Title: Open-label, Single-arm, Multicenter Study to Evaluate the Safety, Tolerability and Efficacy of Evolocumab for LDL-C Reduction, as Add-on to Diet and Lipid-lowering Therapy, in Pediatric Subjects From 10 to 17 Years of Age With Heterozygous Familial Hypercholesterolemia (HeFH) or Homozygous Familial Hypercholesterolemia (HoFH)

HAUSER-OLE

Evolocumab (AMG 145)

Amgen Protocol Number (Evolocumab) 20120124

EudraCT number 2015-002276-25

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Original, Date:	27 May 2015
Amendment 1, Date:	10 September 2015
Amendment 2, Date:	22 June 2016
Amendment 3, Date:	26 April 2017
Amendment 4, Date:	**27 May 2020**

Confidentiality Notice

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

NCT Number: NCT02624869
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 "Open-label, Single-Arm, Multicenter Study to Evaluate the Safety, Tolerability and Efficacy of Evolocumab for LDL-C Reduction, as Add-On to Diet and Lipid Lowering Therapy, in Pediatric Subjects From 10 to 17 Years of Age With Heterozygous Familial Hypercholesterolemia (HeFH) or Homozygous Familial Hypercholesterolemia (HoFH) HAUSER-OLE", dated **27 May 2020**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for 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: Open-label, Single-Arm, Multicenter Study to Evaluate the Safety, Tolerability and Efficacy of Evolocumab for LDL-C Reduction, as Add-On to Diet and Lipid Lowering Therapy, in Pediatric Subjects From 10 to 17 Years of Age With Heterozygous Familial Hypercholesterolemia (HeFH) or Homozygous Familial Hypercholesterolemia (HoFH) HAUSER-OLE

Study Phase: 3b

Indication: Heterozygous familial hypercholesterolemia or homozygous familial hypercholesterolemia in pediatric subjects 10 to 17 years of age

Primary Objective: To describe the safety and tolerability of 80 weeks of SC evolocumab when added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH

Secondary Efficacy Objectives:

- To describe percent change and change from baseline in LDL-C, and on percent change from baseline 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 or HoFH after 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH

Secondary Safety Objectives:

- To describe change from baseline in steroid hormones and the subject incidence of abnormal muscle and liver enzyme levels after 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH
- To describe changes from baseline in carotid intima-media thickness (cIMT) after 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH
- To describe change from baseline in growth and pubertal development parameters at measured timepoints with 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH

Other Safety Objectives:

- To evaluate the incidence of abnormal neurological examination findings after 80 weeks of SC evolocumab added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH
- To assess cognitive function, assessed using the change from baseline in the components of the Cogstate battery at each scheduled administration, after 80 weeks of SC evolocumab added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH

Exploratory Objectives:

- To describe change and percent change at measured timepoints in LDL-C, total cholesterol, non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio, triglycerides, VLDL-C, HDL-C, ApoA1, lipoprotein(a) [Lp(a)], with 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH
- To describe change at measured timepoints in proprotein convertase subtilisin/kexin type 9 (PCSK9) and high sensitivity C-reactive protein (hsCRP) with 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH
- To describe the incidence of abnormal neurological examination findings with 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH
- To investigate the relationship between novel and established biochemical cardiovascular and lipid biomarkers and effects of evolocumab in pediatric subjects 10 to 17 years of age with HeFH

- In subjects consenting to the optional pharmacogenetics analysis, to investigate potential correlations of study data including the subject response to evolocumab with genetic variation in markers of (PCSK9) signaling, low-density lipoprotein receptor (LDLR) turnover, cholesterol metabolism, inflammation, and plaque stability

Hypothesis: The primary clinical hypothesis is that SC evolocumab will be well tolerated when added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH

Primary Endpoint: **T**reatment emergent adverse events at week 80

Secondary Efficacy Endpoints:

- Percent change from baseline at week 80 in:
  - LDL-C
  - non-HDL-C
  - ApoB
  - total cholesterol/HDL-C ratio
  - ApoB/ApoA1 ratio
- Change from baseline in LDL-C at week 80

Secondary Safety Endpoints:

- Change from baseline in steroid hormones (estradiol in females, testosterone in males; follicle-stimulating hormone [FSH], luteinizing hormone [LH], adenocorticotropic hormone [ACTH], dehydroepiandrosterone sulfate [DHEA-S], cortisol in all subjects) at week 80
- **A**bnormal muscle and liver enzyme levels (creatine kinase [CK], aspartate aminotransferase [AST], or alanine aminotransferase [ALT]) at week 80
- Change in cIMT from baseline at week 80
- Change from baseline in growth (height and weight) and pubertal development (Tanner staging) at weeks 24, 48, and 80

Study Design: This is an open-label, single-arm, multicenter study. Subjects are eligible for screening if they have completed Study 20120123 (and did not experience a treatment-related serious adverse event) or if they are 10 to 17 years of age at time of enrollment and have HoFH. The minimum expected enrollment of HeFH rollover subjects is approximately 70% of subjects enrolled in Study 20120123 or approximately **111** subjects. In addition, approximately 10 subjects with HoFH (and without prior participation in an evolocumab study) will be enrolled for an expected total enrollment of approximately **124** subjects. Depending on willingness of subjects completing Study 20120123 to receive open-label evolocumab, final enrollment may be smaller or greater.

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

Sample Size: Approximately **124** subjects are anticipated to enroll in this trial. This corresponds to an estimated 70% rollover for subjects with HeFH from the parent study 20120123 and approximately 10 subjects with HoFH enrolling in this study. Depending on rollover rate from Study 20120123, final enrollment may be smaller or greater.

Summary of Subject Eligibility Criteria: Males and females who have completed Study 20120123 (and did not experience a treatment-related serious adverse event) and males and females of 10 to 17 years of age with diagnosis of HoFH and receiving optimized standard of care lipid-lowering therapy per locally applicable guidelines are eligible for this study. Diagnosis of HoFH must be by genetic confirmation or a clinical diagnosis based on a history of an untreated LDL cholesterol concentration greater than 500 mg/dL (13 mmol/L) together with either xanthoma before 10 years of age in the subject, or evidence of heterozygous familial

hypercholesterolemia in both parents. At screening, HoFH subjects must be on a low-fat diet and receive background lipid-lowering therapy (such as statins, cholesterol absorption inhibitors, bile acid sequestrants, nicotinic acid, or combinations thereof). Lipid-lowering therapy must be stable for ≥ 4 weeks prior to screening. Fasting LDL-C for HoFH subjects 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 exclusion criteria for subjects with HoFH (those not rolling over from a prior evolocumab study): estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m^2; CK > 3x ULN; AST or ALT > 2x ULN; (all screening by central laboratory); known active infection or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction; subject has taken a cholesterylester transfer protein (CETP) inhibitor in the last 12 months, or mipomersen or lomitapide in the last 5 months prior to LDL-C screening, or has received any therapy to inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9) within 12 weeks prior to screening; subject has a 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, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion. The following are major exclusion criteria for all subjects: subjects cannot be receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study (except Study 20120123); female subjects of childbearing potential cannot be pregnant or breast feeding or planning to become pregnant or planning to breast feed and must be willing to use acceptable method(s) of effective birth control (may include true sexual abstinence) during treatment with evolocumab and for an additional 15 weeks after the end of treatment with evolocumab.

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

Amgen Investigational Product Dosage and Administration: Investigational product (evolocumab) will be administered subcutaneously using a spring-based prefilled 1.0 mL autoinjector/pen (AI/Pen) or automated mini-doser (AMD) (upon availability). Each prefilled AI/Pen will contain 140 mg / 1.0 mL deliverable volume of evolocumab. The AMD will contain 420 mg / 3.5 mL deliverable volume of evolocumab. Subjects will have the opportunity to switch between the AI/Pen and AMD at any scheduled time point where evolocumab is supplied to the subject, provided the appropriate supply is available. Dosing will be as follows:

- Evolocumab 420 mg SC QM (3 AI/Pen injections or 1 AMD administration)

Non Amgen Non-investigational Products: 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 who have completed Study 20120123 (and did not experience a treatment-related serious adverse event) and have signed parental/guardian consent/permission and subject consent/assent for Study 20120124, will be enrolled. Subjects with HoFH being considered for participation in this study, and who have signed parental/guardian consent/permission and subject consent/assent, will be assessed for inclusion and exclusion criteria. Medical and medication history will be obtained. Subjects will undergo screening laboratory assessments, including a SC administration of placebo to evaluate tolerability of the SC injection in subjects with HoFH only. Lipid eligibility screening must be conducted after subject has been on a low-fat diet and receiving stable lipid-lowering therapy for ≥ 4 weeks. Subjects should maintain their diet, lipid-lowering therapy, and exercise regimen throughout screening and all phases of study participation. Eligible subjects will start receiving open-label evolocumab, in addition to their background lipid-lowering therapy.

Day 1 is defined as the day of first administration of evolocumab. Subsequent study visits are at weeks 4, 12, 24, 36, 48, 60, 72, and 80 (EOS, end-of-study). 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.

Adverse Events/Serious Adverse Events/Adverse Device Effects (ADE) and concomitant therapy will be collected at every study visit. Other assessments and procedures are done as per Schedule of Assessments (Table 2) and include vital signs, dietary instruction, physical exam,

body height and weight, 12-lead electrocardiograms (ECGs), chemistry, hematology, anti-evolocumab antibodies, biomarker sample collection, serum pregnancy testing (females of childbearing potential), urinalysis, specific laboratory assessments, assessment of growth and pubertal development (Tanner staging), carotid intima-media thickness (cIMT), and IP administration. Specific laboratory assessments will include estradiol for girls, testosterone for boys, creatinine phosphokinase, FSH, LH, ACTH, DHEA-S, and cortisol. If the subject consented to pharmacogenetics analyses and DNA has not already been obtained after consenting in Study 20120123, 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 list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 2).

Statistical Considerations:

General Considerations

Statistical analyses in this open label study are descriptive in nature. No statistical hypothesis testing or missing value imputation is planned.

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

For efficacy analyses, the baseline value is defined as:

- Subjects that participated in parent Study 20120123 and with baseline data from the parent study: the baseline is defined as the baseline of the qualifying parent study.
- Subjects not enrolling from a parent study or without baseline data from the parent study: the baseline is defined as the baseline in this study.

The full analysis set (FAS) includes all subjects with HeFH from parent study 20120123 who are enrolled **and dosed,** and all subjects with HoFH who are enrolled and dosed in this study. Analysis of all the endpoints with FAS will be provided. Subjects will be summarized according to whether subject rolled over from a parent study and their treatment allocation from a parent study when applicable.

Interim Analysis and Early Stopping Guidelines

The interim analysis will be conducted when all the enrolled subjects in the study have opportunity to experience 28 weeks of investigation product exposure or have early terminated from the study. At that time, the database related to the interim analyses of the study will be cleaned, processed and a snapshot will be taken. Unless specified otherwise, the FAS will be the default analysis set in this study. Similar to the primary analysis, the interim data will be summarized by cohort (HeFH and HoFH). Statistical analysis in this interim analysis is descriptive in nature for all safety and efficacy endpoints if applicable. No statistical hypotheses testing, or missing value imputation is planned. There is no study stopping rule for either futility or efficacy and the current design or execution of the study will continue without any changes regardless of the result of the interim analysis.

Analysis of Primary Endpoint

Subject incidence of all treatment emergent adverse events will be tabulated by system organ class and preferred term at week 80. Tables of fatal adverse events, serious adverse events, device related adverse events, adverse events leading to withdrawal from investigational product, and significant treatment emergent adverse events will also be provided. Adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

Analyses of Secondary Endpoints

Growth and pubertal development parameters will be summarized at weeks 24, 48, and 80. Other secondary endpoints will be summarized at week 80. Descriptive statistics will be presented.

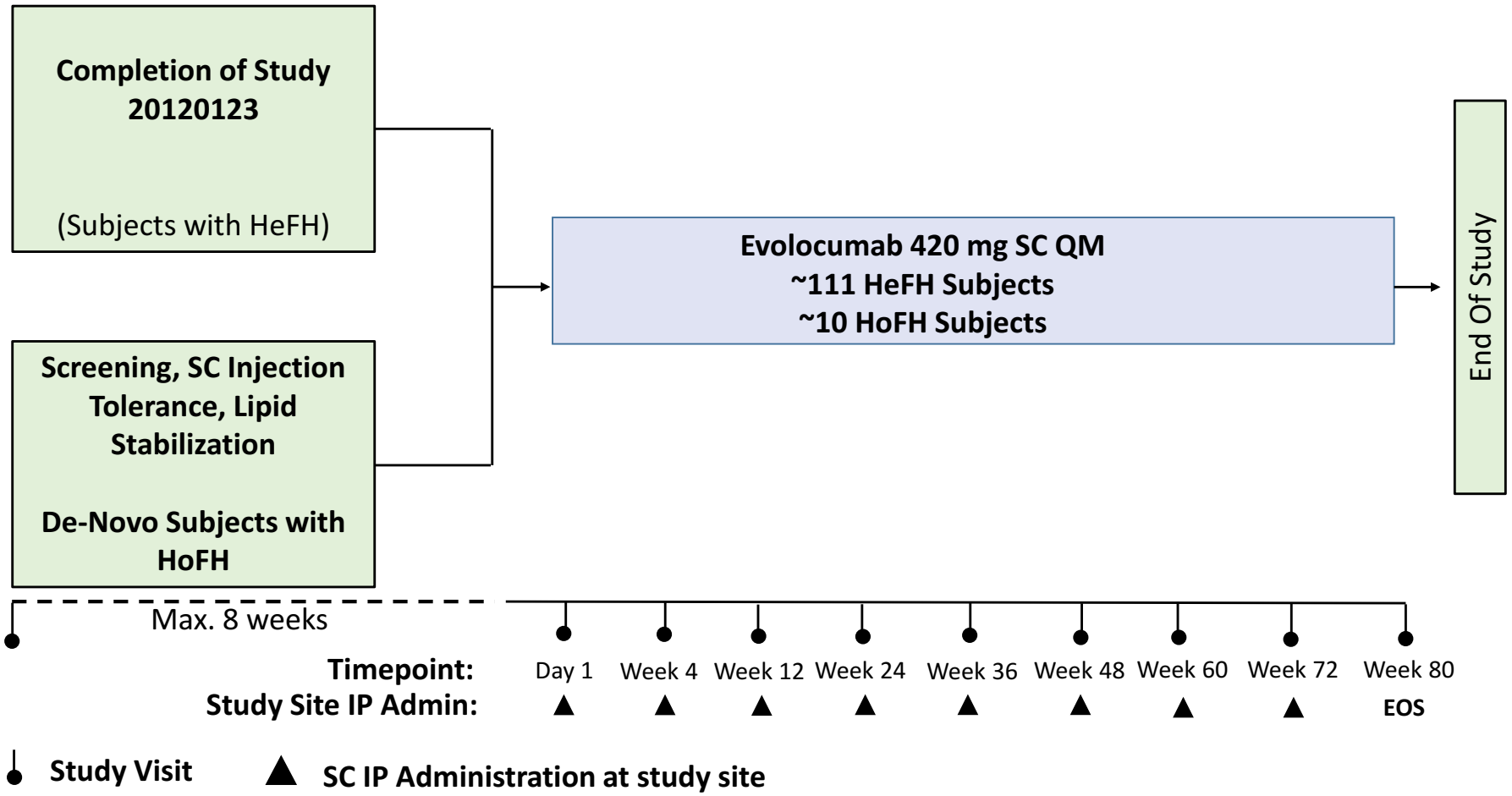
An independent DMC which is external to Amgen will formally review the accumulating data to ensure there is no avoidable increased risk for harm to subjects.

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

Sponsor: Amgen

Data Element Standards Version(s)/Date(s):	Version 5 / 20 March 2015

Study Design and Treatment Schema



EOS = End of Study; HeFH = Heterozygous Familial Hypercholesterolemia; HoFH = Homozygous Familial Hypercholesterolemia; IP = Investigational Product; QM = every 4 weeks; SC = subcutaneous

Study Glossary

Abbreviation or Term	Definition/Explanation
ADE	Adverse device effect
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
CETP	Cholesterylester transfer protein
cIMT	carotid intima-media thickness
CK	Creatine kinase
CHD	Coronary heart disease
CRF	Case report form
CRP	C-reactive protein
CTCAE	NCI Common Terminology Criteria for Adverse Events
DILI	Drug-induced liver injury
DMC	Data monitoring committee (Efficacy and Safety Evaluation Committee)
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
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
End of Study for Individual Subject	Defined as the last day that protocol-specified procedures are conducted for an individual subject

Abbreviation or Term	Definition/Explanation
End of Study (primary completion)	The end of the study (primary completion) is defined as the last day on which an enrolled subject in this study completes the end-of-study visit (week 80) or terminates the study early
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 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; when applicable, this paper based form can be used under restricted conditions (eg, when EDC system is down) and faxed to Amgen
FAS	Full analysis set
FH	Familial hypercholesterolemia
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
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
ICF	Informed consent form
ICH	International Council for Harmoni**s**ation
IEC	Independent ethics committee
IFU	Instructions for Use
Ig	Immunoglobulin
IM	Intramuscular
IMP	Investigational medicinal product
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.
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.
IRB	Institutional Review Board

Abbreviation or Term	Definition/Explanation
IP	Investigational product (evolocumab, administered with the medical device**s** used in this study – the prefilled autoinjector/pen [AI/pen] or automated mini-doser [AMD] [upon availability])
IPIM	Investigational Product Instruction Manual
IVRS/IWRS	Interactive Voice Response System / Interactive Web Response System
IV	Intravenous
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LDLR	LDL receptor
LLN	Lower limit of normal
LOF	Loss of function
Lp(a)	Lipoprotein(a)
MedDRA	Medical dictionary for regulatory activities
NASH	Nonalcoholic steatohepatitis
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamic
PFS	Pre-filled syringe
PI	Principal investigator
PK	Pharmacokinetic
QM	QM is defined as every 4 weeks with a window of ± 3 days for each dose until week 4, then ± 7 days after week 4. Note: day 1 and week 80 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
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

Abbreviation or Term	Definition/Explanation
TC	Total cholesterol
TIA	Transient ischemic attack
TNF	Tumor necrosis factor
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol
WBC	White blood cell

TABLE OF CONTENTS

List of Tables

List of Appendices

1. OBJECTIVES

1.1 Primary

To describe the safety and tolerability of 80 weeks of SC evolocumab when added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH.

1.2 Secondary Efficacy

- To describe percent change and change from baseline in LDL-C, and on percent change from baseline 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 or HoFH after 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH

1.3 Secondary Safety

- To describe change from baseline in steroid hormones and the subject incidence of abnormal muscle and liver enzyme levels after 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH
- To describe changes from baseline in carotid intima-media thickness (cIMT) after 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH
- To describe change from baseline in growth and pubertal development parameters at measured timepoints with 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH

1.4 Other Safety

- To evaluate the incidence of abnormal neurological examination findings after 80 weeks of SC evolocumab added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH
- To assess cognitive function, assessed using the change from baseline in the components of the Cogstate battery at each scheduled administration, after 80 weeks of SC evolocumab added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH

1.5 Exploratory

- To describe change and percent change at measured timepoints in LDL-C, total cholesterol, non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio, triglycerides, VLDL-C, HDL-C, ApoA1, lipoprotein(a) [Lp(a)], with 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH
- To describe change at measured timepoints in proprotein convertase subtilisin/kexin type 9 (PCSK9) and high sensitivity C-reactive protein (hsCRP) with 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH
- To describe the incidence of abnormal neurological examination findings with 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH

- To investigate the relationship between novel and established biochemical cardiovascular and lipid biomarkers and effects of evolocumab in pediatric subjects 10 to 17 years of age with HeFH
- In subjects consenting to the optional pharmacogenetics analysis, to investigate potential correlations of study data including the subject response to evolocumab with genetic variation in markers of (PCSK9) signaling, low-density lipoprotein receptor (LDLR) turnover, cholesterol metabolism, inflammation, and plaque stability

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, 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). Because premature atherosclerosis and especially coronary artery disease are part of the natural history of FH, events related to coronary artery disease and its complications (eg, manifestations of myocardial ischemia such as chest pain and myocardial infarction; percutaneous and surgical revascularization procedures, etc.) are expected to occur in this population at some frequency regardless of drug exposure.

In the adult population, hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are currently the treatment of choice for patients with HeFH and HoFH patients (Grundy et al, 2004). 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 Background

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.

Refer to the evolocumab Investigator's Brochure for more information on 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 and adolescent population. In Amgen's development program for evolocumab, 2 studies to date have included adolescent 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. Per protocol, of the 14 subjects participating in Study 20110271, 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, as of 01 July 2014, 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 were reported. 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 investigational product (IP), and are both known consequences of the subjects' underlying FH.

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 adult studies, 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.

2.4 Rationale

FH is a genetic disorder which typically requires lifelong treatment, sometimes beginning in childhood. Therefore, it is important to study the long-term 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; cognition) are appropriate.

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 (Studies 20110233 and 20110271), evolocumab lowered LDL-C and other lipid parameters in subjects aged 12-17 years. At the time of enrollment in Study 20120124, subjects with HeFH will have completed the double-blind, placebo-controlled study 20120123 in which they will have been randomized to evolocumab or placebo for 24 weeks. Study 20120124 is designed to provide longer-term clinical experience with evolocumab in subjects 10 to 17 years of age. The primary endpoint of Study 20120124 is the incidence of treatment emergent adverse events at week 80. Assessments of several lipid parameters, including LDL-C, Lp(a), non-HDL-C, ApoB, total cholesterol/HDL-C ratio, and ApoB/ApoA1 ratio were chosen as additional endpoints to evaluate stability of the treatment effect over the duration of the study.

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 the range already observed in the evolocumab development program.

2.5 Clinical Hypotheses

The primary hypothesis is that SC evolocumab will be well tolerated when added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is an open-label, single-arm, multicenter study. Subjects are eligible for screening if they have completed Study 20120123 (and did not experience a treatment-related serious adverse event) or if they are 10 to 17 years of age at time of enrollment and have HoFH. The minimum expected enrollment of HeFH (rollover) subjects is approximately 70% of subjects enrolled in Study 20120123 or approximately **111** subjects. In addition, approximately 10 subjects with HoFH (and without prior participation in an evolocumab study) will be enrolled for an expected total enrollment of approximately **124** subjects. Depending on willingness of 20120123 subjects to continue evolocumab administration, final enrollment may be smaller or greater.

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

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 56 sites in North America, Latin America, Europe, Australia, South Africa, 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 enroll 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”.

Approximately **124** subjects are anticipated to enroll in this trial. This corresponds to an estimated 70% rollover for subjects with HeFH from the parent study 20120123 and

approximately 10 subjects with HoFH enrolling in this study. Depending on rollover rate from Study 20120123, final enrollment may be smaller or greater.

3.4 Replacement of Subjects

There will be no replacement of subjects.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

HeFH (rollover) subjects should enroll in Study 20120124 at the time of the week 24 (end of study [EOS]) visit in Study 20120123. For all subjects, after enrollment, the duration of study participation for a subject will be 80 weeks or approximately 18 ½ months.

3.5.2 End of Study

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), whether the study concluded as planned in the protocol or was terminated early.

The primary completion date is the same as the end of study date and is the date when the last enrolled subject has completed the end-of-study visit (week 80) (ie, last subject last visit).

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

End of Study: The end of the study date is defined as the last day on which an enrolled subject in this study completes the end-of-study visit (week 80) 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 (IVR)/Interactive Web Response (IWR) system.

Before any study-specific activities/procedure, the appropriate written informed consent (and assent, when applicable) must be obtained (see Section 11.1). For subjects who

are not of legal age, informed consent from a legally acceptable representative must be obtained, in addition to assent of the child, where locally required.

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria

All Subjects:

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.

Subjects with HeFH:

103 Completed Study 20120123 while still on assigned investigational product and did not experience a treatment-related serious adverse event.

Subjects with HoFH:

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

105 Diagnosis of HoFH by genetic confirmation or a clinical diagnosis based on a history of an untreated LDL cholesterol concentration > 500 mg/dL (13 mmol/L) together with either xanthoma before 10 years of age or evidence of heterozygous familial hypercholesterolemia in both parents.

106 Subject must be on a low-fat diet and receiving background lipid-lowering therapy (such as statins, cholesterol absorption inhibitors, bile acid sequestrants, nicotinic acid, or combinations thereof).

107 Lipid-lowering therapy, including statin dose, must be unchanged for ≥ 4 weeks prior to LDL-C screening; fibrates must be stable for at least 6 weeks prior to screening.

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

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

4.1.2 Exclusion Criteria

All Subjects:

201 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); except Study 20120123. Other investigational procedures or treatments while participating in this study are excluded.

202 Female subject who has experienced menarche and unwilling to use acceptable method(s) of effective birth control during treatment with evolocumab and for an additional 15 weeks after the end of treatment with evolocumab. 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.

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

204 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).

205 Subject will not be available for or likely not to comply with protocol-required study visits or procedures, to the best of the subject and investigator's knowledge (Note: Day 1 and week 80 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).

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

Subjects with HoFH:

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

208 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.

209 CK > 3 times the ULN at screening.

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

211 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.

212 Subject has received evolocumab or any other therapy to inhibit PCSK9 within 12 weeks of screening.

213 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, Evolocumab 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 and/or subject assent form before commencement of study-specific activities/procedures.

Subjects with HeFH will keep the same subject identification number from Study 20120123. Subjects with HoFH who enter into the screening period for the study will receive a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by the IVR/IWR system. The investigator or designee must contact the IVR/IWR system 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.

Sites participating in Study 20120123 and in this study will be assigned the same site number as the one used in Study 20120123.

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 case report form (CRF).

All subjects participating in Study 20120124 will receive open-label evolocumab.

6. TREATMENT PROCEDURES

6.1 Classification of Products and/or Medical Devices

The Amgen investigational product used in this study is evolocumab (Amgen investigational medicinal product [IMP]). The medical devices used in this study to deliver or administer the IMP are the prefilled autoinjector/pen (AI/Pen) or the automated mini-doser (AMD) (upon availability).

The Non-Amgen Non-investigational product(s) used in this study include the subjects' pharmacological background lipid-lowering therapies, including statin therapy.

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 Amgen investigational product.

6.2 Amgen Investigational Product Evolocumab

Evolocumab will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical IP distribution procedures. Evolocumab will be presented for fixed dose, subcutaneous injection as a sterile, preservative-free solution in a prefilled AI/Pen or AMD. The prefilled, single use, disposable, handheld mechanical (spring-based) AI/Pen contains a 140 mg / 1.0 mL deliverable volume of evolocumab. The AMD is a single use, disposable, on body electro-mechanical injection device containing 420 mg / 3.5 mL deliverable volume of evolocumab.

IP (evolocumab) 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 or AMD.

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

6.2.1 Dosage, Administration, and Schedule

IP (evolocumab) 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 all other procedures, including vital signs, electrocardiogram (ECG), Cogstate testing, cIMT imaging, blood draw procedures, and apheresis. Apheresis is permitted only for subjects with HoFH; blood draw procedures are to occur before apheresis. All subjects

will be held for observation for at least 30 minutes after IP administration before being discharged at the first dosing visit.

Each QM administration of IP with the AI/Pen will consist of 3 injections of 140 mg evolocumab in 1.0 mL for a total of 420 mg / 3.0 mL of evolocumab administered. The SC injections should be administered in a consecutive fashion with all injections completed within 30 minutes.

Each QM administration of IP with the AMD will consist of 1 injection of 420 mg / 3.5 mL of evolocumab.

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.

Subjects will have the opportunity to switch between the AI/Pen and AMD at any scheduled time point where evolocumab is supplied to the subject, provided the appropriate supply is available. The first self-administration after switching the device should be done at a regularly scheduled visit under the supervision of the investigator or qualified study center staff.

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 Non Amgen Non-investigational Products

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) discovered during study participation (as part of usual practice or standard of care) 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 Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR, and transaminases) has not been identified (Table 1).

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)

If investigational product(s) is/are withheld, the subject is to be followed according to recommendations in Appendix A for possible drug-induced liver injury (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 6.5.2).

Table 1. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3x ULN at any time	> 2x ULN
		OR
INR	--	> 1.5 (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8x ULN at any time > 5x ULN but < 8x ULN for ≥ 2 weeks > 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule > 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice).	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values > 3x ULN (when baseline was < ULN)
	OR	
ALP	> 8x ULN at any time	--

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

6.5.2 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 Amgen investigational product and other protocol-required therapies, as appropriate, should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 1) should not 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.

6.7 Medical Devices

Evolocumab will be provided by prefilled AI/Pen or AMD (upon availability) (Section 6.2).

Other non-investigational medical devices may be used in the conduct of this study as part of standard of care. These 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(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug(s) or device(s) or combination product(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 AMD 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 or AMD)
- missing labels, illegible labels, incorrect labels, and/or suspect labels
- change in IP appearance, for example color change or visible presence of foreign material
- unexpected quantity or volume, for example number of tablets or amount of fluid in the prefilled AI/Pen or AMD
- 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 and/or device 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, Medical Devices, and/or Procedures During Study Period

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

- treatments for inhibition of PCSK9 or any investigational therapies other than study provided investigational product
- mipomersen or lomitapide
- prescribed amphetamines, or amphetamine derivatives, and weight loss medications.

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 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 2. Schedule of Assessments

Study Day / Week / Other Timepoint[a]	Screening		D1/Parent Study EOS	W4[c] (±3d)	W12 (±7d)	W24 (±7d)	W36 (±7d)	W48 (±7d)	W60 (±7d)	W72 (±7d)	W80 (EOS) (±7d)
	HoFH	HeFH[b]									
General Procedures											
Informed parental/guardian consent/permission and subject consent/assent – HoFH subjects	X										
Informed parental/guardian consent/permission and subject consent/assent – HeFH subjects		X	X								
Enrollment			X[d]								
Medical history	X										
Vital Signs (sitting BP, HR)	X	X	X	X	X	X		X			X
Review for AEs/SAEs/ADEs	X[e]	X[e]	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X
Dietary instruction	X	X	X		X	X	X	X	X	X	
Physical exam (including neurologic examination)	X										X
Height, weight, cIMT, Tanner staging			X[f]			X		X			X
Neurocognitive assessment (Cogstate battery)	X		X[g]			X		X[g]			X
12 lead ECG			X								X
Central Laboratory[h]											
Fasting lipids[h]	X	X[i]	X		X			X			X
ApoA1, ApoB100, Lp(a)[h]			X		X						X
PK (evolocumab), PCSK9			X		X						X
Chemistry, including fasting glucose[h]	X	X			X			X			X
Hematology	X	X						X			X
Estradiol (females) / testosterone (males)		X[i]	X								X
HbA1c, FSH, LH, ACTH, DHEA-S, cortisol, hsCRP, fasting vitamins A/D/E/K[j]		X[i]	X								X
CK	X	X[i]	X		X			X			X
Biomarkers (blood)[k]			X								X
Anti-evolocumab antibodies			X								X
HCV testing[l]	X										
HCV viral load[l]			X					X			X
Serum pregnancy[m]	X	X									X
Urine pregnancy[m]			X[n, o]	X	X	X	X	X	X	X	
Urinalysis, urine microalbumin, urine creatinine, urine albumin/creatinine ratio			X								X

Page 1 of 2

Footnotes displayed on the next page of the Table

Table 2. Schedule of Assessments

Study Day / Week / Other Timepoint[a]	Screening		D1/Parent Study EOS	W4[c] (±3d)	W12 (±7d)	W24 (±7d)	W36 (±7d)	W48 (±7d)	W60 (±7d)	W72 (±7d)	W80 (EOS) (±7d)
	HoFH	HeFH[b]									
Investigational Product											
Screening placebo AI/Pen (HoFH subjects only)	X										
IP administration on-site / instruction as needed			X	X	X	X	X	X	X	X	
AI/Pen or AMD dispensation[p]			X[q]	X	X	X	X	X	X	X	
AI/Pen or AMD reconciliation					X	X	X	X	X	X	X

Page 2 of 2

ACTH = adrenocorticotropic hormone, ADE = adverse device effect, AE = adverse event, AI/Pen = autoinjector/pen, ALT = alanine aminotransferase, AMD = automated mini-dose, ApoA1 = apolipoprotein A-1, ApoB100 = apolipoprotein B100, AST = aspartate aminotransferase, BP = blood pressure, cIMT = Carotid Intima-Media Thickness, CK = creatine kinase, D = day, DHEA-S = dehydroepiandrosterone sulfate, ECG = electrocardiogram, EOS = end-of-study (for the individual subject), FSH = follicle-stimulating hormone, HbA1c = hemoglobin A1C, HCV = hepatitis C virus, HeFH = heterozygous familial hypercholesterolemia, HoFH = homozygous familial hypercholesterolemia, HR = heart rate, hsCRP = high sensitivity C-reactive protein, ICF = informed consent form, IP = investigational product, LH = luteinizing hormone, Lp(a) = lipoprotein(a), PCSK9 = proprotein convertase subtilisin/kexin type 9, PK = pharmacokinetic, SAE = serious adverse event, ULN = upper limit of normal, W = week

[a] D1 = day of first administration of IP; this visit should also coincide with EOS visit for parent study in subjects rolling over from Study 20120123; procedures NOT conducted as part of EOS visit for parent study should be completed at this visit.

[b] For rollover subjects only, when time between Study 20120123 EOS visit and Study 20120124 day 1 visit exceeds 4 weeks.

[c] Week 4 training visit applies to HoFH subjects only (due to lack of prior experience of in-home use of IP).

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

[e] Only AEs possibly related to study procedures, SAEs, and ADEs (placebo injections for HoFH subjects) are collected during the screening period (from signing of ICF).

[f] Study 20120124 day 1 cIMT is not required for rollover subjects completing the 20120123 EOS cIMT (regardless of time between Study 20120123 EOS and Study 20120124 day 1).

[g] HoFH subjects only.

[h] Blood samples must be taken prior to IP administration and apheresis, if applicable. Note: apheresis is permitted only for subjects with HoFH.

[i] For rollover subjects that have performed the screening visit will not have to repeat the labs that were performed at screening at day 1: fasting lipids, hormones, HbA1, FSH, LH, ACTH, DHEA-S, CK, Cortisol, hsCRP, fasting vitamins A,D,E,K.

[j] If a subject with HoFH is not fasting on day 1, reschedule. All other subjects or timepoints: if the subject is not fasting, 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.

[k] If the subject consented to pharmacogenetics analyses, deoxyribonucleic acid (DNA) will be extracted from some of the blood samples, eg, biomarker samples.

[l] 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.

[m] Pregnancy testing in females of childbearing potential; if urine test is positive, perform confirmatory serum pregnancy test.

[n] For rollover subjects: urine pregnancy test at day 1 is not required in lieu of serum pregnancy at Study 20120123 EOS visit if completed within 7 days of initiation of evolocumab in Study 20120124.

[o] For rollover subjects that have performed the screening visit: urine pregnancy test at day 1 is not required in lieu of serum pregnancy at screening visit if completed within 7 days of day 1.

[p] Subjects will have the opportunity to switch between the AI/Pen and AMD at any scheduled time point where evolocumab is supplied to the subject, provided the appropriate supply is available. The first self-administration after switching the device should be done at a regularly scheduled visit under the supervision of the investigator or qualified study center staff.
[q] HeFH subjects only.

7.2 General Study Procedures

It is the responsibility of the investigator to ensure that all procedures are performed according to the protocol. Written informed consent must be obtained 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 are described below and the timing of the procedures is provided in Table 2.

Subjects must be fasting for ≥ 9 hours before each study visit where fasting samples are being taken. 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. If IP is administered during a study visit, administration must be after completion of all other visit procedures, including vital signs, ECG, Cogstate testing, cIMT imaging, blood draw procedures, and apheresis. Apheresis is permitted only for subjects with HoFH; blood draw procedures are to occur before apheresis.

All on-study visits and dosing should be scheduled from study day 1. Day 1 and week 80 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. Weeks are counted from day 1, the first day of IP administration, eg, 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 the visit window as specified in the Schedule of Assessments (Table 2). 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 (HoFH subjects only), all study procedures for a visit must be completed on the same day.

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.

All screening, if applicable, 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 PCSK9 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 3 below outlines the specific analytes for serum chemistry, hematology, urinalysis, and other testing to be conducted.

Table 3. 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	Differential	Estradiol (females)
BUN or Urea		Casts	• Neutrophils	Testosterone (males)
Creatinine		Crystals	• Bands	Cortisol
Uric acid		Urine Creatinine	• Eosinophils	Luteinizing hormone (LH)
Total bilirubin		Urine microalbumin	• Basophils	Adrenocorticotropic hormone (ACTH)
Direct bilirubin		Urine Albumin/ Creatinine ratio	• Lymphocytes	Dehydroepiandrosterone sulfate (DHEA-S)
CK			• Monocytes	hsCRP
ALP				Fasting vitamins A, D, E, and K
LDH				Lp(a)
AST (SGOT)				Anti-evolocumab antibodies
ALT (SGPT)				PCSK9
				Evolocumab (PK)
				HbA1c
				Pregnancy test (females of childbearing potential)
				FSH
				HCV antibody[2]
				HCV viral load[3]

[1] Day 1 and week 80 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 HoFH subjects only at high risk for (see Section 7.2.1.1), or with history of HCV infection and in HoFH subjects with ALT or AST > 2x ULN at any time during screening. Please note that HoFH subjects with ALT or AST > 2x ULN must be screen failed unless the elevation is transient as confirmed by retesting per Section 7.2.1.3.
[3] Viral load will be tested at the time points indicated in Table 2 in subjects who are positive for HCV.

7.2.1 Screening and Enrollment

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.

Subjects completing Study 20120123 (rollover subjects) should be informed of Study 20120124 so that the informed consent process and screening can be completed in time for the subject, if interested and eligible, to be enrolled in Study 20120124 at the time of the last 20120123 study visit (week 24; end-of-study). Only subjects from Study 20120123 that did not experience a treatment-related serious adverse event will be eligible. For subjects rolling over from Study 20120123, if the period between Study 20120123 EOS visit and Study 20120124 day 1 visit exceeds 4 weeks, certain screening tests (as outlined in Table 2) will need to be repeated.

Subjects with HoFH considered for enrollment in Study 20120124 should complete screening and the subject enrolled 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, subjects with HoFH who are considered for the study 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 enrollment. 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 Laboratory Testing (Subjects With HoFH Only)

Screening fasting lipids and glucose must be collected after ≥ 9 hour fasting by the subject. 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 enrollment.

All prohibited lipid-lowering therapy (see Section 6.9) must be discontinued ≥ 4 weeks before lipid screening laboratories are taken or as indicated in Section 4.1.1 and/or Section 4.1.2, whichever is longer.

Note that eGFR will be calculated by the central laboratory and will be provided to the site for eligibility determination.

Screening includes blood laboratory collection for hepatitis C virus (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

* 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 7.2.1.3.

7.2.1.3 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 enrolled within the allowed screening period. Retesting of laboratory samples must occur at least 1 week after previous sample.

7.2.1.4 Rescreening

HoFH 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 enrolled 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.

7.2.1.5 Screen Fail

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

7.2.1.6 Enrollment

Subjects who continue to meet all eligibility criteria at the end of screening will be enrolled (Section 5).

7.2.2 Treatment and End of Study

Rollover subjects (HeFH subjects) should complete their day 1 procedures for Study 20120124 and initiate open-label evolocumab administration at the end of the week 24 (EOS) visit in Study 20120123 (see Section 7.2.1 for guidance). HoFH subjects will visit the study site upon enrollment for day 1 procedures and initiation of open-label evolocumab administration while continuing their background lipid-lowering treatment. Day 1 in Study 20120124 is defined as the day of first administration of open-label evolocumab (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 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.

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 80 should be completed at the time of withdrawal.

Subjects will end the study with the week 80 visit. Note that the week 80 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 2 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 PCSK9 signaling, LDLR turnover, cholesterol metabolism,

inflammation, and plaque stability. It is not possible at this stage to anticipate what these advances will be; however, considerable benefit could accrue to future sufferers of coronary artery disease if these markers can be correlated with the data from the study. It is also important to clarify any potential drug interactions in this population of subjects who will be on a number of other drugs. For biomarker analysis, where local regulations permit, blood will be collected at each of the time points indicated in Table 2 so that biomarkers related to, but not limited to PCSK9 signaling, LDLR turnover, cholesterol metabolism, inflammation, and plaque stability such as certain glycosylated proteins, matrix metalloproteinases, additional markers of inflammation such as myeloperoxidase, bromo and nitro-tyrosine, tumor necrosis factor (TNF), and cellular adhesion molecules 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 PCSK9 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 2) 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 PCSK9 signaling, LDLR turnover, cholesterol metabolism, inflammation, and plaque stability such as certain glycosylated proteins, matrix metalloproteinases, additional markers of inflammation such as myeloperoxidase, bromo and nitro-tyrosine, TNF, and cellular adhesion molecules, the dose response and/or prediction of response to PCSK9 inhibition, 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 Lipid Measurements

For subjects rolling over from Study 20120123, central laboratory results of the lipid panel, as well as ApoA1, ApoB, Lp(a), and PCSK9 will be unblinded when the subject has reached week 12 in Study 20120124. For these subjects, vitamins A, D, E, and K will also be blinded until the Study 20120123 database is locked. 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 until week 12 in Study 20120124 and, if a lipid panel is drawn, all reasonable steps must be undertaken to avoid informing the subject and study personnel of the results.

7.7.2 Measurement of Vital Signs

Blood pressure (BP) and heart rate (HR) will be measured as per Schedule of Assessment (Table 2). Use of an automated oscillometric device for BP measurement is preferred and recommended. 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. For subjects with HoFH, 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. For subjects rolling over from Study 20120123, the same arm should be used for measurement as in Study 20120123.

7.7.3 Height and Weight Measurements

Height and weight measurement will be obtained at the time points specified in the Schedule of Assessments (Table 2). 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.

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 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 CRF 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 Physical and Neurologic Examination

Physical examination (at screening and EOS) should include a neurologic examination. The neurologic 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. Any clinically significant changes in the physical examination per the investigator's opinion should be recorded on the Adverse Event CRF.

7.7.7 Cognitive Assessments (Cogstate Battery)

The Cogstate battery is a largely language-independent battery of neurologic tests administered via computer which has been validated for use in the age group to be studied in Study 20120124. The Cogstate battery has a significant normative database, and has been used in over 190 clinical trials to detect both enhancement and deterioration associated with drug effects. Subject performance on the Cogstate battery is also independent of education level, estimated intelligence quotient (IQ) and language or culture of origin (Yamashita et al, 2011; Yoshida et al, 2011; Boivin et al, 2010; Bangirana et al, 2009; Dingwall et al, 2009; Lim et al, 2009), allowing accurate classifications of cognitive dysfunction or cognitive change with reference only to a child's age and gender.

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 school children (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 ADHD ([Mollica et all, 2004]: eight to 12 year olds; [Snyder et al, 2008]: six to 16 year olds), as well as the effects of computerized cognitive rehabilitation in pediatric cerebral malaria survivors as young as five years old (Bangirana et al, 2009).

Additionally, regulatory authorities have approved the use of Cogstate tests for monitoring and evaluating the safety of CNS penetrant drugs in a range of pediatric indications, including epilepsy (NCT01389596), neurogenic detrusor over-activity (NCT01565694), bipolar depression (NCT02046369), schizophrenia (NCT01911429) and hyponatremia (NCT02012959) and in children as young as four years old. In sports, Cogstate tests are being used to make return-to-play decisions in suspected concussion.

In Study 20120124, 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.

For rollover (HeFH) subjects, the Cogstate battery will be administered at the week 24 visit and at EOS. For HoFH subjects, the Cogstate battery will be administered at screening (practice assessment), day 1, week 24, week 48, and EOS.

7.7.8 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.

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 2) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments (Table 2) 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 Treatment or Study

8.3.1 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)
- withdrawal of consent from study
- death
- lost to follow-up
- decision by Sponsor (other than subject request, safety concern, lost to follow-up)

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

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

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 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 Serious Adverse Events

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

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

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

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

9.2 Safety Event Reporting Procedures

9.2.1 Adverse Events

9.2.1.1 Reporting Procedures for All Adverse Events (Serious or Non-serious Adverse Events)

Refer to Sections 9.2.1.2 and 9.2.1.3 for additional information regarding the reporting of serious adverse events.

For subjects enrolling in Study 20120124 after completion of Study 20120123 (HeFH subjects) the investigator is responsible for ensuring that all adverse events and all adverse device effects observed by the investigator or reported by the subject that occur after the first dose of investigational product/study treatment/protocol-required therapies through the end of Study 20120124 are reported using the Event CRF.

For subjects not rolling over from Study 20120123 (HoFH subjects), the investigator is responsible for ensuring that all adverse events possibly related to study procedures, adverse device effects, and serious adverse events are reported from signing of the ICF. All other adverse events are reported that occur after enrollment. The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur from signing of the ICF or that occur after enrollment through the end of Study 20120124 are reported using the Event CRF.

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 and/or the device[s]: the prefilled AI/Pen or AMD), or other protocol-required therapies, protocol-required procedure or activity, and
- action taken.

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

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 Summary CRF.

The investigator must assess whether the adverse event is possibly related to IMP (evolocumab). 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 evolocumab (investigational medicinal product)? The investigator must assess whether the adverse event is possibly related to the prefilled AI/Pen or the AMD (investigational device(s) used to administer evolocumab). 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 investigational device? Relatedness means that there are facts or reasons to support a relationship between IP and the event.

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

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

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

9.2.1.2 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 Event CRF.

If the electronic data capture (EDC) system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen via an electronic Serious Adverse Event (eSAE) Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix B for a sample of the eSAE Contingency Report Form. For EDC studies where 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 IMP(evolocumab). 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 evolocumab (investigational medicinal product)? The investigator must assess whether the serious adverse event is possibly related to the prefilled AI/Pen or the AMD (investigational device[s] used to administer evolocumab). 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 investigational device(s)? Relatedness means that there are facts or reasons to support a relationship between IP and the event.

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

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

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

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

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.

9.2.1.3 Reporting Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen. In some countries (eg, European Union [EU] member states), investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event. See Appendix B for a sample of the eSAE Contingency Report Form.

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.

9.3 Pregnancy and Lactation Reporting

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

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur through 15 weeks after the last dose of evolocumab.

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). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a female subject becomes pregnant during the study, the investigator should attempt to obtain information regarding the birth outcome and health of the infant. If a male subject's female partner becomes pregnant, the investigator should discuss obtaining information regarding the birth outcome and health of the infant from the pregnant partner.

Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth,

or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.

If a female subject breastfeeds while taking evolocumab, report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur through 15 weeks after the last dose of evolocumab.

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). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoint

- **T**reatment emergent adverse events at week 80

10.1.1.2 Secondary Endpoints

10.1.1.2.1 Secondary Efficacy Endpoints

- Percent change from baseline at week 80 in:
  - LDL-C
  - Non-HDL-C
  - ApoB
  - Total cholesterol/HDL-C ratio
  - ApoB/ApoA1 ratio
- Change from baseline in LDL-C at week 80

10.1.1.2.2 Secondary Safety Endpoints

- Change from baseline in steroid hormones (FSH, LH, ACTH, DHEA-S, cortisol, estradiol/testosterone [females/males, respectively]) at week 80
- **A**bnormal muscle and liver enzyme levels (CK, AST, ALT) at week 80
- Change from baseline in cIMT at week 80
- Change from baseline in growth (height and weight) and pubertal development (Tanner staging) at weeks 24, 48 and 80

10.1.1.3 Exploratory Endpoints

- Change from baseline and percent change from baseline at each scheduled assessment in the following:
  - LDL-C
  - Total cholesterol
  - Non-HDL-C
  - ApoB
  - Total cholesterol/HDL-C ratio
  - ApoB/ApoA1 ratio
  - Triglycerides
  - VLDL-C
  - HDL-C
  - ApoA1
  - Lp(a)
- Change from baseline at each scheduled assessment in the following:
  - Proprotein convertase subtilisin/kexin type 9 (PCSK9)
  - High sensitivity C-reactive protein (hsCRP)

10.1.1.4 Other Safety Endpoints

- Select safety laboratory values and vital signs at each scheduled assessment
- Incidence of anti-evolocumab antibody (binding and neutralizing) formation
- **A**bnormal neurological examination findings
- ECG parameters (such as RR, PR, QRS, QT, and QTc intervals) at each scheduled assessment
- Change from baseline score in the components of the Cogstate battery at each scheduled administration

10.1.1.5 Pharmacokinetics Endpoints

- Serum concentration of evolocumab at each scheduled assessment

10.1.2 Analysis Sets

The full analysis set (FAS) includes all subjects with HeFH from parent study 20120123 who are enrolled and **dosed** all subjects with HoFH who are enrolled and dosed in this study.

10.2 Sample Size Considerations

Approximately **124** subjects are anticipated to enroll in this trial. This corresponds to at least 70% rollover for subjects with HeFH from the parent study 20120123 and at least 10 subjects with HoFH enrolling in this study.

10.3 Planned Analyses

10.3.1 Data Monitoring Committee (DMC)

An external independent DMC has been established to formally review the accumulating data from this study 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. Details are provided in the DMC charter.

10.3.2 Interim Analysis and Early Stopping Guidelines

The interim analysis will be conducted when all the enrolled subjects in the study have opportunity to experience 28 weeks of investigation product exposure or have early terminated from the study. At that time, the database related to the interim analyses of the study will be cleaned, processed and a snapshot will be taken. Unless specified otherwise, the FAS will be the default analysis set in this study. Similar to the primary analysis, the interim data will be summarized by cohort (HeFH and HoFH). Statistical analysis in this interim analysis is descriptive in nature for all safety and efficacy endpoints if applicable. No statistical hypotheses testing or missing value imputation is planned. There is no study stopping rule for either futility or efficacy and the current design or execution of the study will continue without any changes regardless of the result of the interim analysis.

10.3.3 Primary Analysis

To evaluate the safety, tolerability and effect of 80 weeks of SC evolocumab when added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH, the primary analysis will be conducted when all the enrolled subjects in the study have either completed all the scheduled visits up to and including week 80 or have early terminated from the study. Unless specified otherwise, the FAS will be the default analysis set in this study and data will be summarized by cohort (HeFH and HoFH).

The primary analysis will include estimation for all the endpoints. No formal hypotheses will be tested in this study.

10.4 Planned Methods of Analysis

10.4.1 General Considerations

Statistical analyses in this open label study are descriptive in nature. No statistical inference or missing value imputation is planned.

Subject disposition, demographics and baseline characteristics will be summarized.

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

For efficacy analyses, the baseline value is defined as:

- Subjects that participated in parent Study 20120123 and with baseline data from the parent study: the baseline is defined as the baseline of the qualifying parent study.
- Subjects not enrolling from a parent study or without baseline data from the parent study: the baseline is defined as the baseline in this study.

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

10.4.2 Primary Endpoint

The current Medical Dictionary for Regulatory Activities (MedDRA) version at the time of the data lock will be used to code all adverse events (AE) to a system organ class and a preferred term. The following analyses will be performed on FAS.

Treatment emergent adverse events will be tabulated by system organ class and preferred term at week 80. Tables of fatal adverse events, serious adverse events, device related adverse events, adverse events leading to withdrawal from investigational product, and significant treatment-emergent adverse events will also be provided.

10.4.3 Secondary Endpoints

10.4.3.1 Secondary Efficacy Endpoints

Summary statistics on FAS will be provided for the secondary efficacy endpoints.

Efficacy laboratory parameters (LDL-C, non-HDL-C, ApoB, total cholesterol/HDL-C ratio and ApoB/ApoA1 ratio) will be summarized using descriptive statistics at week 80.

10.4.3.2 Secondary Safety Endpoints

Summary statistics on FAS will be provided for the secondary safety endpoints.

Change from baseline in steroid hormone levels (FSH, LH, ACTH, DHEA-S, cortisol, estradiol in females, testosterone in males), and cIMT at week 80 will be summarized

using descriptive statistics at week 80. Summary of abnormal muscle and liver enzymes will also be provided.

Change from baseline in growth parameters (height and weight) will be summarized using descriptive statistics at weeks 24, 48 and 80. Shift from baseline in Tanner staging at weeks 24, 48 and 80 will be summarized.

10.4.4 Other Safety Endpoints

All analysis of the other safety endpoints will use the FAS.

Laboratory Parameters

Selected safety laboratory parameters will be summarized using descriptive statistics.

Vital Signs

Vital signs will be summarized using descriptive statistics.

Neurologic examination

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

Cogstate battery

Change from baseline score in the components of the Cogstate battery at each scheduled administration will be summarized using descriptive statistics.

Anti-evolocumab antibodies

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

ECG

Summaries over time and/or changes from baseline over time will be provided for all ECG parameters.

Subjects' maximum change from baseline in QTcF will be categorized and the number and percentage of subjects in each group will be summarized.

Subjects' maximum post baseline values will also be categorized and the number and percentage of subjects in each group will be summarized.

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.

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 Council for Harmonization 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.

CRF 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, and subject identification list
- Study files containing the protocol with all amendments, Evolocumab 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 CRFs must be maintained and be readily available.

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

12.3 Study Monitoring and Data Collection

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (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 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 or the investigator applies an electronic signature in the EDC system if the study is set up to accept an electronic signature. This signature indicates that investigator inspected or reviewed the data on the CRF, the data queries, and agrees with the content.

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 2), 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 may facilitate 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 Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (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 need to meet conditions 1, 2, 3, and 4.
- When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must 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 must qualify for authorship, and all those who qualify are to be listed.
- Each author must 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

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.

Abramson, M. J., Benke, G. P., Dimitriadis, C., Inyang, I. O., Sim, M. R., Wolfe, R. S., & Croft, R. J. (2009). Mobile telephone use is associated with changes in cognitive function in young adolescents. Bioelectromagnetics, 30(8), 678-86. doi:10.1002/bem.20534

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;18:355-375.

Bangirana P, Giordani B, John CC, Page C, et al. Immediate neuropsychological and behavioral benefits of computerized cognitive rehabilitation in Ugandan pediatric cerebral malaria survivors. J Dev Behav Pediatr. 2009; 30(4): 310-8.

Boivin, M. J., Busman, R. A., Parikh, S. M., Bangirana, P., Page, C. F., Opoka, R. O., & Giordani, B. (2010). A pilot study of the neuropsychological benefits of computerized cognitive rehabilitation in Ugandan children with HIV. Neuropsychology, 24(5), 667-73. doi:10.1037/a0019312.

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.

Dingwall, K., Lewis, M., Maruff, P. & Cairney, S. Reliability of repeated cognitive testing in healthy Indigenous Australian adolescents. Australian Psychologist 44, 224–234 (2009).

Evolocumab Investigator's Brochure. Thousand Oaks, CA. Amgen Inc.

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.

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.

International Committee of Medical Journal Editors, Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. 2013. http://www.icmje.org/

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, T. V., Heo, M., Whiteford, L. M., & Faith, M. S. (2012). Effects on cognitive performance of eating compared with omitting breakfast in elementary schoolchildren. J Dev Behav Pediatr, 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.

Lim, Y. Y. et al. A method for cross-cultural adaptation of a verbal memory assessment. Behavior research methods 41, 1190–200 (2009).

Mayes, L., Snyder, P. J., Langlois, E., & Hunter, N. (2007). Visuospatial working memory in school-aged children exposed in utero to cocaine. Child Neuropsychology, 13(3), 205-18. doi:10.1080/09297040600888753

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.

Mollica, C., Maruff, P., & Vance, A. (2004). Development of a statistical approach to classifying treatment response in individual children with ADHD. Human Psychopharmacology, 19, 445-456.

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, J. K., Hickling, S., Li, J., Ambrosini, G. L., Jacques, A., & Oddy, W. H. (2014). Prospective associations between dietary patterns and cognitive performance during adolescence. Journal of Child Psychology and Psychiatry, and Allied Disciplines. 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.

Snyder AM, Maruff P, Pietrzak RH, Cromer JR, et al. 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): 211-26.

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.

Yamashita, Y., Mukasa, A., Anai, C., Honda, Y., Kunisaki, C., Koutaki, J., et al. (2011). Summer treatment program for children with attention deficit hyperactivity disorder: Japanese experience in 5 years. Brain Dev, 33(3), 260-7. doi:10.1016/j.braindev.2010.09.005

Yoshida, T. et al. Criterion and construct validity of the CogState Schizophrenia Battery in Japanese patients with schizophrenia. PloS one 6, e20469 (2011).

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 AEs (CTCAE) Version 4.0 for AE grading and information. The CTCAE is available at the following link: http://ctep.cancer.gov/protocolDevelopment/electronic_applications\ctc.htm.

Pediatric Drug-induced Liver Injury Reporting & Additional Assessments Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation according to the criteria specified in Section 6.5.1 require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded).
- The appropriate CRF (eg, 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 9.1.3.

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 Table 1 or who experience AST or ALT elevations > 3x ULN or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels.

Assessments that are to be performed during this period include:

1. Repeat liver tests AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours.
2. In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve.
3. Obtain pediatric gastroenterologist or pediatric hepatologist consult.

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:
  - Complete blood count with differential to assess for eosinophilia
  - Serum total immunoglobulin IgG, Anti-nuclear antibody, Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 to assess for autoimmune hepatitis
  - Serum acetaminophen (paracetamol) levels
  - A more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents
    - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting, and fever
    - Prior and/or concurrent use of alcohol, recreational drugs and special diets
    - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
  - Viral serologies
  - Creatinine phosphokinase, haptoglobin, LDH, and peripheral blood smear
  - Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

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

Appendix B. Sample Electronic Serious Adverse Event Contingency Report Form

AMGEN Study # 20120124 Evolocumab (AMG 145)	Electronic Serious 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

<< For completion by COM prior to providing to sites: 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. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day___ Month___ Year___

Serious 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 death. 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	Is event serious?	Is event a potential endpoint?	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? Evolocumab (AMG 145): No✓ Yes✓ Prefilled Autoinjector/ Pen (Alpen): No✓ Yes✓ Automated Mini-Doser (AMD): 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				
				☐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

FORM-056006 Version 7.0 Effective Date: 1 February 2016

Page 1 of 3

AMGEN
Study # 20120124
Evolocumab (AMG 145)

Electronic Serious 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/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)	☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Prefilled Autoinjector/Pen (AI/Pen) *(Amgen medical device)*	☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Automated Mini-Doser (AMD) *(Amgen medical 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✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med 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											
Unit											
Date (Day Month Year)											

AMGEN Study # 20120124 Evolocumab (AMG 145)	Electronic Serious 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 –	Title	Date
_____ *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.*		

Appendix C. Sample 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: 20120124

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

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

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

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

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

5. Pregnancy Information

Pregnant female's LMP mm / dd / yyyy_____ ☐ Unknown

Estimated date of delivery mm_____ / dd_____/ yyyy ___ ☐ Unknown ☐ N/A

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

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

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

****

Effective Date: March 27, 2011

Page 1 of 1

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: 20120124

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

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

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

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

****

Effective Date: 03 April 2012, version 2.

Page 1 of 1

Appendix 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 4

Protocol Title: Open-label, Single-arm, Multicenter Study to Evaluate the Safety, Tolerability and Efficacy of Evolocumab for LDL-C Reduction, as Add-on to Diet and Lipid-lowering Therapy, in Pediatric Subjects From 10 to 17 Years of Age With Heterozygous Familial Hypercholesterolemia (HeFH) or Homozygous Familial Hypercholesterolemia (HoFH)

HAUSER-OLE

Amgen Protocol Number (Evolocumab) 20120124

EudraCT number 2015-002276-25

Amendment Date: 27 May 2020

Rationale:

The following changes were made to the protocol, dated 27 May 2020.

- Added interim analysis for all enrolled subjects
- Updated number of subjects expected to roll over from Study 20120123 into study 20120124 to approximately 111 subjects and 10 subjects with Homozygous Familial Hypercholesterolemia (HoFH) with an expected total enrollment of approximately 124 subjects.
  - Updated Study Schema figure with new enrollment number
- Align with current protocol template:
  - Removed language regarding the collection of Disease Related Events (DRE).
  - Added statement “This protocol was developed, reviewed, and approved in accordance with Amgen’s standard operating procedures.”
  - Deleted “subject incidence of” wording in the endpoints as endpoints are intended to present summary statistics of individual subject data.
  - Removed details from study monitoring and data collection to restrict Amgen (or designee) correcting obvious data errors in the clinical trial database
- Change in key Sponsor contact details

Amendment 3

Protocol Title: Open-label, Single-arm, Multicenter Study to Evaluate the Safety, Tolerability and Efficacy of Evolocumab for LDL-C Reduction, as Add-on to Diet and Lipid-lowering Therapy, in Pediatric Subjects From 10 to 17 Years of Age With Heterozygous Familial Hypercholesterolemia (HeFH) or Homozygous Familial Hypercholesterolemia (HoFH)

Amgen Protocol Number Evolocumab 20120124

2015-002276-25

Amendment Date: 26 April 2017

Rationale:

This is Amendment 3 for Evolocumab Study 20120124. The primary change to the protocol is to clarify that investigational product (IP) will be administered using either an autoinjector/pen (AI/Pen) or automated mini-doser (AMD).

In addition, the following were clarified to ensure alignment with study procedures:

- Update the number of sites expected for the study
- Add AMD product information and option for device use, upon availability
- Clarify IP administration performed during a study visit must occur after all other procedures
- Clarify Cogstate testing and carotid intima-media thickness (cIMT) imaging will be performed prior to IP administration during a study visit
- Clarify apheresis is only permitted for subjects with homozygous familial hypercholesterolemia (HoFH)
- Add QM administration by AMD will consist of 1 injection of 420 mg / 3.5 mL deliverable volume of evolocumab
- Clarify enrollment should be on day 1 or as close as possible to day 1 and no earlier than 5 days prior to day 1
- Align safety definitions and reporting procedures with current protocol template
- Administrative, typographical, and formatting changes were made throughout the protocol

Amendment 2

Protocol Title: Open-label, Single-arm, Multicenter Study to Evaluate the Safety, Tolerability and Efficacy of Evolocumab for LDL-C Reduction, as Add-on to Diet and Lipid-lowering Therapy, in Pediatric Subjects From 10 to 17 Years of Age With Heterozygous Familial Hypercholesterolemia (HeFH) or Homozygous Familial Hypercholesterolemia (HoFH)

HAUSER-OLE

Amgen Protocol Number (Evolocumab) 20120124

EudraCT number 2015-002276-25

Amendment Date: 22 June 2016

Rationale:

This protocol is being amended to:

- Clarify primary endpoint language.
- Add language that defines baseline lab values for rollover and de novo subjects.
- Clarify/update eligibility criteria:
  - Rollover subjects should not have experienced treatment-related serious adverse events in Study 20120123.
  - Fix typo regarding liver function tests.
  - Clarified exclusion criteria regarding lab values; removed language regarding retesting as this is addressed in Section 7.2.1.3.
- Clarify that biomarker samples will only be collected where permitted by local law.
- Update number of sites in study and which countries are participating; as well as clarifying that sites from parent Study 20120123 will retain their same site number in the current study.
- Clarify that all 3 investigational product (IP) injections must be completed within 30 minutes and that all subjects will be held for observation for at least 30 minutes after first IP administration.
- Update Schedule of Assessments and Study Procedures:
  - Allow for a 4-week screening window for rollover subjects and for those subjects who exceed the 4-week window, which procedures must be redone.
  - Update collection points for creatinine kinase.
  - Clarify language in several footnotes.
  - Add additional analytes for urinalysis.
  - Remove thyroid stimulating hormone (TSH) as an analyte.

  - Clarify when lipid panel results will be unblinded.
  - Clarify that blood draw procedures must be performed before apheresis (if applicable).
- Update protocol to align with current protocol template language:
  - Safety: hepatotoxicity, medical devices, product complaints, safety event definitions and reporting.
  - Publication policy.
- Update safety reporting forms.
- Make administrative and editorial changes throughout the protocol.

Amendment 1

Protocol Title: Open-label, Single-arm, Multicenter Study to Evaluate the Safety, Tolerability and Efficacy of Evolocumab for LDL-C Reduction, as Add-on to Diet and Lipid-lowering Therapy, in Pediatric Subjects From 10 to 17 Years of Age With Heterozygous Familial Hypercholesterolemia (HeFH) or Homozygous Familial Hypercholesterolemia (HoFH)

Amgen Protocol Number Evolocumab (AMG 145) 20120124

EudraCT number 2015-002276-25

Original, Date:	27 May 2015
Amendment 1, Date:	**10 September 2015**

Rationale:

- To address regulatory feedback.
- To add safety assessments.