain the originally assigned subject identification number.

7.1.1.3 Screen Fail

Subjects who fail any of the eligibility criteria during screening or rescreening need to be screen failed in IVRS before they can be re-consented and re-registered in IVRS for rescreening.

7.1.2 Enrollment (EOS Parent/Day 1 OL)

Day 1 for this open-label (OL) study and the end of study visit for the parent study should occur on the same day. All efforts should be made to minimize any time gaps between the parent study EOS and Day 1 in the OL study. The Day 1 OL visit will need to occur within 1 month of the parent EOS or the subject will need to undergo screening procedures (Section 7.1.1) prior to enrollment. The following procedures will be performed during the end of study (EOS) visit in the parent study and at the Day 1 visit for all subjects that completed screening procedures:

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

- Concomitant medications
- Physical exam for subjects that did not undergo screening
- Body weight for subjects that did not undergo screening
- Measurement of height, weight, and Tanner stage for adolescent subjects (see the study glossary for definition of adolescence and Appendix E for guidance on Tanner staging). If Tanner staging cannot be performed on Study Day 1, it should be performed along with height and weight at the next scheduled study visit.
- Documentation of historical assessments of height, weight and Tanner stage for adolescent subjects (see the study glossary for definition of adolescence and Appendix E for guidance on Tanner staging). If documentation of historical assessments cannot be obtained on Study Day 1, it should be done as soon as possible after enrollment
- 12-lead electrocardiogram (ECG) in triplicate using centralized ECG services equipment for subjects that did not undergo screening
- Blood draw for serum pregnancy (females of childbearing potential only) and FSH (for applicable subjects)
- Urinalysis
- Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, chemistry, coagulation, hematology, PK (AMG 145; PCSK9), hsCRP, Lp(a), biomarkers, and anti-AMG 145 antibodies
- IP administration

Day 1 - subjects will have the risks and benefits of participating in this study explained to them. Subjects that meet inclusion/exclusion criteria will need to sign a new OLE informed consent form, if they already have not done so, before AMG 145 study drug is administered at the site.

Below are additional analytes, not collected during the parent study's EOS visit that will need to be collected for all subjects at Day 1:

- Fasting Vitamin E
- HbA1c

7.1.2.1 Weeks 2 and 10 (± 7 Days) Non-parent Subjects Only – Mandatory for All Apheresis Subjects, Optional for Non-apheresis Subjects

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- AEs/**ADEs/**SAEs
- Concomitant medications
- Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, Lp(a), PK (AMG 145) and PCSK9
- Administer IP to subjects (as applicable for Q2W subjects)

7.1.2.2 Weeks 4, 6, 8 (± 7 Days) – for all Subjects

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- AEs/**ADEs/**SAEs
- Concomitant medications
- Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, Lp(a), PK (AMG 145) and PCSK9.
- Administer IP to subjects (At week 6 IP administered only for Q2W subjects).

7.1.2.3 Week -1, and Week 9 (± 2 Days) – for Apheresis Subjects Only

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- AEs/**ADEs/**SAEs
- Concomitant medications
- Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, PK, Lp(a), AMG 145 (week 9 only), PCSK9, and serum pregnancy (females of childbearing potential only) and FSH (only if required to ensure menopause in a female subject [see exclusion criterion 4.2.18]) by central laboratory (for week -1)

7.1.2.4 Interval Visits – All Subjects (Weeks 16 and 20 ± 7 Days)

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- AEs/**ADEs/**SAEs
- Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, Lp(a), PK (AMG 145) and PCSK9
- Concomitant medications
- Administer IP to subjects.

7.1.2.5 Quarterly Visits - All Subjects (Week 12, 24, 36, etc ± 7 Days)

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- Measurement of height, weight, and Tanner stage should be performed every 48 weeks for adolescent subjects (see the study glossary for definition of adolescence and Appendix E for guidance on Tanner staging)
- AEs/**ADEs/**SAEs
- Concomitant medications
- Blood draw for serum pregnancy (performed every 6 months for females of childbearing potential only) **– Additional pregnancy testing may be performed at the discretion of the investigator**
- Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, chemistry, hematology, PK (AMG 145), PCSK9, coagulation, hsCRP, Lp(a), HbA1c, and anti-AMG 145 antibodies
- Blood draw for biomarkers at week 12 only
- Fasting Vitamin E at weeks 12, 24, 48 (year 1), 72, and 96 (year 2)
- Administer IP to subjects. – Please note starting at week 24 subjects will receive a 12 week supply of IP to be self-administered every 2 to 4 weeks, as applicable

7.1.2.6 End of Study (Week 260)/Early Term OL Visit – All Subjects

- Vital signs: sitting blood pressure (BP), heart rate (HR)
- AEs/**ADEs/**SAEs
- Concomitant medications
- Physical exam
- Measurement of, height, weight, and Tanner stage for adolescent subjects (see the study glossary for definition of adolescence and Appendix E for guidance on Tanner staging)
- Body weight
- Blood draw for serum pregnancy (for females of childbearing potential only)
- Blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, chemistry, hematology, PK (AMG 145), PCSK9, coagulation, hsCRP, Lp(a), HbA1c, fasting Vitamin E, and anti-AMG 145 antibodies
- Urinalysis
- 12 Lead ECG in triplicate using centralized ECG services equipment

7.1.3 Standardization of Study Procedures

7.1.3.1 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.

7.1.3.2 Blood Sample Use

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

Amgen may do additional testing on the remaining samples (ie, residual and back-up) to investigate and better understand hypercholesterolemia metabolic disorders, the dose response and/or prediction of response to AMG 145, characterize antibody response,

and characterize aspects of the molecule (eg, metabolites). Results from this analysis will be documented and maintained, but may not be reported as part of this study.

7.1.3.3 Lipid Measurements

Investigators and staff involved with this trial should remain blinded to locally obtained lipid panels until the week 8 visit for all subjects that transition from an ongoing blinded (or blinded portion) parent study into this study, in order to avoid potential unblinding of the ongoing parent study.

If a lipid panel is drawn during the first 8 weeks, all reasonable steps must be undertaken to avoid informing the subject and study personnel of the results.

7.1.3.4 Laboratory Assessments

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

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

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

Table 3. Analyte Listing

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

Central laboratory results of the lipid panel, ApoA1, ApoB, Lp(a), and hsCRP will not be reported to the investigator prior to week 8 for subjects coming from a blinded (or blinded portion) of a parent study, since some laboratory results may inadvertently unblind investigators to treatment assignment in the parent study. Subjects coming from a blinded (or blinded portion) parent study will have AMG 145 and PCSK9 levels blinded until week 4 since some laboratory results may inadvertently unblind investigators to treatment assignment in the parent study. Vitamin E samples will be blinded to investigators and subjects in the first 96 weeks of the study. Investigators should not perform local testing of these analytes during this time.

7.1.3.5 Tanner Staging (Sexual Maturity Ratings)

Tanner staging is widely used to assess physical development during puberty in 5 stages (from preadolescent to adult). Also known as Sexual Maturity Ratings (SMRs), Tanner stages are a way of assessing the degree of maturation of secondary sexual characteristics (see Appendix E for guidance). The developmental stages of the adolescent's sexual characteristics will be rated and recorded separately (ie, one stage for pubic hair and one for breasts in females, one stage for pubic hair and one for

genitals in males), because these characteristics may differ in their degree of maturity. For adolescent subjects (as defined in the study glossary), Tanner staging should continue to be performed yearly (every 48 weeks) throughout the study. If Tanner staging cannot be performed on Study Day 1, it should be performed at the next scheduled study visit (along with height and weight), and then every 48 weeks starting at the week 48 visit.

For adolescent subjects, in addition to prospective assessments of Tanner stage, height, and weight, historical assessments (ie, including pre-study measurements) will be recorded. Measurements of, height, weight and Tanner stage made at age 8 years or older that are recorded in the patient's chart should be documented in the appropriate eCRF(s).

7.2 Antibody Testing Procedures

Blood samples will be collected quarterly during the first year and yearly thereafter from all subjects for the measurement of anti-AMG 145 binding antibodies. All subjects who have received at least 1 administration of AMG 145 will have samples assayed for binding and, if positive, neutralizing antibodies. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity**,** and presence of immune complexes. Sites will be notified of any positive neutralizing antibody results to AMG 145. If results are not provided, no neutralizing antibodies to AMG 145 have been detected. Additional blood samples may be obtained to rule out anti-AMG 145 antibodies during the study. Subjects who test positive for neutralizing antibodies to AMG 145 at the final scheduled study visit will be asked to return for additional follow-up testing. This testing should occur approximately every 3 months starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable or (2) the subject has been followed for a period of at least 1 year (± 4 weeks). More frequent testing (eg, every month) or testing for a longer period of time may be requested in the event of safety-related concerns. Follow-up testing will not be required where it is established that the subject did not receive AMG 145. All follow-up results, both positive and negative will be communicated to the sites.

7.3 Pharmacokinetic Sampling

7.3.1 All Subjects

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

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

7.4 Biomarkers Development Studies

7.4.1 Biomarker Sample Collection

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

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

The samples collected will not be suitable for any DNA or other genetic testing and it is specifically stated that these specimens will not be used for this purpose.

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

7.4.2 Sample Storage and Destruction

The biomarker samples and any other components from the cells may be stored for up to 20 years from the end of the study to research scientific questions related to hypercholesterolemia, metabolic disorders, and/or AMG 145. The subject retains the

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

8. REMOVAL AND REPLACEMENT OF SUBJECTS

8.1 Removal of Subjects

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

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

Subjects may decline to continue receiving IP or other protocol-required procedures at any time during the study. If this occurs, the investigator will discuss with the subject appropriate procedures for discontinuation from IP or other protocol-required procedures and should encourage the subject to continue with collection of data, including endpoints and adverse events. These subjects, as well as those who have stopped receiving IP or other protocol-required procedures for other reasons (eg, investigator or sponsor concern) should continue the schedule of study observations. If the subject is unable or

unwilling to continue the schedule of observation, the investigators should clarify what type of follow-up the subject is agreeable to: in person, by phone/mail, through family/friends, in correspondence/communication with other physicians, and/or from review of the medical records.

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

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

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

8.2 Replacement of Subjects

There will be no replacement of subjects.

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition (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 signing informed consent 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 [and/or toxicity per protocol],
- Assessment of relatedness to the device (prefilled AI/Pen or Personal Injector),
- Assessment of relatedness to investigational product (AMG 145) **and/or any study-mandated activity and/or procedure,** and
- Action taken.

The adverse event grading scale used will be the N**ational** C**ancer** I**nstitute** Common Terminology Criteria for AEs (**NCI-**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 **IP (**AMG 145**)**. This relationship is indicated by a “yes” or “no” response to the question: Is there a reasonable possibility that the event may have been caused by AMG 145?

The investigator must assess whether the adverse event is possibly related to the prefilled AI/Pen or Personal Injector used to administer IP. The relationship is indicated by a “yes” or “no” response to the question: Is there a reasonable possibility that the event may have been caused by the device?

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

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

or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) should be recorded as the adverse event.

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

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

9.2 Serious Adverse Events

9.2.1 Definition of Serious Adverse Events

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

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

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

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

If adverse events correspond to Grade 4 "life threatening" CTCAE grading scale criteria (eg, laboratory abnormality reported as grade 4 without manifestation of life threatening status), it will be left to the investigator's judgment to also report these abnormalities as

serious adverse events. For any adverse event that applies to this situation, comprehensive documentation of the event's severity status must be recorded in the subject's medical record.

9.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 days after the last dose of AMG 145 or EOS, whichever is later, are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the applicable 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 serious adverse event must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the applicable Serious Adverse Event Report Form. See Appendix C for a sample of the Serious Adverse Event Report Form.

The investigator must assess whether the serious adverse event is possibly related to IP **(**AMG 145**)**. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by AMG 145?

The investigator must assess whether the serious adverse event is possibly related to the prefilled AI/Pen or Personal Injector used to administer IP. The relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the device?

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

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

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

If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen. To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements

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

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

9.3 Pregnancy and Lactation Reporting

If a pregnancy occurs in a female subject, or a male subject **fathers a child**, while the subject is taking **AMG 145** and for an additional 15 weeks after the **last dose of** AMG 145, report the pregnancy to Amgen as specified below.

The pregnancy should be reported to Amgen's **G**lobal **Patient Safety** within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix D). **Amgen's Global Patient Safety** will seek to **obtain pregnancy and birth outcome information**.

If a lactation case occurs while a female subject is taking **AMG 145** and for an additional 15 weeks after the **last dose of** AMG 145**,** report the lactation case to Amgen as specified below.

Any lactation case should be reported to Amgen's **G**lobal **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 treatment emergent adverse events

10.1.2 Secondary Endpoints

- Percent change in LDL-C from baseline at each scheduled visit
- Percent change in non-HDL-C from baseline at each scheduled visit
- Percent change in Lp(a) from baseline at each scheduled visit
- Percent change in ApoB from baseline at each scheduled visit
- Percent change in total cholesterol/HDL-C ratio from baseline at each scheduled visit
- Percent change in ApoB/ApoA1 ratio from baseline at each scheduled visit
- Response rate of subjects with 15% or greater reduction in LDL-C by scheduled visit

10.1.3 Exploratory Endpoints

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

Lipid and other efficacy laboratory parameters:

- Percent change from baseline at each scheduled visit in
  - Total cholesterol
  - VLDL-C
  - HDL-C
  - ApoA1
  - Triglycerides

- Change from baseline at each scheduled visit in the following parameters:
  - LDL-C
  - Total cholesterol
  - non-HDL-C
  - ApoB
  - Total cholesterol/HDL-C ratio
  - ApoB/ApoA1 ratio
  - VLDL-C
  - HDL-C
  - ApoA1
  - Triglycerides
  - Lp(a)
  - PCSK9

Pharmacokinetics Endpoints

- Serum concentration of AMG 145 and PCSK9 at selected time points

10.1.4 Analysis Set

The evaluable analysis set (EAS) includes all subjects enrolled in this study. This analysis set will be used for all analyses.

10.1.5 Baseline Covariates

Baseline covariates include, but are not limited to:

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

Subject's mutation status and apheresis status at baseline may be applied for subgroup analysis depending on the distribution of the subjects.

10.2 Sample Size Considerations

An approximate total of 310 subjects will enroll into this study such that the long-term safety, tolerability and efficacy of AMG 145 among subjects with severe familial hypercholesterolemia can be assessed.

The 95% confidence intervals for an approximate 5% incidence rate under various sample sizes using the binomial distribution for particular adverse events are provided in the table below:

Sample size	Total Number of Subjects Reporting Adverse Event	Estimated Adverse Event Incidence Rate	
		Incidence Rate	95% Confidence Interval
300	15/300	5%	(0.03, 0.07)
310	16/310	5.2%	(0.03, 0.08)
320	16/320	5%	(0.03, 0.07)

10.3 Interim Analysis and Early Stopping Guidelines

There will be periodic interim analyses performed during this 5 year open label 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 study are descriptive in nature. No statistical inference or missing value imputation is planned. **The final analysis for the study will be performed at the end of the study (defined as when the last subject has completed the assessments for week 260 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).**

Subject disposition, demographics and baseline characteristics will be summarized.

Summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation or standard error, minimum, and maximum. For categorical variables, the frequency and percentage will be given.

Subjects will be summarized according to whether subject rolled over from a parent study and their treatment allocation from a parent study when applicable.

For efficacy analyses, the baseline value is defined as:

- Subjects that participated in a qualifying parent study (including 20110233) and with baseline data from the parent study: the baseline is defined as the baseline of the qualifying parent study
- Subjects not enrolling from a parent study or without baseline data from the parent study: the baseline is defined as the baseline in this study

For non-efficacy analyses, baseline values for all subjects are defined as this study baseline values.

The percent change and absolute change from baseline in laboratory based exploratory endpoints at each scheduled visit will be summarized. Summaries of vital signs, ECGs, and anti-AMG 145 antibodies will be also provided.

10.4.2 Analysis of Key Study Endpoints

10.4.2.1 Primary Endpoint Analyses

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

10.4.2.2 Secondary Endpoint Analyses

Secondary endpoints will be summarized at each scheduled visit. Descriptive statistics will be presented.

10.4.2.3 Exploratory Safety Analyses

Safety Laboratory Parameters

Laboratory parameters will be summarized using descriptive statistics at each measurement time point. 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 (starting of the exposure of AMG 145) to the end of study.

Vital Signs

Vital signs will be summarized using descriptive statistics at each measurement time point.

Electrocardiogram

RR, PR, QRS, QT, and QTc intervals will be summarized at each measurement time point. Frequency tables for maximal QTc and maximal change in QTc at post-dose period using the categories suggested in the ICH E14 guidelines will be provided by treatment group.

PK Parameters

Summary statistics of PK concentration and PCSK9 will be provided.

Anti-AMG 145 Antibodies

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

Concomitant Medications

Concomitant medications of interest will be summarized.

10.4.2.4 Other Exploratory Analyses

Lipid Parameters

The percent change from baseline in lipid parameters other than specified as secondary endpoints and change from baseline in all lipid parameters at each scheduled visit will be summarized. Descriptive statistics will be presented.

Adjudicated Events

Death, myocardial infarction, hospitalization for unstable angina, coronary revascularization, stroke, TIA, and hospitalization for heart failure will be adjudicated by an independent CEC. Subject incidence of these clinical events will be summarized.

Non-coronary revascularizations will be collected on the eCRF and will not be adjudicated. Subject incidence of non-coronary revascularizations will be summarized.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

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

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

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

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

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

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

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

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

11.3 Subject Confidentiality

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

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

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to

his/her study-related records, including personal information, without violating the confidentiality of the subject.

11.4 Investigator Signatory Obligations

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

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

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

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

12.2 Study Documentation and Archive

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

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

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

- Subject files containing completed study-related worksheets, informed consent forms, and subject identification list

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

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

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

12.3 Study Monitoring and Data Collection

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

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

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

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

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the electronic CRFs must be maintained and readily available.
- Updates to electronic CRFs (eCRF) will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review will be performed on subject data received at Amgen. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the

protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications will be created in the EDC system database for site resolution and closed by Amgen reviewer.

- The principal investigator signs only the Investigator Verification Form for this electronic data capture study. This signature will indicate that the principal investigator inspected or reviewed the data on the CRF, the data queries, and the site notifications, and agrees with the content.

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

12.4 Language

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

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

12.5 Publication Policy

To coordinate dissemination of data from this study, Amgen encourages the formation of a publication committee 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.

12.6 Compensation

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

13. REFERENCES

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

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

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

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

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

Goldstein J, Hobbs H, Brown, M. 2001. Familial hypercholesterolemia. In *The metabolic and molecular bases of inherited disease*. C. Scriver, A. Beaudet, W. Sly, and D. Valle, editors. McGraw-Hill. New York, New York, USA. 2863–2913.

Giugliano RP, Desai NR, Payal Kohli P, et al. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study. *Lancet* 2012;380:2007–2017.

Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110:227–239.

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

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

Ito MK, McGowan MP, Moriarty PM; National Lipid Association Expert Panel on Familial Hypercholesterolemia. Management of familial hypercholesterolemias in adult patients: recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5(3 Suppl):S38–S45

Koren MJ, Scott R, Kim JB, et al. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 as monotherapy in patients with hypercholesterolaemia (MENDEL): a randomised, double-blind, placebo-controlled, phase 2 study. *Lancet* 2012;380:1995–2006.

Lakoski SG, Lagace TA, Cohen JC, Horton JD, Hobbs HH. Genetic and Metabolic Determinants of Plasma PCSK9 Levels. *J Clin Endocrinol Metab*. 2009;94(7):2537-2543.

Levey AS, Bosch JP, Lewis JB. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med.* 1999;130:461-470.

Leitersdorf E, Van Der Westhuyzen DR, Coetzee,GA, Hobbs HH. Two Common Low Density Lipoprotein Receptor Gene Mutations Cause Familial Hypercholesterolemia in Afrikaners. *J Clin Invest.* 1989;84:954-961.

Leitersdorf E, Tobin EJ, Davignon J, Hobbs HH. Common Low-density Lipoprotein Receptor Mutations in the French Canadian Population. *J Clin Invest.* 1990;85:1014-1023

Lifshitz F, editor. *Pediatric Endocrinology, Volume 2: Growth, Adrenal, Sexual, Thyroid, Calcium, and Fluid Balance Disorders.* 5th ed. New York, NY: Informa Healthcare; 2007.

Neil A, Cooper J, Betteridge J, et al. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. *European Heart Journa*l. 2008; 29:2625–2633.

Rader DJ, Cohen J, Hobbs HH. Monogenic hypercholesterolemia: new insights in pathogenesis and treatment. *J Clin Invest.* 2003;111:1795–1803.

Raal FJ, Pilcher GJ, Illingworth DR, et al. Expanded-dose simvastatin is effective in homozygous familial hypercholesterolaemia. *Atherosclerosis.* 1997;135:249-256.

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

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

14. APPENDICES

Appendix A. Schedule of Assessments

PARENT ROLLOVER SUBJECTS ONLY:

Study Day / Timepoint	Screening[a]	EOS Parent (Day 1 OL)[b]	Interval Visits (Weeks 4, 6, 8, 16, 20)	Quarterly Visits[c] (Every 12 weeks)	EOS/ ET OL
General Procedures					
Informed consent	X	X			
Vital Signs (HR, BP)	X	X	X	X	X
AEs/**ADEs/**SAEs	X	X	X	X	X
Concomitant medication	X	X	X	X	X
Physical exam	X	X[b]			X
Body weight	X	X[b]			X
Growth parameters		X[n]		X[n]	X[n]
12 Lead ECG	X	X[b]			X
Central Laboratory					
Fasting plasma lipids, ApoA1, Lp(a), ApoB[d]	X	X	X[e]	X	X
PK samples (AMG 145), PCSK9	X[m]	X	X[e]	X	X
Chemistry	X	X		X	X
Hematology	X	X		X	X
HbA1c	X	X		X	X
Coagulation	X	X		X	X
hsCRP		X		X	X
Fasting Vitamin E		X[f]		X[f]	X
Biomarkers (blood)		X		X[g]	
Anti-AMG 145 antibodies		X		X[h]	X
Serum pregnancy (females of childbearing potential) and FSH	X[i,j]	X[i]		X[j]	X
Urinalysis, eGFR	X[k]	X			X
Investigational Product					
IP administration, QM or Q2W[l]		X	X	X	

Footnotes defined on the next page.

a Screening is for parent study subjects that fall outside the 1 month rollover-window.

b D1 = day of first administration of investigational product for the open-label; parent study subjects will undergo EOS procedures for their parent study and need to have signed a new OL consent before study drug is administered at the site. If the subject misses the 1 month window and undergoes screening procedures the physical exam, weight, and ECG will not need to be repeated on Day 1.

c Quarterly visits will start at week 12 and occur every 12 weeks thereafter. Starting at week 24, all subjects will have the option of self-administering AMG 145 Prior to week 24, subjects that are treated with AMG 145 420 mg administered SC Q2W will have to self-administer study drug between some visits.

d Investigators and staff involved with this trial should remain blinded to locally obtained lipid panels until the week 8 visit for all subjects that transition from an ongoing blinded (or blinded portion) parent study into this study, in order to avoid potential unblinding of the ongoing parent study.

e Week 4, 6, 8, 16, and 20 – labs mandatory for all subjects.

f Vitamin E will only be collected at EOS Parent/Day 1 and at weeks 12, 24, 48 (year 1), 72, and 96 (year 2) .

g Biomarkers will only be collected at month 3 (week 12).

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

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

j Pregnancy testing will occur every 6 months and during screening. **Additional pregnancy testing may be performed at the discretion of the investigator.**

k eGFR at screening only.

l Dose frequency may vary based on titration. Please refer to section 6.1.1.

m PCSK9 only.

n For adolescent subjects (as defined in the study glossary), growth parameters (height, weight, and Tanner staging; see Appendix E) will be performed on D1, every 48 weeks, and at EOS. Documentation of historical assessments of height, weight and Tanner stage for adolescent subjects should be obtained on D1 (or as soon as possible after enrollment). If Tanner staging cannot be performed on Study Day 1, it should be performed along with height and weight at the next scheduled study visit, and then every 48 weeks starting at the week 48 visit. Adult subjects should follow the schedule for Physical Exam and Body weight as above, and will not undergo Tanner staging.

NON-PARENT / NON-APHERESIS SUBJECTS ONLY:

Study Day / Timepoint	Screening[a]	Day 1 OL[b]	Optional Visits (Weeks 2,10[c])	Interval Visits (Weeks 4, 6, 8, 16, 20)	Quarterly Visits[d] (Every 12 weeks)	EOS/ ET OL
General Procedures						
Informed consent	X					
Vital Signs (HR, BP)	X	X	X	X	X	X
AEs/**ADEs/**SAEs	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X
Physical exam	X					X
Body weight	X					X
Growth parameters[o]		X[o]			X[o]	X[o]
12 Lead ECG	X					X
Central Laboratory						
Fasting plasma lipids, Lp(a), ApoA1, ApoB[e]	X	X	X	X[f]	X	X
PK samples (AMG 145), PCSK9	X[g]	X	X	X[f]	X	X
Chemistry	X	X			X	X
Hematology	X	X			X	X
HbA1c	X	X			X	X
Coagulation	X	X			X	X
hsCRP		X			X	X
Fasting Vitamin E		X[h]			X[h]	X
Biomarkers (blood)		X			X[i]	
Anti-AMG 145 antibodies		X			X[j]	X
Serum pregnancy (females of childbearing potential) and FSH	X[k,l]	X[k]			X[l]	X
Urinalysis, eGFR	X[m]	X				X
Investigational Product						
IP administration, QM or Q2W[n]		X		X	X	

Footnotes defined on the next page.

a Screening is for all non-parent study subjects.

b D1 = day of first administration of investigational product for the open-label.

c Week 2 and week 10 assessments and visits are not compulsory. They may be performed according to the subject's availability.

d Quarterly visits will start at wk 12 and occur every 12 wks thereafter. Starting at week 24, all subjects will have the option of self-administering AMG 145 Prior to week 24, subjects that are treated with AMG 145 420 mg administered SC Q2W will have to self-administer study drug between some visits.

e Investigators and staff involved with this trial should remain blinded to locally obtained lipid panels until the week 8 visit for all subjects that transition from an ongoing blinded (or blinded portion) parent study into this study, in order to avoid potential unblinding of the ongoing parent study.

f Week 4. 6. 8, 16, and 20 labs are mandatory for all subjects**.**

g PCSK9 only.

h Vitamin E will only be collected at EOS Parent/Day 1 and at weeks 12, 24, 48 (year 1), 72, and 96 (year 2).

I Biomarkers will only be collected at month 3 (week 12).

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

k FSH = in applicable subjects for study entry only – see exclusion criteria**.**

l Pregnancy testing will occur every 6 months and during screening for non-parent subjects**. Additional pregnancy testing may be performed at the discretion of the investigator.**

m eGFRr at screening only.

n Dose frequency may vary based on titration. Please refer to section 6.1.1**.**

o For adolescent subjects (as defined in the study glossary), growth parameters (height, weight, and Tanner staging; see Appendix E) will be performed on D1, every 48 weeks, and at EOS. Documentation of historical assessments of height, weight and Tanner stage for adolescent subjects should be obtained on D1 (or as soon as possible after enrollment). If Tanner staging cannot be performed on Study Day 1, it should be performed along with height and weight at the next scheduled study visit, and then every 48 weeks starting at the week 48 visit. Adult subjects should follow the schedule for Physical Exam and Body weight as above, and will not undergo Tanner staging.

NON-PARENT / ALL APHERESIS SUBJECTS ONLY:

Study Day / Timepoint	Screening[a,c] (week -2)	Screening[a] (week -1)	Day 1 OL[b]	Interval Visits (Weeks 2, 4, 6, 8, 9, 10, 16, 20)	Quarterly Visits[c] (Every 12 weeks)	EOS/ ET OL
General Procedures						
Informed consent	X					
Vital Signs (HR, BP)	X	X	X	X	X	X
AEs/**ADEs/**SAEs	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X
Physical exam	X					X
Body weight	X					X
12 Lead ECG	X					X
Growth parameters[o]			X[o]		X[o]	X[o]
Central Laboratory						
Blood draws (lipids, PCSK9, and PK) will be collected both before and after apheresis						
Fasting plasma lipids, Lp(a), ApoA1, ApoB[d]	X	X	X	X[e]	X	X
PK samples (AMG 145), PCSK9	X[g]	X[g]	X	X[e]	X	X
Chemistry	X		X		X	X
Hematology	X		X		X	X
HbA1c	X		X		X	X
Coagulation	X		X		X	X
hsCRP			X		X	X
Fasting Vitamin E			X[h]		X[h]	X
Biomarkers (blood)			X		X[i]	
Anti-AMG 145 antibodies			X		X[j]	X
Serum pregnancy (females of childbearing potential) and FSH		X[k,l]	X[k]		X[l]	X
Urinalysis, eGFR	X[m]		X			X
Investigational Product						
IP administration, QM or Q2W[n]			X	X	X	

Footnotes defined on the next page.

a All apheresis subjects must have their apheresis schedule aligned with the Q2W dosing of AMG 145. In addition, week -2 screening should happen on an apheresis day. Week -1 should not occur on an apheresis day. Screening procedures may occur at any time during the 6 week screening window, with the exception of lipids labs, which need to be drawn both at week -2 and week -1.

b D1 = day of first administration of investigational product (AMG 145 Q2W).

c Quarterly visits will start at week 12 and occur every 12 weeks thereafter. Starting at week 24, all subjects will have the option of self-administering AMG 145 Prior to week 24, subjects that are treated with AMG 145 420 mg administered SC Q2W will have to self-administer study drug between some visits or visit the site. Visits should still coincide with apheresis sessions and AMG 145 should be provided after (but on the same day) as apheresis.

d Investigators and staff involved with this trial should remain blinded to locally obtained lipid panels until the week 8 visit for all subjects that transition from an ongoing blinded (or blinded portion) parent study into this study, in order to avoid potential unblinding of the ongoing parent study.

e Weeks -2, -1, 2, 4, 6, 8, 9, 10,16 and 20 labs are mandatory for apheresis subjects.

g PCSK9 only.

h Vitamin E will only be collected at EOS Parent/Day 1 and at weeks 12, 24, 48 (year 1), 72, and 96 (year 2) .

l Biomarkers will only be collected at month 3 (week 12).

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

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

l Pregnancy testing will occur every 6 months and during screening for non-parent subjects. **Additional pregnancy testing may be performed at the discretion of the investigator.**

m GFR screening only.

n Please refer to dosing section 6.1.1. IP will not be administered at week 9.

o For adolescent subjects (as defined in the study glossary), growth parameters (height, weight, and Tanner staging; see Appendix E) will be performed on D1, every 48 weeks, and at EOS. Documentation of historical assessments of height, weight and Tanner stage for adolescent subjects should be obtained on D1 (or as soon as possible after enrollment). If Tanner staging cannot be performed on Study Day 1, it should be performed along with height and weight at the next scheduled study visit, and then every 48 weeks starting at the week 48 visit. Adult subjects should follow the schedule for Physical Exam and Body weight as above, and will not undergo Tanner staging.

Appendix B. Additional Safety Assessment Information

Adverse Event Toxicity Grading Scale

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

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

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

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

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST/ALT and TBL elevation according to the criteria specified in Section 6.1.3.2 (3x ULN for AST/ALT, 2x ULN for TBL, and **ALP < 2x 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 and/or background lipid therapy is withheld due to potential DILI or who experience AST/ALT elevations >3x ULN should undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels. Assessments that should be performed during this period include:

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

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

Appendix C. Sample Serious Adverse Event Report Form

AMGEN
evolocumab (AMG 145)
20110271

Clinical Trial Serious Adverse Event Report (3–IMP)
Notify Amgen Within 24 Hours of knowledge of the event

☐New
☐Follow-up

US: +1 888 814 8653

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Date of Birth (Day Month Year)	Sex	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 / 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: evolocumab (AMG 145) (No / Yes)	Pre-filled autoinjector /pen (AI/pen) (No / Yes)	3.5 mL personal injector (No / 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 / Yes)	Continuing (No / Yes)	Dose	Route	Freq.	Treatment Med (No / 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) 20110271	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:

Test / Unit / Date (Day Month Year)											

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

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: 20110271

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

2. Contact Information

Investigator Name _____ Site # _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

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

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

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

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

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

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

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

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Effective Date: March 27, 2011

Page 1 of 1

AMGEN® Lactation Notification Worksheet

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

1. Case Administrative Information

Protocol/Study Number: 20110271

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

2. Contact Information

Investigator Name _____ Site # _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

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

5. Breast Feeding Information

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

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Effective Date: 03 April 2012, version 2. Page 1 of 1

Appendix E. Tanner Staging (Sexual Maturity Ratings)

The table below or equivalent locally used guidance should be used for the assessment of sexual maturity (Tanner Staging) in this study. The table is adapted from Lifshitz (2007).

FEMALES:

Stage	BREAST	PUBIC HAIR STAGING	CONCOMITANT CHANGES
1	Prepubertal, papilla elevation	No pigmented hair	
2	Budding; larger areole; palpable and visible elevated contour	Pigmented hair, mainly labial	Accelerating growth rate
3	Enlargement of the breast and areola	Coarser, spread of pigmented hair over mons	Peak growth rate, thicker vaginal mucosa, axillary hair
4	Secondary mound of areola and papilla	Adult type but smaller area	Menarche (stage 3 or 4) decelerating growth rate
5	Mature	Adult distribution	

MALES:

Stage	GENITAL SIZE	PUBIC HAIR STAGING	CONCOMITANT CHANGES	PRADER ORCHIDOMETER
1	Prepubertal	No pigmented hair	Long testis axis < 1.5 cm	1 – 3 mL
2	Early testicular, penile, and scrotal growth	Minimal pigmented hair at base of penis	Early voice changes; testes length 2.5 – 3.3 cm	3 – 6 mL
3	Increased penile length and width; scrotal and testes growth	Dark, coarse, curly hair extends midline above penis	Light hair on upper lip, acne, maximal growth, testes length 3.3 – 4.0 cm	8 – 12 mL
4	Increased penis size including breadth; pigmented scrotum	Considerable, but less than adult distribution	Early sideburns; testes 4.0 – 4.5 cm	> 12 mL
5	Adult size and shape	Adult distribution, spread to medial thighs or beyond	Beard growth; testes > 4.5 cm	> 15 mL

Amendment 6

Protocol Title: A Multicenter, Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of AMG 145 on LDL-C in Subjects With Severe Familial Hypercholesterolemia

Amgen Protocol Number (AMG 145) 20110271

EudraCT Number: 2011-005400-15

Amendment Date: 02 December 2015

Rationale:

The protocol is being amended to:

- Clarify end of study language to specify the study will end when the last patient has completed assessments at week 260.
- Draw attention to collection of adverse device effects (ADEs) by adding ADEs to the Schedule of Assessments and the general study procedures when reviewing for adverse events (AEs) and serious adverse events (SAEs). This information is already being collected under AEs.
- Update criteria for possible drug-induced liver injury (DILI).
- Clarify language regarding product complaints.
- Allow for additional pregnancy testing at the discretion of the investigator.
- Correct Tanner Staging criteria for males.
- Update pregnancy and lactation reporting language and added new sample reporting forms.
- Correct typographic, grammatical, and formatting errors throughout the protocol.

Description of Changes:

Section: Global

Change: Version dates updated throughout document from 11 May 2015 to **02 December** 2015

Section: Global

Change: Typographic, grammatical, and formatting errors were corrected throughout the protocol.

Section: Global

Change: Corrected abbreviations throughout the protocol (defined on first use, definition removed on subsequent uses).

Section: Global

Change: Added **ADEs** throughout protocol to be reviewed along with AEs and SAEs.

Section: Title Page, below Study Title

Add:

Evolocumab (AMG 145)

Section: Title Page, Key Sponsor Contact

Replace:

PPD

One Amgen Center Drive,
Thousand Oaks, CA 91320-1799, USA
PPD

With:

PPD

240 Cambridge Science Park
Cambridge, CB4 OWD, UK
PPD

Section: Title Page

Add:

Date:	15 November 2011
Amendment 1 Date:	17 July 2012
Amendment 2 Date:	07 December 2012
Amendment 3 Date:	16 September 2013
Amendment 4 Date:	15 April 2014
Amendment 5 Date:	11 May 2015
Amendment 6 Date:	**XX December 2015**

Section: Protocol Synopsis, Study Design

Replace:

A multicenter, open-label study designed to assess the long-term safety, tolerability, and efficacy of AMG 145. The study will continue for 5 years or until AMG 145 becomes commercially available, whichever is earlier.

With:

A multicenter, open-label study designed to assess the long-term safety, tolerability, and efficacy of AMG 145. The study will continue **until the date when the last subject has completed the assessments for week 260 (approximately 5 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**.

Section: Protocol Synopsis, Summary of Subject Eligibility Criteria, last paragraph

Replace:

Female subjects cannot be pregnant or breast-feeding or planning to become pregnant or breastfeed and premenopausal females of childbearing potential must be willing to use an acceptable method(s) of birth control during treatment and for an additional 15 weeks after the end of treatment with AMG 145 (IP).

With:

Female subjects cannot be pregnant or breast-feeding or planning to become pregnant or breastfeed and premenopausal females of childbearing potential must be willing to use an acceptable method(s) of birth control during treatment **with AMG 145 (IP)** and for an additional 15 weeks after the **last dose of** AMG 145 (IP).

Section: Protocol Synopsis, Parent Study 20110233 Subjects

Add:

Subjects coming from parent study 20110233 will initiate this study with **AMG 145** 420 mg SC monthly (QM) dosing.

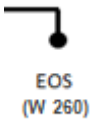
Section: Protocol Synopsis, Apheresis Subjects

Add:

Subjects on apheresis should initiate treatment with **AMG 145** 420 mg SC Q2W in this study to correspond with their apheresis schedule.

Section: Study Design and Treatment Schema

Add:



Section: Study Glossary

Add:

ADE	**Adverse device effect**
ET OL	**Early termination open label**
NCI-CTCAE	N**ational** C**ancer** I**nstitute** Common Terminology Criteria for A**dverse** E**vent**s

Section: Study Glossary

Replace:

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

With:

End of treatment	Defined as the last **dose** for the protocol-specified treatment phase of the study for an individual subject
EOS	End of study

Section: 2.2 AMG 145 Background, 2nd paragraph

Add:

Details of the biochemistry, nonclinical pharmacology, nonclinical pharmacokinetics (PK), and nonclinical toxicology with AMG 145 are contained in the **Evolocumab (AMG 145)** Investigator's Brochure, 2013.

Section: 2.3 Rationale

Replace:

This study is being conducted to gather information on the long-term safety of AMG 145 and to provide subjects that participated in 20110233 or another Amgen qualifying study with an opportunity to receive treatment until AMG 145 becomes commercially available.

With:

This study is being conducted to gather information on the long-term safety of AMG 145 and to provide subjects that participated in 20110233 or another Amgen qualifying study with an opportunity to receive treatment **with** AMG 145 **for up to approximately 5 years**.

Section: 3.1 Study Design, 1st paragraph

Replace:

A multicenter, open-label study designed to assess the long-term safety, tolerability, and efficacy of AMG 145. The study will continue for 5 years or until AMG 145 becomes commercially available, whichever is earlier.

With:

A multicenter, open-label study designed to assess the long-term safety, tolerability, and efficacy of AMG 145. The study will continue **until the date when the last subject has completed the assessments for week 260 (approximately 5 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**.

Section: 3.4 Study Duration for Participants

Replace:

The study will continue for 5 years or until AMG 145 becomes commercially available, whichever is earlier.

With:

The study will continue for **260 weeks (approximately** 5 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**.

Section: 3.5 End of Study

Replace:

The study will continue for 5 years or until AMG 145 becomes commercially available, whichever is earlier.

With:

The study will **continue until the date when the last subject has completed the assessments for week 260 (approximately 5 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.

Section: 4.2 Exclusion Criteria

Add:

4.2.2 Subject is pregnant or breastfeeding, or planning to become pregnant or breastfeed during treatment with AMG 145 **(IP)** and for an additional 15 weeks after the end of treatment with AMG 145 (IP)

Section: 6.1.3.2 Elevation of Liver Function Tests, 2nd paragraph

Replace:

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

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

AND

- AST or ALT > 3x ULN

AND

- no other cause for the combination of laboratory abnormalities is immediately apparent; important potential causes for abnormal AST/ALT or TBL values include, but are not limited to:

With:

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

- TBL **≥** 2x ULN
- AND **increased** AST or ALT > 3x ULN **if baseline values were less than the ULN**
- AND **ALP < 2x ULN**
- **AND** no other cause for the combination of **the above** laboratory abnormalities is immediately apparent; important **alternative** causes for abnormal AST/ALT **and/**or TBL values include, but are not limited to:

Section: 6.2 Product Complaints, Including Device Complaints, 1st paragraph

Add:

A product complaint is defined as any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug**(s)** or device**(s)** after it is released for distribution

to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. **This includes drug(s) or device(s) provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.**

Section: 6.2 Product Complaints, Including Device Complaints, 4th paragraph

Add:

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

Section: 7.1.2.5 Quarterly Visits - All Subjects (Week 12, 24, 36, etc ± 7 Days)

Add:

- Blood draw for serum pregnancy (performed every 6 months for females of childbearing potential only) **– Additional pregnancy testing may be performed at the discretion of the investigator**

Section: 7.1.2.6 End of Study (Week 260)/Early Term OL Visit – All Subjects, Title

Add:

End of Study **(Week 260)**/Early Term OL Visit – **A**ll Subjects

Section: 9.1.2 Reporting Procedures for Adverse Events, 2nd paragraph

Add:

- Assessment of relatedness to investigational product (AMG 145) **and/or any study-mandated activity and/or procedure,** and

Section: 9.1.2 Reporting Procedures for Adverse Events, 4th paragraph

Replace:

The investigator must assess whether the adverse event is possibly related to AMG 145. This relationship is indicated by a “yes” or “no” response to the question: Is there a reasonable possibility that the event may have been caused by AMG 145 and/or other study drugs?

With:

The investigator must assess whether the adverse event is possibly related to **IP (**AMG 145**)**. This relationship is indicated by a “yes” or “no” response to the question: Is there a reasonable possibility that the event may have been caused by AMG 145?

Section: 9.3 Pregnancy and Lactation Reporting

Replace:

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-required therapies and for an additional 15 weeks after the end of treatment with IP: AMG 145, report the pregnancy to Amgen as specified below.

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

If a lactation case occurs while a female subject is taking protocol-required therapies and for an additional 15 weeks after the end of treatment with IP (AMG 145) report the lactation case to Amgen as specified below.

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

With:

If a pregnancy occurs in a female subject, or a male subject **fathers a child**, while the subject is taking **AMG 145** and for an additional 15 weeks after the **last dose of** AMG 145, report the pregnancy to Amgen as specified below.

The pregnancy should be reported to Amgen's **G**lobal **Patient Safety** within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix D). **Amgen's Global Patient Safety** will seek to **obtain pregnancy and birth outcome information**.

If a lactation case occurs while a female subject is taking **AMG 145** and for an additional 15 weeks after the **last dose of** AMG 145, report the lactation case to Amgen as specified below.

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

Section: 10.4.1 General Approach/Considerations, 1st paragraph

Add:

Statistical analyses in this open label study are descriptive in nature. No statistical inference or missing value imputation is planned. **The final analysis for the study will be performed at the end of the study (defined as when the last subject has completed the assessments for week 260 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).**

Section: Appendix A. Schedule of Assessments, footnotes

Add:

Pregnancy testing will occur every 6 months and during screening. **Additional pregnancy testing may be performed at the discretion of the investigator.**

Section: Appendix B. Additional Safety Assessment Information, Drug-induced Liver Injury Reporting & Additional Assessments

Add:

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**,** 2x ULN for TBL**,** and **ALP < 2x ULN**) require the following:

Section: Appendix B. Additional Safety Assessment Information, Drug-induced Liver Injury Reporting & Additional Assessments

Replace:

Additional Clinical Assessments and Observation

- 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

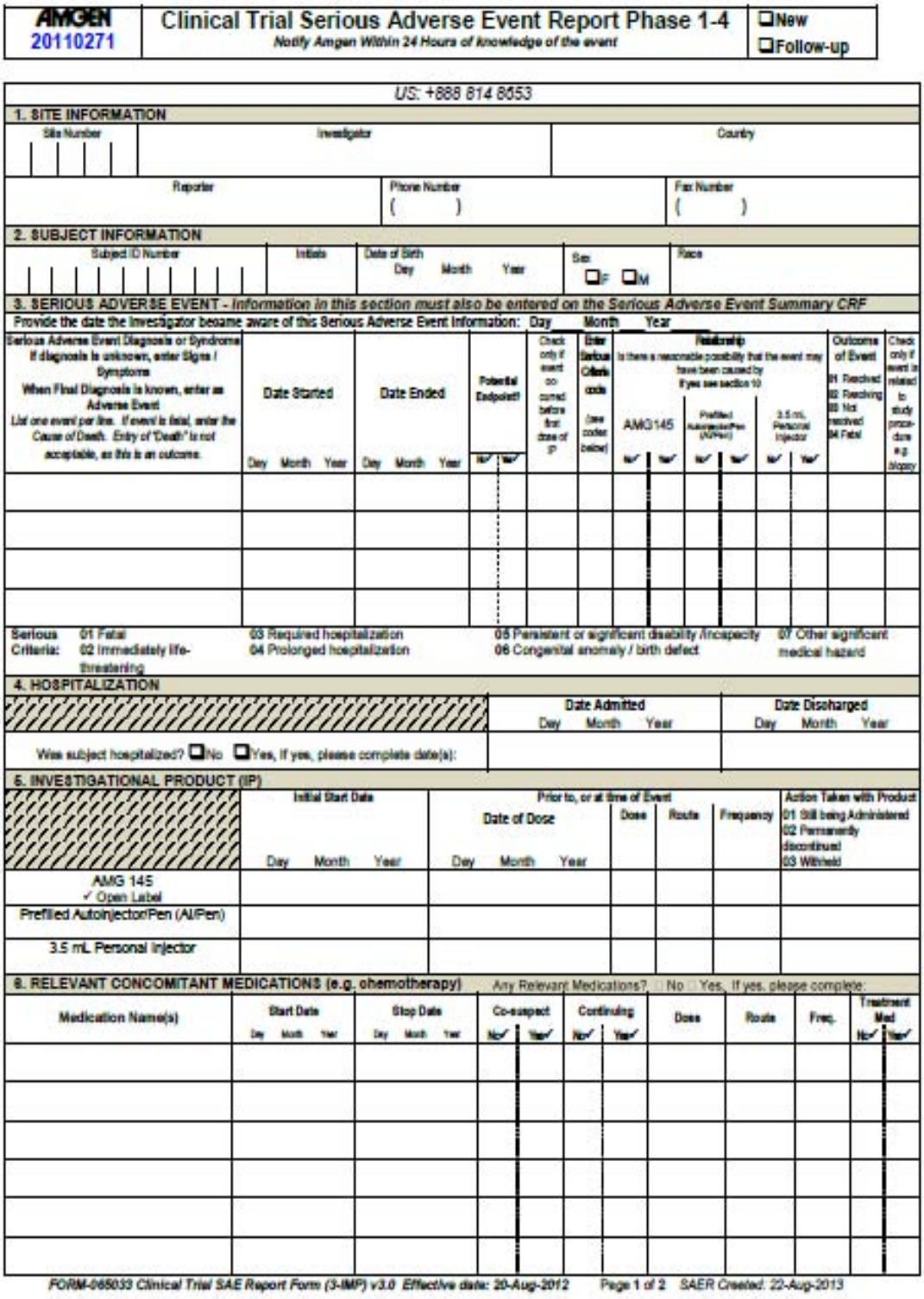
With:

Additional Clinical Assessments and Observation

- Repeat liver chemistries within 24-48 hours (ALT, AST, ALP, TBL); in cases of TBL ≥ 2x ULN**, ALP < 2x ULN,** or AST/ALT much greater than 3x ULN, retesting should be performed within 24 hours

Section: Appendix C. Sample Serious Adverse Event Report Form

Replace:



AMGEN 20110271

Clinical Trial Serious Adverse Event Report Phase 1-4

Notify Amgen Within 24 Hours of Knowledge of the event

☐ New ☐ Follow-up

US: +888 814 8653

1. SITE INFORMATION

Site Number | Investigator | Country

Reporter | Phone Number ( ) | Fax Number ( )

2. SUBJECT INFORMATION

Subject ID Number | Initials | Date of Birth Day Month Year | Sex ☐F ☐M | Race

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

Provide the date the Investigator became aware of this Serious Adverse Event Information: Day Month Year

Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event 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 ✓ 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 IP (see section 10) AMG145 No ✓ Yes ✓	Prefilled Autoinjector/Pen (AI/Pen) No ✓ Yes ✓	3.5 mL Personal Injector No ✓ Yes ✓	Outcome of Event 01 Resolved 02 Resolving 03 Not resolved 04 Fatal	Check only if event is related to study procedure e.g. 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
AMG 145 ✓ Open Label						
Prefilled Autoinjector/Pen (AI/Pen)						
3.5 mL Personal Injector						

8. RELEVANT CONCOMITANT MEDICATIONS (e.g. chemotherapy) Any Relevant Medications? ☐No ☐Yes, If yes, please complete:

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

FORM-065033 Clinical Trial SAE Report Form (3-IMP) v3.0 Effective date: 20-Aug-2012 Page 1 of 2 *SAER Created: 22-Aug-2013*

AMGEN 20110271	Clinical Trial Serious Adverse Event Report Phase 1-4 *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 Form (3-IMP) v3.0 Effective date: 20-Aug-2012 Page 2 of 2 *SAER Created:* 22-Aug-2013

With:

AMGEN
evolocumab (AMG 145)
20110271

Clinical Trial Serious Adverse Event Report (3–IMP)
Notify Amgen Within 24 Hours of knowledge of the event

☐ New
☐ Follow-up

US: +1 888 814 8653

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Date of Birth (Day Month Year)	Sex	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 ✓ / 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: evolocumab (AMG 145) (No ✓ / Yes ✓)	Pre-filled autoinjector /pen (AI/pen) (No ✓ / Yes ✓)	3.5 mL personal injector (No ✓ / 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 ✓ / Yes ✓)	Continuing (No ✓ / Yes ✓)	Dose	Route	Freq.	Treatment Med (No ✓ / 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) 20110271	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:

Test / Unit / Date (Day Month Year)											

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

Section: Appendix D. Pregnancy and Lacation Notification Worksheets

Replace:

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ 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

With:

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20110271

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

2. Contact Information

Investigator Name _____ Site # _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

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

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

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

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

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

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

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

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Effective Date: March 27, 2011 Page 1 of 1

AMGEN® Lactation Notification Worksheet

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

1. Case Administrative Information

Protocol/Study Number: 20110271

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

2. Contact Information

Investigator Name _____ Site # _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

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

5. Breast Feeding Information

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

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Effective Date: 03 April 2012, version 2.

Page 1 of 1

Section: Appendix E. Tanner Staging (Sexual Maturity Ratings)

Delete:

MALES:

Stage	GENITAL SIZE	PUBIC HAIR STAGING	CONCOMITANT CHANGES	PRADER ORCHIDOMETER
1	Prepubertal~~, papilla elevation~~	No pigmented hair	Long testis axis < 1.5 cm	1 – 3 mL

Amendment 5

Protocol Title: A Multicenter, Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of AMG 145 on LDL-C in Subjects with Severe Familial Hypercholesterolemia

Amgen Protocol Number 20110271

EudraCT Number: 2011-005400-15

Amendment Date: 11 May 2015

Rationale:

This document provides the rationale and detailed list of changes for Amendment 5, dated 11 May 2015, from Amendment 4 of the study protocol, dated 15 April 2014.

The purpose of this amendment is:

1. To remove the external Data Monitoring Committee (DMC) following the DMC's expressed preference to not review open-label, uncontrolled safety data. Safety monitoring will continue to be performed by AMGEN. Even though review of this specific study will 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 will be discussed with the DMC and the committee will incorporate that data when making its recommendations to AMGEN. Additional minor editorial and typographical changes were also made.
2. To add measurements of height, weight and Tanner staging for adolescent subjects, and to allow for documentation of historical assessments of height, weight and Tanner staging in adolescent subjects. A definition of 'adolescent' was also provided.

Amendment

Title: A Multicenter, Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of AMG 145 on LDL-C in Subjects With Severe Familial Hypercholesterolemia

AMG 145

Amgen Protocol Number 20110271
EudraCT Number: 2011-005400-15

TAUSSIG

Trial **A**ssessing long term **US**e of PCSK9 Inhibition in **S**ubjects w**I**th **G**enetic LDL Disorders

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 Amendment 3 of the study protocol, dated 16 September 2013.

The purpose of the amendment is to:

- Update the sample size
- Update the number of sites
- Update the dosing language
- Update the analyte table
- Minor corrections

Amendment 3

Title: A Multicenter, Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of AMG 145 on LDL-C in Subjects With Severe Familial Hypercholesterolemia

AMG 145

Amgen Protocol Number 20110271
EudraCT Number: 2011-005400-15

TAUSSIG

Trial **A**ssessing long term **US**e of PCSK9 Inhibition in **S**ubjects w**I**th **G**enetic LDL Disorders

Amendment 3 Date: 16 September 2013

Rationale:

This document provides the rationale and detailed list of changes for Amendment 3, dated 16 September 2013, from Amendment 2 of the study protocol, dated 07 December 2012.

The purpose of the amendment is to:

- Add Lp(a) as a secondary endpoint
- Update the exploratory endpoints
- Include subjects with severe hypercholesterolemia
- Update the sample size to accommodate additional high need subjects
- Exclude Lomitapide and CETP inhibitors
- Add AI and AMD language
- Clarify dose adjustment language
- Update the safety reporting section with Amgen's new template language
- Add CEC language
- Update the study schemas
- Update the background section
- Add addition criteria for withholding IP
- Remove the apheresis substudy

Amendment 2

Title: A Multicenter, Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of AMG 145 on LDL-C in Subjects With Severe Familial Hypercholesterolemia

AMG 145

Amgen Protocol Number 20110271
EudraCT Number: 2011-005400-15

TAUSSIG

Trial **A**ssessing long term **US**e of PCSK9 Inhibition in **S**ubjects w**I**th **G**enetic LDL Disorders

Amendment 2 Date: 07 December 2012

Rationale

This document provides the rationale and detailed list of changes for Amendment 2, dated 07 December 2012, from Amendment 1 of the study protocol, dated 17 July 2012.

The purpose of the amendment is to:

- Update the at home dosing information
- Change the dosing terminology from Q4W to QM
- Add an additional secondary endpoint
- Add more flexible dosing language for subjects that enter study 20110271 from study 20110233
- Highlight that lipid lowering concomitant medications cannot be adjusted during the first 12 weeks of the study

Amendment 1

Protocol Title: A Multicenter, Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of AMG 145 on LDL-C in Subjects With Severe Familial Hypercholesterolemia

Amgen Protocol Number: 20110271
EudraCT Number: 2011-005400-15

TAUSSIG

Trial **A**ssessing long term **US**e of PCSK9 Inhibition in **S**ubjects w**I**th **G**enetic LDL Disorders

Amendment Date: 17 July 2012

Rationale:

This document provides the rationale and detailed list of changes for Amendment 1, dated 17 July 2012, from the original protocol, dated 15 November 2011.

The purpose of the amendment is to:

- Adjust the study title so that it more reflective of the actual study population
- Add a study acronym
- Clarify that labs will be blinded for subjects coming from a blinded (or blinded portion) of a parent study
- Add an optional apheresis substudy
- Increase the sample size from 75 subjects to 125 based on new patient interest in the study
- Add a screening period for subjects that either do not come from a parent study or for parent study subjects that do not rollover into 20110271 within 3 days
- Change the dosage and dosing schedule to accommodate the eclectic patient population
- Update the AMG 145 background section with new data based on the P2 interim analysis.
- Decrease the frequency of Anti-AMG 145 antibody collection after year 1
- Update the patient inclusion criteria
- Highlight that anytime there are 2 consecutive LDL-C values below 25 mg/dL for an individual subject that the DMC will be notified.
- Highlight that Vit E values will be blinded
- Update the safety reporting timelines as well as the pregnancy and lactation language per Amgen's most recent template
- Divide the schedule of assessments into 3 groups; rollover subjects, non-roll-over non-apheresis subjects, and apheresis subjects