Title: A Double-blind, Randomized, Placebo-controlled, Multicenter Study Assessing the Impact of Additional LDL-Cholesterol Reduction on Major Cardiovascular Events When Evolocumab (AMG 145) is Used in Combination With Statin Therapy in Patients with Clinically Evident Cardiovascular Disease

Amgen Protocol Number (Evolocumab) 20110118

EudraCT number 2012-001398-97

FOURIER

Further Cardiovascular **Ou**tcomes **R**esearch with PCSK9 **I**nhibition in Subjects With **E**levated **R**isk

Clinical Study Sponsor:

Amgen Inc
One Amgen Center Drive
Thousand Oaks, CA 91320, USA
Phone: +1-805-447-1000

Investigator's Agreement

I have read the attached protocol entitled "A Double-blind, Randomized, Placebo-controlled, Multicenter Study Assessing the Impact of Additional LDL-Cholesterol Reduction on Major Cardiovascular Events When Evolocumab (AMG 145) is Used in Combination With Statin Therapy in Patients with Clinically Evident Cardiovascular Disease", , and agree to abide by all provisions set forth therein.

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

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

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

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

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

Signature

Name of Principal Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: A Double-blind, Randomized, Placebo-controlled, Multicenter Study Assessing the Impact of Additional LDL-Cholesterol Reduction on Major Cardiovascular Events When Evolocumab (AMG 145) is Used in Combination With Statin Therapy in Patients with Clinically Evident Cardiovascular Disease

Study Phase: 3

Indication: Dyslipidemia

Primary Objective: To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization, whichever occurs first, in subjects with clinically evident cardiovascular disease.

Secondary Objectives:

- To evaluate the effect of treatment with evolocumab, compared with placebo, in subjects with clinically evident cardiovascular disease on the risk for:
  - cardiovascular death, myocardial infarction, or stroke
  - **cardiovascular death**
  - death by any cause
  - **myocardial infarction**
  - **stroke**
  - **coronary revascularization**
  - cardiovascular death or hospital admissions for worsening heart failure
  - fatal or non-fatal ischemic stroke or transient ischemic attack (TIA)

Hypotheses: The primary hypothesis is that additional LDL-C lowering with evolocumab when used in addition to other treatment for dyslipidemia is well tolerated and decreases the risk of cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary revascularization in subjects with clinically evident cardiovascular disease.

Primary Endpoint: The primary endpoint is time to cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary revascularization, whichever occurs first.

Secondary Endpoints:

The key secondary endpoint **is**:

- time to cardiovascular death, myocardial infarction, or stroke, whichever occurs first

Other secondary endpoints are:

- **time to cardiovascular death**
- time to death by any cause
- **time to first myocardial infarction**
- **time to first stroke**
- **time to first coronary revascularization**
- time to cardiovascular death or **first** hospitalization for worsening heart failure, whichever occurs first
- time to ischemic fatal or non-fatal stroke or TIA, whichever occurs first

Study Design: This is a phase 3, multicenter, double-blind, randomized, placebo controlled, parallel group, cardiovascular outcomes study for evolocumab in subjects with clinically evident cardiovascular disease as evidenced by a history of myocardial infarction, non-hemorrhagic stroke, or symptomatic peripheral arterial disease (PAD; defined below). At randomization, subjects must be receiving stable, optimized lipid lowering background therapy per Protocol Appendix E, that is expected to be unchanged for the duration of study participation (up to approximately 5 years). Subjects must receive at least an effective statin dose, ie, at least atorvastatin 20 mg daily or equivalent. Where locally approved, highly effective statin therapy, defined as at least atorvastatin 40 mg daily or equivalent, is recommended. For subjects with LDL-C > 100 mg/dL (2.6 mmol/L) and not receiving highly effective statin therapy (atorvastatin ≥ 40 mg daily or equivalent), the investigator must attest that higher dose statin therapy is not appropriate for this subject (eg, subject refused, dose not tolerated, dose not available in that country, other significant concern).

Eligible subjects will be randomized with an allocation ratio of 1:1 to either receive evolocumab or placebo. Randomization will be stratified by the final screening LDL-C level (< 85 mg/dL [2.2 mmol/L] vs ≥ 85 mg/dL) and by geographical region. Evolocumab and placebo will be blinded. Central laboratory results of the lipid panel, ApoA1, ApoB, lipoprotein(a), and high sensitivity C-reactive protein (hsCRP) will be blinded post-treatment and not reported to the investigator until unblinding of the clinical database. Investigators should not perform non-protocol testing of these analytes during a subject's study participation and until at least 12 weeks after the subject's last administration of IP or the end of study, whichever is later. Investigators will be informed if triglycerides are > 1000 mg/dL (11.3 mmol/L) so that appropriate subject follow-up can be initiated (see Protocol Section 6.3). The study includes collection of biomarker samples, unless prohibited by local law or regulations, and, where approved by the independent ethics committee and/or institutional review board (IEC/IRB) and applicable regulatory and other authorities, all subjects will be invited to consent to pharmacogenetic analyses. The study will end when at least 1630 subjects have experienced a **key** secondary endpoint event of cardiovascular death, myocardial infarction, or stroke. Subjects will be encouraged to complete all planned visits regardless of their adherence to investigational product (IP) administration. Vital status should be obtained periodically and must be obtained at the end of the study for all subjects including those who withdraw consent, unless prohibited by local law.

All deaths and components of primary and secondary endpoints will be adjudicated by an independent external Clinical Events Committee (CEC), using standardized definitions. Instructions regarding submission of potential endpoints (PEPs) will be provided. **In addition, new onset diabetes will also be adjudicated.** An external independent Data Monitoring Committee (DMC) will formally review the accumulating data from this and other ongoing studies with evolocumab to ensure there is no avoidable increased risk for harm to subjects. The independent DMC will be chaired by an external academic cardiologist who is an expert in lipids and clinical trials. Analyses for the DMC will be provided by an independent biostatistical group (IBG), which is external to Amgen. An Executive Committee (EC) has been formed to advise Amgen on trial design and implementation, to conduct independent data analysis, and for assistance in the communication of trial results. An external independent Lipid Monitoring Committee (LMC) will be formed to review lipid results to ensure study design parameters are met. The LMC will be advisory to Amgen and the EC. Details for each committee will be provided in a committee charter. Concentration values are provided in mmol/L for investigator convenience. Conventional concentrations (mg/mL) will be used for the protocol, including eligibility determination.

Sample Size: Up to approximately 27,500 subjects will be randomized

Summary of Subject Eligibility Criteria: Males and females, ≥ 40 to ≤ 85 years of age, are eligible to screen for this study. For inclusion, subjects must have a history of clinically evident cardiovascular disease as signified by myocardial infarction, non-hemorrhagic stroke, or symptomatic PAD (intermittent claudication with ankle-brachial index [ABI] < 0.85, or peripheral arterial revascularization procedure or amputation due to atherosclerotic disease) and ≥ 1 major

risk factor or ≥ 2 minor risk factors. Major risk factors are: diabetes (type 1 or type 2), age ≥ 65 years, the qualifying MI or stroke within 6 months of screening, current daily cigarette smoking, an additional prior MI or non-hemorrhagic stroke (excluding the qualifying diagnosis) or symptomatic PAD if enrolled with history of MI or non-hemorrhagic stroke. Minor risk factors are: history of non-MI related coronary revascularization, residual coronary artery disease with ≥ 40% stenosis in ≥ 2 large vessels, HDL-C < 40 mg/dL (1.0 mmol/L) for men and < 50 mg/dL (1.3 mmol/L) for women, hsCRP > 2.0 mg/L, LDL-C ≥ 130 mg/dL (3.4 mmol/L) or non-HDL-C ≥ 160 mg/dL (4.1 mmol/L), metabolic syndrome as defined in the study protocol. A subject's LDL-C must be ≥ 70 mg/dL (1.8 mmol/L) or non-HDL-C ≥ 100 mg/dL (2.6 mmol/L) on stable lipid lowering therapy per Appendix E at final screening. Fasting triglycerides must be ≤ 400 mg/dL (≤ 4.5 mmol/L).

Subjects must not be randomized within 4 weeks of their most recent MI or stroke. Other major exclusions are New York Heart Failure Association (NYHA) class III or IV or last known left ventricular ejection fraction < 30%; uncontrolled or recurrent ventricular tachycardia, systolic blood pressure (SBP) > 180 mmHg or diastolic BP (DBP) > 110 mmHg; untreated hyper- or hypothyroidism, defined as thyroid stimulating hormone < lower limit of normal (LLN) or > 1.5 times upper limit of normal (ULN), respectively, and free thyroxine (T4) levels outside normal range at screening, estimated glomerular filtration rate (eGFR) < 20 mL/min/1.73m^2, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3x ULN, creatine kinase (CK) > 5x ULN; personal or family history of hereditary muscular disorders; recipient of any major organ transplant (eg, lung, liver, heart, bone marrow); severe, concomitant non-cardiovascular disease that is expected to reduce life expectancy to less than 3 years; known history of hemorrhagic stroke; major active infection, or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction; use of a cholesteryl ester transfer protein (CETP) inhibitor, mipomersen or lomitapide within 12 months prior to randomization; prior use of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition treatment other than evolocumab or use of evolocumab < 12 weeks prior the final lipid screening. Female subjects cannot be pregnant or breast feeding, planning to become pregnant or planning to breastfeed and pre-menopausal females of childbearing potential must be willing to use acceptable method(s) of birth control **and not breastfeed** during treatment with IP and for an additional 15 weeks after the end of treatment.

For a full list of eligibility criteria, please refer to Section 4.1 and Section 4.2.

Amgen Investigational Product Dosage and Administration: Evolocumab and placebo will be administered using a spring-based prefilled 1.0 mL autoinjector/pen (prefilled AI/Pen) or 3.5 mL Personal Injector (Personal Injector).

Evolocumab will be administered at 1 of 2 regimens:

Evolocumab 140 mg SC Q2W (1 prefilled AI/Pen injection) or

Evolocumab 420 mg SC QM (3 prefilled AI/Pen injections or 1 Personal Injector injection)

Placebo will be administered at 1 of 2 regimens:

Placebo SC Q2W (1 prefilled AI/Pen injection) or

Placebo SC QM (3 prefilled AI/Pen injections or 1 Personal Injector injection)

Subjects will choose whether to initiate treatment at the Q2W or QM schedule and will have the opportunity every 3 months to switch between Q2W and QM, provided the required approvals and supplies of IP are available at the study site.

Non Amgen Non-investigational Product Dosage and Administration:

Subjects will receive background lipid therapy with a statin as per Protocol Appendix E. Atorvastatin will be provided at 20 mg, 40 mg, or 80 mg QD. Other statins, if applicable, will not be provided unless required by local regulations.

Control Group: Placebo

Procedures: Subjects being considered for entry into the study and who have had the risk and benefits of participating in the study explained will enter screening by signing and dating an

informed consent form for this study. A separate consent form may be offered for entering screening and lipid therapy titration, followed before randomization by a consent form for full study participation. Subjects taking stable (≥ 4 weeks) lipid lowering therapy per Appendix E when entering screening and with no changes planned or expected for the duration of the study can proceed directly to final screening and, if eligible, randomization. These subjects can complete screening, be randomized, and start investigational product in two visits. Subjects requiring any change in their lipid therapy will complete a lipid therapy titration before proceeding to final screening. During lipid therapy titration, a subject's lipid therapy can be adjusted as necessary, including increasing the dose of non-study supplied statin or study-supplied atorvastatin at intervals of 2 to 4 weeks until the subject's lipids are considered optimally managed as per Appendix E. Titration visits should be scheduled as needed approximately every 2 weeks. These subjects must have completed ≥ 2 weeks on their optimized lipid therapy before final screening and be maintained on their optimized lipid therapy ≥ 4 weeks before randomization and, subsequently, throughout the duration of the study.

To ensure tolerance of SC injections, subjects will receive a 1-time placebo injection by AI/Pen prior to randomization to IP. At the completion of screening and before randomization, all subjects must have signed informed consent for full study participation. Subjects who meet all eligibility criteria will be randomized to receive either evolocumab or placebo. It is expected that all procedures up to randomization should be completed within approximately 15 weeks of first signing informed consent.

Scheduled laboratory assessments are during screening, on day 1, week 4, week 12, and week 24 and subsequently every 24 weeks (approximately every 6 months [Q6M]).

Other procedures are performed as detailed in the protocol and include vital signs, adverse events (AEs)**,** serious adverse events (SAEs), concomitant therapy, evaluation of fasting lipids, dietary instruction and compliance reminder for allowed lipid-lowering medication they may be taking, physical exam, measuring waist circumference, body height and weight, other laboratory assessments, including assessment for anti-evolocumab antibodies, biomarker sample collection, serum pregnancy testing (females of childbearing potential), urinalysis, and IP administration. Subjects at increased risk for or with history of hepatitis C virus (HCV) infection or with ALT or AST > 2x ULN at any time during screening will be tested for prior or existing HCV infection and viral load will be evaluated in those who show evidence thereof. If the subject consented to pharmacogenetics analyses, DNA will be extracted from some of the blood samples. ECGs will be collected centrally in approximately 5000 subjects at selected timepoints, in other subjects only locally at screening, on day 1, and if clinically indicated. IP administration, if applicable, will be done after all other visit procedures have been completed.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and Appendix A.

Statistical Considerations:

The primary efficacy analysis set is the full analysis set (FAS), which includes all randomized subjects. Unless specified otherwise, the FAS will be the default analysis set and all subjects will be analyzed according to their initial randomized treatment allocation. Safety analyses will be performed on the safety analysis set which includes all randomized subjects with at least 1 dose of IP.

In order to preserve the overall type I error rate at 0.05 in the final analysis **of the primary and secondary endpoints**, the following multiplicity adjustment approach will be applied: The primary endpoint (quintuple composite of cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, and coronary revascularization) will be compared by the treatment groups at a significance level of 0.05. If the primary endpoint reaches statistical significance at the 0.05 level, the **key** secondary endpoint **(composite of cardiovascular death, myocardial infarction, and stroke)** will be tested at a significance level of 0.05. If the **key** secondary endpoint reaches statistical significance level of 0.05, then the **endpoint of cardiovascular death will be tested at a significance level of 0.05. If it reaches statistical significance level of 0.05, the following testing will be conducted in parallel under the**

Bonferroni split: (1) The endpoint of all-cause death will be tested at a significance level of 0.04, (2) Other remaining secondary endpoints (time to first myocardial infraction, time to first stroke, time to first coronary revascularization, time to cardiovascular death or first hospitalization for worsening heart failure, and time to fatal or non-fatal ischemic stroke or TIA) will be tested at an overall significance level of 0.**01** applying the Hochberg method (Hochberg, 1988).

The primary analysis of all time-to-event endpoints (including the primary and secondary endpoints) will be the log-rank test stratified by the randomization stratification factors. Kaplan-Meier (K-M) time-to-event curves will be presented by randomized treatment and K-M estimates (95% CI) will be provided. In addition, a hazard ratio and 95% CI will be estimated from a Cox model stratified by the randomization stratification factors. All adjudicated events will be reported.

The exploratory endpoints of the change and percent change from baseline of LDL-C and other lipid parameters will be compared using the repeated measures linear mixed effects model, including terms for treatment group, stratification factors, scheduled visit, and the interaction of treatment with scheduled visit. Missing values will not be imputed when the repeated measures linear mixed effects model is used. Subgroup and covariate analyses will be performed, if applicable.

Safety summaries will include the incidence of AEs, summaries of laboratory parameters (including shift tables), vital signs, ECGs and anti-evolocumab antibodies.

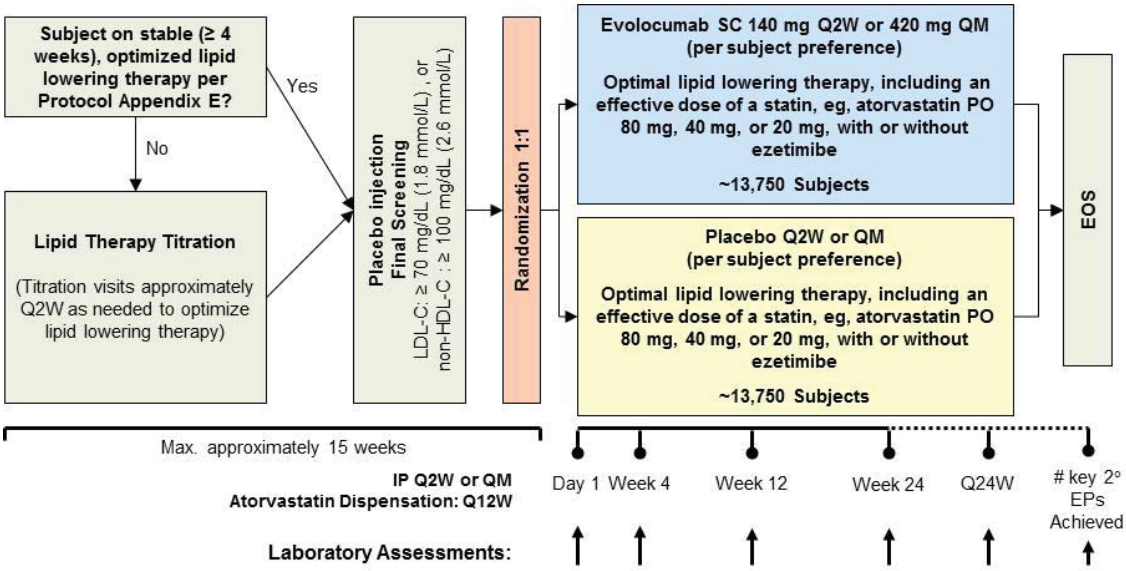
An external independent DMC has been established to formally review the accumulating data from this and other ongoing studies with evolocumab to ensure there is no avoidable increased risk for harm to subjects. Analyses for the DMC will be provided by the IBG, which is external to Amgen. A LMC will be established to monitor the LDL-C separation between treatment groups over the course of the study.

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

Sponsor: Amgen

Study Design and Treatment Schema

Enrollment, Treatment, and Visit Schedule



Subject Enrollment Algorithm

MI, stroke, or symptomatic peripheral arterial disease

Option 1:
At least 1 Major Risk Factor

- Diabetes (type 1 or type 2)
- Current daily cigarette smoking
- Age ≥ 65 years
- MI or stroke within 6 months of screening
- Additional MI or stroke prior to qualifying MI or stroke
- Symptomatic PAD (intermittent claudication with ABI < 0.85 or peripheral revascularization or amputation due to atherosclerosis) if eligible by MI or stroke history

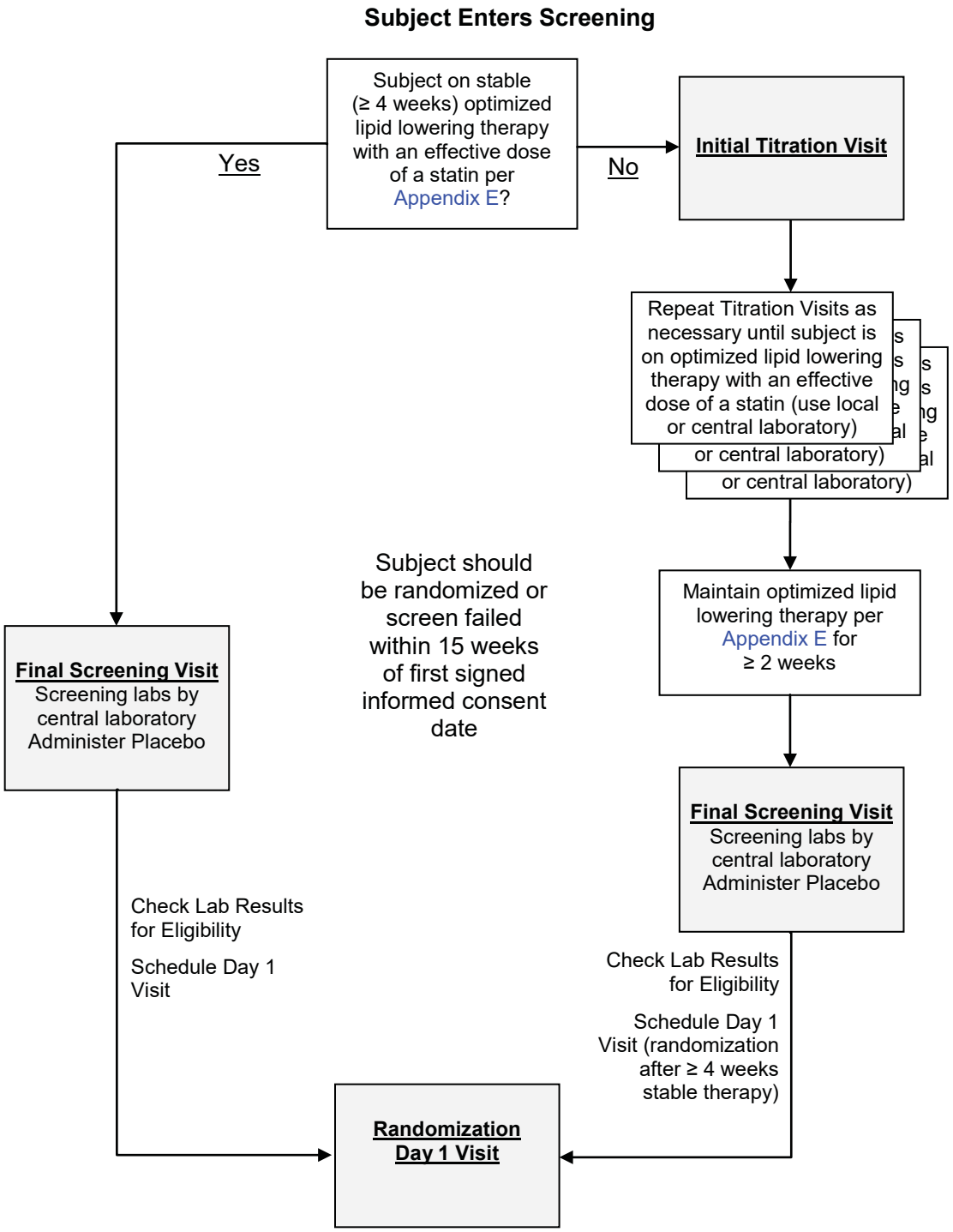
Or:

Option 2:
At least 2 Minor Risk Factors

- Non MI-related coronary revascularization
- Residual CAD (≥ 40% stenosis in ≥ 2 large vessels)
- HDL-C men < 40 mg/dL (1.0 mmol/L); women < 50 mg/dL (1.3 mmol/L)
- hsCRP > 2.0 mg/L
- LDL-C ≥ 130 mg/dL (3.4 mmol/L) or non-HDL-C ≥ 160 mg/dL (4.1 mmol/L)
- Metabolic syndrome

Screen Subject

Background Lipid Lowering Therapy



Study Glossary

Abbreviation or Term	Definition/Explanation
ABI	Ankle-brachial index
AE	Adverse event
AHA	American Heart Association
AI/Pen	autoinjector/pen
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase (serum glutamic-pyruvic transaminase)
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
AST (SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
AUC	Area under the curve
BP	Blood pressure
CABG	Coronary artery bypass graft
CBC	Complete blood count
CEC	Clinical Events Committee
CETP	Cholesteryl ester transfer protein
CHD	Coronary heart disease
CK	Creatine kinase
C_{max}	Maximal concentration
CRP	C-reactive protein
CTCAE	NCI Common Terminology Criteria for AEs
CTTC	Cholesterol Trialists Treatment Collaboration
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DHA	Docosahexaenoic acid
DILI	Drug-induced liver injury
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate; eGFR will be calculated by the central laboratory and provided to the investigator.

Abbreviation or Term	Definition/Explanation
End of study	Amgen will set **a** date for **initiating end of** study **procedures** based on the anticipated date reaching the required number of the triple composite **key** secondary endpoint. **The** date **of the last end of study visit** is the primary completion date **and is** considered the end of study.
End of study for individual subject	Defined as the day that a subject completes the study **or** the subject dies**, is lost to follow-up,** or withdraws full consent before the end of the study. Subjects will **have** complete**d** the study **if their** end of study visit **is** after the date **for initiating end** of study **procedures**.
End of treatment	Defined as the day a subject receives the last treatment with investigational product before the subject completes the study or ends the treatment early.
EPA	Eicosapentaenoic acid
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HCV	Hepatitis C virus
HDL-C	High density lipoprotein cholesterol
HepG2 cells	Human hepatocellular carcinoma cell line
HR	Heart Rate
hsCRP	High sensitivity CRP
IBG	Independent Biostatistical Group
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC/IRB	Independent Ethics Committee / Institutional Review Board
IFU	Instructions for use
INR	International normalized ratio
IP	Investigational product
IPIM	Investigational Product Instruction Manual
IVRS/IWRS	Interactive Voice Response System / Interactive Web Response System

Abbreviation or Term	Definition/Explanation
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
MI	Myocardial infarction
NASH	Nonalcoholic steatohepatitis
NCEP ATP III	National Cholesterol Education Program Adult Treatment Panel III (see Grundy et al, 2004)
NCEP ATP III TLC diet	NCEP ATP III Therapeutic Lifestyle Changes diet
NOAEL	No-observed-adverse-effect level
PAD	Peripheral arterial disease
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
PEP	Potential endpoint
PKPD	Pharmacokinetic / pharmacodynamic
PO	Oral administration
Q2W	Q2W is defined as every 2 weeks with a window of ± 3 days for each visit
Q4W	Every 4 weeks, (Evolocumab Background Section)
QD	Each day
QM	QM is defined as every 4 weeks with a window of ± 3 days for each visit
QW	Every week
RBC	Red blood cells
SAE	Serious adverse event
SBP	Systolic blood pressure
SC	Subcutaneous
SE	Standard error
SD	Standard deviation

Abbreviation or Term	Definition/Explanation
Source Data	Information from an original record or certified a copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline (E6)). Examples of source data include Subject ID, Randomization ID, and Stratification Value.
Study day 1	Defined as the first day that protocol-specified investigational product is administered to the subject
T4	Thyroxine
TBL	Total bilirubin
TIA	Transient ischemic attack
TIMI Study Group Hotline	**Communication system at the Thrombolysis in Myocardial Infarction Study Group of Brigham and Women's Hospital, Boston, Massachusetts, USA, that is providing trial support to all participating active trial sites worldwide**
T_{max}	Time to maximum concentration
TNF	Tumor necrosis factor
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol
WBC	White blood cell

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1. OBJECTIVES

1.1 Primary Objective

To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization, whichever occurs first, in subjects with clinically evident cardiovascular disease.

1.2 Secondary Objectives

Secondary objectives are to evaluate the effect of treatment with evolocumab, compared with placebo, in subjects with clinically evident cardiovascular disease on the risk for:

- cardiovascular death, myocardial infarction, or stroke
- **cardiovascular death**
- death by any cause
- **myocardial infarction**
- **stroke**
- **coronary revascularization**
- cardiovascular death or hospital admissions for worsening heart failure
- fatal or non-fatal ischemic stroke or transient ischemic attack (TIA)

1.3 Exploratory Objectives

Exploratory objectives are:

- **To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for coronary death in subjects with clinically evident cardiovascular disease**
- **To evaluate the effect of treatment with evolocumab, compared with placebo, on the total number of events from the components of the primary endpoint (myocardial infarction, hospitalization for unstable angina, stroke, coronary revascularization, and cardiovascular death), in subjects with clinically evident cardiovascular disease**
- To evaluate the effect of treatment with evolocumab, compared with placebo, on proprotein convertase subtilisin/kexin type 9 (PCSK9) levels, on hemoglobin A1c (HbA1c), on percent of subjects attaining an LDL-C treatment goal of < 70 mg/dL (1.8 mmol/L), and on change and percent change from baseline of LDL-C, total cholesterol, non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio, triglycerides, VLDL-C, HDL-C, ApoA1, Lp(a), and high sensitivity C-reactive protein (hsCRP) in subjects with clinically evident cardiovascular disease
- To investigate the relationship between novel and established biochemical cardiovascular and lipid biomarkers and effects of evolocumab
- 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.

1.4 Safety Objective

To evaluate the safety and tolerability of evolocumab, compared with placebo, in subjects with clinically evident cardiovascular disease.

2. BACKGROUND AND RATIONALE

2.1 Cardiovascular Disease

Collectively, cardiovascular diseases (CVD) are regarded as a world-wide epidemic; and though over the last 2 decades CVD mortality has declined (primarily in developed countries), it still represents the leading cause of death and disability in the world, as well as over 10% of the global total disease burden. In 2008, the World Health Organization (WHO) estimated 57 million deaths world-wide, of which 36 million were due to non-communicable causes. CVD accounted for over 17 million of these deaths, nearly 80% of which were due to heart attacks and strokes alone (responsible for 7.3 million and 6.2 million deaths, respectively).

A large proportion of CVD is preventable, and the investment in prevention measures has been regarded as the most sustainable solution for dealing with the CVD epidemic. Elevated cholesterol is among the leading risk factors for cardiovascular deaths (6th), with an estimated prevalence of 39% globally among all adults (even greater in high-income countries). CVD perhaps represents the single leading threat to the health of the world; the unmet medical need in this arena is immense (World Health Organization, 2011). The facts below from the American Heart Association (AHA) Heart and Stroke Facts Update from 2011 illustrate the magnitude of the problem in the US (Roger et al, 2011).

(i) In excess of one in three individuals in the US has some form of CVD. Coronary heart disease (CHD) affects almost 17 million Americans. Of those almost 8 million suffer from myocardial infarction; nearly 10 million from angina pectoris; nearly 6 million from heart failure; and 6 to 7 million from stroke. The aging of the population and the explosive increase in the prevalence of obesity and type 2 diabetes and their related complications (hypertension, hyperlipidemia, and atherosclerotic vascular disease) will only serve to increase the prevalence of CVD.

(i) CVD claims more lives each year than cancer, chronic lower respiratory disease, and accidents combined. Over 2200 Americans die of CVD each day Mortality data show that CVD accounted for more than one in three deaths (over 800,000) in the United States. Since 1900, CVD has been the number 1 killer in the United States every year, with the exception of 1 year only (1918).

(ii) CHD caused approximately 1 of every 6 deaths in the United States. CHD mortality was slightly more than 400,000. It is estimated that each year

785,000 and 470,000 Americans will have a new and recurrent acute coronary syndrome, respectively. An additional 195,000 silent first myocardial infarctions are estimated to occur each year.

(iii) Approximately 795,000 people experience a new or recurrent stroke each year. About 610,000 of these are first attacks, and 185,000 are recurrent attacks. Preliminary data from 2006 indicate that stroke accounted for about 1 of every 18 deaths in the United States.

The situation in the European Union (EU) is similar. CHD by itself remains the single most common cause of deaths in the EU (Allender et al, 2008). Each year CVD causes over 4.3 million deaths in Europe and over 2.0 million deaths in the EU. CVD causes nearly half of all deaths in Europe (48%) and in the EU (42%). CVD is the main cause of death in women in all countries of Europe and is the main cause of death in men in all countries except France, the Netherlands and Spain. CVD is the main cause of the disease burden (illness and death) in Europe (23%) and the second main cause of the disease burden in those EU countries with very low child and adult mortality (17%). CVD mortality, incidence and case fatality are falling in most Northern, Southern and Western European Countries, but this is not the case in Central and Eastern European countries.

Dyslipidemia is a major modifiable risk factor for the development of CVD. It is estimated that about 100 million Americans and about 34 million Americans have a total cholesterol in excess of 200 mg/dL (approximately 5.2 mmol/L) and 240 mg/dL (approximately 6.2 mmol/L), respectively. In Europe, up to 50% of the population aged 35-64 years has a total cholesterol > 250 mg/dL (6.5 mmol/L) (Tolonen et al, 2005). This high prevalence of dyslipidemia translates into a significant cardiovascular morbidity and mortality, as described above. Dyslipidemia is associated with more than 50% of the global cases of CHD and more than 4 million deaths per year worldwide.

To decrease the morbidity and mortality associated with CVD, over 50 million patients in the US, Europe, and Japan are currently treated with dyslipidemia therapies. The rationale for treatment of dyslipidemia, particularly elevated LDL-C, extends from extensive clinical trial data in both primary and secondary prevention that demonstrates the reduction in total cholesterol, non-HDL-C, and most importantly, LDL-C through pharmacological therapies, particularly statins, lowers the risk of CVD events (Kannel et al, 1974; Kannel et al, 1979; Kannel, 1995). The most recent Cholesterol Treatment Trialists' (CTT) Collaboration (CTT, 2010) meta-analysis which included 21 randomized controlled trials of statin versus control involving nearly 170,000 patients

showed that for every ~ 1 mmol/L reduction of LDL-C there was a ~20% reduction in the risk of major vascular events (coronary death, non-fatal myocardial infarction, coronary revascularization, or stroke). Importantly, this meta-analysis, which also evaluated 5 trials that compared more versus less intensive statin therapy, did not find a LDL-C threshold for risk reduction; additional vascular risk reduction is possible in patients with low LDL-C. The opportunity for further cardiovascular risk reduction is also consistently seen in the numerous primary and secondary prevention studies where subjects are treated with statins to their LDL-C goal, the results of which have manifested in durable, dramatic changes in medical practice which have consequently saved millions of lives.

Despite achieving their LDL-C goals, approximately two-thirds of these patients on lipid reduction therapy still have cardiovascular events (Libby, 2005). While it is unlikely that this residual risk is entirely due to the additional LDL-C reduction needed beyond the LDL-C goal articulated in recent treatment guidelines (NCEP, 2002; Grundy et al, 2004), CTT Collaboration (2010) data suggest that novel agents that are capable of providing additional LDL-C lowering on top of statins may further reduce cardiovascular morbidity and mortality. Furthermore, some individuals are intolerant to statin therapy and cannot achieve their respective LDL-C goals (eg, Bruckert et al, 2005; Franc et al, 2003).

Non-statin treatment options are currently available to lower LDL-C but their potency is limited, such that LDL-C reductions occur on the order of 15% to 20%. Such agents include ezetimibe, bile acid sequestering agents (resins), niacin, and plant stanols. Ezetimibe is in a class of lipid-lowering compounds that selectively inhibits the intestinal absorption of cholesterol and related phytosterols. The bile acid sequestering agents (BAS) bind to bile acids (which are normally produced in the liver using cholesterol, and secreted into the small intestine to aid in digestion). By binding to bile acids, BAS reduce their supply. In turn, this stimulates the liver to produce more bile acids, which uses more cholesterol. Niacin blocks the breakdown of fats in adipose tissue. These fats are used to build very-low-density lipoproteins (VLDL) in the liver, which are precursors of LDL cholesterol. Because niacin blocks the breakdown of fats, it causes a decrease in free fatty acids in the blood and, as a consequence, decreases the secretion of VLDL-C and cholesterol by the liver. By lowering VLDL-C levels, niacin also increases the level of high-density lipoprotein (HDL). Plant stanols derived from wood pulp and vegetable oils lower total and LDL cholesterol by inhibiting cholesterol absorption from the intestine due to their structural similarity with cholesterol.

Considering the remaining cardiovascular risk despite the availability of statin therapy and given that non-statin treatment options have modest efficacy (ezetimibe, BAS, plant stanols) and/or are poorly tolerated (niacin and BAS), there is an unmet medical need for a potent, effective non-statin agent that will get a significant proportion of patients to LDL-C goal and further reduce cardiovascular risk. This need is especially evident among individuals at high risk for future cardiovascular events; namely, those who have already suffered from a myocardial infarction, non-hemorrhagic stroke, or peripheral arterial revascularization procedure or amputation due to atherosclerotic disease. Based on the current data, evolocumab may fulfill this need and may provide an important addition to the treatment of hypercholesterolemia for patients with a past medical history of cardiovascular disease.

2.2 Evolocumab Background

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

Evolocumab is a fully human monoclonal immunoglobulin (Ig) G2 that binds specifically to human PCSK9 and prevents the interaction of PCSK9 with LDLR. Details of the biochemistry, nonclinical pharmacology, nonclinical pharmacokinetics (PK), and nonclinical toxicology with evolocumab are contained in the **Evolocumab (**AMG 145**)** Investigator's Brochure. Evolocumab binds to human, monkey, and hamster PCSK9 with high affinity (K_d < 100 pM). Evolocumab caused a dose-dependent inhibition of PCSK9 binding to the LDLR and of PCSK9-mediated reduction in low-density lipoprotein (LDL) uptake in HepG2 cells (human hepatocellular carcinoma cell line) in culture. In cynomolgus monkeys and in hamsters, in vivo administration of evolocumab resulted in reduced serum lipoprotein cholesterol levels in a dose-dependent manner. Based on a comprehensive package of PK, pharmacodynamics (PD), and toxicology studies **Evolocumab** (AMG 145 Investigator's Brochure), a program to develop evolocumab as a treatment for dyslipidemia was initiated.

2.2.1 First-in-Human (FIH) Study 20080397

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

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

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

For mean unbound PCSK9, the single administrations of evolocumab produced decreases that were also dose-related with respect to magnitude and overall duration. Baseline PCSK9 values were in the range of approximately 200 to 280 ng/mL for all groups. In the 210-mg dose group and in the 420-mg groups (SC or IV), mean PCSK9

decreased within hours after dosing to values below the lower limit of quantitation (LLOQ) (15 ng/mL), remained below the LLOQ until day 11, and subsequently returned to or toward baseline.

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

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

For further details on study 20080397, please consult the AMG 145 Investigator's Brochure.

2.2.2 Multiple-dose Phase 1b Study 20080398

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

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

280 mg Q2W, and 420 mg Q4W) was consistent with the PK profiles of evolocumab in the single-dose Phase 1a study.

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

For further details on study 20080398, please consult the AMG 145 Investigator's Brochure.

2.2.3 Phase 2 Studies Included in the Aggregate Interim Analysis Supporting Phase 3 Dose Selection

Amgen's phase 2 program for evolocumab included several 12-week studies in different patient populations as well as longer-term studies.

a protocol-specified interim analysis was performed to facilitate phase 3 dose selection via an assessment of the safety, tolerability, and efficacy of 6 evolocumab dosing regimens from the ongoing phase 2 program. This interim analysis included safety, tolerability, and efficacy data from 5 studies (Table 1). The results of the interim analysis were corroborated in the final analysis of phase 2 data. Primary analysis results of all studies included in this interim analysis have been published (Koren et al, 2012; Giugliano et al, 2012; Sullivan et al, 2012; Raal et al, 2012).

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

	20101154	20101155	20090158	20090159	20110110
Trial Name	MENDEL	LAPLACE-TIMI 57	RUTHERFORD	GAUSS	OSLER
Sample Size	411	631	168	165	~1100
Patient Population	Monotherapy (Subjects not on statins)	Combination Therapy (Subjects on statins ± ezetimibe)	Subjects with HeFH	Subjects with statin intolerance	Open-label extension Subjects from studies 20101154, 20101155, 20090158, 20090159
Fasting LDL-C	≥ 100 mg/dL and < 190 mg/dL	≥ 85 mg/dL (≥ 85 to <100 mg/dL limited to 20%)	≥ 100 mg/dL	≥ 100 mg/dL; Not at LDL-C goal (NCEP ATP III)	≥ 75 mg/dL
Randomization Ratio	9 arms, equal allocation	8 arms, equal allocation	3 arms, equal allocation	5 arms, equal allocation	2:1
Treatment Duration	12 weeks	12 weeks	12 weeks	12 weeks	52 weeks
Treatment Groups	70mg Q2W	70mg Q2W			
	105mg Q2W	105mg Q2W			
	140mg Q2W	140mg Q2W			
	Placebo Q2W	Placebo Q2W			
	280mg Q4W	280mg Q4W		280mg Q4W	
	350mg Q4W	350mg Q4W	350mg Q4W	350mg Q4W	
	420mg Q4W	420mg Q4W	420mg Q4W	420mg Q4W	420mg Q4W + SOC
	Placebo Q4W	Placebo Q4W	Placebo Q4W		SOC Only
	Ezetimibe QD			Placebo Q4W + Ezetimibe QD	
				420mg Q4W + Ezetimibe QD	

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

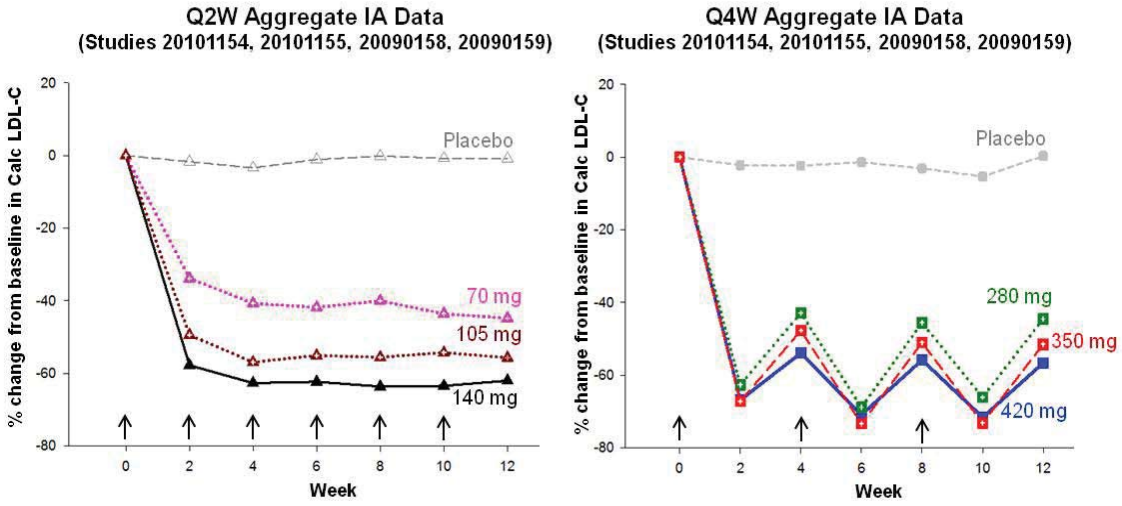
As of the snapshot dates, 606 subjects from the 4 phase 2 parent studies had rolled over into the long-term extension study (20110110). The mean time on study for subjects in Study 20110110 was 1.4 months plus an additional three months from the parent study. This translates into approximately 31% and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

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

2.2.3.1 Phase 2 Aggregate Interim Analysis Efficacy Results

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

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



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

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

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

	Treatment Difference (Estimate) Relative to Placebo[a, b]					
	Evolocumab Q2W vs Placebo Q2W			Evolocumab Q4W vs Placebo Q4W		
Lipid parameter	Evolocumab 70 mg (N = 43)	Evolocumab 105 mg (N = 43)	Evolocumab 140 mg (N = 42)	Evolocumab 280 mg (N = 41)	Evolocumab 350 mg (N = 41)	Evolocumab 420 mg (N = 42)
Calc LDL-C	-40.96	-50.53	-59.54	-44.25	-51.14	-55.99
95% CI	(-46.82, -35.10)	(-56.41, -44.65)	(-65.45, -53.62)	(-50.26, -38.24)	(-56.95, -45.33)	(-61.84, -50.13)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Total Chol	-25.27	-30.75	-36.80	-28.12	-32.31	-34.78
95% CI	(-29.47, -21.06)	(-34.97, -26.54)	(-41.04, -32.55)	(-32.17, -24.06)	(-36.23, -28.39)	(-38.74, -30.83)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
ApoB	-33.04	-41.70	-50.83	-33.24	-38.87	-42.22
95% CI	(-38.05, -28.03)	(-46.73, -36.68)	(-55.89, -45.77)	(-38.41, -28.08)	(-43.86, -33.88)	(-47.25, -37.19)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
non-HDL-C	-35.96	-43.60	-53.45	-38.02	-44.30	-47.79
95% CI	(-41.25, -30.67)	(-48.91, -38.29)	(-58.80, -48.10)	(-43.18, -32.85)	(-49.29, -39.31)	(-52.82, -42.76)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

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

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

	Treatment Difference (Estimate) Relative to Placebo[a, b]					
	Evolocumab Q2W vs Placebo Q2W			Evolocumab Q4W vs Placebo Q4W		
Lipid parameter	Evolocumab 70 mg (N = 43)	Evolocumab 105 mg (N = 43)	Evolocumab 140 mg (N = 42)	Evolocumab 280 mg (N = 41)	Evolocumab 350 mg (N = 41)	Evolocumab 420 mg (N = 42)
VLDL	-27.73	-22.53	-43.74	-14.40	-18.03	-22.77
95% CI	(-43.71, -11.74)	(-38.79, -6.27)	(-60.06, -27.42)	(-27.39, -1.40)	(-30.69, -5.37)	(-35.57, -9.96)
p-value	<0.001	0.007	<0.001	0.030	0.005	<0.001
Lp(a)	-15.21	-24.12	-30.69	-21.96	-27.58	-27.23
95% CI	(-24.18, -6.24)	(-33.12, -15.12)	(-39.85, -21.53)	(-29.59, -14.33)	(-34.90, -20.26)	(-34.69, -19.76)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Triglycerides	-14.89	-12.18	-25.27	-7.28	-12.11	-9.14
95% CI	(-28.37, -1.41)	(-25.71, 1.34)	(-38.89, -11.65)	(-18.07, 3.50)	(-22.53, -1.69)	(-19.64, 1.37)
p-value	0.031	0.077	<0.001	0.180	0.023	0.088
HDL-C	5.72	7.13	9.84	2.79	4.82	5.52
95% CI	(0.82, 10.61)	(2.22, 12.04)	(4.89, 14.78)	(-1.43, 7.00)	(0.74, 8.90)	(1.41, 9.63)
p-value	0.022	0.005	<0.001	0.190	0.021	0.009
ApoA1	2.98	4.09	5.22	2.42	4.18	5.28
95% CI	(-1.01, 6.96)	(0.10, 8.09)	(1.19, 9.24)	(-0.73, 5.56)	(1.14, 7.22)	(2.22, 8.34)
p-value	0.140	0.045	0.011	0.130	0.007	<0.001

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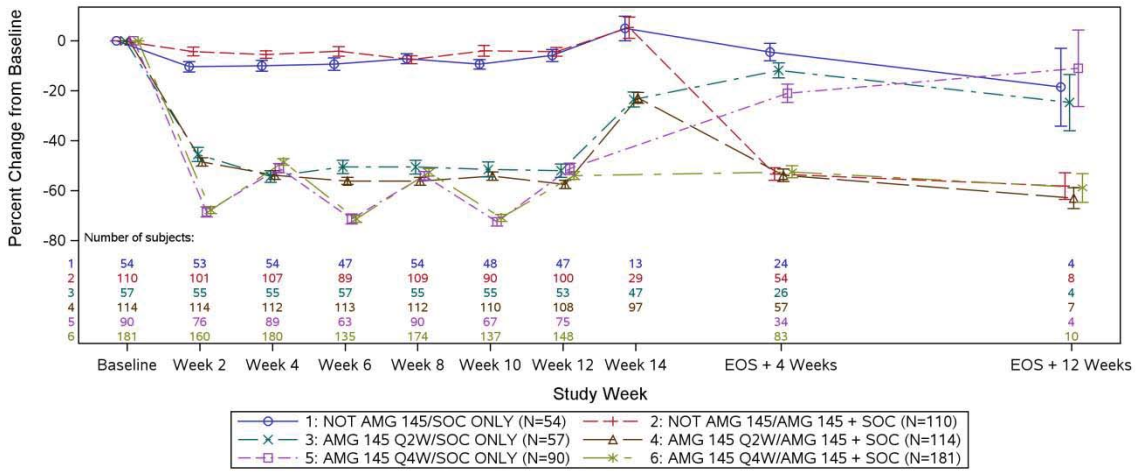
Source: Modified from integrated analysis Tables 14-4.14.1, 14-4.15.6, 14-4.9.1, 14-4.8.1, 14-4.18.6, 14-4.24.6, 14-4.17.6, 14-4.16.6, and 14-4.20.6.

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

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

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



2.2.3.3 Aggregate Safety Data from Completed Phase 2 Studies

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

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

- In completed phase 2 studies, the overall incidence of serious adverse events was similar between the evolocumab and placebo groups (2.1% and 1.3%, respectively). No individual serious adverse event was reported in more than 2 (0.2%) subjects treated with evolocumab in these studies.

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

2.3 Dose Rationale

Dose selection for the phase 3 studies was based on an interim analysis of safety, tolerability, and efficacy data from the 4 parent phase 2, placebo-controlled studies (20090158, 20090159, 20101154, and 20101155), performed on These results of the interim analysis were corroborated in the final analysis of phase 2 data. Further result details for these studies can be found in the AMG 145 Investigator's Brochure. The SC doses of evolocumab and placebo administered in the 4 parent studies are detailed in Table 1.

In the aggregate interim analysis, reductions in LDL-C from baseline at week 12 were greatest for the highest doses evaluated within each dosing frequency (ie, 140 mg Q2W and 420 mg Q4W) (Figure 3). Pairwise comparisons of decreases in LDL-C among the 6 evolocumab cohorts showed statistically significant differences between groups at week 12. The lowest doses within each dosing frequency (70 mg Q2W and 280 mg Q4W) were significantly less effective than the higher doses in each cohort (p values < 0.016). Within the Q2W doses, the 140 mg dose showed statistically greater decreases in LDL-C compared with the 70 mg and 105 mg doses ($p < 0.001$ and $p = 0.006$, respectively). Within the Q4W doses, the 350 mg and 420 mg doses showed statistically greater decreases in LDL-C than the 280 mg dose ($p = 0.016$ and $p < 0.001$, respectively). While the maximal effects measured 2 weeks after the preceding dose were similar for the 350 mg and 420 mg doses, there was better maintenance of LDL-C lowering throughout the dosing interval for 420 mg Q4W as determined by trough effects at the end of each dosing interval (weeks 4, 8, 12). This greater maintenance of LDL-C lowering resulted in statistically lower LDL-C concentrations at the end of each dosing interval (p values ≤ 0.032) in the 420 mg cohorts compared with the 350 mg cohorts (Figure 3; Table 3).

Figure 3. Mean Percent Change from Baseline in Calculated LDL-C by Scheduled Visit and Treatment Group (Placebo Q2W / Evolocumab 140 mg Q2W / Placebo Q4W / Evolocumab 350 mg Q4W / Evolocumab 420 mg Q4W) Studies 20101154, 20101155, 20090158, 20090159 (Integrated Interim Observed Analysis Set)

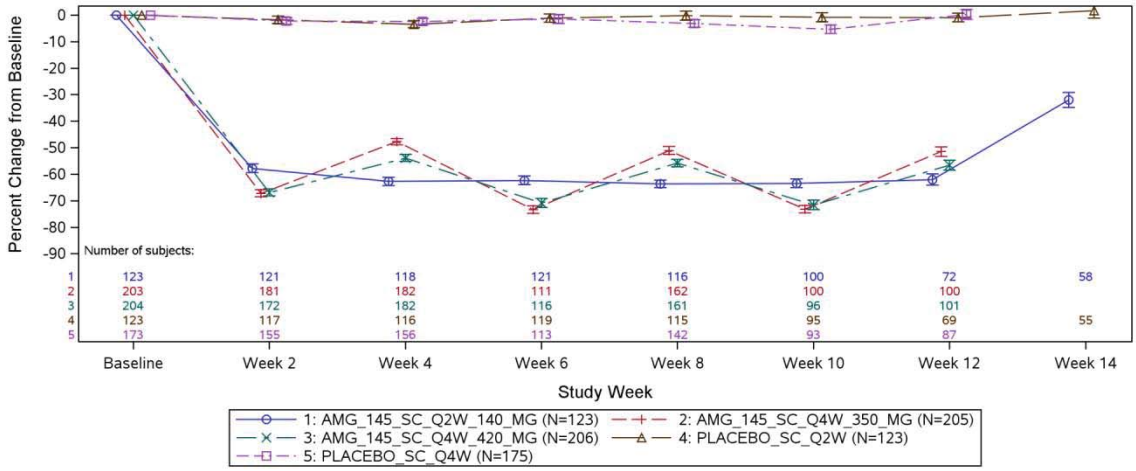


Table 3. Pairwise Comparisons of Repeated Measures Model Without Imputation (Integrated Interim Observed Analysis Set)

Dose comparisons	Weeks	n1/n2	LS mean difference (SE)	p-value	Dose with greater LDL-C reduction
140 mg Q2W vs. 350 mg Q4W	2	121/181	9.85(1.99)	< 0.001	350 mg Q4W
	4	118/182	-14.92(1.90)	< 0.001	140 mg Q2W
	6	121/111	8.67(2.17)	< 0.001	350 mg Q4W
	8	116/162	-12.30(2.12)	< 0.001	140 mg Q2W
	10	100/100	7.59(2.27)	0.001	350 mg Q4W
	12	72/100	-12.30(2.59)	< 0.001	140 mg Q2W
140 mg Q2W vs. 420 mg Q4W	2	121/172	8.91(2.01)	< 0.001	420 mg Q4W
	4	118/182	-8.79(1.90)	< 0.001	140 mg Q2W
	6	121/116	8.39(2.16)	< 0.001	420 mg Q4W
	8	116/161	-8.17(2.12)	< 0.001	140 mg Q2W
	10	100/96	6.70(2.28)	0.003	420 mg Q4W
	12	72/101	-5.96(2.59)	0.021	140 mg Q2W
350 mg Q4W vs. 420 mg Q4W	2	181/172	-0.94(1.79)	0.600	No difference
	4	182/182	6.13(1.68)	< 0.001	420 mg Q4W
	6	111/116	-0.28(2.10)	0.895	No difference
	8	162/161	4.13(1.92)	0.032	420 mg Q4W
	10	100/96	-0.88(2.20)	0.689	No difference
	12	100/101	6.34(2.36)	0.007	420 mg Q4W

Decreases in other lipid parameters, including total cholesterol, ApoB, non-HDL-C, and VLDL-C, and increases in HDL-C and ApoA1, were also statistically greater in the evolocumab treatment groups compared with placebo and generally dose-dependent within each dosing frequency (ie, Q2W or Q4W).

The efficacy results observed in the parent studies are supported by dose-response models which were constructed based on week 12 UC LDL-C concentrations for each of the Q2W and Q4W dosing regimens studied in the two largest phase 2 studies (Study 20101154 and Study 20101155). In the dose-response model, the 140 mg Q2W and 420 mg Q4W dosing regimens were predicted to provide the greatest reduction in LDL-C. Additional support for the doses was obtained from a semi-mechanistic PK/PD model which linked evolocumab serum concentrations to calculated LDL-C reduction over time. The results were in agreement with the dose-response model, with the greatest predicted response achieved 140 mg Q2W and 420 mg Q4W dosing.

Analyses of safety data from the integrated analyses of data from the 4 parent studies showed a slightly higher overall incidence of treatment-emergent adverse events in the evolocumab groups (50%) than in the placebo groups (43%); however, the safety profile among the 6 dosing regimens of evolocumab was similar. More specifically, there was no apparent dose relationship between the incidence of treatment emergent adverse events and the dose or frequency of evolocumab, and no trend in the incidence of treatment emergent adverse events $\geq$ grade 2, $\geq$ grade 3 or $\geq$ grade 4 across treatment groups.

Based on the totality of the safety, tolerability, and efficacy data available from integrated analyses of the 4 placebo-controlled phase 2 studies, the 140 mg Q2W and 420 mg Q4W (QM) doses provide the greatest efficacy with respect to LDL-C lowering and other lipid parameters, with an acceptable safety profile. As a result, the 140 mg Q2W and 420 mg QM doses were selected for use in the proposed phase 3 registrational studies. Amgen is developing 2 dosing frequencies in order to provide the convenience and choice of every 2 weeks or monthly administration for doctors and patients.

The no-observed-adverse-effect level (NOAEL) observed in a 6-month cynomolgus monkey toxicology study (300 mg/kg weekly SC) provides significant exposure multiples (86x for exposure (AUC) and 254x for C_{max}) over the anticipated human exposures.

2.4 Statin Background

For randomization into the FOURIER trial, subjects must be receiving background lipid lowering therapy as per Appendix E which must include at least an effective statin dose, ie, at least atorvastatin 20 mg daily or equivalent. Where locally approved, highly effective statin therapy, defined as at least atorvastatin 40 mg daily or equivalent, is recommended. The clinical benefits of statin treatment in primary prevention as well as secondary prevention have been documented in multiple trials (Weart and Hogan, 2011). A recent meta-analysis confirmed a beneficial effect on all-cause mortality as well as combined fatal and non-fatal cardiovascular endpoints in primary prevention (Taylor et al, 2011). Reported adverse events arising from statin therapy are infrequent and rarely severe (Weart and Hogan, 2011). Though some studies have suggested an association between lower LDL cholesterol levels and hemorrhagic stroke or intracranial hemorrhage (Iso et al, 1989; Collins et al (Heart Protection Collaborative Study Group), 2004; Amarenco et al, 2006), several contemporary studies utilizing high doses of potent statins as well as 2 large meta-analyses have not observed this association (Waters et al, 2006; CTTC, 2010; Hackam et al, 2011). Other meta-analyses have suggested that statin use can also affect the incidence of new onset diabetes (Sattar et al, 2010; Preiss et al, 2011). Combined, these analyses followed over 120,000 participants without a baseline diagnosis of diabetes for a mean duration of at least 4 years. Both studies found a small increased absolute risk for development of diabetes in patients treated with statins; however, this risk was outweighed by the overwhelming reduction in major adverse cardiovascular events resulting from statin use in patients at moderate to high cardiovascular risk. Regarding other safety profile data available for statins, a pooled analysis of 49 atorvastatin trials demonstrated that the overall safety profiles for the 10- and 80-mg/day doses are comparable, with the exception of a slightly increased rate of elevations in levels of the hepatic enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) for the higher dose (Newman et al, 2006). The most common adverse effects experienced by patients taking statins are those associated with the musculoskeletal system, and these effects occur with all statins. Symptoms are usually restricted to muscle pain, weakness and/or cramps. Myalgia, which according to various definitions may include some or all of these relatively minor symptoms, typically affects 5% to 10% of patients receiving statins (Weart and Hogan, 2011).

During participation in the FOURIER trial, subjects will continue their stable statin therapy. Before any changes to the statin therapy, Amgen or designee **(Thrombolysis**

in Myocardial Infarction [TIMI] Study Group Hotline) should be **consulted**, if possible. **If a change is made, the reason for the change must be provided in the eCRF.**

Refer to the regional manufacturer package insert for additional information.

2.5 Rationale

It is widely accepted that the benefit of statin therapy is derived from LDL-C reduction. Observational data sets correlating LDL-C levels with the incidence of cardiovascular events as well as several landmark clinical trials that have examined the effects of LDL-C reduction from statin therapy (vs. placebo) have demonstrated a proportional and linear relationship between LDL-C and cardiovascular events. It is also notable that seminal secondary outcome studies designed to compare cardiovascular event rates on maximum versus low dose statin therapy, such as TNT, IDEAL and PROVE-IT TIMI 22, have demonstrated that incremental LDL-C reduction derived from maximal statin therapy is associated with both a clinical and statistically significant benefit in composite endpoints such as the aggregate of death, MI, stroke, coronary revascularization, and hospitalization for unstable angina (HR ~0.8). A meta analysis of more than 170,000 subjects in 26 randomized controlled studies of statins have shown that "further reductions in LDL cholesterol safely produce definite further reductions in the incidence of heart attack, of revascularization, and of ischemic stroke, with each 1.0 mmol/L reduction reducing the annual rate of these major vascular events by just over a fifth. There was no evidence of any threshold within the cholesterol range studied (Cholesterol Treatment Trialists' Collaboration, 2010). Given that evolocumab is expected to reduce LDL-C by even more than 1.0 mmol (39 mg/dL) in patients already on an intense dose statin therapy (based on phase 1b results), it is expected that the FOURIER trial will demonstrate that evolocumab administration will produce a significant reduction of cardiovascular events, compared to placebo, in high risk patients receiving optimized statin background therapy.

Because event rates are changing over time with changes in the standard of care, the introduction of new therapies, or for other, unknown reasons, it will not be possible to assess the effect of LDL-C lowering with evolocumab on clinical outcomes without a comparison to a placebo arm. For randomization into the FOURIER trial, subjects must be on treatment for their dyslipidemia that must include at least an effective or highly effective statin dose, ie, at least daily atorvastatin 20 mg or 40 mg, respectively, or equivalent (see Appendix E).

The primary endpoint in this study is the composite of cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, and coronary revascularization. This combined endpoint has been selected on the basis of the anticipated event rate as well as the modifiability of the associated event rate in response to LDL-C reduction. This endpoint (or very similar) has been utilized in multiple, large cardiovascular outcomes studies using different modalities for lipid reduction.

2.6 Clinical Hypotheses

2.6.1 Primary

The primary hypothesis is that additional LDL-C lowering with evolocumab when used in addition to other treatment for dyslipidemia is well tolerated and decreases the risk of cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary revascularization in subjects with clinically evident cardiovascular disease.

2.6.2 Secondary

Secondary hypotheses are that additional LDL-C lowering with evolocumab when used in addition to other treatment for dyslipidemia

- decreases the risk of cardiovascular mortality, myocardial infarction, or stroke
- **decreases the risk of cardiovascular mortality**
- decreases the risk of all-cause mortality
- **decreases the risk of myocardial infarction**
- **decreases the risk of stroke**
- **decreases the risk of coronary revascularization**
- decreases the risk of cardiovascular mortality or hospitalization for worsening heart failure
- decreases the risk of fatal or non-fatal ischemic stroke or transient ischemic attack

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 3, multicenter, double-blind, randomized, placebo controlled, parallel group, cardiovascular outcomes study for evolocumab in subjects with clinically evident cardiovascular disease as evidenced by a history of myocardial infarction, non-hemorrhagic stroke, or symptomatic peripheral arterial disease (PAD;Section 4.1.3). At randomization, subjects must be receiving stable, optimized lipid lowering background therapy per Appendix E, that is expected to be unchanged for the duration of study participation (up to approximately 5 years). Subjects must receive at least an effective statin dose, ie, at least atorvastatin 20 mg daily or equivalent. Where locally approved,

highly effective statin therapy, defined as at least atorvastatin 40 mg daily or equivalent, is recommended. For subjects with LDL-C > 100 mg/dL and not receiving highly effective statin therapy (atorvastatin ≥ 40 mg daily or equivalent), the investigator must attest that higher dose statin therapy is not appropriate for this subject (eg, subject refused, dose not tolerated, dose not available in that country, other significant concern).

Eligible subjects will be randomized with an allocation ratio of 1:1 to either receive evolocumab or placebo. Randomization will be stratified by the final screening LDL-C level (< 85 mg/dL [2.2 mmol/L] vs ≥ 85 mg/dL) and by geographical region. Evolocumab and placebo will be blinded. Central laboratory results of the lipid panel, ApoA1, ApoB, lipoprotein(a), and high sensitivity C-reactive protein (hsCRP) will be blinded post-treatment and not reported to the investigator until unblinding of the clinical database. Investigators should not perform non-protocol testing of these analytes during a subject's study participation and until at least 12 weeks after the subject's last administration of IP or the end of study, whichever is later. Investigators will be informed if triglycerides are > 1000 mg/dL (11.3 mmol/L) so that appropriate subject follow-up can be initiated (see Section 6.3). The study includes collection of biomarker samples, unless prohibited by local law or regulations, and, where approved by the independent ethics committee and/or institutional review board (IEC/IRB) and applicable regulatory and other authorities, all subjects will be invited to consent to pharmacogenetic analyses. The study will end when at least 1630 subjects have experienced a **key** secondary endpoint event of cardiovascular death, myocardial infarction, or stroke. Subjects will be encouraged to complete all planned visits regardless of their adherence to investigational product (IP) administration. Vital status should be obtained periodically and must be obtained at the end of the study for all subjects unless prohibited by local law.

All deaths and components of primary and secondary endpoints (myocardial infarction, stroke, revascularization, hospitalization for unstable angina, hospitalization for heart failure, and transient ischemic attack [TIA]) will be adjudicated by an independent external Clinical Events Committee (CEC), using standardized definitions. **In addition, new onset diabetes will also be adjudicated (Section 7.1.5.9).** An external independent Data Monitoring Committee (DMC) will formally review the accumulating data from this and other ongoing studies with evolocumab to ensure there is no avoidable increased risk for harm to subjects. An Executive Committee (EC) has been formed to advise Amgen on trial design and implementation, to conduct confirmatory

data analyses at the end of the trial, and for assistance in the communication of trial results. The EC is co-chaired by 2 external academic cardiologists who are experts in lipids and/or clinical trials and includes at least 3 additional external members with similar expertise. An external independent Lipid Monitoring Committee (LMC) will be formed to review unblinded lipid results by treatment group to ensure design parameters are being met. The LMC will be advisory to Amgen and the EC. It will not have access to clinical outcomes data. The LMC may review treatment compliance and other relevant non-outcomes data. It may recommend increasing the number of randomized subjects or the duration of treatment and follow-up. A similar LMC is a design characteristic of an ongoing study for lipid lowering with ezetimibe/simvastatin combination therapy (Cannon et al, 2008; Califf et al, 2010). In addition, the LMC may be involved in the follow-up for subjects meeting lipid (eg, triglycerides) alert thresholds by the central laboratory. Analyses for the DMC and LMC will be provided by the Independent Biostatistical Group (IBG), which is external to Amgen. Details for each committee will be provided in a committee charter.

Concentration values are provided in mmol/L for investigator convenience. Conventional concentrations (mg/mL) will be used for the protocol, including eligibility determination.

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

The study endpoints are defined in Section 10.1.

3.2 Number of Centers

Up to approximately 1,300 centers will participate in this study worldwide. Additional sites may be invited to participate to ensure study timelines are met. Sites that do not enroll subjects within 3 to 6 months of being open for enrollment may be closed.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”. There will be up to approximately 27,500 subjects randomized in this study. Justification for the sample size can be found in Section 10.2.

3.4 Estimated Study Duration

3.4.1 Study Duration for Participants

The enrollment period is anticipated to be approximately 26 months. The study duration will be approximately 56 months from the date the first subject is randomized (approximately 30 months from the completion of enrollment). Therefore, it is expected

that treatment and follow-up for the first enrolled subjects will be approximately 56 months, for the last enrolled subjects approximately 30 months. Experiencing a non-fatal primary endpoint does not end study participation for a study subject. Subjects will continue treatment and follow-up procedures until the study ends as per Section 3.4.2. All subjects will be followed from randomization **until** the study **ends** unless the subject has withdrawn consent, irrespective of whether the subject is continuing to receive study treatment. Depending on the rates of accumulating endpoints, the follow-up time for individual subjects and the duration of the study may be longer or shorter than anticipated.

3.4.2 End of Study

The study is event driven and will conclude when at least 1630 subjects have experienced an event adjudicated as qualifying for the **key** secondary endpoint (composite of cardiovascular death, myocardial infarction, or stroke). It is expected that at that time, approximately 3550 subjects will have experienced an event adjudicated as qualifying for primary endpoint (composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, and coronary revascularization). Amgen will monitor the overall event rate and will set **a** date for **initiating end of** study **procedures** based on the anticipated date reaching the required number of endpoints above.

After the date for **initiating end of** study **procedures** has been determined, subjects will be scheduled for a final study visit (end of study [EOS] visit). If a subject cannot be contacted, the subject is considered lost to follow-up as of the date of the last contact.

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). Before any study-specific procedure, the appropriate written informed consent must be obtained (see Section 11.1).

4.1 Inclusion Criteria

4.1.1 Signed informed consent

4.1.2 Male or female ≥ 40 to ≤ 85 years of age at signing of informed consent

4.1.3 History of clinically evident cardiovascular disease as evidenced by ANY of the following:

- diagnosis of myocardial infarction
- diagnosis of non-hemorrhagic stroke (TIA does not qualify as stroke for inclusion)

- symptomatic peripheral arterial disease (PAD), as evidenced by intermittent claudication with ankle-brachial index (ABI) < 0.85, or peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease

Note: the proportion of subjects with history of MI or non-hemorrhagic stroke > 5 years prior to screening will be determined by the sponsor

4.1.4 At least 1 major risk factor or at least 2 minor risk factors below:

Major Risk Factors (1 Required):

- diabetes (type 1 or type 2)
- age ≥ 65 years at randomization (and ≤ 85 years at time of informed consent)
- MI or non-hemorrhagic stroke within 6 months of screening
- additional diagnosis of myocardial infarction or non-hemorrhagic stroke excluding qualifying MI or non-hemorrhagic stroke[a]
- current daily cigarette smoking
- history of symptomatic PAD (intermittent claudication with ABI < 0.85, or peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease) if eligible by MI or stroke history

Minor Risk Factors (2 Required):

- history of non-MI related coronary revascularization[a]
- residual coronary artery disease with ≥ 40% stenosis in ≥ 2 large vessels
- Most recent HDL-C < 40 mg/dL (1.0 mmol/L) for men and < 50 mg/dL (1.3 mmol/L) for women by central laboratory before randomization
- Most recent hsCRP > 2.0 mg/L by central laboratory before randomization
- Most recent LDL-C ≥ 130 mg/dL (3.4 mmol/L) or non-HDL-C ≥ 160 mg/dL (4.1 mmol/L) by central laboratory before randomization
- metabolic syndrome[b]

4.1.5 Most recent fasting LDL-C ≥ 70 mg/dL (≥ 1.8 mmol/L) or non-HDL-C ≥ 100 mg/dL (≥ 2.6 mmol/L) by central laboratory during screening after ≥ 2 weeks of stable lipid lowering therapy per Appendix E

4.1.6 Most recent fasting triglycerides ≤ 400 mg/dL (4.5 mmol/L) by central laboratory before randomization

[a] Note: there is no time limit on additional qualifying medical history.

[b] Definition: metabolic syndrome for this protocol is defined as ≥ 3 of the following (Alberti et al, 2009):

- waist circumference > 102 cm (> 40 in.) for men and > 88 cm (> 35 in.) for women (Asian men, including Japanese > 90 cm; Asian women, except Japanese > 80 cm; Japanese women > 90 cm)
- triglycerides ≥ 150 mg/dL (1.7 mmol/L) by central laboratory at final screening
- HDL-C < 40 mg/dL (1.0 mmol/L) for men and < 50 mg/dL (1.3 mmol/L) for women by central laboratory at final screening *(Note: if the HDL-C level is one of criterion used to make the diagnosis of metabolic syndrome, it cannot be used as a separate risk factor)*
- systolic blood pressure (SBP) ≥ 130 mmHg or diastolic BP (DBP) ≥ 85 mmHg or hypertension treated with medication
- fasting glucose ≥ 100 mg/dL (≥ 5.6 mmol/L) by central laboratory at final screening

4.2 Exclusion Criteria

4.2.1 Subject must not be randomized within 4 weeks of their most recent MI or stroke

4.2.2 NYHA class III or IV, or last known left ventricular ejection fraction < 30%

4.2.3 Known hemorrhagic stroke at any time

4.2.4 Uncontrolled or recurrent ventricular tachycardia

4.2.5 Planned or expected cardiac surgery or revascularization within 3 months after randomization

4.2.6 Uncontrolled hypertension defined as sitting systolic blood pressure (SBP) > 180 mmHg or diastolic BP (DBP) > 110 mmHg

4.2.7 Use of cholesteryl ester transfer protein (CETP) inhibition treatment**,** mipomersen, or lomitapide within 12 months prior to randomization. Fenofibrate therapy must be stable for at least 6 weeks prior to final screening at a dose that is appropriate for the duration of the study in the judgment of the investigator. Other fibrate therapy (and derivatives) are prohibited

4.2.8 Prior use of PCSK9 inhibition treatment other than evolocumab or use of evolocumab < 12 weeks prior to final lipid screening

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

4.2.10 Severe renal dysfunction, defined as an estimated glomerular filtration rate (eGFR) < 20 mL/min/1.73m^2 at final screening

4.2.11 Active liver disease or hepatic dysfunction, defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 times the ULN as determined by central laboratory analysis at final screening

4.2.12 Recipient of any major organ transplant (eg, lung, liver, heart, bone marrow, renal)

4.2.13 Personal or family history of hereditary muscular disorders

4.2.14 LDL or plasma apheresis within 12 months prior to randomization

4.2.15 Severe, concomitant non-cardiovascular disease that is expected to reduce life expectancy to less than 3 years

4.2.16 CK > 5 times the ULN at final screening

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

4.2.18 Malignancy (except non-melanoma skin cancers, cervical in-situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma) within the last 10 years

4.2.19 Subject has received drugs via a systemic route that have known major interactions with background statin therapy (see Appendix F) within 1 month prior to randomization or is likely to require such treatment during the study period

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

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

- menopause is defined as 12 months of spontaneous and continuous amenorrhea in a female ≥ 55 years old or 12 months of spontaneous and continuous amenorrhea with a follicle-stimulating hormone (FSH) level > 40 IU/L (or according to the definition of "postmenopausal range" for the laboratory involved) in a female < 55 years old unless the subject has undergone bilateral oophorectomy
- acceptable methods of preventing pregnancy include not having intercourse, birth control pills, injections, implants, or patches, intrauterine devices (IUDs), tubal ligation/occlusion, sexual activity with a male partner who has had a vasectomy, condom or occlusive cap (diaphragm or cervical/vault caps) used with spermicide

4.2.22 Subject is pregnant or breast feeding, or planning to become pregnant **or** to breastfeed during treatment with IP and/ or within 15 weeks after the end of treatment with IP

4.2.23 Known sensitivity to any of the active substances or their excipients to be administered during dosing

4.2.24 Subject likely to not be available to complete all protocol-required study visits or procedures, to the best of the subject's and investigator's knowledge

4.2.25 History or evidence of any other clinically significant disorder, condition or disease other than those outlined above that, in the opinion of the Investigator or Amgen physician, if consulted, may compromise the ability of the subject to give written informed consent, would pose a risk to subject safety, or interfere with the study evaluation, procedures or completion.

5. SUBJECT ENROLLMENT

Before subjects may be entered into the study, Amgen requires a copy of the site's written independent ethics committee and/or institutional review board (IEC/IRB) approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable (see Section 11.2). All subjects must personally sign and date the consent form before commencement of study-specific procedures. AEs related to study procedures and serious AEs (SAEs) will be collected upon signing the informed consent form. A subject is considered enrolled upon randomization.

All subjects who enter into the screening period for the study, defined as when the subject signs the IEC/IRB approved informed consent form, will receive a unique subject identification number before any study procedures are performed. The subject identification number will be assigned by the Interactive Voice Response System / Interactive Web Response System (IVRS/IWRS). 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 at the time of rescreening or randomization. Unique 11-digit subject identification numbers will be assigned in sequential order for each site

This number will not necessarily be the same as the randomization number assigned for the subject.

5.1 Randomization

Assignment to the 2 treatment arms will be based on a computer-generated randomization schedule prepared by Amgen before the start of the study. Randomization to these arms will be 1:1.

The following are the treatment arms:

- Placebo, SC
- Evolocumab, SC

A subject may only receive 1 randomization number and each randomization number will only be assigned to 1 subject. Randomization will be stratified by the final screening

LDL-C level (< 85 mg/dL [2.2 mmol/L] vs ≥ 85 mg/dL) and by geographical region, defined as follows:

- Europe - all European countries, Israel
- North America - US and Canada
- Latin America
- Asia Pacific - all Asian countries, Australasia, and South Africa.

Once eligibility into the study has been confirmed, a site representative will make the randomization call to the IVRS/IWRS to assign a randomization number to the subject. The randomization call to the IVRS/IWRS is accomplished by entering the pertinent information detailed in the IVRS/IWRS user manual. A confirmation will be communicated to the site to verify that the correct information has been entered and to confirm the assignment of a randomization number. A subject will be considered randomized into the study when a randomization number is assigned.

Please refer to Section 5.2 below for details on when and how the randomization code may be broken.

5.2 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject. Unblinding at the study site for any other reason will be considered a protocol deviation.

Refer to the IVRS/IWRS manual for instructions on unblinding.

The principal investigator is strongly encouraged to contact the Amgen study manager before unblinding any subject's treatment assignment, but must do so within 1 working day after the event.

6. TREATMENT PROCEDURES

Evolocumab and evolocumab placebo are IPs in this study.

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

6.1 Evolocumab and Placebo

Evolocumab and placebo will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical IP distribution procedures. Evolocumab will be presented as a sterile, preservative-free solution in a single use, disposable, handheld mechanical (spring-based) 1.0 mL prefilled autoinjector/pen (AI/Pen) or 3.5 mL Personal

Injector (Personal Injector) for fixed dose, subcutaneous injection. The prefilled AI/Pen contains a 1.0 mL deliverable volume of 140 mg/mL evolocumab in 220 mM proline, 20 mM acetate, 0.01% (w/v) polysorbate 80, pH 5.0. The Personal Injector with prefilled cartridge assembly is a single-use, disposable, on-body electro-mechanical injection device that is co-packaged with a prefilled Crystal Zenith (CZ) cartridge assembly containing 3.5 mL deliverable volume of 120 mg/mL evolocumab in 220 mM proline, 20 mM acetate, 0.01% (w/v) polysorbate 80, pH 5.0. Respective placebo will be presented in an identical prefilled AI/Pen containing a 1.0 mL deliverable volume of 1.1% (w/v) sodium carboxymethylcellulose, 250 mM proline, 10 mM acetate, and 0.01% (w/v) polysorbate 80, pH 5.0 or in an identical Personal Injector containing a 3.5 mL deliverable volume of 0.7% (w/v) sodium carboxymethylcellulose, 250 mM proline, 10 mM acetate, and 0.01% (w/v) polysorbate 80, pH 5.0.

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

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

The investigator may be required to record the box number of IP (prefilled AI/Pen or Personal Injector) on the subject's Drug Administration electronic case report form (eCRF).

6.1.1 Dosage, Administration, and Schedule

IP will be administered SC in accordance with instructions in the IPIM. IP administration at each visit should be done after vital signs and ECG, and must be done after blood draw procedures, if applicable. At the first 2 or 3 IP administrations (day 1, week 2 if administered Q2W, week 4), subjects will be instructed and supervised in the use of the prefilled AI/Pen or Personal Injector and, after administration of IP, should be kept for observation for at least 30 minutes before being discharged. After the week 4 visit, IP can be administered at a location external to the study site, using the prefilled AI/Pen or Personal Injector provided by the study. It is suggested, that the IP administration is done by the subject under site staff supervision at each of the regular study visits to ensure continued proper use of the injection device. The first self-administration after

switching the dose and frequency (140 mg Q2W to 420 mg QM or vice versa) should be done at a regularly scheduled visit under the supervision of the investigator or qualified study center staff. If the device that will be used after switching has not been used by the subject previously, the first self-injection must be under supervision of the investigator or qualified study center staff.

Evolocumab will be administered either at 140 mg in 1.0 mL (1 administration by prefilled AI/Pen) or at 420 mg in 3.0 mL or 3.5 mL (3 administrations by prefilled AI/Pen or 1 administration by Personal Injector) QM and placebo will be administered either at 1.0 mL (1 administration by prefilled AI/Pen) or at 3.0 mL or 3.5 mL (3 administrations by prefilled AI/Pen or 1 administration by Personal Injector) QM. The 3 injections for the QM administration, if applicable, can be administered into different injection sites. The SC injections should be administered in a consecutive fashion with all injections completed within 30 minutes.

Subjects will choose whether to start their IP administration at the Q2W or QM frequency and will have an opportunity every 12 weeks to switch between the Q2W and QM frequencies, provided the required approvals and supply of IP are available at the study site.

The Q2W and QM schedules of IP administration, as well as the schedule of study visits, are determined by the date of first IP administration. Administrations that are taking place during a scheduled visit should occur within the visit window for the respective visit. For all other administrations, IP should be administered within ± 7 days of the scheduled administration date.

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

6.1.2 Dosage Adjustments

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

Subjects who are Late for a Scheduled Dose of Investigational Product

If a subject is late for administration of IP, administration should occur as soon as possible. QM doses should not be administered within less than 7 days of a previous dose. If a QM dose is scheduled to be administered during a visit and the subject arrives for the visit earlier than 7 days after a previous dose, the dose should not be administered, but all other study procedures should be conducted. The missed dose should be taken after the visit, at least 7 days after the most recent previous administration. Similarly, more than 2 Q2W doses should not be administered within any 7-day period. If a Q2W subject arrives for a visit with IP administration and more than 1 dose of IP was administered within the prior 7 days, the dose should not be administered but all other study procedures should be completed. Administration of IP should occur as soon as possible but at least 7 days after the most recent previous administration.

Subjects who Miss a Scheduled Dose of Investigational Product Completely

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

6.2 Background Lipid-lowering Therapy

At randomization, subjects must be receiving stable, optimized lipid lowering background therapy per Appendix E, that is expected to be unchanged for the duration of study participation (up to approximately 5 years). Subjects must receive at least an effective statin dose, ie, at least atorvastatin 20 mg daily or equivalent. Where locally approved, highly effective statin therapy, defined as at least atorvastatin 40 mg daily or equivalent, is recommended. For subjects with LDL-C > 100 mg/dL and not receiving highly effective statin therapy (atorvastatin ≥ 40 mg daily or equivalent), the investigator must attest that higher dose statin therapy is not appropriate for this subject (eg, subject refused, dose not tolerated, dose not available in that country, other significant concern).

No statins other than the ones listed in Appendix E are allowed during study participation. Subjects who receive atorvastatin during the study can elect to have it provided by the sponsor at doses of 20 mg, 40 mg, or 80 mg.

Before making any changes to this therapy after randomization, the Amgen medical monitor or designee **(TIMI Study Group Hotline)** should be consulted, if possible. **If a change is made, the reason for the change must be provided in the eCRF.**

Lipid treatment other than that specified in Appendix E is not required for the FOURIER trial. All other drugs that are allowed per protocol and that are prescribed for the subject, including ezetimibe and any other allowed lipid therapy, must be commercially available and used at dosages approved by local regulatory authorities. These therapies and any allowed alternative statin (other than atorvastatin) are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these drugs.

Subjects who Miss a Dose of Background Statin Therapy

Subjects who miss a dose of background statin will be advised to take the missed dose as soon as they can; subsequent doses will be taken at the usual time. However, if the next scheduled dose would be due in less than 6 hours, the subject will be advised to omit the missed dose entirely and to take the next dose at the normal time.

6.3 Lipid Monitoring and Compliance with Lipid-lowering Therapy

Throughout the study, the central laboratory will compare LDL-C concentrations with the subject's prior assessed LDL-C without unblinding the study team, investigator, or site staff. If the measured LDL-C exceeds a preset trigger, the site will be notified by an automated system to instruct the patient on compliance (study drug, statin, ezetimibe and other allowed lipid therapy, if applicable, and diet). To maintain the blind, the same reminder will be provided to additional subjects in each treatment arm, using an appropriate algorithm to balance the frequency of alerts for both treatment groups, active and placebo. Subjects will also be monitored for very low LDL-C (< 25 mg/dL [0.6 mmol/L]). Data on these subjects will be provided to the DMC and additional laboratory values, including vitamin E, may be evaluated in blood samples already collected.

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

A Lipid Monitoring Committee (LMC) will be established to monitor the LDL-C separation between treatment groups over the course of the study (see Section 3.1). In addition, the LMC may be involved in the follow-up for subjects meeting lipid (eg, triglycerides)

alert thresholds by the central laboratory. Details will be provided in the DMC and LMC charters.

6.4 Criteria for Withholding of Investigational Product and Background Lipid Therapy

Reports from the central laboratory after each visit must be reviewed as soon as possible after receipt and before the next administration of IP. If any of the criteria below are met for withholding IP**,** statin, or other applicable background lipid therapy, the subject must be instructed to stop the applicable treatment and an additional visit must be scheduled for the required laboratory evaluations. If a subject is experiencing elevations of laboratory values below (Sections 6.4.1 and 6.4.2) and is receiving other lipid therapies that may result in such elevations, eg, ezetimibe, fenofibrate, or niacin, the additional therapies should also be evaluated for a potential role in these elevations and considered for discontinuation. Fenofibrate, ezetimibe, or niacin can result in elevation of CK or liver function tests. If a subject experiences elevations in triglycerides > 500 mg/dL (5.65 mmol/L) and is concomitantly receiving a bile acid binding resin, the bile acid binding resin should be evaluated for discontinuation.

6.4.1 Elevation of Creatine Kinase (CK)

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

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

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

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

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

6.4.2 Elevation of Liver Function Tests

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

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

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

AND

- AST or ALT > 3x ULN

AND

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

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

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

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

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

6.4.3 Criteria for Rechallenge After Withholding or Discontinuation of IP (Evolocumab or Placebo), Statin and Other Lipid Background Therapy

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

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

6.5 Product Complaints, Including Device Complaints

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

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

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

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

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

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

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

6.6 Concomitant Therapy, Physical Exercise, and Diet

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.7.

Subjects should remain on the same statin background therapy (drug and dose) with or without ezetimibe and other allowed lipid lowering therapy as taken at baseline from end of screening until the EOS **(see Sections 6.7 and 6.8)**. Before making any changes to a subject's prescription lipid-lowering therapy, the Amgen medical monitor or designee **(TIMI Study Group Hotline)** should be **consulted**, if possible. **If a change is made, the reason for the change must be provided in the eCRF.**

Allowed lipid lowering therapy, including drugs that may alter lipid levels should be stable for at least 2 weeks before final screening assessments and should remain constant through the study. Examples include: psyllium preparations including Metamucil® (> 2 tbs per day), plant stanols (such as Benecol), niacin, bile acid binding resins, fenofibrate (fenofibrate must be stable ≥ 6 weeks prior to final screening), or omega-3 fatty acids.

The use of antacids is not recommended within the period of 2 hours before and 2 hours after dosing with statins.

Subjects should adhere to the NCEP ATP III TLC diet or an equivalent diet. Subjects will be required to refrain from unaccustomed intensive exercise (eg, heavy lifting or long runs) 48 hours prior to each visit.

6.7 Prohibited Treatments During Study Period

The following treatments are not permitted during the study:

- other treatments for inhibition of PCSK9 than study provided investigational product
- mipomersen, lomitapide, fibrates and derivatives other than fenofibrate; fenofibrate therapy must be stable for at least 6 weeks prior to final screening at an optimized dose that is appropriate for the duration of the study
- all lipid therapies not taken at the time of assessing eligibility for enrollment into the FOURIER trial (Final Screening Visit), including any statins not listed in Appendix E, **with the exception of ezetimibe described below**.

In general, the lipid-lowering regimen should not be changed during the course of the study. Given results from the IMPROVE-IT study (Cannon et al, 2015) addition of ezetimibe after a subject experiences an acute coronary syndrome (ACS) on study may be considered. Please contact the Amgen medical monitor or designee

(TIMI Study Group Hotline) if **initiation of ezetimibe or** any **other** of **the above** therapies **is being considered** during the study. Note that **study staff should remain blinded to lipid results during the study and changes made to lipid therapy should not be made on the basis of unblinded lipid results. Additionally,** a change in lipid lowering background therapy does not necessarily require ending IP (except in case of non-study provided PCSK9 inhibition therapy) or changing the statin background therapy.

6.8 Non-recommended Treatments During Study Period

The treatments in Appendix F are not recommended because of their potential impact on metabolism of specific statins.

If a subject is enrolled and subsequently requires a treatment that is not recommended based on their particular statin (eg, a strong cytochrome P450 3A4 inhibitor in a patient on atorvastatin), the treating physician should give consideration to using an equivalent concomitant drug, eg, a drug that does not inhibit cytochrome P450 3A4 so that the subject can continue taking statin background therapy. If this is not possible, it may be necessary to withdraw or change statin background therapy while the concomitant drug is required.

There is no need to discontinue treatment with IP should a subject require a non-recommended drug, eg, a strong cytochrome P450 3A4 inhibitor since monoclonal antibody therapeutics are not metabolised through cytochrome P450 and, thus, are unaffected by the use of cytochrome P450 inhibitors.

7. STUDY PROCEDURES

7.1 General Study Procedures

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

- Screening, potential lipid therapy titration if needed, and placebo run-in period
- double-blind treatment and follow-up period

For the purpose of this study, a week is defined as 7 calendar days.

Written informed consent must be obtained and will be implemented before protocol specific procedures are carried out. The risks and benefits of participating in the study will be verbally explained to each potential subject prior to entering into the study. The study includes collection of biomarker samples**,** unless prohibited by local law or

regulations, and, where approved by the independent ethics committee and/or institutional review board (IEC/IRB) and applicable regulatory and other authorities, subjects will be invited to consent to pharmacogenetic analyses. The procedures to be performed at each clinic visit are described below and are summarized in Appendix A. If IP is administered during a study visit, administration must be after completion of vital signs, ECG, and blood draw procedures, as applicable.

Subjects must be fasting for ≥ 9 hours before each study visit where fasting laboratory samples are obtained. If the subject is not fasting for any screening visit or the day 1 visit, no laboratory samples should be collected and the subject must return as soon as possible in a fasting state for the visit. If the subject is not fasting for any visit with evaluation of lipids after study day 1, all visit procedures, including investigational product administration, should be completed except for the fasting lipid blood sample. Please make sure to schedule an extra visit for the fasting sample collection, if possible within the window for the respective visit. Note that procedures for any visit can be done on different calendar days within the respective visit window if necessary for scheduling or for convenience.

7.1.1 Screening, Lipid Therapy Titration, and Placebo Run-in Period

Subjects who are considered for entry into the study and have had the risk and benefits of participating in the study explained will either directly complete final screening (Section 7.1.1.3) and placebo run-in (Section 7.1.1.4) or will first enter lipid therapy titration. Screening or lipid therapy titration will start by signing and dating an informed consent form for this study. Patient history should be obtained by review of the subject's prior medical records or, if unavailable, by patient report (taking the subject's past medical history).

Subjects Entering Final Screening and Placebo Run-in Directly

Subjects entering screening already on optimized lipid lowering background therapy per Appendix E, considering the high risk patient population enrolled in FOURIER, with no change for the prior ≥ 4 weeks and with no change planned or expected for the duration of the study (up to approximately 5 years) can directly proceed to final screening. If eligible, these subjects can be enrolled in 2 visits.

Subjects Entering Lipid Therapy Titration

Subjects requiring change in their current lipid therapy will complete lipid therapy titration before proceeding to the final screening visit. This includes subjects wishing to switch to

study supplied atorvastatin from another statin and subjects requiring statin up-titration or any other changes to their lipid lowering background therapy. A separate consent form may be offered for entering screening and lipid therapy titration followed by a consent form for full study participation.

Once the lipid lowering therapy is optimized per Appendix E, the subject has to complete ≥ 2 weeks on this unchanged therapy before returning for the final screening visit and ≥ 4 weeks (including the prior 2 weeks) before randomization. The final screening visit laboratory assessments can be identified as the last lipid panel by central laboratory obtained on optimized therapy before randomization. Patients can be randomized ≥ 4 weeks after the last change in lipid therapy. No further changes should be planned or expected for the duration of the FOURIER study (up to approximately 5 years), even if the subject experiences a possible nonfatal endpoint event. *Note: 4 weeks of stable therapy can include the first day the final therapy has been initiated.*

7.1.1.1 Initial Titration Visit for Subjects Requiring Up-Titration or Switching of Their Lipid Lowering Therapy

The following subjects need to follow the up-titration/switching procedure:

1. Subjects who are not considered to be on optimal background lipid therapy and require a change in their lipid modifying medication
2. Subjects who desire to switch from a statin other than atorvastatin to study supplied atorvastatin
3. Subjects already on atorvastatin and wishing/requiring titration to a higher dose of study supplied atorvastatin to be considered optimally managed

After signing informed consent, these subjects will undergo initial screening procedures to confirm likely eligibility at the end of the titration phase, including laboratory evaluations and will enter a titration phase during which their non-study supplied statin or study supplied atorvastatin dose will be modified at intervals of 2 weeks until they are considered optimally managed (note that lipid levels are stable within 10 days after initiating or titrating atorvastatin [Stern et al, 2000]).

The following procedures will be performed at or before the initial titration visit:

- Written informed consent
- Medical history
- Vital signs (sitting BP, heart rate [HR])
- Review for AEs/SAEs (AEs possibly related to study procedures and SAEs are collected during screening and lipid therapy titration)
- Concomitant therapy

- Subject will be counseled on the importance of maintaining a "heart-healthy" diet throughout the course of the study
- Physical examination
- Blood draw for fasting lipids (≥ 9 hour fasting sample), chemistry (including fasting glucose), and hematology by central laboratory *(Note: eGFR will be calculated by the central laboratory and will be provided to the site for eligibility determination)*
- Subject will start or modify lipid background therapy including non-study supplied statin or study supplied atorvastatin per Appendix E and will be counseled on the value of compliance
- Consider placebo run-in as per Section 7.1.1.4 below (can be completed at any time before randomization)

7.1.1.2 Subsequent Titration Visits

The central laboratory or a local laboratory can be used for subsequent titration visit assessments. Subjects who are not eligible for the study based on laboratory results or for other reasons discovered after the initial titration visit will be screen failed unless they are retested as per Section 7.1.1.5 below. The dose of non-study supplied statin or study supplied atorvastatin can be adjusted and other changes made per Section 6.2 and Appendix E during titration to optimize lipid therapy. Lipid level assessments and study procedures can be repeated after treatment changes in order to achieve an optimal lipid therapy regimen for each subject. Titration visits can be scheduled as needed.

The following procedures will be performed during titration visits:

- Vital signs (see Section 7.1.5.1): sitting BP, heart rate (HR)
- Review for AEs/SAEs (AEs possibly related to study procedures and SAEs are collected during screening and lipid therapy titration)
- Concomitant therapy
- Blood draw for fasting lipids (≥ 9 hour fasting sample; sample can be analyzed locally or by central laboratory)
- Uptitrate non-study supplied statin or study supplied atorvastatin and dispense atorvastatin, if applicable, to achieve local treatment goal or optimized lipid lowering therapy (consider adding ezetimibe per local standard of care, if necessary to achieve treatment goal).
- Consider placebo run-in as per Section 7.1.1.4 below if not completed already (can be completed at any time before randomization)

7.1.1.3 Final Screening Visit

All subjects will undergo final screening, either entering directly or after lipid therapy titration. Laboratory assessments for the final screening visit will be by central laboratory. For randomization, laboratory values must be within eligibility criteria

(see Sections 7.1.1.5 and 7.1.1.6 for retesting and rescreening, respectively). Eligible subjects should be randomized and the day 1 visit scheduled at the appropriate time after final screening procedures as specified below.

The following procedures will be performed during final screening:

- Written informed consent for the FOURIER study, if not obtained previously
- Medical history / change to medical history
- Vital signs (sitting BP, heart rate [HR])
- Review for AEs/SAEs (AEs possibly related to study procedures and SAEs are collected during screening and lipid therapy titration)
- Concomitant therapy
- Physical examination, including neurological exam and Modified Rankin Scale to measure disability, if not done at a prior visit
- Body height, waist circumference (both can be obtained at any time during screening and baseline procedures; may be needed for cardiovascular risk assessment for eligibility)
- Body weight
- 12-lead ECG (sites who have been provided with centralized ECG services equipment specifically for this study will collect and transfer triplicate ECGs as instructed. All other sites will perform an ECG using local equipment and will file the printed ECG in the subject's medical records)
- Blood draw for fasting lipids (≥ 9 hour fasting sample), hsCRP, chemistry (including fasting glucose), hematology, TSH, T4, serum pregnancy (females of childbearing potential only) and FSH (only if required to ensure menopause in a female subject [see exclusion criterion 4.2.21]) by central laboratory *(Note: eGFR will be calculated by the central laboratory and will be provided to the site for eligibility determination)*
- Blood draws for hepatitis C virus (HCV) antibodies in subjects at high risk for, or with history of, HCV infection and in subjects with AST or ALT > 2x ULN at any time during screening[a]
- Urine sample for urinalysis
- Subject will be counseled on the importance of compliance and maintaining a "heart-healthy" diet throughout the course of the study
- Placebo run-in as per Section 7.1.1.4 below if not completed already (can be completed at any time before randomization)
- Subject will continue optimized lipid therapy as per Appendix E.

[a] High risk subjects are defined in Section 7.1.5.8.

Subjects with an LDL-C or non-HDL-C concentration eligible for study participation and who continue to meet all other eligibility criteria will be scheduled for treatment randomization and baseline (day 1) procedures as specified below.

7.1.1.4 Placebo Run-in

In order to reduce the burden of unnecessary procedures on subjects who subsequently elect not to participate in the study or continue with study procedures, all subjects will enter a placebo run-in period to confirm tolerance of SC administration prior to randomization. The placebo run-in consists of a one-time SC administration of 1 mL placebo by prefilled AI/Pen during the combined screening/lipid therapy titration/placebo run-in period. This placebo run-in can be administered at any visit during screening or lipid therapy titration but must be done before randomization. This injection will follow the same procedures as injections of IP during the treatment period. Further details will be provided in the IPIM.

7.1.1.5 Retesting

If, in the investigator's judgment, lab abnormalities are likely to be transient, (ie, subject participated in vigorous exercise and CK is elevated immediately afterwards), laboratory tests can be retested. Triglycerides, CK, and liver function and other laboratory values can be retested during screening as long as the subject can be evaluated for eligibility and randomized within the allowed screening period. Subjects with laboratory values outside of eligibility range who, in the opinion of the investigator, require major medication changes (eg, up-titration of blood pressure medications, up-titration of diabetes medications) can be put on a higher dose of medication and retested or rescreened after at least 1 month.

7.1.1.6 Rescreening

Subjects who screen fail due to the LDL-C and non HDL-C concentration below the limit for eligibility during final screening cannot be rescreened for this study. Subjects may not have their statins down-titrated to be rescreened except with documented intolerance to the statin dose.

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

7.1.1.7 Screen Fail

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

7.1.2 Randomization and Baseline Procedures (Day 1)

It is expected that all procedures up to randomization should be completed within approximately 15 weeks of first signing the informed consent.

Day 1 is defined as the day of first administration of IP. The date of first administration of IP will be recorded in IVRS/IWRS and will determine the schedule of subsequent study visits.

The first administration of IP should be as soon as possible after randomization but not later than within 5 calendar days.

Subjects who complete the screening, placebo run-in, and, if applicable, therapy titration procedures and continue to meet the inclusion/exclusion criteria will be randomized and will visit the study site for baseline procedures and treatment start with IP.

The following procedures will be performed for the day 1 visit:

- Randomization (can be done before the date of the visit but see time limitation above)
- Vital signs (sitting BP, HR)
- Review for AEs/SAEs/potential endpoints (PEPs)
- Review of concomitant therapy
- Encourage subject to maintain a “heart-healthy” diet
- Body weight
- Blood draw for fasting lipids (≥ 9 hour fasting sample), chemistry (including fasting glucose), hematology, HbA1c, anti-evolocumab antibodies, serum pregnancy (females of childbearing potential only), ApoA1, ApoB, Lp(a), biomarkers, hsCRP, and viral load in subjects positive for HCV antibody
- At sites with centralized ECG services equipment provided by sponsor for this study, additional blood draw for PK and PCSK9
- 12-lead ECG in triplicate (at sites with centralized ECG services equipment provided by sponsor for this study use this equipment to collect and transmit the ECG recordings)
- Urine samples for urinalysis and urine microalbumin
- Dispense statin (if applicable) and counsel on importance of treatment compliance (including ezetimibe and other allowed lipid therapy, if applicable)
- Administer IP (must be after completion of vital signs, ECG, and blood draw procedures; see Section 6.1.1 for instruction and supervision of subjects)

No additional blood will be collected for the pharmacogenetic analyses. For subjects who have consented to the pharmacogenetic portion of this study, deoxyribonucleic acid (DNA) will be extracted from blood samples already collected on day 1 or another visit (see Section 7.1.5.7 “Blood Sample Use” and Section 7.4.2 “Pharmacogenetic Studies”).

7.1.3 Treatment and Follow-up

Subjects will initiate treatment with IP at the Q2W or QM schedule and can switch between the 2 dosing regimens every 3 months, provided that the required approvals and supply of IP are available at the site. Subjects should be encouraged to provide advance notice of their preference to change the schedule to ensure the necessary supply is available at the site. Reasons for switching the IP administration regimen will be recorded in the eCRF.

Laboratory assessments are at week 4, week 12, and week 24, and then every 24 weeks. IP will be administered by prefilled AI/Pen or Personal Injector according to the Q2W or QM schedule during study visits and at other scheduled times generally at a location external to the study site. If agreed to by Amgen, additional visits may be scheduled to administer IP at the study site.

7.1.3.1 Week 2 Visit (± 3 Days)

The following procedures will be performed at the week 2 visit:

- Vital signs (sitting BP, HR)
- Review for AEs/SAEs/PEPs
- Review of concomitant therapy
- Encourage subject to maintain a “heart-healthy” diet
- Dispense statin (if applicable) and counsel on importance of treatment compliance (including ezetimibe and other allowed lipid therapy, if applicable)
- Administer IP (must be after completion of vital signs; see Section 6.1.1 for instruction and supervision of subjects) if subject is receiving IP Q2W

7.1.3.2 Week 4 Visit (± 3 Days)

The following procedures will be performed at the week 4 visit:

- Vital signs (sitting BP, HR)
- Review for AEs/SAEs/PEPs
- Review of concomitant therapy
- Encourage subject to maintain a “heart-healthy” diet
- Dispense statin (if applicable) and counsel on importance of treatment compliance (including ezetimibe and other allowed lipid therapy, if applicable)
- Blood draw for fasting lipids (≥ 9 hour fasting sample)
- Administer IP (must be after completion of vital signs and blood draw procedures; see Section 6.1.1 for instruction and supervision of subjects)
- Allocate/dispense IP (prefilled AI/Pens or Personal Injectors)

7.1.3.3 Week 12 Visit (± 5 Days)

The following procedures will be performed at the week 12 visit:

- Vital signs (sitting BP, HR)
- Review for AEs/SAEs/PEPs
- Review of concomitant therapy
- Encourage subject to maintain a “heart-healthy” diet
- Blood draw for fasting lipids (≥ 9 hour fasting sample), chemistry (including fasting glucose), hematology, ApoA1, ApoB, Lp(a), and viral load in subjects positive for HCV antibody
- At sites with centralized ECG services equipment provided by sponsor for this study:
  - additional blood draw for PK and PCSK9
  - collection and transmission of 12-lead ECG in triplicate
- Dispense statin (if applicable) and counsel on importance of treatment compliance (including ezetimibe and other allowed lipid therapy, if applicable)
- Reconcile used IP and allocate/dispense IP
- Administer IP (it is recommended to administer IP during the visit; if taken during visit, IP must be administered after completion of vital signs, ECG, if applicable, and blood draw procedures)

7.1.3.4 Week 24 Visit (± 5 Days)

The following procedures will be performed at the week 24 visit:

- Vital signs (sitting BP, HR)
- Review for AEs/SAEs/PEPs
- Review of concomitant therapy
- Encourage subject to maintain a “heart-healthy” diet
- Body weight
- Blood draw for fasting lipids (≥ 9 hour fasting sample), chemistry (including fasting glucose), **HbA1c,** hematology, ApoA1, ApoB, Lp(a), biomarkers, anti-evolocumab antibodies, serum pregnancy (females of childbearing potential only), and viral load in subjects positive for HCV antibody
- At sites with centralized ECG services equipment provided by sponsor for this study:
  - additional blood draw for PK and PCSK9
  - collection and transmission of 12-lead ECG in triplicate
- Urine sample for urinalysis
- Dispense statin (if applicable) and counsel on importance of treatment compliance (including ezetimibe and other allowed lipid therapy, if applicable)

- Reconcile used IP and allocate/dispense IP
- Administer IP (it is recommended to administer IP during the visit; if taken during visit, IP must be administered after completion of vital signs, ECG, if applicable, and blood draw procedures)

7.1.3.5 Week 36 Visit (± 7 Days)

The following procedures will be performed at the week 36 visit:

- Vital signs (sitting BP, HR)
- Review for AEs/SAEs/PEPs
- Review of concomitant therapy
- Encourage subject to maintain a “heart-healthy” diet
- Dispense statin (if applicable) and counsel on importance of treatment compliance (including ezetimibe and other allowed lipid therapy, if applicable)
- Reconcile used IP and allocate/dispense IP
- Administer IP (it is recommended to administer IP during the visit; if taken during visit, IP must be administered after completion of vital signs)

7.1.3.6 Week 48 Visit (± 7 Days)

The following procedures will be performed at the week 48 visit:

- Vital signs (sitting BP, HR)
- Review for AEs/SAEs/PEPs
- Review of concomitant therapy
- Encourage subject to maintain a “heart-healthy” diet
- Body weight
- Blood draw for fasting lipids (≥ 9 hour fasting sample), chemistry (including fasting glucose), hematology, hsCRP, ApoA1, ApoB, Lp(a), HbA1c, anti-evolocumab antibodies, serum pregnancy (females of childbearing potential only), and viral load in subjects positive for HCV antibody
- Urine sample for urinalysis and urine microalbumin
- Dispense statin (if applicable) and counsel on importance of treatment compliance (including ezetimibe and other allowed lipid therapy, if applicable)
- Reconcile used IP and allocate/dispense IP
- Administer IP (it is recommended to administer IP during the visit; if taken during visit, IP must be administered after completion of vital signs and blood draw procedures)

7.1.3.7 Q12W Visits (± 7 Days)

The following procedures will be performed for all subjects at Q12W visits until the end of the study:

- Vital signs (sitting BP, HR)
- Review for AEs/SAEs/PEPs
- Review of concomitant therapy
- Encourage subject to maintain a "heart-healthy" diet
- Dispense statin (if applicable) and counsel on importance of treatment compliance (including ezetimibe and other allowed lipid therapy, if applicable)
- Reconcile used IP and allocate/dispense IP
- Administer IP (it is recommended to administer IP during the visit; if taken during visit, IP must be administered after completion of vital signs and blood draw procedures, if applicable)

7.1.3.8 Q24W Visits (± 7 Days)

The following procedures will be performed for all subjects at Q24W visits until the end of the study, in addition to the Q12W visit procedures:

- Body weight
- Blood draw for fasting lipids (≥ 9 hour fasting sample), chemistry (including fasting glucose), **HbA1c,** hematology, serum pregnancy (females of childbearing potential only), and viral load in subjects positive for HCV antibody
- Urine sample for urinalysis

7.1.3.9 Q48W Visits (± 7 Days)

The following procedure will be performed for all subjects at Q48W visits until the end of the study, in addition to the Q12W and Q24W visit procedures:

- Blood draw for anti-evolocumab antibodies

7.1.4 End of Study (EOS) Visit

The study is event driven and will conclude when at least 1630 subjects have experienced a **key** secondary endpoint event of cardiovascular death, myocardial infarction, or stroke. Amgen will monitor the overall event rate and will set **a** date for **initiating end of** study **procedures** based on the anticipated date above. After the decision to end the study has been made, subjects will be scheduled for a final study visit (End of study [EOS] visit)**. If the EOS visit is less than** 30 days after the last received dose of IP**, the subject will be contacted (eg, by phone) at 30 days (+ 7 days) after last IP for safety follow-up unless the subject is enrolled in an Amgen extension study at that time**.

The following procedures will be performed at the EOS visits:

- Vital signs (sitting BP, HR)
- Review for AEs/SAEs/PEPs
- Review of concomitant therapy
- Physical exam, including neurological exam and Modified Rankin Scale to measure disability
- Body weight
- Blood draw for lipids (≥ 9 hour fasting sample), chemistry (including fasting glucose), hematology, ApoA1, ApoB, Lp(a), hsCRP, HbA1c, anti-evolocumab antibodies, serum pregnancy (females of childbearing potential only), biomarkers, for viral load in subjects positive for HCV antibody, and for HCV antibodies in subjects tested for HCV antibodies at screening but not found positive
- For subjects selected for centralized ECGs:
    - additional blood draw for PK and PCSK9
- Urine sample for urinalysis and urine microalbumin

At the end of the study, vital status must be obtained for all subjects within the limits of local law. This includes subjects who may have discontinued study visits with or without withdrawing consent and should include interrogation of public databases, if necessary. If deceased, the date and reported cause of death should be obtained

7.1.5 Standardization of Study Procedures

7.1.5.1 Measurement of Vital Signs

Blood pressure (BP) and heart rate (HR) will be measured at each visit. Use of an automated oscillometric device for BP measurement is preferred and recommended. BP will initially be recorded in both of the subject's arms unless a concomitant condition favors the use of a particular arm. The arm with the higher systolic reading at screening will then be used for BP determinations throughout the study. The appropriate size cuff should be used. BP and HR measurements will be determined after the subject has been seated for at least 5 minutes. The subject's pulse should be measured for 30 seconds and the number multiplied by 2 to obtain heart rate. Before randomization, BP measurement can be repeated if the previous reading is outside of the eligibility range. The repeat BP measure should be taken at least 2 minutes following the previous measure.

7.1.5.2 Waist Circumference

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

measurement, the lowest rib margin is first located and marked with a pen. The iliac crest is then palpated in the midaxillary line, and also marked. It is recommended to apply an elastic tape horizontally midway between the lowest rib margin and the iliac crest, and tie firmly so that it stays in position around the abdomen about the level of the umbilicus. The elastic tape thus defines the level of the waist circumference, which can then be measured by positioning the measuring tape over the elastic tape. Subjects are asked to breathe normally, and to breathe out gently at the time of the measurement to prevent them from contracting their muscles or from holding their breath. Measurements should be performed using the same procedure throughout the study. The reading is taken to the nearest centimeter or ½ inch and entered in the source document.

7.1.5.3 Concomitant Therapy

Targeted concomitant therapy and medications will be recorded on the CRF. The following groups of concomitant medications will be recorded:

- lipid lowering medications
- cardiovascular medications
- analgesics / antipyretics
- anticoagulants / antiplatelet
- antibiotics
- antidepressants
- vitamins
- hormone replacement therapy
- oral corticosteroids

7.1.5.4 Subject Compliance with Statin Dosing

The investigator (or designee) must instruct the subject on proper dosing of and compliance with taking background lipid therapy.

7.1.5.5 Electrocardiograms

ECGs will be collected centrally in approximately 5000 subjects at selected timepoints per Schedule of Assessments (Appendix A). At sites that have been provided with centralized ECG services equipment specifically for this study, this equipment will be used to acquire all protocol-specified ECGs and transmit them to the centralized ECG services provider. All other sites will perform an ECG at screening and day 1 only, using local equipment, and will file the printed ECG in the subject's medical records. If clinically indicated, additional ECGs may be performed.

The investigator 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/CRO to be manually read by a central reader.

Centrally collected ECGs only:

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

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

7.1.5.6 Lipid Measurements

Only the screening and other pre-randomization lipid concentrations will be reported to the site for background treatment and eligibility decision (note: in subjects undergoing therapy titration, the initial LDL-C and non-HDL-C levels obtained at initial titration visit do not determine eligibility). For subjects who are rescreened, data from the first screening period will not be used for the analysis. Central laboratory results of the lipid panel, as well as ApoA1, ApoB, lipoprotein(a), and high sensitivity C-reactive protein (hsCRP) will be blinded post-treatment until unblinding of the clinical database and will not be reported to the investigator post-screening. In addition, investigators and staff involved with this trial and all medical staff involved in the subject's medical care should refrain from obtaining lipid panels between randomization and at least 12 weeks after the subject's last administration of IP or the ends the study, whichever is later (to avoid potential unblinding). If a lipid panel is drawn, all reasonable steps must be undertaken to avoid informing the subject and study personnel of the results.

7.1.5.7 Blood Sample Use

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

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

7.1.5.8 Laboratory Assessments

All screening and on-study laboratory samples will be processed and sent to the central laboratory except as detailed for titration visits in Section 7.1.1.2. Amgen or designee will be responsible for 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 4 below outlines the specific analytes for serum chemistry, hematology, urinalysis, and other testing to be conducted.

Table 4. Analyte Listing

Chemistry	Coagulation	Urinalysis	Hematology	Other Labs
Sodium	PT/INR (per Appendix B)	Specific gravity	Hemoglobin	Fasting lipids
Potassium		pH	Hematocrit	Total cholesterol
Chloride		Blood	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		hsCRP
BUN or Urea		Casts		Lp(a)
Creatinine		Crystals		Anti-evolocumab antibodies
Uric acid				PCSK9
Total bilirubin				Evolocumab (PK)
Direct bilirubin				HbA1c
CK				Vitamin E (see Section 6.3)
ALP				Pregnancy test (females of childbearing potential)
LDH				FSH (if needed per exclusion 4.2.21)
AST (SGOT)				TSH
ALT (SGPT)				T4
				HCV antibody[a]
				HCV viral load[b]

[a]HCV antibodies are measured before initiating treatment with investigational product in subjects at high risk for, or with history of, HCV infection and in subjects with ALT or AST > 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
- Received clotting factors made before 1987
- Received blood/organs before July 1992 or were exposed to blood known to be infected with HCV
- Were ever on chronic hemodialysis
- Are known to be infected with HIV
- Have a known HCV-infected sexual partner

[b]Viral load will be tested at the time points indicated in Appendix A in subjects who are positive for HCV antibody.

Some laboratory results may inadvertently unblind investigators to treatment assignment to evolocumab. Central laboratory results of the lipid panel, ApoA1, ApoB, Lp(a), and hsCRP will not be reported to the investigator and will be blinded post-screening. Investigators will be informed if triglycerides are > 1000 mg/dL (11.3 mmol/L) so that appropriate subject follow-up can be initiated (see Section 6.3). Investigators should not perform non-protocol testing of these analytes during a subject's study participation from first administration of IP until at least 12 weeks after the subject's last administration of IP or the end of study, whichever is later.

7.1.5.9 Reporting Procedures for Potential Endpoints and Potential New Onset Diabetes

Events that **occur after randomization and up to the completed EOS visit and** are potential endpoints: all cause death, myocardial infarction, stroke, revascularization, hospitalization for unstable angina, hospitalization for heart failure and TIA will be reported only as PEPs in similar way as serious adverse events (Section 9.2.2) but will be identified by the investigator as PEP. These events must be recorded in the eCRF within 24 hours of knowledge of the event. Information regarding dates of onset and resolution, severity, action taken, investigator assessment of relatedness and assessment of seriousness will be collected. The DMC will be requested to follow the occurrence of these events to see if specific action needs to be taken during the course of the study. **I**f a reported PEP is negatively adjudicated (does not meet the definitions of an endpoint) **the event will be reclassified as AE or SAE and will be reported to regulatory agencies as required, if applicable.**

In addition to the potential endpoints above, potential new onset diabetes events – which will be identified based on elevated fasting blood glucose, elevated HbA1C, new adverse event related to hyperglycemia, or initiation of new medication for hyperglycemia – among study subjects not known to have pre-existing diabetes mellitus will be adjudicated to identify cases of new onset diabetes. Such events should be recorded in the eCRF within 24 hours of knowledge of the event. Information regarding the related patient medical history, medications, and local lab assessments will be collected. When such events are identified by Amgen or the CEC, investigators will be asked if they believe an adverse event of new onset diabetes should be reported and may be prompted for additional information.

7.2 Antibody Testing Procedures

Blood samples will be collected per Appendix A from all subjects 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.

7.3 Evolocumab Pharmacokinetic and PCSK9 Sampling

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

7.4 Biomarker Development and Pharmacogenetic Studies

7.4.1 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 14.5 mL of blood will be

collected from all subjects at each of the timepoints indicated in Section 7.1 and in Appendix A unless prohibited by local law or regulations. 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, and tumor necrosis factor (TNF) cellular adhesion molecules may be studied.

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

7.4.2 Pharmacogenetic Studies

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic 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.

7.4.3 Sample Storage and Destruction

These biomarker development samples and any other components from the cells may be stored for up to 20 years from the end of the study to research scientific questions related to cardiovascular disease, hyperlipidemia, other metabolic disorders, and/or evolocumab. The subject retains the right to request that the sample material be destroyed at any time by contacting the principal investigator. The sponsor will be the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the principal investigator or at the end of the storage period or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). Following the request from the subject, the principal investigator will provide the sponsor with the required study and subject numbers so that any remaining plasma and blood samples and any other components from the cells can be located and destroyed. If a commercial product is developed from

this research project, the sponsor will own the commercial product. The subject will have no commercial rights to such product and will have no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 11.3 for subject confidentiality.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

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

Subjects 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 (Appendix A) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments (Appendix A) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, indirect follow-up through family, friends, and/or healthcare providers, 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 tocontinue 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.

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(s) or procedural assessments include any of the following:

- subject request
- safety concern (eg, due to an adverse event, protocol deviation, non-compliance, requirement for alternative therapy, protocol-specified criteria (see Section 6.4), pregnancy)
- 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:

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

8.4 Replacement of Subjects

There will be no replacement for randomized subjects.

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of Adverse Events

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

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

than anticipated (ie, more than usual fluctuation of disease) during the study, or involves an intervention such as elective cosmetic surgery or a medical procedure while on study is not considered an adverse event.

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

9.1.2 Reporting Procedures for Adverse Events

Adverse events and serious adverse events (see Section 9.2) considered related to study procedures are reported after signing of the informed consent. All other adverse events are reported after randomization. The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent or randomization, as specified above, through the EOS are reported using the applicable eCRF (eg, Adverse Event Summary eCRF). The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution,
- Severity,
- Assessment of relatedness to **I**P
- Assessment of relatedness to the device (prefilled AI/Pen or Personal Injector), and
- Action taken.

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

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

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

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

The investigator must assess whether the adverse event, if reported during screening (AEs possibly related to study procedures and SAEs only), is possibly related to any study-mandated screening procedure. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may be related to screening procedures?"

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

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

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

Adverse events considered related to IP or any Amgen-provided protocol-required product or device will be followed until resolved, improved to baseline, or stabilized.

9.2 Serious Adverse Events

9.2.1 Definition of Serious Adverse Events

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

- 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 B for DILI reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

If adverse events correspond to grade 4 "life threatening" CTCAE grading scale criteria (eg, laboratory abnormality reported as Grade 4 without manifestation of life threatening status), it will be left to the investigator's judgment to also report these abnormalities as serious adverse events. For any adverse event that applies to this situation, comprehensive documentation of the event's severity status must be recorded in the subject's medical record.

9.2.2 Reporting Procedures for Serious Adverse Events

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

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

If the electronic data capture (EDC) system is unavailable to the site staff to report a 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 C for a sample of the electronic Serious Adverse Event Contingency Report Form. If the first notification of a serious adverse event is reported to Amgen via the eSerious Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

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

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

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

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

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

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

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

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

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IEC/IRBs in compliance with all reporting requirements according to local regulations and good clinical practice. The investigator should notify the appropriate IEC/IRB of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures and statutes.

9.3 Pregnancy and Lactation Reporting

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

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

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

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

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Subsets, and Covariates

10.1.1 Primary Endpoint

The primary endpoint is the time to cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary revascularization, whichever occurs first. (*Note: The primary endpoint includes all adjudicated strokes, ischemic and hemorrhagic.)*

10.1.2 Secondary Endpoints

The key secondary endpoint **is**:

- time to cardiovascular death, myocardial infarction, or stroke, whichever occurs first

Other secondary endpoints are:

- **time to cardiovascular death**
- time to death by any cause
- **time to first myocardial infarction**
- **time to first stroke**
- **time to first coronary revascularization**
- time to cardiovascular death or **first** hospitalization for worsening heart failure, whichever occurs first
- time to ischemic fatal or non-fatal stroke or TIA, whichever occurs first

10.1.3 Exploratory Endpoints

- **Time to coronary death**
- **Total number of events from the components of the primary endpoint (myocardial infarction, hospitalization for unstable angina, stroke, coronary revascularization, and cardiovascular death)**
- LDL-C response (LDL-C < 70 mg/dL [1.8 mmol/L]) at each scheduled assessment
- Change and percent change from baseline at each scheduled assessment in each of the following parameters:
  - LDL-C
  - total cholesterol
  - non-HDL-C
  - ApoB
  - total cholesterol/HDL-C ratio
  - ApoB/ApoA1 ratio
  - triglycerides
  - VLDL-C

  - HDL-C
  - ApoA1
  - Lp(a)
- PCSK9 change from baseline at each scheduled assessment
- HbA1C at each scheduled assessment
- hsCRP at each scheduled assessment

10.1.4 Safety Endpoints

- Subject incidence of treatment emergent adverse events
- Safety laboratory values and vital signs at each scheduled assessment
- ECG parameters (such as RR, PR, QRS, QT and QTc intervals) at each scheduled assessment
- Incidence of anti-evolocumab antibody (binding and neutralizing) formation

10.1.5 Pharmacokinetics Endpoints

- Serum concentration of evolocumab at selected time points

10.1.6 Analysis Sets

Efficacy Analysis Set

Efficacy analyses will be performed on the full analysis subject set (FAS), which is defined as all randomized subjects. All subjects will be analyzed according to their randomized treatment assignment.

Safety Analysis Set

Safety analyses will be performed on randomized subjects who received ≥ 1 dose of investigational product. For safety analyses, subjects will be grouped according to their randomized treatment group assignment with the following exception: if a subject receives treatment throughout the study that is different than the randomized treatment group assignment, then the subject will be grouped by the actual treatment group.

10.1.7 Baseline Covariates

Baseline covariates include, but are not limited to:

- Stratification factors of the final screening LDL-C level (< 85 mg/dL [2.2 mmol/L] vs ≥ 85 mg/dL) and geographical region
- Age: < 65 years, ≥ 65 years
- Sex
- Race
- Prior MI: < 2 years, ≥ 2 years
- Baseline PCSK9: < baseline median, ≥ baseline median

- Baseline LDL-C: < baseline median, ≥ baseline median
- Ezetimibe use at baseline: yes, no

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

10.2 Sample Size Considerations

The calculation of sample size is based on the **key** secondary endpoint in this study (triple composite of cardiovascular death, myocardial infarction, or stroke) and assumes a placebo event rate of approximately 2% per year (LaRosa et al, 2005; Cannon et al, 2004; de Lemos et al, 2004; Pedersen et al, 2005; SEARCH et al, 2010; Wiviott et al, 2007; Stone et al, 2011; Alberts et al, 2009; Baigent et al, 2011; MarketScan database [population; Thomson Reuters Healthcare Inc., Ann Arbor, MI 48018, USA]; United Health Care database [population; OptumInsight, Eden Prairie, MN 55344, USA), a 26-month enrollment period, and a total 3% of loss to follow-up rate over the study duration of approximately 56 months. The hazard ratio for the triple composite endpoint in this study design is assumed to be 0.8. It is an estimate based on the recent CTT Collaboration (2010) meta-analysis which assessed the relationship between LDL-C reduction and the cardiovascular events concluded that the relative risk decreases by 1% for every 1.8 mg/dL reduction in LDL-C. However, it is assumed that the attenuation of treatment effect will occur because of a 3-month treatment lag at the beginning of the trial and non-compliance of 10% per year during the course of the study. The overall type I error is controlled at a 0.05 significance level. After accounting for these factors, and based on a two-sided log-rank test of demonstrating the superiority of evolocumab over placebo, a total sample size of 27,500 subjects, with approximately 1630 subjects experiencing a **key** secondary endpoint event, is required to ensure approximately 90% power (Shih, 1995). Assuming an annualized event rate of approximately 4.5% and a hazard ratio of 0.8 for the primary endpoint, at the time of 1630 key secondary events observed among total of 27,500 subjects, there will be approximately 3550 primary events observed which will ensure a power of 99.8% to demonstrate superiority of evolocumab over placebo in the primary endpoint.

Based on the accumulating event rate in the pooled treatment groups, the sample size may be altered in order to complete the trial with at least 1630 key secondary events observed in approximately 56 months. Alternatively, Amgen may choose to lengthen the

study duration to ensure at least 1630 key secondary events observed and other assumptions are met.

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Individual subject treatment assignments will be maintained by the IVRS. Members of the Amgen study team will not have access to unblinded data until the study is unblinded for the final analysis. Any unplanned unblinding occurring during the study period will be documented and reported in the final clinical study report.

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

10.4 Interim Analysis and Early Stopping Guidelines

There is no planned interim analysis or stopping rule for efficacy or futility in this study. An external independent DMC has been established to formally review the accumulating data from this and other ongoing studies with evolocumab to ensure there is no avoidable increased risk for harm to subjects. The independent DMC is chaired by an external academic cardiologist who is an expert in lipids and clinical trials. Analyses for the DMC will be provided by the IBG, which is external to Amgen.

Details will be provided in the DMC charter.

10.5 Planned Methods of Analysis

10.5.1 General Approach/Considerations

The study will conclude when at least 1630 subjects have experienced a **key** secondary endpoint event of cardiovascular death, myocardial infarction, or stroke. At that time, the database will be cleaned, processed and a snapshot will be taken; the study will also be unblinded. Based on the snapshot, unless specified otherwise, efficacy analyses will be performed on the FAS by randomized treatment group; and safety analyses will be performed on the safety analysis set.

Subject disposition, demographics, baseline characteristics, and exposure to IP will be summarized.

All continuous variables will be summarized using descriptive statistics, including the number of observations (n), mean, standard deviation (SD), standard error (SE), median, the 1st (Q1) and 3rd (Q3) quartiles, minimum, and maximum. All categorical variables will be summarized using the number and percent of subjects.

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

All deaths and components of primary and secondary endpoints (myocardial infarction, stroke, revascularization, hospitalization for unstable angina, hospitalization for heart failure, and TIA) will be adjudicated by an independent external Clinical Events Committee (CEC), using standardized definitions. **In addition, new onset diabetes will be adjudicated by the same CEC.** The CEC is external to Amgen and primarily comprises both academic clinical physicians (to include cardiologists) and medical reviewers trained on the clinical trial protocol, the CEC charter, and CEC processes. The chairman of the CEC is responsible for overseeing the operations in conformance with the CEC charter and for supervising the flow of data between the sponsor/data management and the CEC. Committee members are qualified in the appropriate subspecialty and free of conflict of interest. The CEC is blinded to treatment allocation and reviews events according to pre-specified criteria defined in the CEC charter.

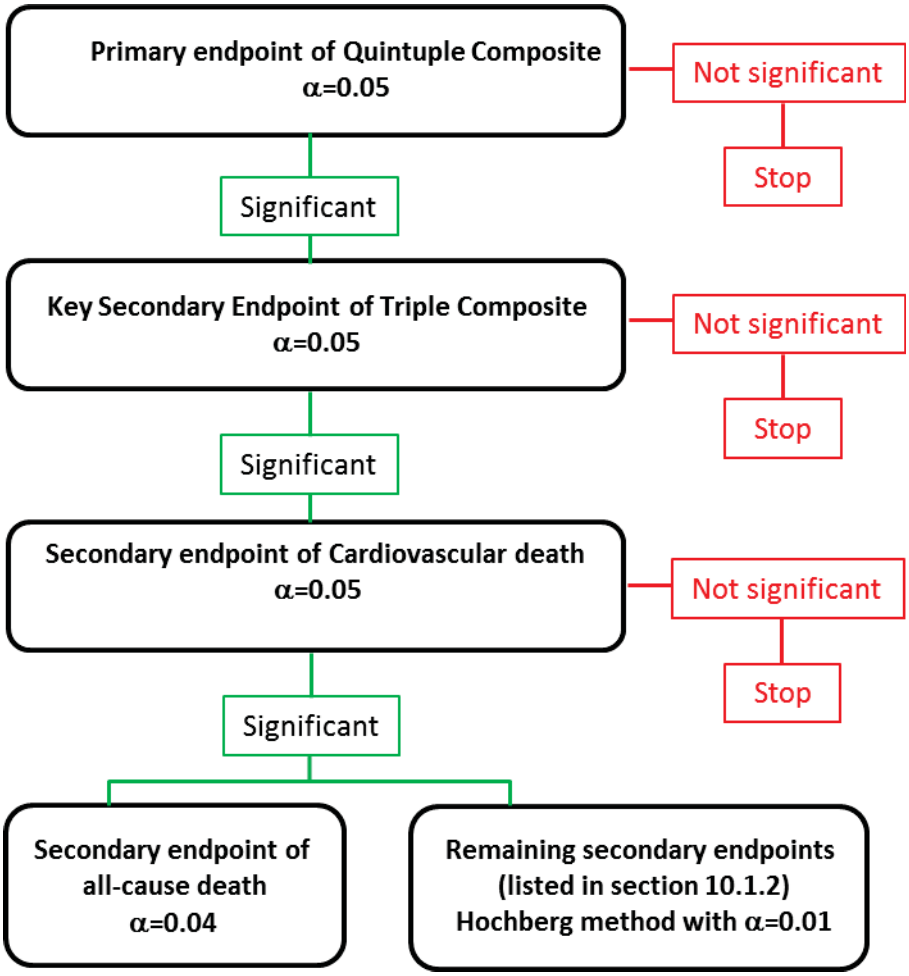
Multiplicity Adjustment Method

In order to preserve the overall type I error rate at 0.05 in the final analysis of the primary and secondary endpoints, the following multiplicity adjustment approach will be applied: The primary endpoint (quintuple composite of cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, and coronary revascularization) will be compared by the treatment groups at a significance level of 0.05. If the primary endpoint reaches statistical significance at the 0.05 level, the **key** secondary endpoint (triple composite of cardiovascular death, myocardial infarction, and stroke) will be tested at a significance level of 0.05. If the **key** secondary endpoint reaches statistical significance level of 0.05, then the **endpoint of cardiovascular death will be tested at a significance level of 0.05. If the endpoint of cardiovascular death reaches statistical significance level of 0.05, the following testing will be conducted in**

parallel under the Bonferroni split:

- The **endpoint of all-cause death will be tested at a significance level of 0.04.**
- **Other remaining** secondary endpoints (time to **first myocardial infraction, time to first stroke, time to first coronary revascularization**, time to cardiovascular death or first hospitalization for worsening heart failure, and time to fatal or non-fatal ischemic stroke or TIA) will be tested at an overall significance level of 0.01 applying the Hochberg method (Hochberg, 1988).

No multiplicity adjustment will be used for exploratory or sensitivity analyses. The multiplicity adjustment **for primary and secondary endpoints** is shown in the following flowchart:



10.5.2 Analysis of Key Study Endpoints

10.5.2.1 Efficacy Endpoints

10.5.2.1.1 Primary Endpoint

The primary endpoint is the time to cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, and coronary revascularization, whichever occurs first. The primary analysis for this endpoint will employ the intent-to-treat (ITT)

principle and use a survival analysis. For each treatment group, Kaplan-Meier (K-M) curves will be estimated and graphically displayed. The 2 survival functions will be compared using a 2-sided log-rank test stratified by randomization stratification factors. K-M estimates and 95% CIs will be calculated by randomized treatment for event time quartiles. The hazard ratio and its corresponding 95% CI will be estimated from a stratified Cox model, stratified by the randomization stratification factors.

Subjects not experiencing a qualifying event during the study will be censored at their **EOS** date.

Covariate analyses of the primary endpoint using Cox model will be performed as sensitivity analysis. Baseline covariates listed in Section 10.1.7 will be included in the model one at a time. If applicable, subgroup analyses on the primary endpoint will be conducted using the stratification factors and baseline covariates. Sensitivity analyses will be conducted using all-cause death in place of CV death in the composite endpoint. The proportional hazards assumption in the Cox model will be assessed. A piecewise Cox model with pre-defined intervals will be considered given evidence of non-proportional hazards.

10.5.2.1.2 Secondary Endpoint

Secondary endpoints will be analyzed as per primary **analysis of the primary** endpoint. **For analyses of mortality endpoints (time to cardiovascular death and time to death by any cause), subjects not experiencing a qualifying event during the study will be censored at their last confirmed alive date or end of study date, whichever occurs later.**

10.5.2.1.3 Exploratory Endpoints

Exploratory endpoints are **time to coronary death, total number of events from the components of the primary endpoint, and** measurement**s** of lipid parameters listed in Section 10.1.3. **Time to coronary death will be analyzed in the same way as secondary mortality endpoints. Summary statistics for the total number of primary endpoint events will be provided. For lipid parameters, t**he repeated measures linear mixed effects model will be used and will include terms for treatment group, stratification factors, scheduled visit and the interaction of treatment with scheduled visit. Missing values will not be imputed when the repeated measures linear mixed effects model is used. Summary statistics of change and percent change of lipid parameters from baseline will be provided. Subgroup and covariate analyses will be performed, if applicable.

10.5.2.2 Safety Endpoints

Adverse Events

Adverse events will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Subject incidence rates of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, and adverse events leading to withdrawal from investigational product or from study also will be provided.

Safety Laboratory Parameters

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

Vital Signs

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

Electrocardiogram

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

Concomitant Medications

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

Anti-evolocumab antibodies

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

10.5.3 Additional Analyses

Exposure to Investigational Product

Exposure to IP will be summarized for each treatment group.

Pharmacokinetics Endpoints

Pharmacokinetics endpoints will be summarized for each treatment group.

Adjudicated **Cardiovascular** Events

All adjudicated **cardiovascular** events will be summarized for each treatment group.

Adjudicated New Onset Diabetes

All adjudicated cases of new onset diabetes will be summarized for each treatment group.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial generic 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 will be communicated by letter from the Amgen study manager to the investigator. The written informed consent document should be prepared in the language(s) of the potential patient population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any IPs are administered. Where permitted, a separate consent form may be offered for entering screening and lipid therapy titration only, followed by a consent form for full study participation for eligible subjects.

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

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

11.2 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent

form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen IP.

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

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

11.3 Subject Confidentiality

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

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

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

11.4 Pharmacogenetics Confidentiality (for Subjects who Sign a Separate Consent Only)

All pharmacogenetics samples will be no less than single coded prior to their being utilized. Similarly, all results will be no less than single coded and stored in a secure database to ensure confidentiality while enabling destruction of the samples when requested. Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results will not be placed in the subject's medical records

and will 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.

11.5 Investigator Signatory Obligations

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

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

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

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

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

12.2 Study Documentation and Archive

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

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

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

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

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

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

12.3 Study Monitoring and Data Collection

The Amgen representative 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, eCRFs and other pertinent data) provided that subject confidentiality is respected.

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

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

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

Data capture for this study is planned to be electronic:

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

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

12.4 Investigator Responsibilities for Data Collection

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

12.5 Language

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

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

12.6 Publication Policy

To coordinate dissemination of data from this study, a publication committee will be formed. The governance, responsibilities, and membership will be set forth in a Publication Charter. The Publication Committee core will consist of the Executive Committee and appropriate Amgen staff. The committee will solicit input and assistance from other investigators and will collaborate with authors and Amgen staff as defined in the Publication Committee Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship—the criteria described below should be met for every publication.

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

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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

12.7 Compensation

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

13. REFERENCES

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

Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation.* 2009;120:1640-1645.

Alberts MJ, Bhatt DL, Mas JL, et al. Three-year follow-up and event rates in the international REduction of Atherothrombosis for Continued Health Registry. *Eur Heart J.* 2009;30:2318-2326.

Allender S, Scarborough P, Peto V, Rayner M, Leal J, Luengo-Fernandez R and Gray A. European Cardiovascular Disease Statistics 2008 Edition.

Amarenco P, Bogousslavsky J, Callahan A 3rd., et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355:549-559.

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

Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet.* 2011;377:2181-2192.

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

Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO study. *Cardiovasc Drugs Ther*. 2005;19:403-414.

Califf RM, Lokhnygina Y, Cannon CP, et al. An update on the IMProved reduction of outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) design. *Am Heart J.* 2010;159:705-709.

Cannon CP, Blazing MA, Giugliano RP, et al. for the IMPROVE IT Investigators. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med*. 2015;372:2387-2397

Cannon CP, Braunwald E, McCabe CH, et al. Pravastatin or atorvastatin evaluation and infection therapy-thrombolysis in myocardial infarction 22 investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495-1504.

Cannon CP, Giugliano RP, Blazing MA, et al. Rationale and design of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimbe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes. *Am Heart J.* 2008;156:826-832.

Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670-1681.

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.

Collins R, Armitage J, Parish S, Sleight P, Peto R; Heart Protection Study Collaborative Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. Lancet. 2004;363:757-767.

de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA. 2004;292(11):1307-1316.

Franc S, Dejager S, Bruckert E, Chauvenet M, Giral P, Turpin G. A comprehensive description of muscle symptoms associated with lipid-lowering drugs. *Cardiovasc Drugs Ther*. 2003;17:459-465.

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

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

Hackam DG, Woodward M, Newby LK, et al. Statins and intracerebral hemorrhage: collaborative systematic review and meta-analysis. *Circulation.* 2011;124:2233-2242.

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

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

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

Iso H, Jacobs DR Jr, Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. *N Engl J Med*. 1989;320:904-910.

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

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

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

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

LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352:1425-1435.

Libby P. The forgotten majority: unfinished business in cardiovascular risk reduction. *J Am Coll Cardiol*. 2005;46 :1225-1228.

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

Newman C, Tsai J, Szarek M, Luo D, Gibson E. Comparative safety of atorvastatin 80 mg versus 10 mg derived from analysis of 49 completed trials in 14,236 patients. *Am J Cardiol.* 2006;97:61-67.

Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA*. 2005;294:2437-2445.

Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA*. 2011;305:2556-2564.

Raal F, Scott R, Somaratne R, et al. Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia: the Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) randomized trial. *Circulation.* 2012;126:2408-2417.

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

Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet*. 2010;375:735-742.

Shih JH. Sample size calculation for complex clinical trials with survival endpoints. *Control Clin Trials.* 1995;16:395-407

Stern RH, Yang BB, Hounslow NJ, MacMahon M, Abel RB, Olson SC. Pharmacodynamics and pharmacokinetic-pharmacodynamic relationships of atorvastatin, an HMG-CoA reductase inhibitor. *J Clin Pharmacol*. 2000;40:616-623.

Stone GW, Witzenbichler B, Guagliumi G, et al. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial. *Lancet.* 2011;377:2193-2204.

Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group, Armitage J, Bowman L, et al. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin QD in 12,064 survivors of myocardial infarction: a double-blind randomised trial. *Lancet.* 2010;376:1658-1669.

Sullivan D, Olsson AG, Scott R, et al. Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients: the GAUSS randomized trial. *JAMA*. 2012;308:2497-2506.

Taylor F. Ward K. Moore TH. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2011;CD004816.

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.

Waters DD, LaRosa JC, Barter P, et al. Effects of high-dose atorvastatin on cerebrovascular events in patients with stable coronary disease in the TNT (treating to new targets) study. *J Am Coll Cardiol.* 2006;48:1793-1799.

Weart CW. Hogan RJ. Event reduction: revisiting why we treat with statins and harnessing current evidence towards optimal therapy. *Expert Opin Pharmacother*. 2011;12:99-117.

Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001-2015.

World Health Organization. Global Atlas on Cardiovascular Disease Prevention and Control. Mendis S, Puska P, Norrving B editors. Geneva 2011; http://www.who.int/cardiovascular_diseases/publications/atlas_cvd/en/

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

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

14. APPENDICES

Appendix A. Schedule of Assessments

Timepoint/Frequency[a]	Initial Titration	Titration[b]	Final Screen Pbo Run-in	Rand. D1	W2	W4	W12	W24	W36	W48	Q12W	Q24W	Q48W	EOS
General Procedures														
Informed consent	X		X											
Medical history	X		X											
Vital Signs (sitting BP, HR)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review for AEs/SAEs/PEPs	X[c]	X[c]	X[c]	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dietary instruction	X		X	X	X	X	X	X	X	X	X	X	X	
Physical exam; neurological exam and Modified Rankin at final screen & EOS	X		X											X
Body height, waist circumfer.			X											
Body weight			X	X				X		X		X	X	X
12 lead ECG			X	X			X[d]	X[d]						
Randomization				X										
Central Laboratory[e]														
Fasting lipids	X	X	X	X		X	X	X		X		X	X	X
PK[f], PCSK9				X[d]			X[d]	X[d]						X[d]
ApoA1, ApoB, Lp(a)				X			X	X		X				X
hsCRP			X	X						X				X

[a] D1 = day of first administration of IP; for visit windows see Section 7 of the protocol**; If the EOS visit is < 30 days after last IP, the subject will be contacted (eg, by phone) at 30 days (+ 7 days) after last IP for safety follow-up unless the subject is enrolled in an Amgen extension study at that time**

[b] Titration visits can be repeated as needed for optimizing lipid therapy; local or central laboratory can be used

[c] Only AEs possibly related to study procedures and SAEs are collected during the screening period

[d] Only at sites that have been provided with centralized ECG services equipment ; see Section 7

[e] If the subject consented to pharmacogenetics analyses, DNA will be extracted from some of the blood samples, eg, biomarker samples

[f] PK samples must be taken prior to IP administration, if applicable

[g] T4 only tested if TSH < LLN or > 1.5x ULN

[h] HCV antibodies only in high risk subjects (see Section 7.1.5.8), subjects with a positive history of HCV infection, or if ALT or AST > 2x ULN at any time during screening; viral load only in subjects positive for HCV antibody

[i] Serum pregnancy in females of childbearing potential, FSH only at screening if needed (exclusion 4.2.21)

[j] Placebo run-in is a 1-time administration of 1 mL of placebo and can be done at any visit during screening or lipid therapy titration

[k] Includes counseling on the importance of statin dosing/dispensation if applicable; uptitrate during therapy titration if necessary, discuss compliance at each visit

[l] Subjects initiate treatment at the Q2W or QM schedule and can switch every 3 months between Q2W and QM, provided the appropriate approvals and supply of IP are available. IP can be kept at site if administered in office. IP administration at week 2 only if on Q2W schedule.

Appendix A. Schedule of Assessments

Timepoint/Frequency[a]	Initial Titration	Titration[b]	Final Screen Pbo Run-in	Rand. D1	W2	W4	W12	W24	W36	W48	Q12W	Q24W	Q48W	EOS
Central Laboratory[e]														
Biomarkers (blood)				X				X						X
Chemistry, fasting glucose	X		X	X			X	X		X		X	X	X
Hematology	X		X	X			X	X		X		X	X	X
TSH, T4[g]			X											
HbA1c				X				**X**		X		**X**		X
Anti-evolocumab antibodies				X				X		X			X	X
HCV antibodies[h]			X											X
HCV viral load[h]				X			X	X		X		X	X	X
Serum pregnancy, FSH[i]			X	X				X		X		X	X	X
Urinalysis (w. microscopic)			X	X				X		X		X	X	X
Urine microalbumin				X						X				X
Investigational Product														
Placebo run-in[j]	(X)	(X)	(X)											
Statin instruction/dispensation[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	
IP in-office administration[l]				X	X[l]	X	X	X	X	X	X	X	X	
IP dispense/reconcile[l]						X	X	X	X	X	X	X	X	

[a]D1 = day of first administration of IP; for visit windows see Section 7 of the protocol**; If the EOS visit is < 30 days after last IP, the subject will be contacted (eg, by phone) at 30 days (+ 7 days) after last IP for safety follow-up unless the subject is enrolled in an Amgen extension study at that time**

[b]Titration visits can be repeated as needed for optimizing lipid therapy; local or central laboratory can be used

[c]Only AEs possibly related to study procedures and SAEs are collected during the screening period

[d]Only at sites that have been provided with centralized ECG services equipment ; see Section 7

[e]If the subject consented to pharmacogenetics analyses, DNA will be extracted from some of the blood samples, eg, biomarker samples

[f]PK samples must be taken prior to IP administration, if applicable

[g]T4 only tested if TSH < LLN or > 1.5x ULN

[h]HCV antibodies only in high risk subjects (see Section 7.1.5.8) , subjects with a positive history of HCV infection, or if ALT or AST > 2x ULN at any time during screening; viral load only in subjects positive for HCV antibody

[i]Serum pregnancy in females of childbearing potential, FSH only at screening if needed (exclusion 4.2.21)

[j]Placebo run-in is a 1-time administration of 1 mL of placebo and can be done at any visit during screening or lipid therapy titration

[k]**Includes** counseling on the importance of statin dosing/dispensation if applicable; uptitrate during lipid therapy titration if necessary, discuss compliance at each visit

[l]Subjects initiate treatment at the Q2W or QM schedule and can switch every 3 months between Q2W and QM, provided the appropriate approvals and supply of IP are available. IP can be kept at site if administered in office. IP administration at week 2 only if on Q2W schedule.

Appendix B. Additional Safety Assessment Information

Adverse Event Toxicity Grading Scale

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

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

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

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST/ALT and TBL elevation or INR elevation according to the criteria specified in Section 6.4 (3x ULN for AST/ALT and 2x ULN for TBL or INR > 1.5) require the following:

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

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

Additional Clinical Assessments and Period of Close Observation

All subjects in whom IP and/or background lipid therapy is withheld due to potential DILI or who experience AST/ALT elevations >3x ULN should undergo a period of “close

observation" until abnormalities return to normal or to the subject's baseline levels.

Assessments that should be performed during this period include:

- Repeat liver chemistries within 24-48 hours (ALT, AST, ALP, TBL); in cases of TBL > 2x ULN or AST/ALT much greater than 3x ULN, retesting should be performed within 24 hours
  - Subjects should be monitored at least twice weekly; testing frequency may decrease to once per week or less if laboratory abnormalities stabilize or the IP has been discontinued AND the subject is asymptomatic
- Obtain PT/INR, fractionated bilirubin and any other potentially relevant laboratory evaluations of liver function or disease
- Obtain complete blood count (CBC) with differential to assess for eosinophilia
- Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Obtain a more detailed history of:
  - Prior and/or concurrent diseases or illness
  - Exposure to environmental and/or industrial chemical agents
  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - Prior and/or concurrent use of alcohol, recreational drugs and special diets
  - Concomitant medications (including non-prescription medicines & herbal and dietary supplements)
- Initiate full viral and autoimmune hepatitis evaluation (serologies for hepatitis A,B,C, D, E, Epstein-Barr Virus, Herpes Simplex Virus, etc); evaluate for other potential causes of DILI including but not limited to: NASH, hypoxic/ischemic hepatopathy, and biliary tract disease
- Obtain gastroenterology or hepatology consult
- Perform appropriate liver imaging or biopsy if clinically indicated; strongly consider these tests in cases of concurrent transaminase and TBL elevation as specified in Section 6.4.
- Follow the subject until all laboratory abnormalities return to baseline or normal. The "close observation period" should continue for a minimum of 4 weeks after drug discontinuation.

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

Appendix C. Sample eSerious Adverse Event Contingency Reporting Form

AMGEN Study # 20110118 AMG 145	Electronic Serious Adverse Event (eSAE) Contingency Reporting Form **For Restricted Use**

Complete either Section A *or* Section B and follow the instructions provided:

Section A

EDC system (eg, Rave) is active for this study but is not accessible to allow reporting within 24 hours of the Investigator's knowledge of the event. I am submitting (check/complete all that apply):

An event that applies to a specialty CRF page titled _____ (eg, clinical fracture)

Screening event (as defined by the protocol) | OR | On-study event (as defined by the protocol)

- *Complete ONLY Sections 1, 2 and 3 (page 1)*
- *Sign and date the signature section following Section 3*
- *Fax completed page of the form to the number noted in the header above Section 1*

Section B

Access to the EDC system (eg, Rave) has either not begun or has ended for this study. I am submitting (check all that apply):

Screening event (as defined by the protocol)
- This is a new event report
- This is follow-up information for a previously reported event

OR

Event after access to the EDC system (eg, Rave) has ended (*provide subject's End of Study date in Section 2*)
- This is a new event report
- This is follow-up information for a previously reported event

- *Complete ALL sections of the form (all 3 pages)*
- *Sign and date the signature section at the end of the form*
- *Fax completed form (all 3 pages) to the number noted in the header above Section 1*

<<For completion by Amgen 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	Date of Birth	Sex	Race	If applicable, provide End of Study date
	Day Month Year	☐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 Serious Adverse Event Information: Day____ Month____ Year_____

Serious Adverse Event Diagnosis or Syndrome **If diagnosis is unknown, enter Signs / Symptoms** **When Final Diagnosis is known, enter as Adverse Event** *List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.*	**Date Started** Day Month Year	**Date Ended** Day Month Year	Check only if event occurred before first dose of IP	**Enter Serious Criteria code** *(see codes below)*	**Relationship** Is there a reasonable possibility that the event may have been caused by IP?		**Relationship** Is there a reasonable possibility that the event may have been caused by an Amgen device?			**Outcome of Event** Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy
					No✓	Yes✓	No✓	Yes✓	If yes, what device?		

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

If you temporarily cannot access the EDC system (eg, Rave), sign below and submit ONLY this page to the number noted in the header above Section 1.

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.*		

FORM-056006 Page 1 of 3 ***Version 3.0 Effective Date 04-FEB-2013***

AMGEN Study # 20110118 AMG 145	Electronic Serious Adverse Event (eSAE) Contingency Reporting Form **For Restricted Use**

If **access to the EDC system (eg, Rave) has either not begun or has ended for this study, *complete the remainder of this form.***

Site Number	Subject ID Number

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

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

IMP: _____ ☐ (✓) Blinded ☐ (✓) Open Label	Initial Start Date Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld

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

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

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 # 20110118 AMG 145	Electronic Serious Adverse Event (eSAE) Contingency Reporting 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 D. 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: _____

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: _____

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: 03 April 2012, version 2.

Page 1 of 1

Appendix E. Acceptable Lipid Lowering Background Therapy

Background lipid lowering therapy should be optimized for the individual subject consistent with local professional society guidelines. At randomization, all subjects must receive at least an effective statin dose, ie, at least atorvastatin 20 mg daily or equivalent. Where locally approved, highly effective statin therapy, defined as at least atorvastatin 40 mg daily or equivalent, is recommended. For subjects with LDL-C > 100 mg/dL (> 2.6 mmol/L) and not receiving highly effective statin therapy (atorvastatin ≥ 40 mg daily or equivalent), the investigator must attest that higher dose statin therapy is not appropriate for this subject (eg, subject refused, dose not tolerated, dose not available in that country, other significant concern).

Background Statin	Atorvastatin	Simvastatin	Rosuvastatin	Pitavastatin
Acceptable doses	*20 mg*[a] 40 mg[b] 80 mg[b]	*40 mg*[a] 80 mg[b,c]	*5 mg*[a] 10 mg[b] 20 mg[b] 40 mg[b]	*4 mg*[a]

[a]For subjects enrolled with LDL-C > 100 mg/dL, confirmation is required that the selected dose of statin therapy was optimized and is appropriate for the duration of the study.
[b] Highly effective therapy includes atorvastatin 40 mg or 80 mg, rosuvastatin 10 mg, 20 mg or 40 mg, and simvastatin 80 mg monotherapy. In addition, any of the above statin doses administered in combination with ezetimibe would qualify as highly effective therapy.
[c] Use of simvastatin 80 mg was associated with myopathy and is not commonly recommended for use. Simvastatin 80 mg is not available in all countries participating in this study. Approval of simvastatin 80 mg by the local regulatory authority is required for patients using simvastatin 80 mg in this study.

Protocol Section 7.1.1 must be followed for screening, lipid therapy titration, and placebo run-in before randomization. No statins other than the ones listed above **should be used** during study participation. No other lipid therapy is required for the FOURIER trial. Ezetimibe and other commercially available lipid therapy at dosages approved by local regulatory authorities may be added to any of these regimens except excluded medication as per Protocol Section 6.7. These therapies, and statins other than atorvastatin, are not provided or reimbursed by Amgen (except if required by local regulation). Background lipid lowering therapy received at randomization should**, in general,** remain unchanged throughout the entire duration of the study (**see Section 6.7 for further details**).

Appendix F. Drugs With Known Major Interactions With Statin Background Therapy

Atorvastatin:

- strong Cyp3A4 inhibitors (eg, Itraconazole, ketoconazole, and other antifungal azoles, erythromycin, clarithromycin, telithromycin, HIV or HCV protease inhibitors, systemic cyclosporine nefazodone and grapefruit juice in large quantities [> 1 quart or approximately 1 Liter daily])

Simvastatin:

- strong Cyp3A4 inhibitors (eg, Itraconazole, ketoconazole, and other antifungal azoles, erythromycin, clarithromycin, telithromycin, HIV or HCV protease inhibitors, systemic cyclosporine nefazodone and grapefruit juice in large quantities [> 1 quart or approximately 1 Liter daily])
- verapamil
- diltiazem
- danazol
- If simvastatin > 20 mg
    - amlodipine
    - amiodarone
    - ranolazine

Rosuvastatin:

- systemic cyclosporine
- and if rosuvastatin > 10 mg, HIV or HCV protease inhibitors

Pitavastatin:

- systemic cyclosporine
- erythromycin
- rifampin

Note: There is no need to discontinue treatment with IP should a subject require a strong cytochrome P450 3A4 inhibitor since monoclonal antibody therapeutics are not metabolised through cytochrome P450 and, thus, are unaffected by the use of cytochrome P450 inhibitors.