Title: Double-blind, Randomized, Multicenter, Placebo-controlled, Parallel Group Study to Characterize the Efficacy, Safety, and Tolerability of 24 Weeks of Evolocumab for Low Density Lipoprotein-cholesterol (LDL-C) Reduction, as Add-on to Diet and Lipid-lowering Therapy, in Pediatric Subjects 10 to 17 Years of Age With Heterozygous Familial Hypercholesterolemia (HeFH)

Evolocumab (AMG 145)

Amgen Protocol Number (Evolocumab) 20120123

EudraCT number 2014-002277-11

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Original, Date: 09 December 2014

Amendment 1, **Date**: 20 May 2015

Amendment 2, Date **01 September 2015**

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NCT Number: NCT02392559
This NCT number has been applied to the document for purposes of posting on clinicaltrials.gov

Investigator's Agreement

I have read the attached protocol entitled "Double-blind, Randomized, Multicenter, Placebo-Controlled, Parallel Group Study to Characterize the Efficacy, Safety, and Tolerability of 24 Weeks of Evolocumab for Low Density Lipoprotein-Cholesterol (LDL-C) Reduction, as Add-On to Diet and Lipid-Lowering Therapy, in Pediatric Subjects 10 to 17 Years of Age With Heterozygous Familial Hypercholesterolemia (HeFH)", dated **01 September 2015**, and agree to abide by all provisions set forth therein.

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

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

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

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

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

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

Protocol Synopsis

Title: Double-blind, Randomized, Multicenter, Placebo-controlled, Parallel Group Study to Characterize the Efficacy, Safety, and Tolerability of 24 Weeks of Evolocumab for Low Density Lipoprotein-cholesterol (LDL-C) Reduction, as Add-on to Diet and Lipid-lowering Therapy, in Pediatric Subjects 10 to 17 Years of Age With Heterozygous Familial Hypercholesterolemia (HeFH)

Study Phase: 3b

Indication: Heterozygous familial hypercholesterolemia in pediatric subjects

Primary Objective: To evaluate the effect of 24 weeks of subcutaneous (SC) evolocumab compared with placebo, when added to standard of care, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in pediatric subjects 10 to 17 years of age with HeFH.

Secondary Efficacy Objectives: to assess the effects of SC evolocumab compared with placebo, when added to standard of care, on mean percent change from baseline to weeks 22 and 24 and change from baseline to week 24 in LDL-C, and on percent change from baseline to week 24 in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, and ApoB/Apolipoprotein A-1 (ApoA1) ratio, in pediatric subjects 10 to 17 years of age with HeFH

Secondary Safety Objectives: to evaluate the safety of SC evolocumab compared with placebo, when added to standard of care, in pediatric subjects 10 to 17 years of age with HeFH

Secondary Pharmacokinetic Objective: to characterize pharmacokinetic (PK) exposure

Hypotheses: The primary hypothesis is that SC evolocumab will be well tolerated and will result in greater reduction of LDL-C, defined as percent change from baseline to week 24, compared with placebo, when added to standard of care in pediatric subjects 10 to 17 years of age with HeFH.

Primary Endpoint: Percent change from baseline to week 24 in LDL-C

Secondary Endpoints:

- Mean percent change from baseline to weeks 22 and 24 in LDL-C
- change from baseline to week 24 in LDL-C
- percent change from baseline to week 24 in the following:
  - non-HDL-C
  - ApoB
  - total cholesterol/HDL-C ratio
  - ApoB/ApoA1 ratio

Study Design: This is a randomized, multicenter, placebo-controlled, double-blind, parallel group study. Subjects are eligible for screening if they are 10 to 17 years of age at time of randomization and have met the local applicable diagnostic criteria for HeFH. Subjects considered for enrollment will undergo screening assessments, including laboratory screening by central laboratory. Approximately 150 eligible subjects will be randomized in a 2:1 ratio to receive 24 weeks of QM evolocumab or placebo. Randomization will be stratified by screening LDL-C (< 160 mg/dL [4.1 mmol/L] vs ≥ 160 mg/dL) and age (< 14 years vs ≥ 14 years).

The study includes collection of biomarker development samples. Where permitted by local regulations, subjects will be invited to consent to pharmacogenetic analyses.

After completion of Study 20120123, subjects will be offered to participate in an extension study where they will receive open-label evolocumab.

Sample Size: Approximately 150 subjects will be randomized.

Summary of Subject Eligibility Criteria: Males and females of 10 to 17 years of age with diagnosis of HeFH and receiving optimized standard of care lipid lowering therapy per locally applicable guidelines are eligible for this study.

Subjects must have signed informed consent or subject assent for the study and appropriate parental/guardian consent must be available. Subjects must be on a low-fat diet and must receive optimized background lipid-lowering therapy which includes a statin at optimal dose as determined by the managing physician not requiring uptitration in the opinion of the investigator. Lipid-lowering therapy must be stable for ≥ 4 weeks prior to screening. Fasting LDL-C must be ≥ 130 mg/dL (3.4 mmol/L) and fasting triglycerides must be ≤ 400 mg/dL (4.5 mmol/L) as determined by the central laboratory at screening.

The following are the major exclusion criteria: **homozygous familial hypercholesterolemia,** type 1 diabetes or recently diagnosed (within 3 months of randomization) or poorly controlled (HbA1c > 8.5%) type 2 diabetes or newly diagnosed impaired glucose tolerance; thyroid stimulating hormone (TSH) < lower limit of normal (LLN) or TSH > 1.5x upper limit of normal (ULN) and free thyroxine (T4) levels that are outside normal range, estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m^2, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2x ULN, creatine kinase (CK) > 3x ULN (all screening by central laboratory); known active infection, or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction. Subjects are excluded if they have taken any cholesterylester transfer protein (CETP) inhibitor in the last 12 months, mipomersen or lomitapide in the last 5 months, lipid apheresis within the last 12 weeks, or if they have previously received evolocumab or any other investigational therapy to inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9). Subjects cannot be enrolled in another investigational device or drug study, receive other investigational agent(s) or procedures, or be within less than 30 days since ending another investigational device or drug study. Female subjects of childbearing potential cannot be pregnant, planning to become pregnant, breast feeding or planning to breastfeed and must be willing to use acceptable method(s) of effective contraception during treatment with IP (evolocumab or placebo) and for an additional 15 weeks after the end of treatment with IP (evolocumab or placebo).

For a full list of eligibility criteria, please refer to Section 4.1.1 through Section 4.1.2.

Investigational Product

Amgen Investigational Product Dosage and Administration: Evolocumab and placebo are Amgen investigational product (IP). IP will be administered SC using a spring-based prefilled autoinjector/pen (prefilled AI/Pen). Each prefilled AI/Pen will contain 1.0 mL deliverable volume, either 140 mg evolocumab or placebo.

Non-Amgen Non-investigational Product Dosage and Administration: Subjects will continue to use stable background lipid-lowering therapies as prescribed. These therapies will not be provided by Amgen unless required by law.

Procedures: Subjects being considered for participation in this study, and who have signed informed consent or subject assent, will be assessed for inclusion and exclusion criteria. Medical and medication history will be obtained. Subjects will undergo screening assessments, including a SC administration of placebo to evaluate tolerability of the SC injection via the prefilled AI/pen. Lipid eligibility screening must be conducted after the subject has been on a low-fat diet and receiving lipid lowering therapy that includes an optimal dose of a statin not requiring uptitration in the opinion of the investigator and has been stable for ≥ 4 weeks. Subjects should maintain their diet, lipid-lowering therapy, and exercise regimen unchanged throughout screening and all phases of study participation. Eligible subjects will be randomized to receive IP (evolocumab or placebo), in addition to their background lipid lowering therapy. An interactive voice response system and/or interactive web response system (IVRS/IWRS) will allocate subjects to administration of investigational product. Day 1 is defined as the day of first administration of investigational product. Subsequent study visits are at weeks 4, 12, 20, 22, and 24 (EOS, end-of-study). Day 1 and week 24 visits must be scheduled at approximately the same time of day, and should be performed as close as possible to 8 am as the hormones measured have diurnal variation. IP administration is every 4 weeks. Administration at weeks 8 and 16 can be at

the study site (optional visit) or at a location other than the study site. Last administration of IP is at week 20. Subjects who discontinue IP early for any reason will be asked to continue to return for all other study procedures and measurements until the end of the study.

Assessments and procedures include vital signs, adverse events/serious adverse events/**adverse device effects (ADE)/disease related events(DRE)**/cardiovascular (CV) events, and concomitant therapy, dietary instruction, physical exam including neurologic examination and assessment of waist circumference, body height and weight, 12-lead electrocardiograms (ECGs), fasting lipids, chemistry, hematology, anti-evolocumab antibodies, biomarker sample collection, serum pregnancy testing (females of childbearing potential), urinalysis, assessment of growth and pubertal development (Tanner staging), Cogstate neurocognitive assessment, carotid intima-media thickness (cIMT), and IP administration. In addition, specific laboratory assessments will be performed, including estradiol for girls, testosterone for boys, creatinine phosphokinase, follicle-stimulating hormone, luteinizing hormone, adenocorticotropic hormone, dehydroepiandrosterone, and cortisol. If the subject consented to pharmacogenetics analyses, DNA will be extracted from some of the blood samples. IP administration by SC injection, if applicable, will be done after all other procedures have been completed.

For a full description of procedures, please refer to Section 7.

Statistical Considerations:

General Considerations

Efficacy and safety analyses will be performed on the full analysis set (FAS), which includes all randomized subjects who have received at least 1 dose of IP.

The superiority of evolocumab to placebo will be assessed for all efficacy endpoints.

Methods of adjusting for multiplicity due to multiple endpoints are provided in Section 10.5.1

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

Analysis of Primary Efficacy Endpoint

To assess the primary endpoint of percent change from baseline in LDL-C at week 24, a repeated measures linear mixed effects model will be used to compare the efficacy of evolocumab with placebo. Missing values will not be imputed when the repeated measures linear mixed effects model is used.

Analyses of Secondary Efficacy Endpoints

The statistical model for the secondary efficacy endpoints will be similar to the primary endpoint.

Safety Analyses

Safety summaries will include the subject incidence of adverse events, summaries of laboratory parameters, vital signs, and anti-evolocumab antibodies.

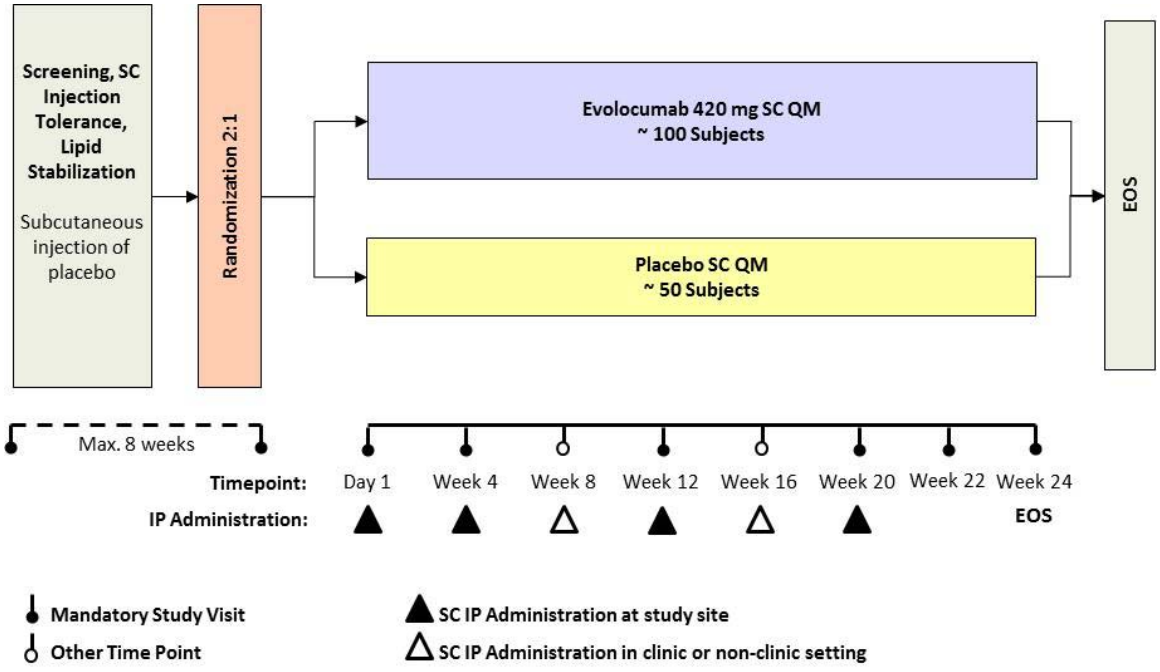
An independent data monitoring committee (DMC) will formally review the accumulating data from this and other completed and ongoing studies with evolocumab to ensure there is no avoidable increased risk for harm to subjects. Analyses for the DMC will be provided by a group which is external to Amgen.

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

Sponsor: Amgen

Data Element Standards Version(s)/Date(s):	Version 4.1 / 20 June 2014

Study Design and Treatment Schema



QM = dosed monthly; IP = investigational product

Study Glossary

Abbreviation or Term	Definition/Explanation
ADE	**Adverse device effect**
ADHD	attention deficit hyperactivity disorder
AE	Adverse event
AI/Pen	Autoinjector pen
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase (serum glutamic-pyruvic transaminase)
AMD	Automated mini doser
ApoA1	Apolipoprotein A-1
ApoB	Apolipoprotein B
AST (SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
BP	Blood pressure
BUN	Blood urea nitrogen
CAD	Coronary artery disease
CAS	Completer analysis set
CEC	Clinical events committee
CETP	Cholesterylester transfer protein
CHD	Coronary heart disease
CK	Creatine kinase
CTCAE	Common Terminology Criteria for Adverse Events
DET	Detection (Test)
DHEA-S	Dehydroepiandrosterone sulfate
DILI	Drug-induced liver injury
DMC	Data monitoring committee (Efficacy and Safety Evaluation Committee)
DNA	Deoxyribonucleic acid
DRE	**Disease related event**
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate; eGFR will be calculated by the central laboratory and provided to the investigator.
Electronic Source Data (eSource)	Source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
End of Follow-up	Defined as when the last subject completes the last protocol-specified assessment in the study

Abbreviation or Term	Definition/Explanation
End of Study (end of trial)	Defined as when the last subject is assessed or receives an intervention for evaluation in the study; if the study includes multiple parts (eg, safety follow-up or survival assessment), the end of study would include these additional parts
End of Study (primary completion)	The end of the study (primary completion) is defined as the last day on which a randomized subject in this study completes the end-of-study visit (week 24) or terminates the study early
End of Study for Individual Subject	Defined as the last day that protocol-specified procedures are conducted for an individual subject
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 the individual subject)
eSAE contingency report form	Electronic serious adverse event contingency report form
FAS	Full analysis set
FH	Familial hypercholesterolemia
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GMLT	Groton Maze Learning Task
HCV	Hepatitis C virus
HDL-C	High density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
HoFH	Homozygous familial hypercholesterolemia
HR	Heart Rate
hsCRP	High sensitivity C-reactive protein
IB	Investigator's Brochure
IBG	Independent Biostatistical Group
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDN	Identification (Test)
IEC	Independent ethics committee
IFU	Instructions for Use
IP	Investigational product (evolocumab or placebo, administered with the medical device used in this study – the prefilled autoinjector/pen [AI/pen])
INR	International normalized ratio
Interactive Voice Response (IVR)	Telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.

Abbreviation or Term	Definition/Explanation
Interactive Web Response (IWR)	Web based technology that is linked to a central computer in real time as an interface to collect and process information.
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
IVRS/IWRS	Interactive Voice Response System / Interactive Web Response System
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
LLN	Lower limit of normal
LOF	Loss-of-function
Lp(a)	Lipoprotein(a)
Monthly	Defined as every 4 weeks with a window of ± 3 days. For practical considerations, study visits are scheduled based on a weekly calendar with a window of +/- 3 days for each visit, thus dosing intervals are allowed to be up to 31 days for the QM regimen.
NASH	Nonalcoholic steatohepatitis
NCI	National Cancer Institute
OCL	One Card Learning (Test)
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamic
PFS	Pre-filled syringe
PI	Principal investigator
PK	Pharmacokinetic(s)
Q2W	Q2W is defined as every 2 weeks with a window of ± 3 days for each visit, thus dosing intervals are allowed to be up to 17 days for the Q2W regimen. Note: Day 1 and week 24 visits must be scheduled at approximately the same time of day, and should be performed as close as possible to 8 am as the hormones measured have diurnal variation.
QM	QM is defined as every 4 weeks with a window of ± 3 days for each visit, thus dosing intervals are allowed to be up to 31 days for the QM regimen. Note: Day 1 and week 24 visits must be scheduled at approximately the same time of day, and should be performed as close as possible to 8 am as the hormones measured have diurnal variation.
RBC	Red blood cells
SAE	Serious adverse event
SC	Subcutaneous
SoC	Standard of care

Abbreviation or Term	Definition/Explanation
Source Data	Information from an original record or 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 identification, Randomization identification, and Stratification Value.
Study Day 1	Defined as the first day that protocol-specified investigational product is administered to the subject
TBL	Total bilirubin
TIA	Transient ischemic attack
TNF	Tumor necrosis factor
TSH	Thyroid Stimulating Hormone
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol
WBC	White blood cell

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1. OBJECTIVES

1.1 Primary

To evaluate the effect of 24 weeks of subcutaneous (SC) evolocumab compared with placebo, when added to standard of care, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in pediatric subjects 10 to 17 years of age with heterozygous familial hypercholesterolemia (HeFH).

1.2 Secondary Efficacy

- to assess the effects of SC evolocumab compared with placebo, when added to standard of care, on mean percent change from baseline to weeks 22 and 24 and change from baseline to week 24 in LDL-C, and on percent change from baseline to week 24 in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, and ApoB/Apolipoprotein A-1 (ApoA1) ratio, in pediatric subjects 10 to 17 years of age with HeFH

1.3 Secondary Safety

- to evaluate the safety of SC evolocumab compared with placebo, when added to standard of care, in pediatric subjects 10 to 17 years of age with HeFH

1.4 Secondary Pharmacokinetic

- to characterize pharmacokinetic (PK) exposure

1.5 Tertiary

- to assess the effects of SC evolocumab compared with placebo, when added to standard of care, on percent change from baseline to week 24 in total cholesterol, very low-density lipoprotein cholesterol (VLDL-C), HDL-C, ApoA1, triglycerides, and lipoprotein(a) [Lp(a)], in pediatric subjects 10 to 17 years of age with HeFH
- to assess the effects of SC evolocumab compared with placebo, when added to standard of care, on mean percent change from baseline to weeks 22 and 24 in non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio, total cholesterol, very low-density lipoprotein cholesterol (VLDL-C), HDL-C, ApoA1, triglycerides, and Lp(a), in pediatric subjects 10 to 17 years of age with HeFH

1.6 Exploratory

[redacted]

2. BACKGROUND AND RATIONALE

2.1 Hypercholesterolemia and the Pediatric Population

Hypercholesterolemia (elevated serum low-density lipoprotein cholesterol [LDL-C]) is an established risk factor for coronary heart disease (CHD) in humans (Grundy et al, 2004), and more than 50 million patients are treated for hypercholesterolemia in the United States and Europe (Kuklina et al, 2011; Kotseva et al, 2009; Tolonen et al, 2005). Cholesterol elevations requiring pharmacologic therapy are uncommon in children. However, patients with familial hypercholesterolemia (FH), an almost exclusively autosomal dominant condition most often resulting from deficient or defective LDLR function (Rader et al, 2003), have elevated LDL-C beginning in childhood. Since FH is a genetic condition, the prevalence among children is very similar to the prevalence among younger adults.

In the pediatric population, FH may be identified by the combination of elevated LDL-C and a positive family history of hypercholesterolemia and/or premature cardiovascular disease. HeFH affects approximately one out of every 200 to 500 people worldwide (National Collaborating Centre, 2008; Nordestgaard et al, 2013; Rader et al, 2003). By comparison, homozygous FH (HoFH) is present in approximately 1 in 1,000,000 individuals (Goldstein et al, 2001). Without treatment, these patients have severe hypercholesterolemia, develop premature coronary artery disease, and are at increased risk for premature cardiovascular death (Rader et al, 2003).

In the adult population, hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are currently the treatment of choice for both heterozygous FH patients and homozygous FH patients (Grundy et al, 2004), as statins inhibit endogenous cholesterol biosynthesis and upregulate LDLR expression (increasing the activity of functional LDLR) (Rader et al, 2003). Although statins reduce mortality in this patient population (Raal et al, 2011), cholesterol levels may remain elevated in FH patients despite therapy with diet, exercise, and medications.

Pediatric guidelines in the United States (Daniels and Greer, 2008; McCrindle et al, 2007; Kavey et al, 2006) recommend considering pharmacologic

treatment after initial treatment with lifestyle modification has failed in patients ≥ 10 years of age with LDL-C that is:

- ≥ 130 mg/dL (3.4 mmol/L) for the highest risk (eg, diabetes mellitus)
- ≥ 160 mg/dL (4.1 mmol/L) for intermediate risk (eg, ≥ 2 other CHD risk factors, family history of premature coronary artery disease [CAD])
- ≥ 190 mg/dL (4.9 mmol/L) for the lowest risk (no cardiovascular risk factors)

Similarly, treatment guidelines from the European Society of Cardiology and European Atherosclerosis Society (ESC/EAS; Reiner et al, 2011) and from the National Institute for Health and Clinical Excellence (NICE; National Collaborating Centre, 2008) recommend statin treatment in patients who are ≥ 10 years of age and have HeFH or HoFH, and consider pharmacologic treatment for subjects with HoFH at earlier ages (Reiner et al, 2011). When a child with FH has exceptionally high LDL-C and/or cardiovascular risk, bile acid sequestrants and ezetimibe are also indicated and may be used in combination.

Thus, while currently available therapies can reduce LDL-C levels, novel therapies that can be used alone or in combination with existing agents to more effectively reduce LDL-C would be valuable for both adults and pediatric patients with severely elevated cholesterol levels.

2.2 Amgen Investigational Product

2.2.1 Background and Nonclinical Studies

Recycling of the hepatic cell surface low-density lipoprotein receptor (LDLR) plays a critical role in regulating serum LDL-C levels. Proprotein convertase subtilisin/kexin type 9 (PCSK9) binds to the LDLR and down regulates hepatic cell surface LDLR, which, in turn, leads to increased levels of circulating LDL-C. Humans with PCSK9 loss-of-function mutations have cholesterol levels lower than normal and reduced incidence of CHD (Abifadel et al, 2009). Evolocumab (formerly referred to as AMG 145) is a fully human monoclonal immunoglobulin G2 (IgG2), developed at Amgen Inc., that specifically binds to PCSK9 preventing its interaction with the LDLR. The inhibition of PCSK9 by evolocumab leads to increased LDLR expression and subsequent decreased circulating concentrations of LDL-C.

Evolocumab binds to human, cynomolgus monkey, and hamster PCSK9 with a similar high affinity (dissociation equilibrium constant [K_D] = 16, 8, and 14 pM, respectively) and

is pharmacologically active in both animal species. Evolocumab exhibited nonlinear PK consistent with target-mediated elimination and a low volume of distribution (V_{ss}/F) indicating limited tissue distribution. A concentration-response relationship was observed between serum unbound evolocumab, free PCSK9, and LDL-C.

Evolocumab-related effects were limited to expected pharmacology (serum LDL-C and total cholesterol lowering). Toxicological assessments included repeated dose studies in the hamster and cynomolgus monkey (up to 3- and 6-months, respectively) at evolocumab dose levels up to 300 mg/kg, a 3-month repeated dose study in the cynomolgus monkey in which evolocumab was dosed in combination with rosuvastatin, a hamster carcinogenicity study, a hamster fertility study, and an enhanced pre-post natal development study in the cynomolgus monkey. No evolocumab-related adverse effect was observed in any study.

Refer to the specific sections of the AMG 145 Investigators Brochure for additional information related to the physical, chemical, and pharmaceutical properties of evolocumab.

2.2.2 Clinical Studies

Evolocumab is intended for long-term use and has been evaluated in approximately 6800 subjects in 26 clinical studies to date. Regulatory submissions have been filed in several jurisdictions, including to the Food and Drug Administration (FDA) in the United States and to the European Medicines Agency (EMA) in Europe. The submissions are based on a phase 3 program which evaluated evolocumab administered every two weeks and monthly in various treatment settings (ie, in combination with statins, statin-intolerant, heterozygous familial hypercholesterolemia [HeFH] or as an adjunct to diet [monotherapy]). Additional studies with evolocumab are ongoing or planned, including studies to provide additional long-term safety and efficacy data, studies to determine the effect of evolocumab on coronary atherosclerosis, and studies to evaluate the effects of evolocumab on lipoprotein metabolism. The FOURIER trial is a large cardiovascular outcomes trial that is ongoing.

The combined PK data including phase 1, 2 and 3 studies have consistently shown that evolocumab displays approximately dose-proportional increases in exposure for repeated dose regimens $\geq$ 140 mg SC.

Pharmacodynamic (PD) studies explored LDL-C and unbound PCSK9 responses after administration of a wide range of SC doses and dosing frequencies. With the 140 mg

once every 2 weeks (Q2W) and 420 mg QM (once monthly) regimens, maximal LDL-C reduction was observed at 1 week or 2 weeks following administration, respectively, and returned towards baseline at the end of the dosing interval.

A side-by-side analysis of efficacy across the individual phase 3 primary hyperlipidemia and mixed dyslipidemia studies demonstrated the following for evolocumab administered 140 mg Q2W and 420 mg QM:

- Evolocumab was superior to placebo in reducing LDL-C (approximately 55% to 75% compared with placebo), total cholesterol, apolipoprotein B (ApoB), non-high density lipoprotein cholesterol (non-HDL-C), total cholesterol/high-density lipoprotein cholesterol (HDL-C), and ApoB/apolipoprotein A1(ApoA1) very low-density lipoprotein cholesterol (VLDL-C), triglycerides, lipoprotein(a) (Lp[a]), and increasing HDL-C and ApoA1.
- Evolocumab reduced LDL-C as early as week 1 following administration, generally achieved maximal response within 1 to 2 weeks after dosing with 140 mg Q2W and 420 mg QM, respectively, and maintained efficacy with long-term use.
- Reductions in LDL-C and improvements in other lipid parameters were reversible upon cessation of treatment, with no evidence of rebound.
- Evolocumab 140 mg Q2W and 420 mg QM dosing regimens were clinically equivalent; no clinically meaningful differences, with respect to reductions in LDL-C and improvements in other lipid parameters, were noted between the 2 doses.
- Evolocumab 140 mg Q2W and 420 mg QM dosing regimens were effective in all subgroups relative to placebo and ezetimibe with no notable differences observed among subgroups (ie, age, race, gender, region, body mass index, current smoking status, baseline CHD risk factors, family history of premature CHD, glucose tolerance status [diabetes mellitus type 2, metabolic syndrome, or neither], hypertension, unbound baseline PCSK9, baseline LDL-C, baseline triglycerides, and National Cholesterol Education Program [NCEP], 2002 high risk status).
- Administration of evolocumab with the prefilled autoinjector/pen (AI/pen) was shown to be safe and effective for its intended use and the conditions of use, including self-administration in the home-use setting.

The results of the analyses conducted in the primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia integrated safety analysis set for evolocumab demonstrated the following with respect to safety:

- In the integrated parent studies, the most common (≥ 2%) adverse events in the combined evolocumab group or control group were nasopharyngitis, upper respiratory tract infection, headache, back pain, and myalgia. Common adverse events in the year 1 standard of care (SoC)-controlled period did not include headache and myalgia; otherwise, common adverse events were the same as integrated parent studies with the addition of arthralgia and hypertension. There were no additional common adverse events during the year 2+ open-label extension (OLE) period.

- The types and incidence of adverse events were consistent across studies where evolocumab was given as monotherapy, in combination therapy with statins (with or without ezetimibe) or in subjects with statin intolerance.
- Most adverse events were grade 1 or 2.
- Serious adverse events, deaths, positively adjudicated clinical events, and adverse events leading to discontinuation of investigational product (IP) were infrequently reported and similar across treatment groups.
- No safety issues were detected for adverse events of interest associated with other lipid-lowering therapies (ie, diabetes adverse events, liver-related adverse events, muscle-related adverse events, neurocognitive adverse events) and those that could theoretically be associated with PCSK9 inhibition/LDL-C receptor upregulation (ie, hepatitis C events). No cognitive adverse events have been reported among adolescents in the completed Study 20110233 or in the ongoing open-label evolocumab-only Study 20110271.
- The device-related adverse events from the 3 SC presentations (ie, pre-filled syringe [PFS], prefilled AI/pen, and automated mini doser [AMD]) were uncommon, mostly grade 1, and generally limited to injection site reactions.
- An evaluation of vitamin E data showed that long-term evolocumab exposure (52 weeks) did not change normalized vitamin E levels, regardless of LDL-C concentration. Similarly, long-term evolocumab exposure (52 weeks) did not affect steroid hormone levels (cortisol, adrenocorticotropic hormone, follicle-stimulating hormone, luteinizing hormone, testosterone, or estradiol), regardless of LDL-C concentration.
- The type and incidence of adverse events observed in subjects with LDL-C concentrations < 25 mg/dL (< 0.6 mmol/L) and < 40 mg/dL (< 1.0 mmol/L) were similar to those observed in subjects with LDL-C concentrations ≥ 40 mg/dL (≥ 1.0 mmol/L). In particular, no safety signal was identified for neurocognitive adverse events, vitamin E levels, or steroid analytes based on LDL-C concentrations.
- Presence of anti-evolocumab antibodies was infrequent, non-neutralizing, and not associated with clinically relevant adverse events.

Refer to the AMG 145 Investigators Brochure for additional information regarding the clinical experience with evolocumab.

2.3 Pediatric Risk Assessment

Loss-of-function (LOF) mutations of the PCSK9 gene are associated with low serum LDL-C levels (≤ 100 mg/dL [2.6 mmol/L]) (Cohen et al, 2005). Subjects with heterozygous PCSK9 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). Importantly, despite complete loss of PCSK9 and associated very low serum LDL-C levels (< 20 mg/dL [0.5 mmol/L]), 2 subjects with LOF mutations in both PCSK9 alleles appear healthy (Hooper et al, 2007; Zhao 2006).

The subjects in this study are a pediatric population. In Amgen's development program for evolocumab, 2 studies to date have included pediatric subjects along with adults. The completed Study 20110233 was a phase 2/3 study of subjects 12 to 80 years of age with HoFH; Part A of Study 20110233 was an open-label pilot study in 8 subjects and Part B of Study 20110233 was a randomized, double-blind, placebo-controlled study of 49 subjects (Raal et al., 2014). The ongoing Study 20110271 is a phase 2/3, multicenter, open-label study of evolocumab in approximately 310 subjects 12 to 80 years of age with severe FH.

To date, 15 subjects < 18 years of age and with HoFH or compound HeFH have been enrolled in Studies 20110233 and 20110271; 10 participated in both studies, 4 participated only in Study 20110271, and 1 participated only in Study 20110233. Based on the most recent data cut off of 01 July 2014, all adolescent subjects in Study 20110271 have HoFH. Per protocol, the non-apheresis subjects (n=10) began the study on 420 mg QM, while the apheresis subjects (n=4) began the study on 420 mg Q2W. In general, no differences in the safety profile have been seen in pediatric subjects relative to adults. In Study 20110271, the subject incidences of treatment emergent adverse events and serious adverse events were 71% and 14% among adolescents, compared to 68% and 10% among all subjects with HoFH. Average exposure to evolocumab was longer among adolescents, median 11.4 months vs 7.5 months in adults with HoFH. Among pediatric subjects, a total of 28 adverse events have been reported in Study 20110271. All but 2 of these events were deemed non-serious and were Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or 2. The 2 serious adverse events (worsening of chest pain and occlusive coronary artery disease) were both CTCAE grade 3 and unrelated to IP, and are both known cardiovascular consequences of the subjects' underlying FH. No serious adverse events were deemed by the investigator to be related to evolocumab.

The dose of 420 mg evolocumab SC was selected based on pharmacokinetic modeling for this pediatric age group (Section 2.4) and is supported by the current safety experience with the same dosing in pediatric subjects in Studies 20110233 and 20110271.

As in studies with adult subject, the subjects in this study will be monitored for the development of anti-evolocumab antibodies. To date, the overall immunogenicity rate is < 1% and the formation of neutralizing anti-evolocumab antibodies has not been observed.

Volumes of blood withdrawn for analysis will be minimized as appropriate for this pediatric population.

2.4 Rationale

FH is a genetic disorder which typically requires lifelong treatment, sometimes beginning in childhood. It is therefore important to study the safety and efficacy of potential treatments for FH in children and adolescents. Because developmental processes that are complete in adults are ongoing in children and adolescents, additional safety assessments (eg, biochemical and clinical assessments of puberty, carotid intimal medial thickness, and cognition) are also appropriate. Data from a dedicated randomized placebo-controlled study of evolocumab and adolescents will support the existing data from nonclinical studies in ages corresponding to human adolescence and clinical data from adolescent subjects participating in the TESLA and TAUSSIG studies.

The safety and efficacy of evolocumab 420 mg SC QM in adults have been extensively studied in phase 2 and phase 3 clinical trials. Additionally, in the two studies that have included pediatric subjects (TESLA and TAUSSIG), evolocumab lowered LDL-C and other lipid parameters in subjects aged 12-17 years. The percent change from baseline in LDL-C has been chosen as the primary assessment for this study because of the extensive body of data from interventional studies and epidemiological evidence demonstrating a strong causal relationship between serum LDL cholesterol, and the risk of CHD. These data also support the relationship with other clinical manifestations of atherosclerosis such as cerebrovascular disease (stroke) or peripheral vascular disease. These relationships are present over a broad range of LDL-C levels. Additionally, current guidelines focus on LDL-C as a target for therapy.

Non-HDL cholesterol (non-HDL-C), ApoB, the ratio of total cholesterol/HDL-C, the ratio of ApoB/ApoA1, and Lp(a) have been included as secondary efficacy endpoints because these markers are known as useful markers of cardiovascular risk under certain circumstances and because they may be employed as future targets for lipid lowering therapy.

Additional endpoints include triglycerides and HDL-C because data in adults demonstrates lowering of triglycerides and raising of HDL-C with evolocumab. In addition, triglycerides and HDL-C are independent risk factors for cardiovascular disease (Austin et al, 1998; Sarwar et al, 2007).

Pharmacokinetic data from the 2 studies with evolocumab that included adults as well as pediatric subjects age 12 years and older (Studies 20110233 and 20110271) show that exposure among pediatric subjects is comparable to that seen in adults of similar weight. Further pharmacokinetic modeling to predict the optimal dosing regimen for pediatric subjects 10 to 17 years of age shows that the exposure with monthly administration of 420 mg evolocumab SC in these subjects is expected to fall within in the range observed to date in the evolocumab development program.

2.5 Clinical Hypotheses

The primary hypothesis is that SC evolocumab will be well tolerated and will result in greater reduction of LDL-C, defined as percent change from baseline to week 24, compared with placebo, when added to standard of care in pediatric subjects 10 to 17 years of age with HeFH

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a randomized, placebo-controlled, double-blind, parallel group, multicenter study. Subjects are eligible for screening if they are 10 to 17 years of age at time of randomization and have met the local applicable diagnostic criteria for HeFH. Subjects considered for enrollment will undergo screening assessments, including laboratory screening by central laboratory. Approximately 150 eligible subjects will be randomized in a 2:1 ratio to receive 24 weeks of QM evolocumab or placebo. Randomization will be stratified by screening LDL-C (< 160 mg/dL [4.1 mmol/L] vs ≥ 160 mg/dL) and age (< 14 years vs ≥ 14 years) at randomization.

The study includes collection of biomarker development samples. Where permitted by local regulations, subjects will be invited to consent to pharmacogenetic analyses.

Events of death, myocardial infarction (MI), hospitalization for unstable angina, coronary revascularization, stroke, transient ischemic attack (TIA), and hospitalization for heart failure will be adjudicated by an independent Clinical Events Committee (CEC). Subject incidence of exploratory endpoint events will be summarized for each treatment group. Processes of event identification and submission to the CEC are described in a CEC **Endpoint Reporting** Manual.

An independent data monitoring committee (DMC) will formally review the accumulating data from this and other completed and ongoing studies with evolocumab to ensure

there is no avoidable increased risk for harm to subjects. Analyses for the DMC will be provided by a group which is external to Amgen.

After completion of Study 20120123, subjects will be offered participation in an extension study where they will receive open-label evolocumab.

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

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

This study will include approximately 30 sites in North America, Latin America, Europe, Australia, and New Zealand, and may include sites in Middle East. Additional sites may be added if necessary to achieve the enrollment goal within the planned time.

Sites that do not randomize subjects within 3 months of being open for enrollment may be closed.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”.

There will be approximately 150 subjects randomized in this study. Justification for the sample size can be found in Section 10.2 Sample Size Considerations.

3.4 Replacement of Subjects

There will be no replacement for randomized subjects.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

After signing the informed consent or subject assent, subjects should be randomized within 8 weeks. Including the screening, study treatment, and follow-up, the maximal total duration of study participation for a subject will be 32 weeks or approximately 8 months.

3.5.2 End of Study

The end of the study (primary completion) is defined as the last day on which a randomized subject in this study completes the end-of-study visit (week 24) or terminates the study early.

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening). This log may be completed and updated via an Interactive Voice Response system (IVRS)/Interactive Web Response system (IWRS).

Before any study-specific activities/procedure, the appropriate written informed consent **(and assent, when applicable)** must be obtained (see Section 11.1). In addition to written informed consent from a legally acceptable representative, the assent of the child also must be obtained, as appropriate if requested by the institutional review board/independent ethics committee (IRB/IEC).

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria

101 Subject has provided **written** informed consent or subject assent prior to initiation of any study-specific activities/procedures.

and/or

102 Subject's legally acceptable representative has provided informed consent when the subject is legally too young to provide informed consent and the subject has provided written subject assent based on local regulations and/or guidelines prior to any study-specific activities/procedures being initiated.

103 Male or female, ≥ 10 to ≤ 17 years of age at time of randomization (includes the year after the subject completes the 17th year after birth but not the day of completing the 18th year after birth).

104 Diagnosis of heterozygous familial hypercholesterolemia by local applicable diagnostic criteria for HeFH (ie, criteria outlined by the Simon Broome Register Group [Scientific Steering Committee, 1991], the Dutch Lipid Clinic Network [World Health Organization, 1999], MEDPED [Williams et al, 1993]), or by genetic testing.

105 On an approved statin with stable dose for ≥ 4 weeks before LDL-C screening and, in the opinion of the investigator, not requiring up-titration.

106 **Subject must be on a low-fat diet, and i**f taking any other lipid-lowering therapy (eg, ezetimibe, bile-acid sequestering resin, omega 3 fatty acids or niacin), this therapy must be unchanged for ≥ 4 weeks prior to LDL-C screening; fibrates must be stable for at least 6 weeks prior to screening.

107 Fasting LDL-C at screening ≥ 130 mg/dL (3.4 mmol/L) as determined by central laboratory.

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

4.1.2 Exclusion Criteria

201 **Homozygous familial hypercholesterolemia**

202 **Lipid apheresis within the last 12 weeks prior to screening**

203 Type 1 diabetes or newly diagnosed (within 3 months of randomization) type 2 diabetes, or poorly controlled type 2 diabetes (HbA1c > 8.5%) or newly diagnosed impaired glucose tolerance (within 3 months of randomization).

204 Untreated or inadequately treated hyperthyroidism or hypothyroidism as defined by thyroid stimulating hormone (TSH) < lower limit of normal (LLN) or > 1.5 times the upper limit of normal (ULN), respectively, and free thyroxine (T4) levels that are outside normal range at screening.

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

206 Persistent active liver disease or hepatic dysfunction, defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 times the ULN as determined by central laboratory analysis at screening, confirmed by a repeat measurement at least 1 week apart.

207 Creatine kinase (CK) > 3 times the ULN at screening, confirmed by a repeat measurement at least 1 week apart.

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

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

210 Subject has taken a cholesterylester transfer protein (CETP) inhibitor such as anacetrapib, dalcetrapib or evacetrapib in the last 12 months, or mipomersen or lomitapide in the last 5 months prior to LDL-C screening.

211 Subject has previously received evolocumab or any other investigational therapy to inhibit PCSK9.

212 Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study(s). Other investigational procedures or treatments while participating in this study are excluded.

213 Female subject who has experienced menarche and unwilling to use acceptable method(s) of effective birth control during treatment with IP (evolocumab or placebo) and for an additional 15 weeks after the end of treatment with IP (evolocumab or placebo). A female who has experienced menarche is considered of childbearing potential.

- Acceptable methods of preventing pregnancy include: true sexual abstinence when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception), or use of hormonal birth control methods (oral, implantable, injectable, transdermal, intravaginal), intrauterine devices (IUDs), intrauterine hormonal-releasing system (IUS), or two (2) barrier methods (one by each partner and at least one of the barrier methods must include spermicide, unless spermicide is not approved in the country or region - the male must use a condom and the female must choose either

a diaphragm OR cervical cap, OR contraceptive sponge. Note: a male and female condom cannot be used together due to the risk of tearing.)

Note: If additional medications are given during treatment which may alter the contraceptive requirements (these additional medications may require an increase in the number of contraceptive methods and/or length of time that contraception is to be utilized ***or length of time breastfeeding is to be avoided*** *after the last dose of protocol-required therapies) the investigator is to discuss these changes with the study subject.*

214 Female subject with a positive pregnancy test

215 Female subject is pregnant or breast feeding, or planning to become pregnant or planning to breastfeed during screening, during treatment with IP (evolocumab or placebo), and within 15 weeks after the end of treatment with IP (evolocumab or placebo).

216 Known sensitivity to any of the active substances or their excipients to be administered during dosing, eg, carboxymethylcellulose.

217 Subject will not be available for protocol-required study visits or procedures, to the best of the subject and investigator's knowledge (Note: Day 1 and week 24 visits must be scheduled at approximately the same time of day, and should be performed as close as possible to 8 am as the hormones measured have diurnal variation).

218 History or evidence of any other clinically significant disorder, condition or disease, or planned or expected procedure that, in the opinion of the Investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written IRB/IEC approval of the protocol, AMG 145 Investigator's Brochure (IB), informed consent form (ICF), and all other subject information and/or recruitment material, if applicable (see Section 11.2). All subjects or parents/legally acceptable representatives must personally sign and date the informed consent form or subject assent form before commencement of study-specific activities/procedures.

Each subject who enters into the screening period for the study receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by the IVRS/IWRS. The investigator or designee must contact the IVRS/IWRS to register subjects once the informed consent, and subject assent if applicable, is signed to obtain the unique subject identification number. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment CRF.

5.1 Randomization/Treatment Assignment

Assignment to the 2 treatment arms (Section 3.1) will be based on a computer-generated randomization schedule prepared by Amgen before the start of the study.

Each subject will receive a unique randomization number and each randomization number will only be assigned to 1 subject. Randomization will be stratified by screening LDL-C (< 160 mg/dL [4.1 mmol/L] vs ≥ 160 mg/dL) and age (< 14 years vs ≥ 14 years) at time of randomization.

Once the investigator decides that a subject has met all eligibility criteria, a site representative will make the randomization call to the IVRS/IWRS to assign a randomization number to the subject. The randomization call to the IVRS/IWRS is accomplished by entering the pertinent information as detailed in the IVRS/IWRS user manual. A confirmation fax or email will be sent to the site to verify that the correct information has been entered and to confirm the assignment of a randomization number.

The randomization date is to be documented in the subject's medical record and on the enrollment electronic case report form (eCRF).

5.2 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject on this study. Unblinding at the study site for any other reason will be considered a protocol deviation. The investigator is strongly encouraged to contact the Amgen Clinical Study Manager before unblinding any subject's treatment assignment, but must do so within 1 working day after the event.

6. TREATMENT PROCEDURES

6.1 Classification of Products and Medical Devices

The Amgen investigational medicinal products used in this study include: evolocumab and matching placebo.

The medical device used in this study is the prefilled autoinjector/pen (AI/Pen).

An Investigational Product Instruction Manual (IPIM) and the Instructions For Use (IFU), documents external to this protocol, contain detailed information regarding the storage, preparation, **destruction,** and administration of investigational product.

6.2 Amgen Investigational Product Evolocumab and Placebo

Evolocumab and placebo will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical IP distribution procedures. Evolocumab 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, SC injection. The prefilled AI/Pen contains a 1.0 mL deliverable volume of 140 mg/mL evolocumab or 1.0 mL deliverable volume of placebo.

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

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

6.2.1 Dosage, Administration, and Schedule

IP (evolocumab or matching placebo) will be administered SC in accordance with instructions in the IPIM and IFU. IP administration by SC injection if performed during a study visit must occur after vital signs, electrocardiogram (ECG), and blood draw procedures, if applicable. After IP administration at the first dosing visit, subjects will be held for observation for at least 30 minutes before being discharged.

Each QM administration of IP will consist of 3 injections of 140 mg evolocumab or placebo in 1.0 mL (administration by prefilled AI/Pen) for a total of 3.0 mL (placebo or 420 mg evolocumab) administered.

In this study, subjects have the option of self-administration, defined as SC administration of IP by the subject, designee or a qualified health care professional in a non-investigator site setting (eg, at home). 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.

Details of preparing IP and the injection procedures are included in the IPIM and IFU provided by Amgen prior to the start of the study. The dosing schedule is described by a schema in the protocol synopsis.

When IP is mandated to be administered at the study site, the date and completion time of administration, the body location of the injection, and whether the injection was fully or partially administered are to be recorded on each subject's CRF.

When IP can be administered at a non-investigator site location, at a minimum, the dates the devices were dispensed and the used devices returned, and for each device whether it was returned fully or partially used are to be recorded on each subject's CRF.

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

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

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

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

6.3 Other Protocol-required Therapies

All lipid-lowering drugs that are allowed per protocol and that the subject may be taking, must be commercially available and are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these drugs. All such therapy needs to be stable and unchanged during the entire time of screening and study participation unless a change is clinically necessary.

6.4 Withholding of Amgen Investigational Product or Statin Background Therapy due to 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, the subject's CK levels should be measured and if CK is > 5x ULN, the subject should be instructed to discontinue statin background therapy and IP. CK must be retested before any statin or IP is administered.

The following rules apply:

CK at prior visit	CK on retest	Amgen Investigational Product and Non-Amgen Statin Background Therapy Administration
> 5x ULN	> 10x ULN	Discontinue statin and IP[a]. Contact Amgen Medical Monitor
	> 5x to ≤ 10x ULN	Discontinue statin and retest CK before statin administration. Consider continuing IP if alternative explanation
	≤ 5x ULN	Consider continuing IP and statin

[a] CK elevations >10x ULN that have been confirmed to be secondary to myocardial infarction do not require discontinuation of Amgen IP or non-Amgen statin background therapy.

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

6.5 Hepatotoxicity Stopping and Rechallenge Rules

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

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

Statin and investigational product should be discontinued permanently and the subject should be followed according to the recommendations in Appendix A (Additional Safety

Assessment Information) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:

- TBL > 2x ULN or INR > 1.5 (testing determined per Appendix A)

AND

- AST or ALT > 3x ULN

AND

- no other cause for the combination of the above laboratory abnormalities is immediately apparent; important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:
  - hepatobiliary tract disease
  - viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
  - right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia.
  - exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
  - heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
  - alpha-one antitrypsin deficiency
  - alcoholic hepatitis
  - autoimmune hepatitis
  - Wilson's disease and hemochromatosis
  - nonalcoholic fatty liver disease including steatohepatitis (NASH)
  - Non-hepatic causes (eg, rhabdomyolysis, hemolysis)

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

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

- AST or ALT > 8x ULN at any time
- AST or ALT > 5x ULN but < 8x ULN for ≥ 2 weeks (or subject unable to adhere to enhanced monitoring schedule)

- ALT or AST > 3x ULN with 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%)
- TBL > 3x ULN at any time
- ALP > 8x ULN at any time

Both statin and investigational product should be withheld pending investigation into alternative causes of DILI. If statin or investigational product is withheld, the subject is to be followed according to recommendations in Appendix A for possible DILI. Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (Section 6.5.3).

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

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

If signs or symptoms recur with rechallenge, then investigational product should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.5.1) should never be rechallenged.

6.6 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.9.

All concomitant therapies are to be collected from start of screening through the end-of-study (EOS), including medications being taken at the time of enrollment. This includes all lipid-regulating medications (eg, statin, ezetimibe, fibrates, cholesterol absorption inhibitors, and bile acid sequestrants). Therapy name, indication, dose, unit, frequency, route, start date and stop date will be collected.

6.7 Medical Devices

IP (evolocumab and placebo) will be provided by prefilled AI/pen (Section 6.2). The prefilled AI/pen is a modified version of the SureClick™ autoinjector, a device that is commercially available for the administration of Aranesp® or Enbrel® drug product by patients or caregivers in a non-healthcare environment, or by healthcare professionals in the clinic environment in the United States (Enbrel® only) and in Europe.

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

6.8 Product Complaints

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

Any product complaints associated with the medicinal product, prefilled AI/Pen or other Amgen provided, protocol-required product in this study must be reported to Amgen within 24 hours of discovery or notification of the complaint. Please do not use the device or product that is subject of a complaint until Amgen confirms that it is permissible to do so.

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

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

If possible, please have the device or medicinal product associated with the complaint available for examination when reporting a product complaint. Maintain device 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 complaints observed by the investigator or reported by the subject that occur after signing of the informed consent

through 30 days after the last dose of IP or EOS, whichever is later, are reported to Amgen within 24 hours of discovery or notification of the product complaint.

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

6.9 Excluded Treatments and/or Procedures During Study Period

The following treatments are not permitted during the study, including screening:

- lipid apheresis
- treatments for inhibition of PCSK9 or any investigational therapies other than study provided investigational product
- mipomersen or lomitapide
- red yeast rice
- other drugs (besides those mentioned above) that significantly affect lipid metabolism (eg, systemic cyclosporine, systemic steroids [intravenous, intramuscular, or oral; *Note: hormone replacement therapy is permitted*], vitamin A derivatives and retinol derivatives for the treatment of dermatologic conditions [eg, Accutane; *Note: Vitamin A as part of a multivitamin preparation is permitted*]).
- prescribed amphetamines, or amphetamine derivatives, and weight loss medications.
- all lipid therapies not taken at the time of screening and enrollment

Please contact the Amgen medical monitor or designee if any of these therapies should be initiated during the study. Note that a change in lipid lowering therapy does not necessarily require ending IP (except in case of non-study provided PCSK9 inhibition therapy).

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

- medications or foods that are known potent inhibitors of CYP3A (eg, Itraconazole, ketoconazole, and other antifungal azoles, macrolide antibiotics erythromycin, clarithromycin, and the ketolide antibiotic telithromycin, HIV or hepatitis C virus (HCV) protease inhibitors, antidepressant nefazodone and grapefruit juice in large quantities (> 1 quart daily [approximately 1 Liter]) should not be used during the study.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Table 1. Schedule of Assessments

Study Day / Week / Other Timepoint[a]	Screen	Rand D1	W4 (±3d)	W8 (±3d)	W12 (±3d)	W16 (±3d)	W20 (±3d)	W22 (±3d)	W24 (EOS) (±3d)
Study Day[a]		*D1*	*D29±3*	*D57±3*	*D85±3*	*D113±3*	*D141±3*	*D155±3*	*D169±3*
General Procedures									
Parental/guardian informed consent/permission & subject assent/consent	X								
Medical history	X								
Vital Signs (sitting BP, HR)	X	X	X		X		X	X	X
Review for AEs/SAEs/**ADEs/DREs**/CV events	X[b]	X	X	(X)[b]	X	(X)[b]	X	X	X
Concomitant therapy	X	X	X		X		X	X	X
Dietary instruction	X	X							
Physical exam (including neurologic examination; see Section 7.7.8)	X								X
Body weight, waist circumference, cIMT, Tanner staging		X							X
Body height		X							X
Cogstate neurocognitive assessment[c]	X	X							X
12 lead ECG		X			X				X
Randomization		X[d]							
Central Laboratory[e]									
Fasting lipids[e]	X	X			X			X	X
ApoA1, ApoB100, Lp(a)[f]		X			X			X	X
PK (evolocumab), [redacted]		X			X			X	X
Chemistry, including fasting glucose[f]	X				X				X
Hematology	X				X				X
HbA1c	X								X
Estradiol (females) / testosterone (males)		X							X
hsCRP, CK, FSH, LH, ACTH, DHEA-S, cortisol**, Fasting vitamins A/D/E/K**		X							X
TSH	X								
Biomarkers (blood)[g]		X							X
Anti-evolocumab antibodies		X			X				X
HCV testing[h]	X								
HCV viral load[h]		X							X
Serum pregnancy[i]	X								X
Urine pregnancy[i]		X			X				
Urinalysis, urine microalbumin		X			X				X
Investigational Product									
Screening placebo injection	X								
AI/Pen Instruction		X	X		X				
AI/Pen dispensation			X		X				
AI/Pen reconciliation					X		X		
IP (AI/Pen) administration on-site		X	X		X		X		
IP (AI/Pen) administration on-site or in non-investigator site setting				X		X			

Footnote defined on the next page.

[a] D1 = day of first administration of IP; a visit window of ± 3 days applies to all other visits. Note: Day 1 and week 24 visits must be scheduled at approximately the same time of day, and should be performed as close as possible to 8 am as the hormones measured have diurnal variation.

[b] only AEs possibly related to study procedures and SAEs are collected during screening (from signing of ICF or subject assent, whichever is later); week 8 and week 16 AEs/SAEs/**ADEs/DREs/**CV events collection only if visit to study site. **ADEs/Product Complaints are reported that occur after signing of the informed consent through 30 days after the last dose of IP or EOS, whichever is later.**

[c] Cogstate cognitive battery tests (see Section 7.7.7)

[d] randomization should be on day 1 or as close as possible to day 1 and must not be earlier than 5 days prior

[e] blood samples must be taken prior to IP administration, if applicable

[f] if subject is not fasting on day 1, reschedule; if subject is not fasting after day 1, do all procedures except fasting labs and IP administration, if applicable; schedule another visit, if possible within the visit window for fasting labs and IP administration

[g] if parental/guardian consent or permission and subject consent or assent to pharmacogenetics analyses has been provided, deoxyribonucleic acid (DNA) will be extracted from some of the blood samples, eg, biomarker samples

[h] HCV antibodies only in subjects at high risk for, or with history of, HCV infection (see Section 7.2.1.2) or if ALT or AST > 2x ULN at any time during screening; viral load only in subjects positive for HCV

[i] pregnancy testing in females of childbearing potential (additional pregnancy tests may be conducted if there is concern that a female subject has become pregnant).

Refer to Sections 7.2 through Section 7.7 and the applicable supplemental laboratory manual, ECG manual, IPIM, and IFU for detailed study procedures.

7.2 General Study Procedures

This is a multi-center, randomized, double-blind, placebo-controlled trial. The study consists of 2 periods:

- screening period
- double-blind treatment period

All on-study visits and dosing should be scheduled from study day 1. Day 1 and week 24 visits must be scheduled at approximately the same time of day, and should be performed as close as possible to 8 am as the hormones measured have diurnal variation. The week 4 visit is 4 weeks after the study day 1 visit, corresponding to study day 29. When it is not possible to perform the study visit at the specified time point, the visit should be performed within ± 3 days (visit window ± 3 days). If a study visit is missed or late, including visits outside the visit window, subsequent visits should resume on the original visit schedule. Missed assessments at prior visits should not be duplicated at subsequent visits. With the exception of screening and rescreen visits, all study procedures for a visit must be completed on the same day.

It is the responsibility of the investigator to ensure that all procedures are performed according to the protocol. 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 study site visit are described below and the timing of the procedures is provided in Table 1. If IP is administered during a study visit, administration must be after completion of vital signs, ECG, and blood draw procedures, as applicable.

Subjects must be fasting for ≥ 9 hours before each study visit. For procedures if the subject is not fasting when presenting at the study site for a visit, please see Section 7.2.1.2 and Section 7.2.2 below.

All screening and on-study laboratory samples will be processed and sent to the central laboratory. Amgen or designee will be responsible for the evaluation of PK (evolocumab) and [redacted] serum levels, anti-evolocumab 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 2 below outlines the specific analytes for serum chemistry, hematology, urinalysis, and other testing to be conducted.

Table 2. Analyte Listing[1]

Chemistry	Coagulation	Urinalysis	Hematology	Other Labs
Sodium	PT/INR (per Appendix A)	Specific gravity	Hemoglobin	Fasting lipids
Potassium		pH	Hematocrit	Total cholesterol
Chloride		Blood	RBC	HDL-C
Bicarbonate		Protein	RDW	LDL-C
Total protein		Glucose	MCV	Triglycerides
Albumin		Bilirubin	MCH	VLDL-C
Calcium		WBC	MCHC	non-HDL-C
Magnesium		RBC	WBC	ApoA1
Phosphorus		Epithelial cells	Platelets	ApoB
Fasting glucose		Bacteria		Estradiol (females)
BUN or Urea		Casts		Testosterone (males)
Creatinine		Crystals		Cortisol
Uric acid				Luteinizing hormone (LH)
Total bilirubin				Adrenocorticotropic hormone (ACTH)
Direct bilirubin				Dehydroepiandrosterone sulfate (DHEA-S)
CK				**Fasting vitamins A, D, E, and K**
ALP				hsCRP
LDH				Lp(a)
AST (SGOT)				Anti-evolocumab antibodies
ALT (SGPT)				[redacted]
				Evolocumab (PK)
				HbA1c
				Pregnancy test (females of childbearing potential)
				FSH
				TSH
				HCV antibody[2]
				HCV viral load[3]

[1] Day 1 and week 24 visits must be scheduled at approximately the same time of day, and should be performed as close as possible to 8 am as the hormones measured have diurnal variation.
[2] HCV antibodies are measured before initiating treatment with IP in subjects at high risk for (see Section 7.2.1.1), or with history of HCV infection and in subjects with ALT or AST > 2x ULN at any time during screening. Please note that subjects with ALT or AST > 2x ULN must be screen failed unless the elevation is transient as confirmed by retesting per Section 7.2.1.4.
[3] Viral load will be tested at the time points indicated in Table 1 in subjects who are positive for HCV.

Since some laboratory results may inadvertently unblind investigators to treatment assignment to evolocumab, central laboratory results of the lipid panel, ApoA1, ApoB, Lp(a), **fasting vitamins A, D, E, and K,** and [redacted] will not be reported to the investigator (or study personnel) post-screening. Investigators should not perform non-protocol testing of these analytes during a subject's study participation from first administration of IP until at least 12 weeks after last IP administration, or the subject's end of study, whichever is later.

7.2.1 Screening Enrollment and Randomization

Subjects who are considered for entry into the study and have the risks and benefits of participating in the study explained**,** will sign and date the informed consent or subject assent form for this study. Screening starts when the subject's legally acceptable representative has provided informed consent and/or the subject has provided informed consent or assent as applicable, whichever is later. Screening should be completed and the subject randomized or screen failed within 8 weeks of the screening start date.

7.2.1.1 Screening Placebo Administration

In order to reduce the burden of unnecessary procedures on subjects who subsequently elect not to participate in the study or continue with study procedures, all subjects will undergo a placebo administration to confirm tolerance of SC administration by SC injection prior to enrollment. This placebo administration can be done before or after screening venipuncture procedures but must be done before randomization. The screening placebo administration consists of 1 injection of 1.0 mL placebo, using 1 prefilled AI/Pen device. This administration is following the same procedures as injections of IP during the treatment period. Further details are provided in the IPIM.

7.2.1.2 Screening

The following procedures are to be completed during the screening period:

- confirmation that the informed consent and subject assent, if applicable, has been signed
- demographic data including sex, age, race, and ethnicity will be collected in order to study their possible association with treatment effectiveness, subject safety, or, for example, to further study biomarker variability
- medical history
- vital signs (sitting blood pressure [BP], heart rate [HR]; see Section 7.7.1)
- review for adverse events/serious adverse events/**ADE** (adverse events possibly related to study procedures and serious adverse events are collected during screening)

- concomitant therapy
- physical examination (including neurologic examination; see Section 7.7.8)
- Cogstate neurocognitive assessment (see Section 7.7.7)
- blood draw for fasting lipids (≥ 9 hour fasting sample), chemistry (including fasting glucose), hematology, HbA1c, TSH, and serum pregnancy (females of childbearing potential only). *Note: eGFR will be calculated by the central laboratory and will be provided to the site for eligibility determination.*
- blood draws for HCV antibodies in subjects at high risk for, or with history of, HCV infection, or with AST or ALT > 2x ULN at any time during screening*
  - High risk subjects for this protocol are those who meet any of the following conditions:
    - ever injected illegal drugs
    - were exposed to blood known to be infected with HCV
    - were ever on chronic hemodialysis
    - are known to be infected with HIV
    - have a known HCV-infected sexual partner
- the subject will be instructed to maintain his/her current diet throughout the course of the study and avoid going on any strict diet or aiming to lose weight during the study
- screening placebo injection as per Section 7.2.1.1; includes instruction/training on AI/Pen device use
- randomization, if eligible (on or as close as possible to Day 1; see Section 7.2.1.3)

* Please note that subjects with ALT or AST > 2x ULN must be screen failed unless the elevation is transient as confirmed by retesting per Section 7.2.1.4.

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

All prohibited lipid lowering therapy (see Section 4.1.2 and Section 6.9) must be discontinued ≥ 4 weeks before screening laboratories are taken or as indicated in Section 4.1.2 and/or Section 6.9, whichever is longer.

7.2.1.3 Randomization

Subjects who continue to meet all eligibility criteria at the end of screening will be randomized and will return to the study site for day 1 procedures while continuing their background lipid-lowering treatment. Randomization should be on day 1 or as close as possible and not earlier than maximally 5 days prior. Subjects can only be randomized 1 time for this study.

7.2.1.4 Retesting

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

7.2.1.5 Rescreening

Subjects with any LDL-C < 130 mg/dL (3.4 mmol/L) during screening are considered screen failures and cannot be rescreened for this study. Suitable subjects who are ineligible at the initial screening for other reasons and have not been randomized can be re-consented and rescreened at a later time unless they withdraw from screening. For subjects who are rescreened, data from the first screening period will not be used for the analysis.

With the exception of the screening placebo injection, rescreened subjects who are re-consented will repeat all screening procedures. Rescreened subjects will maintain the originally assigned subject identification number.

7.2.1.6 Screen Fail

Subjects who fail any of the eligibility criteria during screening or rescreening and have not been randomized need to be screen failed in IVRS/IWRS before they can be re-consented and re-registered in IVRS/IWRS for rescreening.

7.2.2 Treatment and End of Study

Subjects who are randomized will visit the study site for treatment start. The first administration of IP should be on or as close as possible to the day of randomization but not later than 5 calendar days after randomization. Day 1 is defined as the day of first administration of IP. The date of first administration of IP will be recorded in IVRS/IWRS and will determine the schedule of subsequent study visits.

Subjects must be fasting for ≥ 9 hours before each study visit where fasting lipid samples are obtained. If the subject is not fasting for the scheduled study day 1 visit, no visit procedures are performed. The subject must return as soon as possible in a fasting state for study day 1 visit procedures. If the subject is not fasting as required for a visit after study day 1, visit procedures should be completed except for fasting laboratory sample collection and IP administration, if applicable. An extra visit must be completed

for the omitted procedures as soon as possible and, if possible, within the window for the respective visit.

The following procedures will be completed during the 24 week treatment period at the times designated in the Schedule of Assessments (Table 1):

- vital signs (sitting BP, HR; see Section 7.7.1)
- review for adverse events/serious adverse events/**ADE/DRE/**CV events
- review of concomitant therapy
- encourage subject to maintain a stable diet
- physical examination (including neurologic examination; see Section 7.7.8)
- body weight and waist circumference (see Section 7.7.2)
- body height
- Cogstate neurocognitive assessment (see Section 7.7.7)
- 12-lead ECG in triplicate using centralized ECG services equipment
- blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, chemistry, hematology, PK, [redacted] high sensitivity C-reactive protein (hsCRP), **CK, FSH, LH, ACTH, DHEA-S, cortisol, fasting vitamins A, D, E, and K,** Lp(a), biomarkers, anti-evolocumab antibodies, and viral load in subjects positive for HCV
- cIMT
- Tanner staging
- urine sample for urinalysis
- pregnancy testing for females of childbearing potential (serum at screening and EOS; urine at other time points)
- IP administration at the study site (must be after completion of vital signs, ECG, and blood draw procedures, if applicable)
- dispense AI/Pen device with instructions for use

No additional blood will be collected for the pharmacogenetics analyses. For subjects who have consented to the pharmacogenetic portion of this study, DNA will be extracted from blood samples already collected on day 1 or another visit (see Section 7.5 “Pharmacogenetic Studies” and Section 7.6 “Sample Storage and Destruction”).

If a subject withdraws from the study early, all efforts should be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. If possible, the procedures of week 24 should be completed at the time of withdrawal.

Subjects will end the study with the week 24 visit. Note that the week 24 visit must be scheduled at approximately the same time of day as the day 1 visit, as the hormones measured have diurnal variation.

7.3 Antibody Testing Procedures

Blood samples for antibody testing are to be collected per Table 1 for the measurement of anti-evolocumab binding antibodies. All subjects who have received at least 1 administration of evolocumab 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 evolocumab. If results are not provided, no neutralizing antibodies to evolocumab have been detected. Additional blood samples may be obtained to rule out anti-evolocumab antibodies during the study. Subjects who test positive for neutralizing antibodies to evolocumab 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 evolocumab. All follow-up results, both positive and negative will be communicated to the sites. Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-evolocumab antibody response may also be asked to return for additional follow-up testing.

7.4 Biomarker Development

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

It is expected that further advances will occur in the future in investigational techniques that look at markers of [redacted] It is not possible at this stage to anticipate what these advances will be; however, considerable benefit could accrue to future sufferers of coronary artery disease if these markers can be correlated with the data from the study. It is also important to clarify any potential drug interactions in this population of subjects who will be on a number of other drugs. For biomarker analysis 14.5 mL of blood will be collected at each of the time points indicated in Table 1 so that biomarkers related to, but

not limited to [redacted] may be studied.

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

7.5 Pharmacogenetic Studies

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

7.6 Sample Storage and Destruction

Any blood sample collected according to the Schedule of Assessments (Table 1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

If permitted by local law and informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand processes related to [redacted]

[redacted] eg, by evolocumab, characterize antibody response, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

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

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

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

7.7 Standardization of Study Procedures

7.7.1 Measurement of Vital Signs

BP and HR will be measured at each visit. Use of an automated oscillometric device for BP measurement is preferred and recommended. BP will initially be recorded in both of the subject's arms unless a concomitant condition favors the use of a particular arm. The arm with the higher systolic reading at screening will then be used for BP

determinations throughout the study. The appropriate size cuff should be used. BP and HR measurements will be determined after the subject has been seated for at least 5 minutes. The subject's pulse should be measured for 30 seconds and the number multiplied by 2 to obtain heart rate. Before randomization, BP measurement can be repeated if the previous reading is outside of the eligibility range. The repeat BP measure should be taken at least 2 minutes following the previous measure.

7.7.2 Height, Weight, and Waist Circumference

Height and weight measurement will be obtained at the time points specified in the Schedule of Assessments (Table 1). If possible, visits with height and weight measurements should be scheduled at a similar time of day (eg, in the morning). Height is measured to the nearest centimeter with the subject's back against a wall. Use of a stadiometer is preferred and recommended. Height is defined as the maximum distance from the floor to the highest point on the head, when the subject is facing directly ahead. Shoes must be off, feet together, and arms by the sides. Head, upper back, buttocks, and heels should be in contact with the wall when the measurement is made. Two (2) measurements of height should be taken at each timepoint and entered into the CRF. Weight is to be measured to the nearest tenth of a kilogram with the subject wearing light clothing and with shoes removed. A properly calibrated digital scale should be used. The scale should weigh in 0.1 kg increments, have a stable weighing platform that can be easily set to zero, be calibrated through professional service or by standard known weight.

For measurement of waist circumference, subjects should wear minimal clothing to ensure that the measuring tape is correctly positioned. Subjects should stand erect with the abdomen relaxed, arms at the sides, feet together and with their weight equally divided over both legs. To perform the waist measurement, the lowest rib margin is first located and marked with a pen. The iliac crest is then palpated in the midaxillary line, and also marked. It is recommended to apply an elastic tape horizontally midway between the lowest rib margin and the iliac crest, and tie firmly so that it stays in position around the abdomen about the level of the umbilicus. The elastic tape thus defines the level of the waist circumference, which can then be measured by positioning the measuring tape over the elastic tape. Subjects are asked to breathe normally, and to breathe out gently at the time of the measurement to prevent them from contracting their muscles or from holding their breath. Measurements should be performed using the

same procedure throughout the study. The reading is taken to the nearest centimeter or ½ inch and entered in the source document.

7.7.3 Tanner Staging (Sexual Maturity Ratings)

Tanner staging is widely used to assess adolescents' 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 D 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.

7.7.4 Carotid Intima-Media Thickness (cIMT)

Carotid intima-media thickness will be measured by ultrasonography at the timepoints shown in the Schedule of Assessments in Section 7.1. Sonograms will be sent to a core laboratory for analysis. Please refer to the cIMT instruction manual for detailed information on acquiring, storing, and transmitting the sonograms.

7.7.5 Electrocardiograms

At each scheduled visit where ECGs are being obtained ECGs will be performed in a standardized method, in triplicate, and run consecutively (ie, < 30 seconds apart), prior to blood draws or other invasive procedures. Using equipment supplied to each site, all protocol-specified ECGs will be acquired and transmitted to the centralized ECG services provider. The Principal investigator (PI) or designated physician will review acquired ECGs. One (1) signed, original ECG tracing should be retained with the subject's source documents. At the request of the sponsor, the original ECG should be made available to Amgen to be manually read by a central reader.

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

ECGs required for the clinical management of the subject, using centralized ECG services equipment or equipment on-site.

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

7.7.6 Lipid Measurements

Only the screening LDL-C concentration will be reported to the site for the eligibility decision. Central laboratory results of the lipid panel, as well as ApoA1, ApoB, lipoprotein(a), **fasting vitamins A, D, E, and K,** and [redacted] will be blinded post-treatment until unblinding of the clinical database and will not be reported to the investigator post-screening. In addition, investigators and staff involved with this trial and all medical staff involved in the subject's medical care should refrain from obtaining lipid panels from randomization until at least 12 weeks after the subject's last administration of IP or until the subject ends the study, whichever is later (to avoid potential unblinding). If a lipid panel is drawn, all reasonable steps must be undertaken to avoid informing the subject and study personnel of the results.

7.7.7 Neurocognitive Assessments

The Cogstate cognitive battery is a set of neuropsychological tests administered to subjects via computer. In Study 20120123, the battery will consist of the following 4 tests:

- Groton Maze Learning Task (GMLT; Executive Function): The Groton Maze Learning task is a measure of problem solving and reasoning and uses a well-validated maze learning paradigm. In this task, the subject is shown a 10 x 10 grid of boxes on a computer screen. A 28-step pathway is hidden among these 100 possible locations. Each box represents move locations, and the grid refers to the box array (ie, 10 × 10). Subjects are required to find the hidden pathway guided by 4 search rules. These rules are: do not move diagonally, do not move more than 1 box (ie, do not jump), do not move back on the pathway, and return to the last correct location after an error. At each step, only the most recently selected box is shown. Feedback is given with visual and auditory cues (green check marks and red crosses) to indicate whether the selected box is correct or incorrect. The head of path, or the last correct location, flashes with a green check when two errors are made in succession (failing to return errors). There are 20 well-matched alternate pathways available. The software records each move as an error or as a correct move.
- One Card Learning Test (OCL; Visual Memory): The One Card Learning test is a measure of visual recognition memory and uses a well-validated pattern separation paradigm using card stimuli. In this test, the cards are similar to those found in a deck of playing cards. The subject is asked whether the card currently being presented in the center of the screen was seen previously in this test. The subject responds by pressing the Yes or No key. Because no card has been presented yet, the first response is always No.

- Identification Test (IDN; Attention/Vigilance): The Identification test is a measure of visual attention and uses a well-validated choice reaction time paradigm using card stimuli. In this test, the playing cards are all either red or black. The subject is asked whether the card currently being presented in the center of the screen is red. The subject responds by pressing the Yes key when the card is red and No when it is black.
- Detection Test (DET; Psychomotor Speed): The Detection test is a measure of information processing speed and uses a well-validated simple reaction time paradigm using card stimuli. In this test, the playing cards are all red and black. The subject is asked to press the Yes key as soon as the card in the center of the screen flips over.

This battery will be administered 3 times during the study: during screening, on study Day 1 (baseline), and at Week 24 (EOS). Completion of this test battery will take approximately 15 to 20 minutes at each administration. The Cogstate tests do not require complex language skills for administration, and the forms themselves do not use linguistic stimuli or responses.

Cogstate tests have been used to examine the potential adverse effects of mobile telephone use in young adolescents (Abramson et al, 2009), adolescents with eating disorders (Allen et al, 2013), skipping breakfast in elementary schoolchildren (Kral et al, 2012), dietary patterns in adolescents (Nyaradi et al, 2014), and in utero exposure to cocaine (Mayes et al, 2007). The Cogstate tests have also been used to examine the cognitive effects of treatment with stimulant medication in children with attention deficit hyperactivity disorder (ADHD) ([Mollica et al, 2004]: 8 to 12 year olds; [Snyder et al, 2008]: 6 to 16 year olds), as well as the effects of computerized cognitive rehabilitation in pediatric cerebral malaria survivors as young as 5 years old [Bangirana et al, 2009].

Additionally, regulatory authorities have approved the use of Cogstate tests for monitoring and evaluating the safety of central nervous system penetrant drugs in a range of pediatric indications, including epilepsy, neurogenic detrusor over-activity, bipolar depression, schizophrenia, and hyponatremia, and in children as young as 4 years old. In sports, Cogstate tests are being used to make return-to-play decisions in suspected concussion.

7.7.8 Neurologic Examination

Physical examination (at screening and EOS) should include a neurologic examination. The neurologic physical examination should include assessments of motor, sensory, reflexes, coordination, and gait.

On the relevant eCRF, each area should be described as normal or abnormal, and if abnormal, details should be recorded, including whether there is worsening from baseline.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

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

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 1) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments (Table 1) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study. The investigator should ask the subject's consent to perform the procedures listed under the final study visit.

8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

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

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

8.3 Reasons for Removal From Screening, Treatment, or Study

8.3.1 Reasons for Removal From Screening

Reasons for removal from screening include any of the following:

- subject request
- intolerance of placebo injection during screening
- safety concern (eg, due to an adverse event, failure to follow contraception, pregnancy, or breast feeding)
- decision by sponsor (other than subject request or safety concern)
- death
- lost to follow-up

8.3.2 Reasons for Removal From Treatment

Reasons for removal from protocol-required investigational product or procedural assessments include any of the following:

- subject request
- safety concern (eg, due to an adverse event, failure to follow contraception, pregnancy, breast feeding, and/or protocol requirements)
- death
- lost to follow-up
- decision by Sponsor (other than subject request, safety concern, lost to follow-up)

8.3.3 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of Adverse Events

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

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition **or underlying disease**

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

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

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

9.1.2 Definition of Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria **(unless it meets the definition of a Disease Related Event as defined in Section 9.1.3– below) :**

- 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

A disease related event is to be reported as a serious adverse event if:

- **the subject's pre-existing condition becomes worse than what the investigator would consider typical for a subject with the same underlying condition, or**
- **if the investigator believes a causal relationship exists between the investigational medicinal product(s)/protocol-required therapies and the event,**
- **and the event meets at least 1 of the serious criteria above.**

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

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

9.1.3 Definition of Disease-related Events

Disease-related events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. In this study, such events include atherosclerosis (especially of the coronary arteries) and its complications. Examples include manifestations of myocardial ischemia such as chest pain and myocardial infarction, and percutaneous and surgical revascularization procedures. Such events do not meet the definition of an adverse event unless assessed to be more severe than expected for the subject's condition **or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment protocol required therapies and disease worsening**.

Disease Related Events and/or Disease Related Outcomes that do not qualify as Serious Adverse Events:

- **An event which is part of the normal course of disease under study (eg, disease progression in oncology or hospitalization due to disease progression) is to be reported as a Disease Related Event.**
- **Death due to the disease under study is to be recorded on the Event CRF.**

If the outcome of the underlying disease is worse than that which would normally be expected for the subject, or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment protocol required therapies and disease worsening, this must be reported as an Adverse Event or Serious Adverse Event.

9.2 Reporting of Adverse Events

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

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur **from** randomization and all adverse

events possibly related to study procedures from signing of the informed consent or subject assent through the end of study are reported using the applicable eCRF (eg, Adverse Event eCRF).

The investigator must assign the following adverse event attributes:

- adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- dates of onset and resolution (if resolved),
- severity
- assessment of relatedness to investigational product (evolocumab or placebo or the prefilled autoinjector/pen (AI/Pen device), or other protocol-required therapies/**protocol-required procedure or activity**, and
- action taken.

The adverse event grading scale used will be the most current version of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grading scale. The grading scale used in this study is referenced in Appendix A.

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

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

The investigator must assess whether the adverse event is possibly related to any other study-mandated activity (eg, screening or background therapy/protocol-required therapies). This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by study procedure/activity?"

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

clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

The Investigator is expected to follow reported adverse events until stabilization or reversibility. If the severity of an adverse event worsens from the date of onset to the date of resolution, record a single event for each increased level of severity on the Adverse Event eCRF.

9.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 days after the last dose of IP or EOS, whichever is later, are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the applicable eCRF.

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

If the electronic data capture (EDC) system is unavailable to the site staff to report the Serious Adverse Event, the information is to be reported to Amgen via an electronic Serious Adverse Event (eSAE) Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix B for a sample of the Serious Adverse Event Worksheet/electronic Serious Adverse Event Contingency Report Form. If the first notification of a Serious Adverse Event is reported to Amgen via the eSAE Contingency Report Form, the data must be entered into the EDC system when the system is again available.

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

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

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

The investigator is expected to follow reported serious adverse events until stabilization or reversibility. If the severity of a serious adverse event worsens from the date of onset to the date of resolution, record a single event for each increased level of severity on the Adverse Event eCRF.

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 eCRF).

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

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

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

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

9.2.3 Reporting Procedures for Disease-related Events

The investigator is responsible for ensuring that all disease-related events observed by the investigator or reported by the subject that occur after the first dose of investigational medicinal product(s) through **EOS (including any** follow-up **visits)** are reported using the appropriate Event CRF. Additionally, the investigator is required to report a fatal disease-related event on the CRF.

If the outcome of the underlying disease is worse than that which would normally be expected for the subject, or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment protocol required therapies and disease worsening, this must be reported as an Adverse Event or Serious Adverse Event.

9.3 Pregnancy and Lactation Reporting

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking IP (evolocumab or placebo) report the pregnancy to Amgen as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies the last dose of IP (evolocumab or placebo) through 15 weeks after the end of treatment with IP (evolocumab or placebo).

The pregnancy should be reported to Amgen **Global Patient Safety** within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). If a lactation case occurs while the female subject is taking IP (evolocumab or placebo) report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of IP (evolocumab or placebo) through 15 weeks after the end of treatment with IP (evolocumab or placebo).

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

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Efficacy Endpoint

- Percent change from baseline to week 24 in LDL-C

10.1.1.2 Secondary Efficacy Endpoints

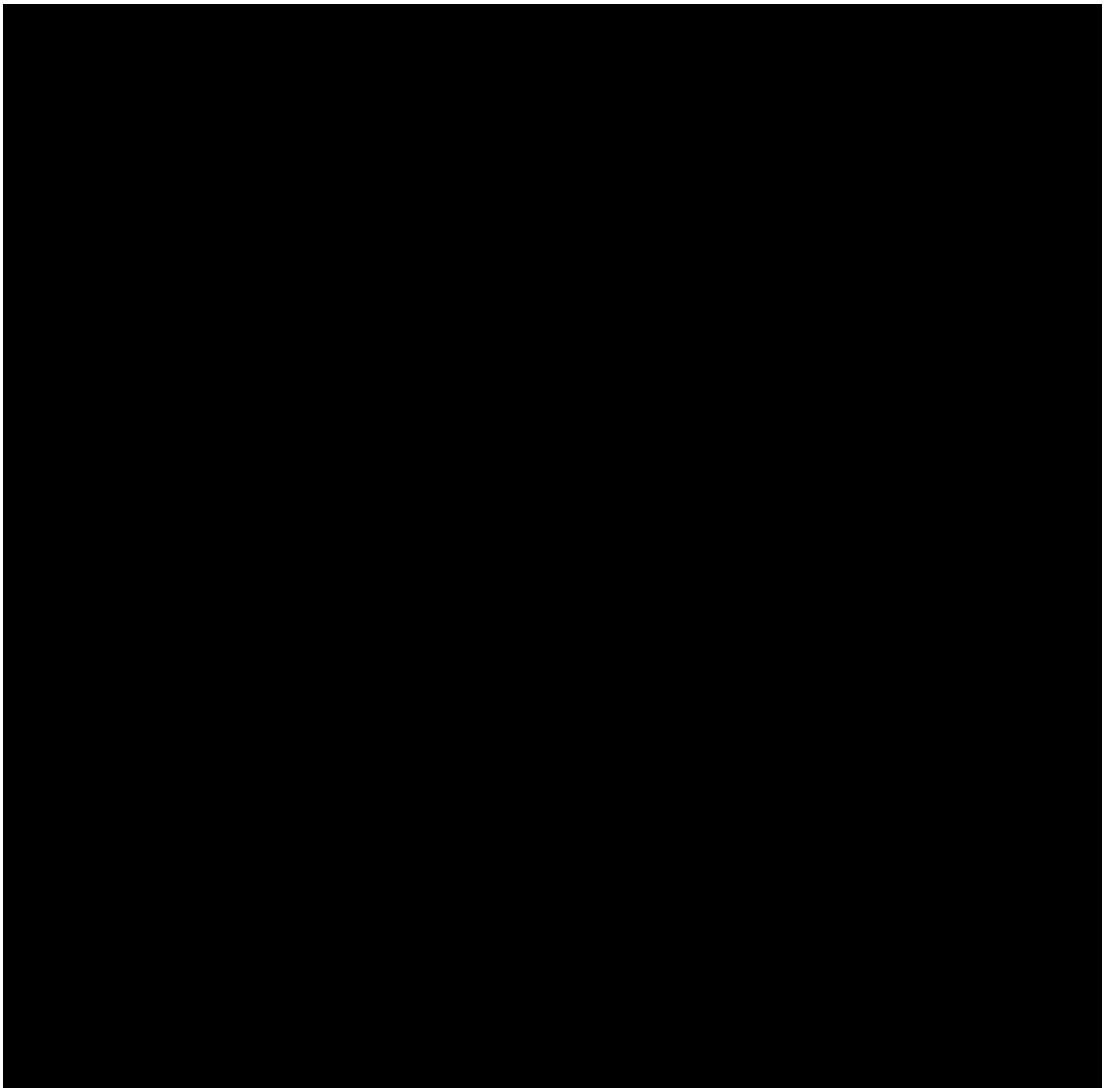
- Mean percent change from baseline to weeks 22 and 24 in LDL-C[1]
- change from baseline to week 24 in LDL-C[2]
- percent change from baseline to week 24 in the following[3]:
  - non-HDL-C
  - ApoB
  - total cholesterol/HDL-C ratio
  - ApoB/ApoA1 ratio

[1,2,3]See Section 10.5.1 for details on multiplicity adjustment.

10.1.1.3 Tertiary Efficacy Endpoints

- Percent change from baseline to week 24 in the following:
  - total cholesterol
  - VLDL-C
  - HDL-C
  - ApoA1
  - triglycerides
  - Lp(a)
- mean percent change from baseline to weeks 22 and 24 in the following:
  - non-HDL-C
  - ApoB
  - total cholesterol/HDL-C ratio
  - ApoB/ApoA1 ratio
  - total cholesterol
  - VLDL-C
  - HDL-C
  - ApoA1
  - triglycerides
  - Lp(a)

10.1.1.4 Exploratory Endpoints



10.1.1.5 Secondary Safety Endpoints

- subject incidence of treatment emergent adverse events
- safety laboratory values and vital signs at each scheduled assessment
- incidence of anti-evolocumab antibody (binding and neutralizing) formation

10.1.1.6 Secondary Pharmacokinetics Endpoints

- Serum concentration of evolocumab at each scheduled assessment

10.1.1.7 Other Safety Endpoints

- Change from baseline score in the components of the Cogstate battery at each scheduled administration

10.1.2 Analysis Sets

The full analysis set (FAS) includes all randomized subjects who received at least 1 dose of IP. This analysis set will be used in both efficacy and safety analyses. In efficacy analyses, subjects will be grouped according to their randomized treatment group assignment. For safety analyses, subjects will be grouped according to their randomized treatment group assignment with the following exception: if a subject receives treatment throughout the study that is different than the randomized treatment group assignment, then the subject will be grouped by the actual treatment group. The completer analysis set (CAS) includes subjects in the FAS who adhered to the scheduled IP regimen and have an observed value for the primary endpoint.

10.1.3 Baseline Covariates and Subgroups

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

- age (< 14 years vs ≥ 14 years)
- sex
- LDL-C by central laboratory (< 160 mg/dL [4.1 mmol/L] vs ≥ 160 mg/dL)
- [redacted]

Subgroup levels may be combined as appropriate for subgroup analyses.

10.2 Sample Size Considerations

This study is to provide clinical experience with evolocumab in approximately 150 pediatric subjects, compared to the current experience described in Sections 2.3 and Section 2.4. Based on the treatment effect from the global phase 3 study in adult subjects with HeFH, evolocumab reduced LDL-C by approximately 55%. A planned total sample size of 150 subjects (100 randomized to evolocumab 420 mg QM and 50 randomized to placebo QM) will provide approximately 99% power in testing the superiority of evolocumab 420 mg QM over placebo. The sample size calculation is performed using a two-sided t-test with a 0.05 significance level, assuming a treatment effect of 40% reduction in LDL-C, a common SD of 20%, and 20% of subjects discontinuing investigational product prior to completion of the study.

The power calculation is derived using nQuery version 7.01.

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Unblinding and potentially unblinding information should not be distributed to the study team, investigators or subjects prior to the study being formally unblinded (eg, the formal unblinding may occur at the final analysis rather than during the primary analysis) except as specified (eg, Section 5.2 and Section 9.2.2).

Individual subject treatment assignments will be maintained by the IVRS/IWRS. Any unplanned unblinding occurring during the study period will be documented and reported in the final clinical study report.

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

10.4 Planned Analyses

10.4.1 Data Monitoring Committee (DMC)

An external independent DMC has been established to formally review the accumulating data from this and other completed and ongoing studies with evolocumab to ensure there is no avoidable increased risk for harm to subjects. The independent DMC is chaired by an external academic cardiologist who is an expert in lipids and clinical trials. Analyses for the DMC are provided by the Independent Biostatistical Group (IBG), which is external to Amgen. Details are provided in the DMC charter.

10.4.2 Primary Analysis

The primary analysis of this study will be conducted when the study is completed. At that time, the database will be cleaned, processed and locked; the study will also be unblinded. Unless specified otherwise, the FAS will be the default analysis set in this study and data will be summarized by randomized treatment group.

10.5 Planned Methods of Analysis

10.5.1 General Considerations

Efficacy and safety analyses will be performed on the FAS. Unless specified otherwise, the FAS will be the default analysis set in this study and data will be summarized by

randomized treatment group. The superiority of evolocumab to placebo will be assessed for all efficacy endpoints.

Subject disposition, demographics, baseline characteristics, and exposure to IP 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.

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

Multiplicity Adjustment Method

To preserve the familywise error rate at 0.05, multiplicity adjustment for the multiple endpoints (primary and secondary efficacy endpoints as enumerated in section 10.1.1.2) will be performed using sequential gatekeeping and Hochberg procedures (Hochberg, 1988) as follows:

- If the treatment effect from the primary analysis of the primary endpoint is significant at a significance level of 0.05, statistical testing of the secondary efficacy endpoint[1] and endpoint[2] will proceed using the sequential procedure with a significance level of 0.05 (ie, secondary endpoint[2] will be tested only if secondary endpoint[1] is statistically significant at 0.05 significance level).
- If the treatment effect from secondary endpoint[2] is significant at a significance level of 0.05, statistical testing of the secondary endpoints[3] will follow the Hochberg procedure at a significance level of 0.05.

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

10.5.2 Primary Efficacy Endpoint Analyses

Primary Analyses

The estimand of primary interest is the difference in mean percent change from baseline in LDL-C at week 24 regardless of treatment adherence for subjects in FAS. A repeated measures linear effects model will be used to compare the efficacy of evolocumab with placebo. The repeated measures model will include terms for treatment group, stratification factor (as appropriate), scheduled visit and the interaction of treatment with scheduled visit. Missing values will not be imputed when the repeated measures linear effects model is used. **The analysis will use LDL-C values measured regardless of treatment adherence.**

Sensitivity Analysis

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

- The primary analysis will be repeated using the CAS
- Non-parametric analyses (Quade test)
- **To evaluate the impact of missing values, a sensitivity analysis under the assumption that subjects who, discontinued IP and have missing endpoint data have a mean zero percent change from baseline will be conducted using multiple imputation**

The difference between the number of randomized subjects and the number of subjects in the FAS will also be assessed and reported in the Clinical Study Report.

Covariate and Subgroup Analysis

If applicable, covariate and subgroup analyses on the primary endpoint will be conducted using baseline covariates.

10.5.3 Secondary Efficacy Endpoints Analyses

The statistical model and testing of the secondary efficacy endpoints will be similar to the primary analysis of the primary endpoint.

Multiplicity adjustment procedures are defined in Section 10.5.1.

10.5.4 Tertiary Efficacy Endpoint Analyses

Analysis of the tertiary efficacy endpoints will be similar to the primary analysis of the primary endpoint. No multiplicity adjustment will be applied.

10.5.5 Secondary Safety and Pharmacokinetic Endpoint Analyses

Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product will also be provided. Subject-level data may be provided instead of tables if the subject incidence is low.

Safety Laboratory Parameters

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

Vital Signs

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

Anti-evolocumab antibodies

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

Pharmacokinetic

Unbound evolocumab serum concentrations by time will be summarized using descriptive statistics.

10.5.6 Other Safety Endpoint Analyses

Neurologic examination

The incidence of abnormal neurologic findings overall and in each exam area will be summarized by treatment group.

Cogstate neurocognitive assessment

For each test, the change from baseline to EOS in the standardized score will be summarized by treatment group.

10.5.7 Exploratory Endpoint Analyses

[redacted]

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Clinical Study Manager or designee to the investigator. The written informed consent document is to be prepared in the language(s) of the potential patient population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational product(s) is/are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.

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

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

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.

In this study, obtaining subject assent from the child and consent from the parents or legally authorized representative, except if the child is very young, as defined by local law will apply. A child is defined as a person who has not attained the legal age for consent for treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will take place. The local IRB/IEC will determine the process for obtaining and documenting the subject assent process for pediatric subject, but should follow the guidelines established by the Department of Health and Human Services (DHHS) Office of Human Research Protections guidelines, which state an explanation of the procedures involved in the study should be made in a language appropriate to the child's age, experience, maturity, and condition.

11.2 Institutional Review Board/Independent Ethics Committee

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

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

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

11.3 Subject Confidentiality

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

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

- For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multi-center studies, the coordinating investigator.

The Coordinating investigator, identified by Amgen, will be any or all of the following:

- 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 IRB/IEC must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IRB/IEC to Amgen.

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

Subjects may be eligible for continued treatment with Amgen investigational product(s) by an extension protocol or as provided for by the local country's regulatory mechanism.

However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

12.2 Study Documentation and Archive

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

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

In this study, the *IVRS/IWRS* system captures the following data points and these are considered source data: subject ID, treatment group assignment, randomization number and date, and IP box assignment.

eCRF entries may be considered source data if the CRF is the site of the original recording (ie, there is no other written or electronic record of data).

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 CRF, informed consent forms or subject assent forms, and subject identification list
- Study files containing the protocol with all amendments, AMG 145 Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB and Amgen
- If kept, proof of receipt, Investigational Product Accountability Record, Return of Investigational Product for Destruction, Final Investigational Product Reconciliation Statement (if applicable), and all drug-related correspondence
- Non-investigational product(s) and or medical device documentation, as applicable.

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

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

12.3 Study Monitoring and Data Collection

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

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

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

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

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the CRFs must be maintained and readily available.
- Updates to CRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that investigator inspected or reviewed the data on the CRF, the data queries, and the site notifications, and agrees with the content.

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

12.4 Investigator Responsibilities for Data Collection

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

12.5 Language

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

12.6 Publication Policy

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

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), which states (August 2013 revision):

- 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; (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3, and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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

12.7 Compensation

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

13. REFERENCES

Abramson MJ, Benke GP, Dimitriadis C, et al. Mobile telephone use is associated with changes in cognitive function in young adolescents. *Bioelectromagnetics*. 2009;30(8):678-686. doi:10.1002/bem.20534

Abifadel M, Rabes JP, Devillers M, et al. Mutations and polymorphisms in the proprotein convertase subtilisin kexin 9 (PCSK9) gene in cholesterol metabolism and disease. *Hum Mutat*. 2009;30(4):520-529.

Allen KL, Byrne SM, Hii H, van Eekelen A, Mattes E, Foster JK. Neurocognitive functioning in adolescents with eating disorders: A population-based study. *Cogn Neuropsychiatry*. 2013;18(5):355-375. doi:10.1080/13546805.2012.698592

Amgen. AMG 145 Investigator's Brochure. Thousand Oaks, CA. Amgen Inc.

Austin MA, Hokanson JE, Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. *Am J Cardiol*. 1998;81:7B-12B.

Bangirana P, Giordani B, John CC, Page C, Opoka RO, Boivin MJ. Immediate neuropsychological and behavioral benefits of computerized cognitive rehabilitation in Ugandan pediatric cerebral malaria survivors. *J Dev Behav Pediatr*. 2009;30(4):310-318.

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

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

Daniels SR, Greer FR. Committee on Nutrition. Lipid screening and cardiovascular health in childhood. *Pediatrics.* 2008;122:198-208.

Goldstein J, Hobbs H, Brown, M. Familial hypercholesterolemia. In: The Metabolic and Molecular Bases of Inherited Disease. Scriver C, Beaudet A, Sly W, Valle D, eds. New York, NY: McGraw-Hill; 2001;2863–2913.

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.

Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika* 1988;75:800-802.

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.

Kavey RE, Allada V, Daniels SR, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation.* 2006;114:2710-2738.

Kotseva K, Wood D, De Backer G, De Bacquer D, Pyörälä K, Keil U, for the EUROSPIRE Study Group. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. *Lancet.* 2009;373:929-940.

Kral TV, Heo M, Whiteford LM, Faith MS. Effects on cognitive performance of eating compared with omitting breakfast in elementary schoolchildren. *J Dev Behav Pediatr*. 2012;33(1):9-16. doi:10.1097/DBP.0b013e31823f2f35

Kuklina EV, Shaw KM, Hong Y. Vital signs: prevalence, treatment, and control of high levels of low-density lipoprotein cholesterol—United States, 1999-2002 and 2005-2008. *JAMA*. 2011;305:1086-1088.

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

Mayes L, Snyder PJ, Langlois E, Hunter N. Visuospatial working memory in school-aged children exposed in utero to cocaine. *Child Neuropsychol*. 2007;13(3):205-218. doi:10.1080/09297040600888753

Mollica CM, Maruff P, Vance A. Development of a statistical approach to classifying treatment response in individual children with ADHD. *Hum Psychopharmacol*. 2004;19(7):445-456.

McCrindle BW, Urbina EM, Dennison BA, et al. Drug therapy of high-risk lipid abnormalities in children and pediatrics: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. *Circulation*. 2007;115:1948-1967.

National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106:3143-3421.

National Collaborating Centre for Primary Care. Identification and Management of Familial Hypercholesterolaemia (FH). London, UK: National Institute for Health and Clinical Excellence (NICE); 2008.

Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J.* 2013;34:3478-3490a.

Nyaradi A, Foster JK, Hickling S, et al. Prospective associations between dietary patterns and cognitive performance during adolescence. *J Child Psychol Psychiatry*. 2014;55(9):1017–1024. doi:10.1111/jcpp.12209

Raal FJ, Pilcher GJ, Panz VR, et al. Reduction in mortality in subjects with homozygous familial hypercholesterolemia associated with advances in lipid-lowering therapy. *Circulation.* 2011;124:2202-2207.

Raal FJ, Honorpour N, Blom DJ, et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. *The Lancet.* 2014: doi:10.1016/S0140-6736(08)61345-8 [Epub ahead of print].

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

Reiner Z, Catapano AL, De Backer G, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J.* 2011;32:1769-1818.

Sarwar N, Danesh J, Eiriksdottir G, et al. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. *Circulation*. 2007;115:450-458.

Scientific Steering Committee. Risk of fatal coronary heart disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. *BMJ.* 1991;303:893-896.

Snyder AM, Maruff P, Pietrzak RH, Cromer JR, Snyder P. Effect of treatment with stimulant medication on nonverbal executive function and visuomotor speed in children with attention deficit/hyperactivity disorder (ADHD). *Child Neuropsychol*. 2008;14(3):211-226.

Tolonen H, Keil U, Ferrario M, Evans A; WHO MONICA Project. Prevalence, awareness and treatment of hypercholesterolaemia in 32 populations: results from the WHO MONICA Project. *Int J Epidemiol.* 2005;34:181-192.

Williams RR, Hunt SC, Schumacher MC, et al. Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. *Am J Cardio*l 1993;72(2):171-176.

World Health Organization. Familial hypercholesterolemia – Report of a Second WHO Consultation, WHO publication no: WHO/HGN/FH/CONS/00.2, Geneva, 1999; http://apps.who.int/iris/handle/10665/66346.

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. Additional Safety Assessment Information

Adverse Event Grading Scale

Refer to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 for adverse event grading and information. The CTCAE is available at the following link: http://ctep.cancer.gov/protocolDevelopment/electronic_applications\ctc.htm.

Pediatric Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

Cases with

AST or ALT ≥ 3 x ULN and TBL > 2 x ULN or INR > 1.5

or

AST or ALT ≥ 3 x ULN with signs and symptoms consistent with hepatitis must 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).

Cases with

AST or ALT > 3 x ULN (if baseline ALT or AST is ≤ 3 x ULN)

AST or ALT > 5 x ULN (if baseline ALT or AST is ≤ 5 x ULN)

are to be reported as adverse events.

The appropriate CRF (eg, Adverse Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.1.2.

Additional Clinical Assessments and Observation

All subjects in whom investigational medicinal product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Sections 6.5.1 and Section 6.5.2 or who experience AST or ALT elevations > 3x ULN (if baseline ALT or AST is ≤ 3 x ULN) or who experience AST or ALT > 5 x ULN (if baseline

ALT or AST is ≤ 5 x ULN) are to undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels.

The following evaluations are to be performed during this period:

1. Repeat liver tests AST, ALT, ALP, bilirubin (total and direct), and INR as clinically necessary until laboratory abnormalities improve .
2. Obtain pediatric gastroenterologist or pediatric hepatologist consult.

The diagnostic approach (including blood tests) to investigate alternative causes for abnormal liver tests is to be determined in consultation with a pediatric gastroenterologist or hepatologist.

The "close observation" is to continue until all laboratory abnormalities return to baseline or normalize and subject's clinical condition improves.

Appendix B. Sample Electronic Serious Adverse Event (eSAE) Contingency Report Form

AMGEN Study # 20120123 evolocumab (AMG 145)	Electronic Adverse Event Contingency Report Form **For Restricted Use**

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site
☐ Is not yet available for this study
☐ Has been closed for this study

SELECT OR TYPE IN A FAX#

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

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

3. ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____ Month____ Year_____

Adverse Event diagnosis or syndrome **If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report** *List one event per line. If event is fatal, enter the cause of eeath. Entry of "death" is not acceptable, as this is an outcome.*	**Date Started** Day Month Year	**Date Ended** Day Month Year	Check only if event occurred before first dose of IP/drug under study	**Is event serious?**	**Is event a potential endpoint?**	**If serious, enter Serious Criteria code** *(see codes below)*	**Relationship** Is there a reasonable possibility that theEvent may have been caused by IP/drug under study or an Amgen device used to administer the IP/drug under study? evolocumab (AMG145) No✓ Yes✓ Autoinjector/ Pen (AiPen) No✓ Yes✓	**Outcome of Event** Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No	☐Yes ☐No				
				☐Yes ☐No	☐Yes ☐No				
				☐Yes ☐No	☐Yes ☐No				

Serious Criteria: **01** Fatal; **02** Immediately life-threatening; **03** Required/prolonged hospitalization; **04** Persistent or significant disability /incapacity; **05** Congenital anomaly / birth defect; **06** Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

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AMGEN Study # 20120123 evolocumab (AMG 145)	Electronic Adverse Event Contingency Report Form **For Restricted Use**

Site Number	Subject ID Number

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/Drug/Amgen Device:		Date of Initial Dose 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	Lot # and Serial #
evolocumab (AMG 145)	☒ blinded							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Prefilled Autoinjector/Pen (AI/Pen) device	☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any 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✓

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												
Date	Unit											
Day Month Year												

AMGEN Study # 20120123 evolocumab (AMG 145)	Electronic Adverse Event Contingency Report Form **For Restricted Use**

	Site Number	Subject ID Number	

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)* Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee - _____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*	Title	Date

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Appendix C. 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: 20120123

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**

Print Form

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: 20120123

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:** _____

Amgen maintains a Lactation Surveillance Program that collects data about women who have been exposed to an Amgen product while breastfeeding. 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: 03 April 2012, version 2. Page 1 of 1

Appendix D. Tanner Stages (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 2

Protocol Title: Double-blind, Randomized, Multicenter, Placebo-controlled, Parallel Group Study to Characterize the Efficacy, Safety, and Tolerability of 24 Weeks of Evolocumab for Low Density Lipoprotein-cholesterol (LDL-C) Reduction, as Add-on to Diet and Lipid-lowering Therapy, in Pediatric Subjects 10 to 17 Years of Age With Heterozygous Familial Hypercholesterolemia (HeFH)

Amgen Protocol Number Evolocumab (AMG 145) 20120123

EudraCT number 2014-002277-11

Original, Date:	09 December 2014
Amendment 1, **Date**:	20 May 2015
Amendment 2, Date:	**01 September 2015**

Rationale:

- To address regulatory feedback.
- To clarify specific details of the statistical analysis
- To add safety assessments

Description of Changes:

Section: Global

Change: Updated the amendment 2 date throughout to 01 September 2015.

Grammatical changes throughout (correction of prior errors or omissions).

Abbreviation ADE and DRE added globally.

Section: Title Page

Replace:

Key Sponsor Contact(s):	[redacted] 1 Sanderson Road (Uxbridge Business Park) Uxbridge UB8 1DH United Kingdom Phone: [redacted] Fax: [redacted] Email: [redacted]
Date:	09 December 2014
Amendment 1:	20 May 2015

With:

Key Sponsor Contact(s):	[redacted] **One Amgen Center Drive** **Mail Stop 27-1-F** **Thousand Oaks, CA 91320, USA** **Phone:** [redacted] **Fax:** [redacted] **Email:** [redacted]
Original, Date:	09 December 2014
Amendment 1, **Date:**	20 May 2015
Amendment 2, Date	**01 September 2015**

Section: Protocol Synopsis, Secondary Efficacy Objectives

Replace:

Secondary Objectives:

to evaluate the safety of SC evolocumab compared with placebo, when added to standard of care, in pediatric subjects 10 to 17 years of age with HeFH

to assess the effects of SC evolocumab compared with placebo, when added to standard of care, on mean percent change from baseline to weeks 22 and 24 and change from baseline to week 24 in LDL-C, and on percent change from baseline to week 24 in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B

(ApoB), total cholesterol/HDL-C ratio, and ApoB/Apolipoprotein A-1 (ApoA1) ratio, in pediatric subjects 10 to 17 years of age with HeFH

- to characterize pharmacokinetic (PK) exposure

With:

Secondary Efficacy Objectives

- ~~to evaluate the safety of SC evolocumab compared with placebo, when added to standard of care, in pediatric subjects 10 to 17 years of age with HeFH~~

Secondary Efficacy Objectives: to assess the effects of SC evolocumab compared with placebo, when added to standard of care, on mean percent change from baseline to weeks 22 and 24 and change from baseline to week 24 in LDL-C, and on percent change from baseline to week 24 in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, and ApoB/Apolipoprotein A-1 (ApoA1) ratio, in pediatric subjects 10 to 17 years of age with HeFH

Secondary Safety Objectives: to evaluate the safety of SC evolocumab compared with placebo, when added to standard of care, in pediatric subjects 10 to 17 years of age with HeFH

Secondary Pharmacokinetic Objective: to characterize pharmacokinetic (PK) exposure

Section: Protocol Synopsis, Summary of Subject Eligibility Criteria:

Replace:

The following are the major exclusion criteria: type 1 diabetes or recently diagnosed (within 3 months of randomization) or poorly controlled (HbA1c > 8.5%) type 2 diabetes or newly diagnosed impaired glucose tolerance; thyroid stimulating hormone (TSH) < lower limit of normal (LLN) or TSH > 1.5x upper limit of normal (ULN) and free thyroxine (T4) levels that are outside normal range, estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m^2, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2x ULN, creatine kinase (CK) > 3x ULN (all screening by central laboratory); known active infection, or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction. Subjects are excluded if they have taken any cholesterylester transfer protein (CETP) inhibitor in the last 12 months, mipomersen or lomitapide in the last 5 months, lipid apheresis within the last 12 weeks, or if they have previously received evolocumab or any other investigational therapy to inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9). Subjects cannot be enrolled in another investigational device or drug study, receive other investigational agent(s) or procedures, or be within less than 30 days since ending another investigational device or drug study. Female subjects of childbearing potential cannot be pregnant, planning to become pregnant, breast feeding or planning to breastfeed and must be willing to use acceptable method(s) of effective contraception during treatment with IP (evolocumab or placebo) and for an additional 15 weeks after the end of treatment with IP (evolocumab or placebo).

With:

The following are the major exclusion criteria: **homozygous familial hypercholesterolemia,** type 1 diabetes or recently diagnosed (within 3 months of randomization) or poorly controlled (HbA1c > 8.5%) type 2 diabetes or newly diagnosed impaired glucose tolerance; thyroid stimulating hormone (TSH) < lower limit of normal

(LLN) or TSH > 1.5x upper limit of normal (ULN) and free thyroxine (T4) levels that are outside normal range, estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m^2, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2x ULN, creatine kinase (CK) > 3x ULN (all screening by central laboratory); known active infection, or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction. Subjects are excluded if they have taken any cholesterylester transfer protein (CETP) inhibitor in the last 12 months, mipomersen or lomitapide in the last 5 months, lipid apheresis within the last 12 weeks, or if they have previously received evolocumab or any other investigational therapy to inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9). Subjects cannot be enrolled in another investigational device or drug study, receive other investigational agent(s) or procedures, or be within less than 30 days since ending another investigational device or drug study. Female subjects of childbearing potential cannot be pregnant, planning to become pregnant, breast feeding or planning to breastfeed and must be willing to use acceptable method(s) of effective contraception during treatment with IP (evolocumab or placebo) and for an additional 15 weeks after the end of treatment with IP (evolocumab or placebo).

Section: Protocol Synopsis, Investigational Product

Replace:

Assessments and procedures include vital signs, adverse events/serious adverse events/cardiovascular (CV) events, and concomitant therapy, dietary instruction, physical exam including neurologic examination and assessment of waist circumference, body height and weight, 12-lead electrocardiograms (ECGs), fasting lipids, chemistry, hematology, anti-evolocumab antibodies, biomarker sample collection, serum pregnancy testing (females of childbearing potential), urinalysis, assessment of growth and pubertal development (Tanner staging), Cogstate neurocognitive assessment, carotid intima-media thickness (cIMT), and IP administration. In addition, specific laboratory assessments will be performed, including estradiol for girls, testosterone for boys, creatinine phosphokinase, follicle-stimulating hormone, luteinizing hormone, adenocorticotropic hormone, dehydroepiandrosterone, and cortisol. If the subject consented to pharmacogenetics analyses, DNA will be extracted from some of the blood samples. IP administration by SC injection, if applicable, will be done after all other procedures have been completed.

With:

Assessments and procedures include vital signs, adverse events/serious adverse events/**adverse device effects (ADE)/disease related events (DRE)**/cardiovascular (CV) events, and concomitant therapy, dietary instruction, physical exam including neurologic examination and assessment of waist circumference, body height and weight, 12-lead electrocardiograms (ECGs), fasting lipids, chemistry, hematology, anti-evolocumab antibodies, biomarker sample collection, serum pregnancy testing (females of childbearing potential), urinalysis, assessment of growth and pubertal development (Tanner staging), Cogstate neurocognitive assessment, carotid intima-media thickness (cIMT), and IP administration. In addition, specific laboratory assessments will be performed, including estradiol for girls, testosterone for boys, creatinine phosphokinase, follicle-stimulating hormone, luteinizing hormone, adenocorticotropic hormone, dehydroepiandrosterone, and cortisol. If the subject consented to pharmacogenetics analyses, DNA will be extracted from some of the blood samples. IP administration by SC injection, if applicable, will be done after all other procedures have been completed.

Section: 1.2 Secondary Efficacy

Replace:

- to evaluate the safety of SC evolocumab compared with placebo, when added to standard of care, in pediatric subjects 10 to 17 years of age with HeFH
- to assess the effects of SC evolocumab compared with placebo, when added to standard of care, on mean percent change from baseline to weeks 22 and 24 and change from baseline to week 24 in LDL-C, and on percent change from baseline to week 24 in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, and ApoB/Apolipoprotein A-1 (ApoA1) ratio, in pediatric subjects 10 to 17 years of age with HeFH
- To characterize pharmacokinetic (PK) exposure

With:

- ~~to evaluate the safety of SC evolocumab compared with placebo, when added to standard of care, in pediatric subjects 10 to 17 years of age with HeFH~~
- to assess the effects of SC evolocumab compared with placebo, when added to standard of care, on mean percent change from baseline to weeks 22 and 24 and change from baseline to week 24 in LDL-C, and on percent change from baseline to week 24 in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, and ApoB/Apolipoprotein A-1 (ApoA1) ratio, in pediatric subjects 10 to 17 years of age with HeFH

1.3 Secondary Safety

- to evaluate the safety of SC evolocumab compared with placebo, when added to standard of care, in pediatric subjects 10 to 17 years of age with HeFH

1.4 Secondary Pharmacokinetic

- to characterize pharmacokinetic (PK) exposure

Section: 1.6 Exploratory

[redacted]

Section: 3.1 Study Design

Replace:

Events of death, myocardial infarction (MI), hospitalization for unstable angina, coronary revascularization, stroke, transient ischemic attack (TIA), and hospitalization for heart failure will be adjudicated by an independent Clinical Events Committee (CEC). Subject incidence of exploratory endpoint events will be summarized for each treatment group. Processes of event identification and submission to the CEC are described in a CEC Manual of Operations.

With:

Events of death, myocardial infarction (MI), hospitalization for unstable angina, coronary revascularization, stroke, transient ischemic attack (TIA), and hospitalization for heart failure will be adjudicated by an independent Clinical Events Committee (CEC). Subject incidence of exploratory endpoint events will be summarized for each treatment group. Processes of event identification and submission to the CEC are described in a CEC **Endpoint Reporting** Manual.

Section: 4 Subject Eligibility

Replace:

Before any study-specific activities/procedure, the appropriate written informed consent must be obtained (see Section 11.1). In addition to written informed consent from a legally acceptable representative, the assent of the child also must be obtained, as appropriate if requested by the institutional review board/independent ethics committee (IRB/IEC).

With:

Before any study-specific activities/procedure, the appropriate written informed consent **(and assent, when applicable)** must be obtained (see Section 11.1). In addition to written informed consent from a legally acceptable representative, the assent of the child also must be obtained, as appropriate if requested by the institutional review board/independent ethics committee (IRB/IEC).

Section: 4.1.1 Inclusion Criteria

Replace:

101 Subject has provided informed consent or subject assent prior to initiation of any study-specific activities/procedures.

106 If taking any other lipid-lowering therapy (eg, ezetimibe, bile-acid sequestering resin, omega 3 fatty acids or niacin), this therapy must be unchanged for ≥ 4 weeks prior to LDL-C screening; fibrates must be stable for at least 6 weeks prior to screening.

With:

101 Subject has provided **written** informed consent or subject assent prior to initiation of any study-specific activities/procedures.

106 **Subject must be on a low-fat diet, and i**f taking any other lipid-lowering therapy (eg, ezetimibe, bile-acid sequestering resin, omega 3 fatty acids or niacin), this therapy must be unchanged for ≥ 4 weeks prior to LDL-C screening; fibrates must be stable for at least 6 weeks prior to screening.

Section: 4.1.2 Exclusion Criteria

Replace:

201 Type 1 diabetes or newly diagnosed (within 3 months of randomization) type 2 diabetes, or poorly controlled type 2 diabetes (HbA1c > 8.5%) or newly diagnosed impaired glucose tolerance (within 3 months of randomization).

213 Female subject who has experienced menarche and unwilling to use acceptable method(s) of effective birth control during treatment with IP (evolocumab or placebo) and for an additional 15 weeks after the end of treatment with IP (evolocumab or placebo). A female who has experienced menarche is considered of childbearing potential.

- Acceptable methods of preventing pregnancy include: true sexual abstinence when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception), or use of hormonal birth control methods (oral, implantable, injectable, transdermal, intravaginal), intrauterine devices (IUDs), intrauterine hormonal-releasing system (IUS), or two (2) barrier methods (one by each partner and at least one of the barrier methods must include spermicide, unless spermicide is not approved in the country or region - the male must use a condom and the female must choose either a diaphragm OR cervical cap, OR contraceptive sponge. Note: a male and female condom cannot be used together due to the risk of tearing.)

Note: If additional medications are given during treatment which may alter the contraceptive requirements (these additional medications may require an increase in the number of contraceptive methods and/or length of time that contraception is to be utilized after the last dose of protocol-required therapies) the investigator is to discuss these changes with the study subject.

With:

201 Homozygous familial hypercholesterolemia

202 Lipid apheresis within the last 12 weeks prior to screening

203 Type 1 diabetes or newly diagnosed (within 3 months of randomization) type 2 diabetes, or poorly controlled type 2 diabetes (HbA1c > 8.5%) or newly diagnosed impaired glucose tolerance (within 3 months of randomization).

213 Female subject who has experienced menarche and unwilling to use acceptable method(s) of effective birth control during treatment with IP (evolocumab or placebo) and for an additional 15 weeks after the end of treatment with IP (evolocumab or placebo). A female who has experienced menarche is considered of childbearing potential.

- Acceptable methods of preventing pregnancy include: true sexual abstinence when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception), or use of hormonal birth control methods (oral, implantable, injectable, transdermal, intravaginal), intrauterine devices (IUDs), intrauterine hormonal-releasing system (IUS), or two (2) barrier methods (one by each partner and at least one of the barrier methods must include spermicide, unless spermicide is not approved in the country or region - the male must use a condom and the female must choose either a diaphragm OR cervical cap, OR contraceptive sponge. Note: a male and female condom cannot be used together due to the risk of tearing.)

  Note: If additional medications are given during treatment which may alter the contraceptive requirements (these additional medications may require an increase in the number of contraceptive methods and/or length of time that contraception is to be utilized ***or length of time breastfeeding is to be avoided*** *after the last dose of protocol-required therapies) the investigator is to discuss these changes with the study subject.*

~~216 Lipid apheresis within the last 12 weeks prior to screening.~~

Section: 6.1 Classification of Products and Medical Devices

Replace:

An Investigational Product Instruction Manual (IPIM) and the Instructions For Use (IFU), documents external to this protocol, contain detailed information regarding the storage, preparation, and administration of investigational product.

With:

An Investigational Product Instruction Manual (IPIM) and the Instructions For Use (IFU), documents external to this protocol, contain detailed information regarding the storage, preparation, **destruction,** and administration of investigational product.

Section: 6.7 Medical Devices

Replace:

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

With:

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

Section: 6.8 Product Complaints

Replace:

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

With:

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

Section: 7.1 Schedule of Assessments

Replace:

Review for AEs/SAEs//CV events	X[b]	X	X	(X)[b]	X	(X)[b]	X	X	X
hsCRP, CK, FSH, LH, ACTH, DHEA-S, cortisol		X							X

b. only AEs possibly related to study procedures and SAEs are collected during screening (from signing of ICF or subject assent, whichever is later); week 8 and week 16 AEs/SAEs/CV events collection only if visit to study site

With:

Review for AEs/SAEs/**ADEs/DREs**/CV events	X[b]	X	X	(X)[b]	X	(X)[b]	X	X	X
hsCRP, CK, FSH, LH, ACTH, DHEA-S, cortisol**, Fasting vitamins A/D/E/K**		X							X

b. only AEs possibly related to study procedures and SAEs are collected during screening (from signing of ICF or subject assent, whichever is later); week 8 and week 16 AEs/SAEs/**ADEs/DREs/**CV events collection only if visit to study site. **ADEs/Product Complaints are reported that occur after signing of the informed consent through 30 days after the last dose of IP or EOS, whichever is later.**

Section: 7.2 General Study Procedures

Replace: Table 2: Analyte Listing[1]

Chemistry	Coagulation	Urinalysis	Hematology	Other Labs
Sodium	PT/INR (per Appendix A)	Specific gravity	Hemoglobin	Fasting lipids
Potassium		pH	Hematocrit	Total cholesterol
Chloride		Blood	RBC	HDL-C
Bicarbonate		Protein	RDW	LDL-C
Total protein		Glucose	MCV	Triglycerides
Albumin		Bilirubin	MCH	VLDL-C
Calcium		WBC	MCHC	non-HDL-C
Magnesium		RBC	WBC	ApoA1
Phosphorus		Epithelial cells	Platelets	ApoB
Fasting glucose		Bacteria		Estradiol (females)
BUN or Urea		Casts		Testosterone (males)
Creatinine		Crystals		Cortisol
Uric acid				Luteinizing hormone (LH)
Total bilirubin				Adrenocorticotropic hormone (ACTH)
Direct bilirubin				Dehydroepiandrosterone sulfate (DHEA-S)
CK				hsCRP
ALP				Lp(a)
LDH				Anti-evolocumab antibodies
AST (SGOT)				[redacted]
ALT (SGPT)				Evolocumab (PK)
				HbA1c
				Pregnancy test (females of childbearing potential)
				FSH
				TSH
				HCV antibody[2]
				HCV viral load[3]

Since some laboratory results may inadvertently unblind investigators to treatment assignment to evolocumab, central laboratory results of the lipid panel, ApoA1, ApoB, Lp(a), and [redacted] will not be reported to the investigator (or study personnel) post-screening. Investigators should not perform non-protocol testing of these analytes during a subject's study participation from first administration of IP until at least 12 weeks after last IP administration, or the subject's end of study, whichever is later.

With:

Table 2: Analyte Listing[1]

Chemistry	Coagulation	Urinalysis	Hematology	Other Labs
Sodium	PT/INR (per Appendix A)	Specific gravity	Hemoglobin	Fasting lipids
Potassium		pH	Hematocrit	Total cholesterol
Chloride		Blood	RBC	HDL-C
Bicarbonate		Protein	RDW	LDL-C
Total protein		Glucose	MCV	Triglycerides
Albumin		Bilirubin	MCH	VLDL-C
Calcium		WBC	MCHC	non-HDL-C
Magnesium		RBC	WBC	ApoA1
Phosphorus		Epithelial cells	Platelets	ApoB
Fasting glucose		Bacteria		Estradiol (females)
BUN or Urea		Casts		Testosterone (males)
Creatinine		Crystals		Cortisol
Uric acid				Luteinizing hormone (LH)
Total bilirubin				Adrenocorticotropic hormone (ACTH)
Direct bilirubin				Dehydroepiandrosterone sulfate (DHEA-S)
CK				**Fasting vitamins A, D, E, and K**
ALP				hsCRP
LDH				Lp(a)
AST (SGOT)				Anti-evolocumab antibodies
ALT (SGPT)				[redacted]
				Evolocumab (PK)
				HbA1c
				Pregnancy test (females of childbearing potential)
				FSH
				TSH
				HCV antibody[2]
				HCV viral load[3]

Since some laboratory results may inadvertently unblind investigators to treatment assignment to evolocumab, central laboratory results of the lipid panel, ApoA1, ApoB, Lp(a), **fasting vitamins A, D, E, and K,** and [redacted] will not be reported to the investigator (or study personnel) post-screening. Investigators should not perform non-protocol testing of these analytes during a subject's study participation from first administration of IP until at least 12 weeks after last IP administration, or the subject's end of study, whichever is later.

Section: 7.2.1.2 Screening

Replace:

- review for adverse events/serious adverse events/(adverse events possibly related to study procedures and serious adverse events are collected during screening)

With:

- review for adverse events/serious adverse events/**ADE** (adverse events possibly related to study procedures and serious adverse events are collected during screening)

Section: 7.2.2 Treatment and End of Study

Replace:

- review for adverse events/serious adverse events/CV events
- blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, chemistry, hematology, PK, [redacted] high sensitivity C-reactive protein (hsCRP), Lp(a), biomarkers, anti-evolocumab antibodies, and viral load in subjects positive for HCV

With:

- review for adverse events/serious adverse events/**ADE/DRE/**CV events
- blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, chemistry, hematology, PK, [redacted] high sensitivity C-reactive protein (hsCRP), **CK, FSH, LH, ACTH, DHEA-S, cortisol, fasting vitamins A, D, E, and K,** Lp(a), biomarkers, anti-evolocumab antibodies, and viral load in subjects positive for HCV

Section: 7.7.2 Waist Circumference

Replace:

7.7.2 Waist Circumference

Subjects should wear minimal clothing to ensure that the measuring tape is correctly positioned. Subjects should stand erect with the abdomen relaxed, arms at the sides, feet together and with their weight equally divided over both legs.

With:

7.7.2 Height, Weight, and Waist Circumference

Height and weight measurement will be obtained at the time points specified in the Schedule of Assessments (Table 1). If possible, visits with height and weight measurements should be scheduled at a similar time of day (eg, in the morning). Height is measured to the nearest centimeter with the subject's back against a wall. Use of a stadiometer is preferred and recommended. Height is defined as the maximum distance from the floor to the highest point on the head, when the subject is facing directly ahead. Shoes must be off, feet together, and arms by the sides. Head, upper back, buttocks, and heels should be in contact with the wall when the measurement is made. Two (2) measurements of height should be taken at each timepoint and entered into the CRF. Weight is to be measured to the nearest tenth of a kilogram with the subject wearing light clothing and with shoes removed. A properly calibrated digital scale should be used. The scale should weigh in 0.1 kg increments, have a stable weighing platform that can be easily set to zero, be calibrated through professional service or by standard known weight.

For measurement of waist circumference, subjects should wear minimal clothing to ensure that the measuring tape is correctly positioned. Subjects should stand erect with the abdomen relaxed, arms at the sides, feet together and with their weight equally divided over both legs.

Section: 7.7.6 Lipid Measurements

Replace:

Only the screening LDL-C concentration will be reported to the site for the eligibility decision. Central laboratory results of the lipid panel, as well as ApoA1, ApoB, lipoprotein(a), and [redacted] will be blinded post-treatment until unblinding of the clinical database and will not be reported to the investigator post-screening. In addition,

investigators and staff involved with this trial and all medical staff involved in the subject's medical care should refrain from obtaining lipid panels from randomization until at least 12 weeks after the subject's last administration of IP or until the subject ends the study, whichever is later (to avoid potential unblinding). If a lipid panel is drawn, all reasonable steps must be undertaken to avoid informing the subject and study personnel of the results.

With:

Only the screening LDL-C concentration will be reported to the site for the eligibility decision. Central laboratory results of the lipid panel, as well as ApoA1, ApoB, lipoprotein(a), **fasting vitamins A, D, E, and K,** and [redacted] will be blinded post-treatment until unblinding of the clinical database and will not be reported to the investigator post-screening. In addition, investigators and staff involved with this trial and all medical staff involved in the subject's medical care should refrain from obtaining lipid panels from randomization until at least 12 weeks after the subject's last administration of IP or until the subject ends the study, whichever is later (to avoid potential unblinding). If a lipid panel is drawn, all reasonable steps must be undertaken to avoid informing the subject and study personnel of the results.

Section: 9.1.1 Definition of Adverse Events

Replace:

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.

With:

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

involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

Section: 9.1.2 Definition of Serious Adverse Events

Replace:

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

With:

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria **(unless it meets the definition of a Disease Related Event as defined in Section 9.1.3– below):**

A disease related event is to be reported as a serious adverse event if:

- **the subject's pre-existing condition becomes worse than what the investigator would consider typical for a patient with the same underlying condition, or**
- **if the investigator believes a causal relationship exists between the investigational medicinal product(s)/protocol-required therapies and the event,**
- **and the event meets at least 1 of the serious criteria above.**

Section: 9.1.3 Definition of Disease-related Events

Replace:

Disease-related events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. In this study, such events include atherosclerosis (especially of the coronary arteries) and its complications. Examples include manifestations of myocardial ischemia such as chest pain and myocardial infarction, and percutaneous and surgical revascularization procedures. Such events do not meet the definition of an adverse event unless assessed to be more severe than expected for the subject's condition.

With:

Disease-related events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. In this study, such events include atherosclerosis (especially of the coronary arteries) and its complications. Examples include manifestations of myocardial ischemia such as chest pain and myocardial infarction, and percutaneous and surgical revascularization procedures. Such events do

not meet the definition of an adverse event unless assessed to be more severe than expected for the subject's condition **or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment protocol required therapies and disease worsening**.

Disease Related Events and/or Disease Related Outcomes that do not qualify as Serious Adverse Events:

- **An event which is part of the normal course of disease under study (eg, disease progression in oncology or hospitalization due to disease progression) is to be reported as a Disease Related Event.**
- **Death due to the disease under study is to be recorded on the Event CRF.**

If the outcome of the underlying disease is worse than that which would normally be expected for the subject, or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment protocol required therapies and disease worsening, this must be reported as an Adverse Event or Serious Adverse Event.

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

Replace:

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after randomization and all adverse events possibly related to study procedures from signing of the informed consent or subject assent through the end of study are reported using the applicable eCRF (eg, Adverse Event eCRF).

The investigator must assign the following adverse event attributes:

- adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- dates of onset and resolution (if resolved),
- severity
- assessment of relatedness to investigational product (evolocumab or placebo) or the prefilled autoinjector/pen (AI/Pen) device, or other protocol-required therapies, and

With:

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur **from** randomization and all adverse events possibly related to study procedures from signing of the informed consent or subject assent through the end of study are reported using the applicable eCRF (eg, Adverse Event eCRF).

The investigator must assign the following adverse event attributes:

- adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- dates of onset and resolution (if resolved),
- severity
- assessment of relatedness to investigational product (evolocumab or placebo or the prefilled autoinjector/pen (AI/Pen device), or other protocol-required therapies/**protocol-required procedure or activity**, and

Section: 9.2.3 Reporting Procedures for Disease-related Events

Replace:

The investigator is responsible for ensuring that all disease-related events observed by the investigator or reported by the subject that occur after the first dose of investigational medicinal product(s) through the safety follow-up visit are reported using the appropriate Event CRF. Additionally, the investigator is required to report a fatal disease-related event on the CRF.

Events assessed by the investigator to be related to the investigational medicinal product(s) or study treatment and determined to be serious require reporting of the event on an Event CRF.

With:

The investigator is responsible for ensuring that all disease-related events observed by the investigator or reported by the subject that occur after the first dose of investigational medicinal product(s) through **EOS (including any** follow-up **visits)** are reported using the appropriate Event CRF. Additionally, the investigator is required to report a fatal disease-related event on the CRF.

~~Events assessed by the investigator to be related to the investigational medicinal product(s) or study treatment and determined to be serious require reporting of the event on an Event CRF.~~

If the outcome of the underlying disease is worse than that which would normally be expected for the subject, or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment protocol required therapies and disease worsening, this must be reported as an Adverse Event or Serious Adverse Event.

Section: 9.3 Pregnancy and Lactation Reporting

Replace:

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of IP (evolocumab or placebo) through 15 weeks after the end of treatment with IP (evolocumab or placebo).

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

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

With:

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies ~~that occur after~~ the last dose of IP (evolocumab or placebo) through 15 weeks after the end of treatment with IP (evolocumab or placebo).

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

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

Section 10.1.1.4 Exploratory Endpoints

[redacted]

Section: 10.1.1.5 Safety Endpoints

Added:

10.1.1.5 **Secondary** Safety Endpoints

Section: 10.1.1.6 Pharmacokinectics Endpoints

Added:

10.1.1.6 **Secondary** Pharmacokinetics Endpoints

Section: 10.1.1.7 Other Safety Endpoints

Added:

- **Change from baseline score in the components of the Cogstate battery at each scheduled administration**

Section: 10.5.2 Primary Efficacy Endpoint Analyses

Replace:

Primary Analyses

To assess the primary endpoint of the percent change from baseline in LDL-C at week 24, a repeated measures linear effects model will be used to compare the efficacy of evolocumab with placebo. The repeated measures model will include terms for treatment group, stratification factor (as appropriate), scheduled visit and the interaction of treatment with scheduled visit. Missing values will not be imputed when the repeated measures linear effects model is used.

Sensitivity Analysis

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

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

With:

Primary Analyses

The estimand of primary interest is the difference in mean percent change from baseline in LDL-C at week 24 regardless of treatment adherence for subjects in FAS. A repeated measures linear effects model will be used to compare the efficacy of evolocumab with placebo. The repeated measures model will include terms for treatment group, stratification factor (as appropriate), scheduled visit and the interaction of treatment with scheduled visit. Missing values will not be imputed when the repeated measures linear effects model is used. **The analysis will use LDL-C values measured regardless of treatment adherence.**

Sensitivity Analysis

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

- The primary analysis will be repeated using the CAS
- Non-parametric analyses (Quade test)
- **To evaluate the impact of missing values, a sensitivity analysis under the assumption that subjects who, discontinued IP and have missing endpoint data have a mean zero percent change from baseline will be conducted using multiple imputation.**

The difference between the number of randomized subjects and the number of subjects in the FAS will also be assessed and reported in the Clinical Study Report.

Section: 10.5.5 Secondary Safety and Pharmacokinetic Endpoint Analyses

Added:

Vital Signs

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

Anti-evolocumab antibodies

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

Pharmacokinetic

Unbound evolocumab serum concentrations by time will be summarized using descriptive statistics.

Added new Section: 10.5.6 Other Safety Endpoint Analyses

Section: Appendices, Appendix D. Tanner Stages (Sexual Maturity Ratings)

Replace:

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

With:

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 #1

Protocol Title: Double-blind, Randomized, Multicenter, Placebo-controlled, Parallel Group Study to Characterize the Efficacy, Safety, and Tolerability of 24 Weeks of Evolocumab for Low Density Lipoprotein-cholesterol (LDL-C) Reduction, as Add-on to Diet and Lipid-lowering Therapy, in Pediatric Subjects 10 to 17 Years of Age With Heterozygous Familial Hypercholesterolemia (HeFH)

Amgen Protocol Number (Evolocumab) 20120123

Amendment Date: 20 May 2015

Rationale:

The following items were added to the protocol at the request of the FDA:

- Hematology, urinalysis and anti-evolocumab antibody assessments at Week 12
- Explicit exclusion of apheresis subjects
- Documentation of historical lipid therapies
- [redacted] (added as an exploratory endpoint)
- Clarification that the calculation of sample size accounts for 20% of randomized subjects discontinuing investigational product prior to completion of the study

The following changes were also made:

- The key Sponsor contact was changed
- The exploratory endpoint of "[redacted]" was deleted.
- Editorial changes or corrections for clarity and accuracy.