Title: A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Safety and Efficacy of Evolocumab (AMG 145) in addition to Optimal Stable Background Statin Therapy in Chinese Subjects with Primary Hypercholesterolemia and Mixed Dyslipidemia

Amgen Protocol Number (Evolocumab) 20150172

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Investigator's Agreement

I have read the attached protocol entitled, "A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Safety and Efficacy of Evolocumab (AMG 145) in addition to Optimal Stable Background Statin Therapy in Chinese Subjects with Primary Hypercholesterolemia and Mixed Dyslipidemia", dated 06 June 2016, 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 sub investigators (including, if applicable, their spouses [or legal partners] and dependent children)

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

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

Signature

Name of Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Safety and Efficacy of Evolocumab (AMG 145) in addition to Optimal Stable Background Statin Therapy in Chinese Subjects with Primary Hypercholesterolemia and Mixed Dyslipidemia

Study Phase: 3

Indication: Primary Hypercholesterolemia and mixed dyslipidemia

Primary Objective: To evaluate the effect of 12 weeks of subcutaneous (SC) evolocumab every 2 weeks or every 4 weeks, compared with placebo, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) when used in addition to optimal stable background statin therapy in Chinese subjects with primary hypercholesterolemia and mixed dyslipidemia.

Secondary Objective(s): To evaluate the effect of 12 weeks of SC evolocumab Q2W or QM, compared with placebo, on change from baseline in LDL-C, achievement of target LDL-C < 70 mg/dL (1.8 mmol/L), LDL-C response (50% reduction of LDL-C from baseline) and percent change from baseline in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol, lipoprotein(a) [Lp(a)], triglycerides, HDL-C, very low-density lipoprotein cholesterol (VLDL-C) when used in addition to optimal stable background statin therapy in Chinese subjects with primary hypercholesterolemia and mixed dyslipidemia.

Hypotheses: The hypothesis is the dosing regimens of evolocumab SC 140 mg Q2W and 420 mg QM will be well tolerated and will result in greater reduction of LDL-C, as defined by the mean percent change from baseline at weeks 10 and 12 and percent change from baseline at week 12, than placebo when used in combination with optimal stable background statin therapy in Chinese subjects with primary hypercholesterolemia and mixed dyslipidemia.

Co-Primary Endpoints:

- Mean percent change from baseline in LDL-C at weeks 10 and 12
- Percent change from baseline in LDL-C at week 12

Secondary Endpoint(s):

- The mean of weeks 10 and 12 and for week 12 for the following:

Tier 1:

- Change from baseline in LDL-C
- Percent change from baseline in non-HDL-C
- Percent change from baseline in ApoB
- Percent change from baseline in total cholesterol
- Achievement of target LDL-C < 70 mg/dL (1.8 mmol/L)
- LDL-C response (50% reduction of LDL-C from baseline)

Tier 2:

- Percent change from baseline in Lp(a)
- Percent change from baseline in triglycerides
- Percent change from baseline in HDL-C
- Percent change from baseline in VLDL-C

Study Design: This is a phase 3, multicenter, double-blind, randomized, placebo-controlled study of evolocumab in Chinese subjects with hypercholesterolemia and mixed dyslipidemia. Subjects who have signed the informed consent form (ICF), will have fasting lipids measured and all inclusion and exclusion criteria assessed. Subjects should maintain their current diet and exercise regimen. Subjects who, in the opinion of the investigator, require statin up-titration or dietary adjustment can be rescreened after 1 month. Subjects can only be rescreened once. Statins may not be down-titrated with subsequent rescreened. Baseline statin therapy is

expected to be continued unchanged throughout the study. Subjects will be randomized 2:2:1:1 into the following treatment arms:

- evolocumab SC 140 mg Q2W,
- evolocumab SC 420 mg QM,
- placebo SC Q2W, or
- placebo SC QM.

Randomization will be stratified by entry cardiovascular (CV) risk (high/very high CV risk vs not high/very high CV risk).

The overall sample size will be approximately 450 subjects (150 subjects for each evolocumab dosing regimen). The sample size for each placebo will be approximately 75 subjects.

Evolocumab and placebo will be administered SC at the study site or in an appropriate non-clinic setting (eg, at home) by spring based prefilled autoinjector/pen (AI/Pen). The dose frequencies of Q2W and QM will not be blinded but the identity of investigational product evolocumab or matching SC placebo) will be blinded.

Subjects must tolerate a SC injection of placebo with a prefilled autoinjector/pen device to be used during the study prior to randomization.

All central laboratory results of Apolipoprotein (Apo) A1, ApoB, Lp (a), PCSK9, high sensitivity C-reactive protein (hsCRP) will be blinded until unblinding of the clinical database and will not be reported to the investigator. Post-investigational product treatment central laboratory results of the lipid panel will be blinded until unblinding of the clinical database and will not be reported to the investigator. Investigators should not perform non protocol testing of these analytes during a subject's study participation and until at least 12 weeks after last investigational product administration, or the subject's end of study (EOS), whichever is later.

Approximately 40 sites in China will participate in this study. Treatment and follow-up period will be 12 weeks with an additional phone call or other subject contact at week 14 for subjects receiving investigational product Q2W. The EOS for subjects on QM investigational product is at the week 12 visit which must be at least 30 days post last dose of investigational product. The EOS for subjects on Q2W investigational product is a telephone call from the site at week 14 (and at least 30 days post last dose of investigational product) for any potential adverse events, adverse device effects (ADEs), serious adverse events and disease related events. Subjects will be encouraged to complete all planned visits regardless of their adherence to investigational product administration.

The primary completion is when all subjects have completed study treatment and have had the opportunity to complete the 12 week visit.

End of trial will occur when the last subject has completed or discontinues study treatment and has had the opportunity to complete the safety follow-up visit.

Sample Size: A total 450 subjects are planned to be enrolled in this study.

Summary of Subject Eligibility Criteria: Males and females, ≥ 18 to years of age are eligible for this study. Subject must be on an approved statin for at least 4 weeks, before LDL-C screening and, in the opinion of the investigator, not require uptitration. Subject must have fasting LDL-C ≥ 80mg/dL at screening, and meet one of the criteria listed in Section 4.1.1 to be considered high/very high CV risk. Subject must have fasting triglycerides ≤ 400 mg/dL (4.5 mmol/L) at screening, and be able to tolerate a screening placebo injection

Major exclusions are myocardial infarction, unstable angina, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) within the last 3 months, planned coronary or other revascularization within 20 weeks of screening, New York Heart Association (NYHA) III or IV heart failure, uncontrolled serious cardiac arrhythmia, diabetes, or hypertension, and severe renal dysfunction.

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

Investigational Product

Amgen Investigational Product Dosage and Administration: Evolocumab and matched placebo will be administered SC using a spring-based prefilled AI/Pen. Each prefilled AI/Pen

contains 1.0 mL of deliverable volume. The Q2W administration will occur via 1 AI/Pen, while the QM administration will occur via 3 AI/Pens.

Non-investigational Product

Amgen Non-investigational Product Dosage and Administration: None

Non-Amgen Non-investigational Product Dosage and Administration: All eligible subjects must be taking a maximum appropriate dose of an approved statin, not requiring uptitration.

All other lipid lowering drugs that are allowed per protocol and that the subject may be taking, must be commercially available. Subjects must be on an approved statin with maximum appropriate (optimal) stable daily dose with or without ezetimibe for at least 4 weeks before LDL-C screening and, in the opinion of the investigator, not requiring uptitration.

They must remain on the same daily statin background therapy (drug and dose), with or without ezetimibe, throughout the study from signing of the ICF until the EOS. If statin therapy is discontinued, or changed during the study, the reason for adjusting medication (eg. adverse event, noncompliance, etc) should be recorded.

Procedures: Subjects being considered for participation and who have signed informed consent, will be assessed for inclusion and exclusion criteria. Medical and medication history will be obtained. During screening, all subjects will undergo physical examination, and central labs including fasting lipids will be collected. If a subject has not met all eligibility criteria at the end of the 4-week window, the subject will be registered as a screen fail. Subjects who screen fail due to the LDL-C below the limit for eligibility during final screening cannot be rescreened for this study. Suitable subjects who are ineligible at the initial screening for other reasons and have not been randomized can be re-consented and rescreened once at a later time unless they withdraw from screening, provided the study is still enrolling subjects. Subjects will undergo SC placebo injection prior to randomization with a device to be used during the study (AI/pen). Subjects who tolerate the placebo injection, complete all screening procedures, and successfully meet all eligibility criteria at the end of screening will be randomized and will return to the study site for Day 1 procedures while continuing their background lipid lowering treatment (if applicable). The dosing regimens are evolocumab 140 mg SC Q2W or 420 mg SC QM. Study visits will occur at screening, baseline (Day 1), Week 8, Week 10, Week 12, and Week 14 (Q2W subjects only). Fasting lipids will be tested for all subjects at baseline, Week 8, Week 10, and Week 12 towards analysis of primary and secondary endpoints. Safety data will be collected at all time points as indicated in the Schedule of Assessments (Table 2).

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 2).

Statistical Considerations:

Analysis Sets

The full analysis set (FAS) includes all randomized subjects who received at least 1 dose of investigational product. This analysis set will be used in both efficacy and safety analyses. In efficacy analyses, subjects will be grouped according to their randomized treatment group assignment. For safety analyses, subjects will be grouped according to their randomized treatment group assignment with the following exception: if a subject receives treatment throughout the study that is different than the randomized treatment group assignment, then the subject will be grouped by the actual treatment group.

The completer analysis set (CAS) includes subjects in the FAS who adhered to the scheduled investigational product regimen and have observed values for the co-primary endpoints.

General Considerations

Efficacy and safety analyses will be performed on the FAS. Unless specified otherwise, the FAS will be the default analysis set in this study and data will be summarized by randomized treatment group. Analyses will be performed separately by each dose frequency (Q2W and QM) unless specified otherwise. The superiority of evolocumab to placebo will be assessed for all efficacy endpoints.

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

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

Missing data will not be imputed for safety endpoints.

Analysis of Co-Primary Efficacy Endpoints

To assess the co-primary endpoints of the mean percent change from baseline in LDL-C at weeks 10 and 12 and the percent change in LDL-C from baseline at week 12, a repeated measures linear effects model will be used on the FAS in each dose frequency to compare the efficacy of evolocumab with placebo. The repeated measures model will include terms for treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit.

Subgroup Analysis

If applicable, subgroup analyses on the co-primary efficacy endpoints will be conducted using the stratification factor and baseline covariates.

Secondary Efficacy Endpoint(s)

The statistical model and testing of the tier 1 secondary efficacy endpoints will be similar to the primary analysis of the co-primary endpoints. The secondary efficacy endpoints of LDL-C response (achievement of LDL-C < 70 mg/dL and achievement of > 50% LDL-C reduction from baseline) will be analyzed using the Cochran-Mantel Haenszel (CMH) test adjusted by the stratification factor.

Analyses of the tier 2 secondary efficacy endpoints will use the same analysis model as the tier 1 endpoints, and testing will use a union-intersection test.

Safety Endpoints

The current Medical Dictionary for Regulatory Activities (MedDRA) version at the time of the data lock will be used to code all adverse events to a system organ class and a preferred term. Subject incidence of all treatment emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product, device-related adverse events, and significant treatment-emergent adverse events will also be provided. Subject incidence of disease-related events and fatal disease-related events will be tabulated by system organ class and preferred term.

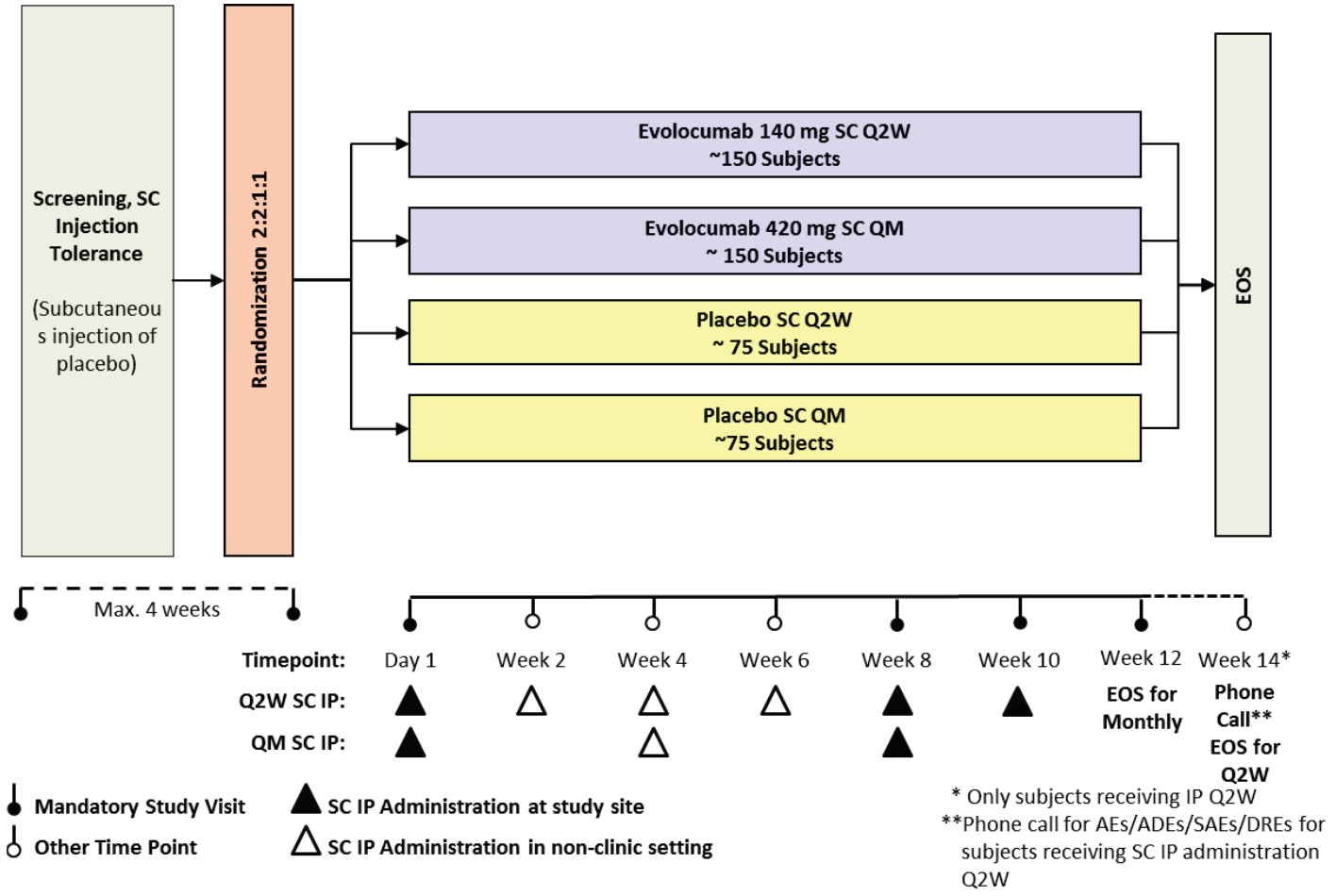
Measurements of selected laboratory parameters and vital signs will be summarized over time. The incidence and percentages of subjects who develop anti-evolocumab antibodies (binding and neutralizing) at any time will be tabulated.

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

Sponsor: Amgen

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

Study Design and Treatment Schema



Abbreviations: ADE=adverse drug event; DRE=disease related event; EOS=end of study; QM=every 4 weeks; Q2W=every 2 weeks; SC=subcutaneous

Study Glossary

Abbreviation or Term	Definition/Explanation
ADE	adverse device effect
AE	adverse event
AI/Pen	autoinjector/pen
ALP	alkaline phosphatase
ALT (SGPT)	alanine aminotransferase (serum glutamic-pyruvic transaminase)
ApoA1	apolipoprotein A1
ApoB	apolipoprotein B
AST (SGOT)	aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
BAS	bile acid sequestrants
BP	blood pressure
CABG	coronary artery bypass graft
CAS	completer analysis set
CBC	complete blood count
CHD	coronary heart disease
CK	creatine kinase
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for adverse events
CTT	Cholesterol treatment trialists
CV	cardiovascular
CVD	cardiovascular disease
CYP3A4	Cytochrome P450 A4
Day 1	defined as the first day that protocol-specified investigational product is administered to the subject at the beginning of each study part
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DRE	disease related event
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate; eGFR will be calculated by the central laboratory and provided to the investigator.
End of study	The end of the study is defined as when the last subject has completed or discontinued study treatment and has had the opportunity to complete the safety follow-up visit.

Abbreviation or Term	Definition/Explanation
End of study for individual subject	Defined as the last day that protocol-specified procedures are conducted for an individual subject or the day the subject withdraws from study early.
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.
Enrollment	A subject is considered enrolled upon randomization
EOS	end of study (for individual subject)
EU	European Union
FAS	full analysis set
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HbA1c	hemoglobin A1c
HCV	Hepatitis C virus
HDL-C	high density lipoprotein cholesterol
HepBsAg	Hepatitis B surface antigen
HepBcAb	Hepatitis B core antibody
HR	heart rate
HRT	Hormone replacement therapy
hsCRP	high sensitivity CRP
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
IMP	investigational medicinal product
IP	investigational product (evolocumab and placebo, administered with the medical device used in this study – the prefilled autoinjector/pen [AI/pen])
IPIM	investigational product instruction manual
IUD	intrauterine device
IUS	Intrauterine hormone releasing system
IVRS/IWRS	interactive voice response system / interactive web response system
IV	intravenous
LDH	lactate dehydrogenase
LDL-C	low-density lipoprotein cholesterol
l	lipoprotein(a)

Abbreviation or Term	Definition/Explanation
MedDRA	medical dictionary for regulatory activities
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
PCR	polymerase chain reaction
PKPD	pharmacokinetic / pharmacodynamic
Q2W	Q2W is defined as every 2 weeks with a window of ± 3 days for each visit
QM	QM is defined as every 4 weeks with a window of ± 3 days for each visit
Randomized	Assignment to treatment group based on computer-generated randomization schedules prepared by Amgen before the start of the study
RBC	red blood cells
RNA	ribonucleic acid
SAE	serious adverse event
SBP	systolic blood pressure
SC	subcutaneous
SD	standard deviation
SEC	self-evident correction
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.
TBL	total bilirubin
ULN	upper limit of normal
VLDL-C	very low-density lipoprotein cholesterol
WBC	white blood cell

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1. OBJECTIVES

1.1 Primary

- To evaluate the effect of 12 weeks of subcutaneous (SC) evolocumab every 2 weeks or every 4 weeks, compared with placebo, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) when used in addition to optimal stable background statin therapy in Chinese subjects with primary hypercholesterolemia and mixed dyslipidemia.

1.2 Secondary

- To evaluate the effect of 12 weeks of SC evolocumab Q2W or QM, compared with placebo, on change from baseline in LDL-C, achievement of target LDL-C < 70 mg/dL (1.8 mmol/L), LDL-C response (50% reduction of LDL-C from baseline) and percent change from baseline in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol, lipoprotein(a) [Lp(a)], triglycerides, HDL-C, very low-density lipoprotein cholesterol (VLDL-C) when used in addition to optimal stable background statin therapy in Chinese subjects with primary hypercholesterolemia and mixed dyslipidemia.

1.3 Exploratory

- To evaluate the effect of 12 weeks of SC evolocumab Q2W or QM, compared with placebo on change from baseline high sensitivity C-reactive protein (hsCRP) and on percent change from baseline in apolipotrotein A1 (Apo A1) when used in addition to optimal stable background statin therapy in Chinese subjects with primary hypercholesterolemia and mixed dyslipidemia.
- To evaluate the effect over time of SC evolocumab Q2W or QM, compared with placebo, on change from baseline in proprotein convertase subtilisin/kexin type 9 (PCSK9) levels and on change from baseline and percent change from baseline of LDL-C, total cholesterol, non-HDL-C, apolipotrotein B (ApoB), VLDL-C, HDL-C, ApoA1, triglycerides and Lp(a) when used in addition to optimal stable background statin therapy in Chinese subjects with primary hypercholesterolemia and mixed dyslipidemia.

1.4 Safety

- To evaluate the safety and tolerability of SC evolocumab Q2W and QM when used in combination with optimal stable background statin therapy in Chinese subjects with primary hypercholesterolemia and mixed dyslipidemia

2. BACKGROUND AND RATIONALE

2.1 Disease

In China, about 230 million people, 1 in 5 adults, have cardiovascular disease (CVD). In 2010, 154.8 per 100,000 deaths per year are estimated to be associated with CVDs in urban areas and 163.1 per 100,000 in rural areas. This number accounts for 20.9%/17.9% (urban/rural) of China's total number of deaths per year. In China, heart attacks and strokes account for the number 1 and 3 causes of death. China now ranks among the top 10 countries in the world for total incidence of CVD. Projected annual

cardiovascular events are predicted to increase by 50% between 2010 and 2030 based on population aging and growth alone in China.

These trends are thought to result from growing urbanization and industrialization which has resulted in a rise in cardiovascular risk factors such as glucose intolerance, dyslipidemia, and hypertension. The rationale for treatment of dyslipidemia, particularly elevated LDL-C, extends from extensive clinical study 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.

A recent Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis (CTT Collaboration, 2010), which included 21 randomized controlled studies of statin versus control involving nearly 170,000 patients, showed that for every ~ 1 mmol/L reduction in LDL-C, there was an approximately 20% reduction in the risk of major vascular events (coronary death, non-fatal myocardial infarction, coronary revascularization, or stroke). Importantly, this meta-analysis, which evaluated 5 studies that compared more versus less intensive statin therapy, did not find a LDL-C threshold; additional vascular risk reduction is possible in patients with low LDL-C.

Statins are the most commonly used drugs for treating dyslipidemia. However, the current status of lipid lowering therapy in China is unsatisfactory. Several studies found that there is a low rate of achieving goal LDL-C levels among Chinese patients in general, and that this is particularly true in those at high risk or very high risk who require intensive LDL-C lowering therapy. For example, results from China Cholesterol Education Program indicate that after moderate statin treatment (ie, 10-20 mg atorvastatin or 20-40 mg simvastatin), the rates of LDL-C goal achievement are only 10.9% (< 70mg/dL) and 36.2% (< 100 mg/dL) and among outpatients at very high risk and high risk, respectively (Hu et al, 2008). Results of the dyslipidemia international study (DYSIS) China study showed that 39.7% of coronary heart disease (CHD) patients with diabetes achieved LDL-C control far lower than in subjects with either CHD or diabetes alone (Zhao S et al, 2014). Poor control rate of LDL-C is associated with increased risk of cardiovascular events, which leads to a heavy burden on families and society.

There are certain limitations of statins. Some Chinese patients respond poorly to the statin therapy.

As an example, the clinical study HPS2-THRIVE showed that almost 9.8% of Chinese patients were reported to have an LDL-C level > 2.0 mmol/L (77mg/dL), and 48.9% exceeded 1.5 mmol/L (58mg/dL) even with a dose of statin such as 40 mg/day simvastatin (HPS2 THRIVE Collaborative Group, 2013). Although increasing the statin dose could help more patients to achieve their LDL-C goal, it is not wise to achieve a higher goal attainment rate by only using high-dose statin, as there is a "Rule of Six%" principle: For each doubling of the statin dose, only an additional 6% further lowering of LDL C is achieved (Knopp, 1999).

Meanwhile, high dose statins lead to increasing adverse effects, including increased liver and muscle related adverse effects (Silva et al, 2007) and a potential increased risk higher of new onset diabetes (Preiss et al, 2011). This is particularly obvious in the Chinese population. The HSP2-THRIVE study, which randomized 10932 Chinese patients, demonstrated a higher rate of adverse events in Chinese subjects who received only LDL-C lowering therapy (namely they were allocated into controlled arm receiving simvastatin or simvastatin plus ezetimibe) than in European patients who underwent the same treatment (HPS2-THRIVE Collaborative Group, 2013). Statin related adverse effects are considered to be the main reason of the discontinuation of the drug. The Clinical Pathways for Acute Coronary Syndromes in China study suggested that side effects were accountable for discontinuation of statin therapy in 23% of patients discharged from hospitals with a diagnosis of acute coronary syndrome (Bi et al, 2009). Drug discontinuation due to adverse effects and poor patient compliance further impact attainment of LDL-C goals; consequently, this will lead to high incidence of cardiovascular events.

2.2 Amgen Investigational Product Background

For further details on evolocumab efficacy and safety results refer to the Evolocumab Investigator's Brochure.

2.3 Rationale

Despite achieving their LDL-C goals, approximately two-thirds of Chinese patients on lipid reduction therapy still have cardiovascular events (Libby, 2005). While it is unlikely that this residual risk is entirely due to LDL-C concentrations above the goal articulated in recent treatment guidelines (Grundy et al, 2004; NCEP, 2002;), CTT Collaboration 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-D (CTT Collaboration, 2010). Furthermore, therapies are

needed for individuals who are intolerant to statin therapy and cannot achieve their respective LDL C goals (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%. Considering the remaining cardiovascular risk despite the availability of statin therapy, and given that non-statin treatment options have modest efficacy (ezetimibe, bile acid sequestrants [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. Based on the current data, evolocumab, a fully human monoclonal antibody to PCSK9, may fulfill this need and may provide an important addition to the treatment of hyperlipidemia/dyslipidemia for individuals with hyperlipidemia.

The rationale for the study design and study population is to investigate the effect of evolocumab on LDL across different levels of cardiovascular risk and baseline LDL levels. The 2007 China Guideline on Prevention and Treatment of Dyslipidemia in Adults categorizes patients as high risk if they have coronary heart disease or coronary heart disease equivalent (documented atherosclerosis other than in the coronary arteries, diabetes mellitus or multiple cardiovascular risk factors). The target LDL levels for these patients is < 80mg/dL for those with a history of acute coronary syndrome or both documented atherosclerosis and diabetes mellitus. The target LDL for other high risk subjects was < 100mg/dL. However since the release of subsequent international guidelines in 2007 the target for the latter high risk patients has in practice been moving lower. Patients without very high or high risk features but receiving optimal stable background statin therapy in China are generally of moderate risk for which the 2007 guidelines recommend a target LDL of < 130 mg/dL. For these reasons the recruitment criteria for this trial is based on level of risk with high and very high risk subjects requiring an LDL at screening of at least 80mg/dL on optimal stable background statin therapy and the subjects without high risk features requiring an LDL of at least 130 mg/dL.

2.4 Clinical Hypotheses

The hypothesis is the dosing regimens of evolocumab SC 140 mg Q2W and 420 mg QM will be well tolerated and will result in greater reduction of LDL-C, as defined by the mean percent change from baseline at weeks 10 and 12 and percent change from baseline at week 12, than placebo when used in combination with optimal stable

background statin therapy in Chinese subjects with primary hypercholesterolemia and mixed dyslipidemia.

3. EXPERIMENTAL PLAN

3.1 Study Design

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

This is a phase 3, multicenter, double-blind, randomized, placebo-controlled study of evolocumab in Chinese subjects with hypercholesterolemia and mixed dyslipidemia. Subjects who have signed the informed consent form (ICF), will have fasting lipids measured and all inclusion and exclusion criteria assessed. Subjects should maintain their current diet and exercise regimen. Subjects who, in the opinion of the investigator, require statin up-titration or dietary adjustment can be rescreened after 1 month. Subjects can only be rescreened once. Statins may not be down-titrated with subsequent rescreened. Baseline statin therapy is expected to be continued unchanged throughout the study. Subjects will be randomized 2:2:1:1 into the following treatment arms:

- evolocumab SC 140 mg Q2W,
- evolocumab SC 420 mg QM,
- placebo SC Q2W, or
- placebo SC QM.

Randomization will be stratified by entry CV risk (high/very high CV risk vs not high/very high CV risk).

The overall sample size will be approximately 450 subjects (150 subjects for each evolocumab dosing regimen). The sample size for each placebo will be approximately 75 subjects.

Evolocumab and placebo will be administered SC at the study site or in an appropriate non-clinic setting (eg, at home) by spring based prefilled autoinjector/pen (AI/Pen). Observed, in-clinic dosing will occur at Day 1 and Week 8 (± 3 days). Subjects randomized to QM will self-administer in an appropriate non-clinic setting (eg, at home) at Week 4 (± 3 days). Subjects randomized to Q2W will self-administer in an appropriate non-clinic setting (eg, at home) at Week 2, 4 and 6 (± 3 days). The dose frequencies of Q2W and QM will not be blinded but the identity of investigational product (evolocumab or matching SC placebo) will be blinded.

Subjects must tolerate a SC injection of placebo with a prefilled AI/Pen device to be used during the study prior to randomization.

All central laboratory results of ApoA1, ApoB, lipoprotein(a), PCSK9, hsCRP will be blinded until unblinding of the clinical database and will not be reported to the investigator. Post-investigational product treatment central laboratory results of the lipid panel will be blinded until unblinding of the clinical database and will not be reported to the investigator. Investigators should not perform non protocol testing of these analytes during a subject's study participation and until at least 12 weeks after last investigational product administration, or the subject's end of study (EOS), whichever is later.

Approximately 40 sites in China will participate in this study. Treatment and follow-up period will be 12 weeks with an additional phone call or other subject contact at week 14 for subjects receiving investigational product Q2W. The EOS for subjects on QM investigational product is at the week 12 visit which must be at least 30 days post last dose of investigational product. The EOS for subjects on Q2W investigational product is a telephone call from the site at week 14 (and at least 30 days post last dose of investigational product) for any potential adverse events, adverse device effects (ADEs), serious adverse events and disease related events (DREs). Subjects will be encouraged to complete all planned visits regardless of their adherence to investigational product administration.

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

Approximately 40 sites in China will participate in this study.

Sites that do not enroll subjects within 3 months of site initiation may be closed.

3.3 Number of Subjects

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

A total of 450 subjects are planned to be enrolled in this study.

3.4 Replacement of Subjects

Subjects who are withdrawn or removed from treatment or the study will not be replaced.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

After signing the ICF, subjects should be randomized within 4 weeks. The maximal total duration of study participation for a subject on QM investigational product schedule will

be 16 weeks (approximately 4 months) which includes screening, study treatment, and safety follow-up. For a subject on Q2W investigational product schedule, the maximum study duration will be 18 weeks (approximately 4.5 months), including a telephone contact by the site at week 14 to obtain potential adverse events, adverse device effects, serious adverse events and disease related events information.

3.5.2 End of Study

Primary Completion: is when all the randomized subjects in the study have completed study treatment and have had the opportunity to complete the 12 week visit.

End of Trial: is when the last subject has completed or discontinued study treatment and has had the opportunity to complete the safety follow-up visit.

4. SUBJECT ELIGIBILITY

Study sites will be expected to maintain a screening log of all potential study subjects that includes limited information about the potential subject (eg, date of screening).

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

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria

101 Male or female ≥ 18 years of age at signing of informed consent form

102 On an approved statin, with or without ezetimibe, at optimal stable daily dose(s) for at least 4 weeks before LDL-C screening and, in the opinion of the investigator, not requiring uptitration

103 Fasting LDL-C as determined by central laboratory at screening ≥ 80 mg/dL

104 Subject meets at least one of the following criteria for high/very high CV risk :

- history of coronary artery disease
- history of ischemic stroke
- diagnosis of peripheral artery disease
- an estimated glomerular filtration rate (eGFR) as determined by central laboratory at screening of ≥ 30 but < 60 ml/min/1.73m2
- diagnosis of diabetes mellitus type 2
- presence of ≥ 3 of the following risk factors:
    - ≥ 45 years of age if male, ≥ 55 years of age if female
    - hypertension
    - smoking
    - family history of premature CVD (1st degree of relative: male < 55yr, female < 65yr)

- HDL cholesterol < 40 mg/dL
- obesity(BMI ≥ 28 kg/m2)

OR

Subject does not meet high/very high CV risk criteria but fasting LDL-C as determined by central laboratory at screening ≥ 130 mg/dl

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

106 Subject tolerates a screening placebo injection

4.1.2 Exclusion Criteria

201. Myocardial infarction, unstable angina, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) or stroke within 3 months prior to randomization

202. Planned coronary or other revascularization within 20 weeks of screening

203. New York Heart Association (NYHA) III or IV heart failure, or last known left ventricular ejection fraction < 30

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

205. Type 1 diabetes, new-onset (hemoglobin [Hb]A1c ≥ 6.5% or fasting plasma glucose (FPG) ≥ 126 mg/dL at screening without known diagnosis) or poorly controlled (HbA1c ≥ 8.5%) type 2 diabetes, as determined by central laboratory at screening

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

207. Subject has taken a cholesterylester transfer protein (CETP) inhibitor in the 12 months prior to randomization

208. Subject has taken in the 6 weeks prior to LDL - C screening: red yeast rice, > 200 mg/day niacin, > 1000 mg/day omega-3 fatty acids (eg, dihydroxyacetone docosahexaenoic acid and eicosapentaenoic acid), stanols or prescription lipid-regulating drugs (eg, bile-acid sequestering resins, fibrates and derivatives) or other cholesterol lowering drugs or lipid-lowering dietary supplements or food additives other than statins and ezetimibe

209. Treatment 3 months prior to LDL-C screening with any of the following drugs: systemic cyclosporine, systemic steroids , (intravenous [IV], intramuscular [IM], or PO) (Note: hormone replacement therapy is permitted), vitamin A derivatives and retinol derivatives for the treatment of dermatologic conditions (eg, Accutane) (Note: vitamin A in a multivitamin preparation is permitted)

210. Uncontrolled hypothyroidism or hyperthyroidism as defined by thyroid stimulating hormone (TSH) < 1.0 time the lower limit of normal (LLN) or > 1.5 times the upper limit of normal (ULN), respectively, at screening

211. Severe renal dysfunction, defined as an eGFR < 30 ml/min/1.73m2 at screening as estimated by Cockcroft-Gault method

212. 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 screening

213. Creatinine Kinase (CK) > 5 times the ULN at screening

214. Malignancy (except non-melanoma skin cancers, cervical in-situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma) within the last 5 years prior to randomization

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

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

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

218. History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

219. Currently receiving treatment in another investigational device or drug study, or less than 30 days before randomization since ending treatment on another investigational device or drug study(s) or planning to receive other investigational procedures while participating in this study

220. Female subject of childbearing potential not willing to use an acceptable method(s) of effective birth control during treatment with investigational product and for an additional 15 weeks after the end of treatment with investigational product (Refer to Section 6.9.1 for specific contraceptive information).
Female subjects of non-childbearing potential who are not required to use contraception during the study and include those who have had a:

- hysterectomy
- bilateral salpingectomy
- bilateral oophorectomy
  or
- who are postmenopausal.
  i. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. [A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.]
  ii. Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during

the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Acceptable methods of effective birth control include:

- sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject. [Periodic abstinence (eg., calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of a study, and withdrawal are not acceptable methods of contraception])
- bilateral tubal ligation/occlusion
- vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- use of hormonal birth control methods (oral, intravaginal (eg. vaginal ring(s), transdermal, injectable, or implantable)
- intrauterine devices (IUDs)
- intrauterine hormonal releasing system (IUS)
- 2 barrier methods (each partner must use 1 barrier method) the male uses a condom and the female must choose either a diaphragm, OR cervical cap, OR contraceptive sponge with spermicide. If spermicide is not commercially available in the country or region, the 2 barrier method without spermicide is acceptable. (A female condom is not an option due to the risk of tearing when both partners use a condom.)

Note: Additional medications given during treatment with investigational product may alter the contraceptive requirements. These additional medications may require a change in the type of contraceptive methods and/or length of time that contraception is to be utilized and/or length of time breastfeeding (nursing) is to be avoided. The investigator is to discuss these contraceptive changes with the study subject.

221. Female subject is pregnant or breast feeding (nursing), planning to become pregnant or planning to breastfeed (nurse) during treatment with investigational product and/or within 15 weeks after the end of treatment with investigational product.

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, ICF, and all other subject information and/or recruitment material, if applicable (see Section 11.2). All subjects must

personally sign and date the ICF before commencement of study specific activities/procedures.

Upon completion of the screening period the subject is evaluated by the investigator and providing the subject continues to meet the inclusion/exclusion criteria, the subject is subsequently eligible to be enrolled in the study. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (defined as the point at which the subject signs the ICF) receives a unique subject identification number before any study-related activities/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. Subjects who, in the opinion of the investigator, require statin up-titration or dietary adjustment can be rescreened after 1 month. Subjects can only be rescreened once.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened. This number will not necessarily be the same as the randomization number assigned for the study.

5.1 Randomization/Treatment Assignment

Subjects will be considered enrolled on the day they are randomized. Assignment to the 4 treatment arms will be based on a computer-generated randomization schedule prepared by Amgen before the start of the study.

Each subject will receive a unique randomization number. Randomization will be stratified by entry CV risk (high/very high CV risk vs not high/very high CV risk).

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

The randomization date is to be documented in the subject's medical record and on the enrollment CRF. Randomization numbers will be provided to the site through an IVRS/IWRS.

5.2 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject on this study.

Unblinding at the study site for any other reason will be considered a protocol deviation.

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

6. TREATMENT PROCEDURES

The Amgen investigational product used in this study is evolocumab and placebo (Amgen investigational medicinal product) in a prefilled Autoinjector/Pen (AI/Pen) (Amgen investigational medical device). In several countries, investigational product is referred to as Investigational Medicinal Product (IMP). In this document, IMP will be referred to as investigational product.

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

Refer to Section 6.1 and Section 6.2 for details regarding investigational product and its dosage and administration.

6.1 Classification of Product(s) and/or Medical Device(s)

The Amgen Investigational Product(s) and/or matched placebo (except if required by local regulation) used in this study include(s): evolocumab and placebo.

The IPIM, a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of evolocumab and matched placebo.

The medical device(s) used in this study include(s): Prefilled AI/pen.

Note: Non-investigational medical device(s) (ie, medical device(s) not under study) or products will be described in Section 6.6.

Additional details regarding the use of the AI/Pen is provided in the IPIM and in the Instructions for Use (IFU).

In several countries, investigational product is referred to as IMP. In this document, IMP will be referred to as investigational product.

6.2 Investigational Product

6.2.1 Amgen Investigational Product [Evolocumab]

Evolocumab and respective placebo will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical investigational product 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 AI/Pen 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.

Placebo will be presented in a 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.

Evolocumab should be stored protected from light and according to the storage and expiration information (where required) provided on the label. Evolocumab should be handled per the instructions provided in the IPIM. AI/pens should be checked for cracks or damage that may occur during shipment or if not handled properly. Damaged product should not be administered. Further details are provided in the IPIM.

6.2.1.1 Dosage, Administration, and Schedule

Investigational product will be administered SC (evolocumab or matched placebo) at the investigator site by a qualified staff member in accordance with instructions in the IPIM. Investigational product administration by SC injection at each visit must be done after vital signs, electrocardiogram (ECG), and blood draw procedures, if applicable. The date, time, and amount of evolocumab or placebo will be recorded on the individual subject's worksheet and/or electronic case report form (eCRF). The box number of investigational product (active drug or placebo) is to be recorded on each subject's Drug Administration electronic case report form (eCRF).

After investigational product administration at each dosing visit, subjects should be observed for at least 30 minutes before being discharged.

In the Q2W regimen, 140 mg of AMG 145 will be administered subcutaneously every 2 weeks via one 1.0 mL prefilled AI/pen.

In the QM regimen, 420 mg of evolocumab will be administered subcutaneously once a month via three 1.0 mL prefilled AI/pens. The prefilled AI/pens injections should be administered in a consecutive fashion with all injections completed within 30 minutes.

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

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

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

If a subject is late for administration of investigational product, administration should occur as soon as possible.

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

Not more than 2 Q2W doses should be administered within any 7-day period. If a Q2W subject arrives for a visit with investigational product administration and more than 1 dose of investigational product was administered within the prior 7 days, the dose should not be administered but all other study procedures should be completed. Administration of investigational product should occur as soon as possible but at least 7 days after the most recent previous administration.

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

6.3 Non-investigational Product(s)

6.3.1 Non-Amgen Non-investigational Product(s)

All eligible subjects must be taking a maximum appropriate dose of an approved statin, not requiring uptitration.

All other lipid lowering drugs that are allowed per protocol and that the subject may be taking, must be commercially available and are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these drugs.

Subjects must be on an approved statin with maximum appropriate (optimal) stable daily dose with or without ezetimibe for at least 4 weeks before LDL-C screening and, in the opinion of the investigator, not requiring uptitration.

They must remain on the same daily statin background therapy (drug and dose), with or without ezetimibe, throughout the study from signing of the ICF until the EOS. If statin therapy is discontinued, or changed during the study, the reason for adjusting medication (eg. adverse event, noncompliance**,** etc.) should be recorded.

Additional details regarding the product(s) are provided in the IPIM.

6.4 Hepatotoxicity Stopping and Rechallenge Rules

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

6.4.1 Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity

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

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, toxoplasmosis, and Parvovirus)

- Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia.
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome,Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic Fatty Liver Disease including Steatohepatitis (NASH)
- Non-hepatic causes (eg, rhabdomylosis, hemolysis)

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

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (Section 6.4.2).

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

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

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

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

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

If signs or symptoms recur with rechallenge, then investigational product should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 1) should never be rechallenged.

6.5 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.8.

6.6 Medical Devices

Investigational product will be administered per prefilled AI/Pen, provided by Amgen. The AI/pen is a single use disposable, handheld mechanical "spring-based" device for fixed dose subcutaneous injection of 1.0 mL deliverable volume.Additional details regarding the use of the AI/Pen is provided in the IPIM and in the IFU. Other non-investigational medical devices may be used in the conduct of this study as part of standard care. These other medical devices (eg, syringes, sterile needles, alcohol prep pads), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

6.7 Product Complaints

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

This includes any drug(s), device(s) or combination product(s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) includes investigational product.

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

- broken container or cracked container,
- subject or healthcare provider cannot appropriately use the product despite training (eg., due to malfunction of the prefilled AI/pen),
- missing labels, illegible labels, incorrect labels, and/or suspect labels,
- change in investigational product 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
- evidence of tampering or stolen material.

If possible, please have the prefilled AI/pen available for visual examination when making a product complaint. Maintain the prefilled AI/pen 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 ICF through 30 days after the last dose of investigational product or EOS, whichever is

later, are reported to Amgen within 24 hours of discovery or notification of the product and/or device complaint.

Any product complaint(s) associated with an investigational product(s) or non-investigational product(s) or device(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

6.8 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

The following treatments are not permitted during the study:

- any investigational therapies other than study provided investigational product
- any lipid lowering therapies not taken at the time of screening and enrollment

Please contact the Amgen medical monitor or designee if any of these therapies should be initiated during the blinded portion of the study. Note that a change in lipid lowering therapy does not necessarily require ending investigational product.

The following treatments are not recommended in subjects treated with statins metabolized by CYP3A4 (eg simvastatin or atorvastatin) because of their potential impact on metabolism of certain statins:

> Medications or foods that are known potent inhibitors of cytochrome P450 A4 (CYP3A) eg, itraconazole, ketoconazole, and other antifungal azoles, macrolide antibiotics erythromycin, clarithromycin, and the ketolide antibiotic telithromycin, HIV or Hepatitis C virus (HCV) protease inhibitors, antidepressant nefazodone and grapefruit juice in large quantities (> 1 quart daily [approximately 1 Liter]) should not be used during the study or other cholesterol lowering drugs or lipid lowering dietary supplements or food additives other than statins and ezetimibe.

6.9 Contraceptive Requirements

6.9.1 Female Subjects

Female subjects of childbearing potential must agree to practice true sexual abstinence (refrain from heterosexual intercourse) or use effective method(s) of contraception during treatment and for an additional 15 weeks after the last dose of protocol-required therapies.

Acceptable methods of effective contraception include: Hormonal (Combined estrogen and progestogen or progesterone-only hormonal contraception given via oral, intravaginal, transdermal, injectable, or implantable route); Intrauterine device (IUD); Intrauterine hormonal-releasing system (IUS); Bilateral tubal occlusion/ligation**;**

Vasectomized partner (provided that partner is the sole sexual partner of the female subject who is of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)**;** Two barrier methods (one by each partner) and the female partner must use spermicide (if spermicide is commercially available) with the barrier method [the male must use a condom (latex or other synthetic material) and the female may select either a diaphragm, cervical cap or contraceptive sponge]. A female condom is not an option because there is a risk of tearing when both partners use a condom. The reliability of true sexual abstinence must be evaluated by the investigator and be the preferred and usual lifestyle of the subject.

If a female subject is suspected of being pregnant, the protocol-required therapies must be stopped immediately and may not be resumed until absence of pregnancy has been medically confirmed.

Females not of childbearing potential are defined as: Any female who is has had a hysterectomy, OR bilateral salpingectomy, OR bilateral oophorectomy, OR are post-menopausal. Post-menopausal women are:

- Age > 55 years with cessation of menses for 12 or more months
- Age < 55 years but no spontaneous menses for at least 2 years
- Age < 55 years and spontaneous menses within the past 1 year, but currently amenorrheic (eg, spontaneous or secondary to hysterectomy), AND with follicle-stimulating hormone levels > 40 IU/L, or postmenopausal estradiol levels < 5 ng/dL, or according to the definition of "postmenopausal range" for the laboratory involved.

6.9.2 Unacceptable Methods of Birth Control for Female Subjects

Birth control methods that are considered unacceptable in clinical trials include: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method.

7. STUDY PROCEDURES

Screening assessments and study procedures outlined in this section and in Table 2 can only be performed after obtaining a signed informed consent. This includes any discontinuation of the subject's medication for the purpose of participation in this study.

It is very important to attempt to perform study procedures and obtain samples at the precise timepoints stipulated in Table 2. When it is not possible to perform the study visit at the exact timepoint, the visit may be performed within the acceptable visit window

as defined in Table 2. If a study visit is missed or late, including visits outside the visit window, subsequent visits should resume on the original visit schedule.

Any assessments at prior visits should not be duplicated at subsequent visits, with the exception of screening and rescreening visits, if possible, all study procedures for a visit should be completed on the same day. Subsequent study visits should resume on the original schedule. Missed assessments at prior visits should not be duplicated at subsequent visits.

7.1 Schedule of Assessments

Table 2. Schedule of Assessments

	Screening	Baseline	Treatment Period				Early Termination
Study Week	Week -4 (Day -28) to Day -1	Day 1	Week 8 ± 3 days	Week 10 ± 3 days	Week 12[a] ± 3 days	Week 14[a, b] ± 3 days Q2W subjects only	
Informed Consent	X						
Demographics	X						
Medical History	X						
Vital Signs	X	X	X	X	X		X
Physical Examination	X	X			X		X
Weight and waist circumference	X	X			X		X
Height	X						
Pregnancy Test : Serum[c]	X						
Pregnancy Test : Urine[d]		X					
Chemistry	X	X	X		X		X
Hematology	X	X	X		X		X
Urinalysis	X	X	X		X		X
Screening placebo injection[e]	X						
HbA1c	X				X		X
Thyroid Stimulating Hormone	X						
HCV[f]	X				X		X
Hepatitis C viral load[g]		X			X		X
hsCRP		X			X		X
Anti-evolocumab antibodies		X			X		X

Footnotes defined on the next page

Table 2. Schedule of Assessments

	Screening	Baseline	Treatment Period				Early Termination
Study Week	Week -4 (Day -28) to Day -1	Day 1	Week 8 ± 3 days	Week 10 ± 3 days	Week 12[a] ± 3 days	Week 14[a, b] ± 3 days Q2W subjects only	
Fasting Lipids, ApoA1, ApoB, Lp(a)	X	X	X	X	X		X
PCSK9		X	X	X	X		X
Safety Data Collection/Recording/Reporting[h]	X	X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X
IP dispensation to subject for non-clinic administration		X					
IP administration[i]		X	X	X[j]			
IP reconciliation			X				X

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Abbreviations: ApoA1= apolipoprotein A1;ApoB= apolipoprotein B1; HbA1C= hemoglobin A1c; hsCRP= high sensitivity CRP; Lp(a)= lipoprotein a; PCSK9= proprotein convertase subtilisin/kexin type 9.

a: End of Study visit for QM subjects (week 12) and visit/phone call for Q2W subjects (Week 14) are to occur no earlier than 30 days post last IP administration

b: Phone call is acceptable

c: Only in females of childbearing potential. Additional pregnancy testing may be performed at the investigators's discretion or as required per local laws and regulations.

d: Only in females of childbearing potential prior to administration of IP/placebo if the serum pregnancy test was performed over 7 days prior to initiation of IP/placebo.

e: Placebo injection to occur following determination of eligibility for all other screening parameters

f: HCV antibodies only in high risk subjects (see Section 7), subjects with a positive history of HCV infection, or if ALT or AST > 2x ULN at any time during screening;

g: Hepatitis C viral load only in HCV positive patients

h: Including assessment/review for adverse events/serious adverse events/disease related events/adverse device effects. Only AEs/ADEs possibly related to study procedures and serious adverse events are collected during the screening period

i: During the treatment period, in addition to the in-clinic administration at D1, W8 and W10 (as applicable), subjects randomized to QM are expected to administer non-clinic IP at W4 and subjects randomized to Q2W IP are expected to administer non-clinic IP at W2,W4,and W6.

j: Only for subjects randomized to Q2W IP

7.2 General Study Procedures

7.2.1 Study Visit Definitions and Windows

After signing the ICF, potential subjects will be evaluated to determine whether they fulfill the entry requirements listed in Section 4.1. At screening, the subject should be reminded that participation in the study is contingent upon his or her screening test results. The screening period begins the day the subject signs the ICF, and ends (after 28 days) when the subject is randomized to receive the first dose of investigational product or fails the enrollment criteria.

Refer to the applicable supplemental central laboratory, IVRS/IWRS, and study manuals for detailed collection and handling procedures.

Subjects should be randomized before or on the day 1 visit, and initiate their first dose of investigational product within 5 days of randomization.

The following visit windows (± 3 days) will apply to all visits during the treatment period of the study:

- Week 8
- Week 10
- Week 12
- Week 14 (Q2W subjects only)

Study procedures for a specific visit may be completed on multiple days as long as all the procedures are completed within the visit window.

7.2.2 Description of Study Procedures

The sections below provide a description of the individual study procedures listed in Section 7.2.3, Section 7.2.4, and Section 7.2.5. Details regarding the collection, recording and reporting of adverse events, adverse device effects, serious adverse events, disease related events and/or other safety findings are provided in Section 9.2.

7.2.2.1 Informed Consent

All subjects or legally acceptable representative must sign and personally date the IRB/IEC approved informed consent and provide subject assent if appropriate before any study specific procedures are performed.

7.2.2.2 Medical History

The Investigator or designee will collect a complete medical history covering the period within 120 days prior to randomization. Additionally, a targeted cardiovascular and diabetes medical history not limited to 120 days prior to randomization will be collected.

Targeted cardiovascular history including but not limited to cardiovascular risk factors, history of cardiovascular disease, revascularization procedures, family history, and diagnostic criteria for familial hypercholesterolemia will be collected.

7.2.2.3 Measurement of Vital Signs

Blood pressure (BP) and heart rate (HR) measurements will be determined after the subject has been seated for at least 5 minutes. The appropriate size cuff should be used. During screening, BP measurements 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.

7.2.2.4 Measurement of Waist Circumference

Subjects should wear minimal clothing to ensure that the measuring tape is correctly positioned. Subjects should stand erect with the abdomen relaxed, arms at the sides, feet together and with their weight equally divided over both legs. To perform the waist measurement, the lowest rib margin is first located. The iliac crest is then palpated in the midaxillary line. 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.

7.2.2.5 Prior Therapies, Substance use History, and Concomitant Medications

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed above in Excluded Treatments and/or Procedures During Study Period.

Prior general and targeted therapies (eg, statins and other lipid lowering therapy), taken 120 days prior to randomization should be collected with the following information: therapy name, indication, dose, unit, frequency, route, start date and stop date.

If a targeted therapy is begun, discontinued, or changed during study, in addition to updates for the above information, the reason for adjusting medication (ie, adverse event, worsening of underlying condition, noncompliance etc) should be recorded.

Concomitant therapies are to be collected from ICF through the EOS.

7.2.2.6 Pregnancy Test

Pregnancy testing will occur in females of childbearing potential only.

7.2.2.7 Laboratory Assessments

Subjects must be fasting overnight (no food or drinks other than water for ≥ 9 hours) before each study visit where fasting lipid samples are obtained. If the subject is not fasting for the screening or the day 1 visit, no visit procedures are performed and the visit should be rescheduled within the applicable protocol windows. If subject is not fasting after day 1, all procedures except fasting labs and investigational product administration, if applicable, will be performed and another visit should be scheduled, within the visit window if possible, for fasting labs and investigational product administration.

All laboratory samples will be sent to the central laboratory. Concentration values are provided in mmol/L for investigator convenience. Conventional concentrations (mg/mL) will be used for the protocol, including for eligibility determination. eGFR will be calculated by the central laboratory and will be provided to the site for eligibility determination. Table 3 below outlines the specific analytes to be tested.

Table 3. Lists of Analytes

Central Laboratory Chemistry	Central Laboratory Urinalysis	Central Laboratory Hematology	Other Central Laboratory Analyses
Sodium	Specific gravity	RBC	Fasting lipids
Potassium	pH	Hemoglobin	• total cholesterol
Chloride	Blood	Hematocrit	• HDL-C
Bicarbonate	Protein	MCV	• LDL-C
Total protein	Glucose	MCH	• triglycerides
Albumin	Bilirubin	MCHC	• VLDL-C
Calcium	WBC	RDW	• non-HDL-C
Adjusted Calcium	RBC	Platelets	ApoA1
Magnesium	Epithelial cells	WBC	ApoB
Phosphorus	Bacteria		Lp(a)
Fasting Glucose	Casts		hsCRP
BUN or Urea	Crystals		PCSK9
Creatinine			HbA1c
Uric acid			Serum and urine pregnancy tests (females of
Total bilirubin			childbearing potential)
Direct bilirubin			HCV antibody
CK			HCV viral load
Alk phos			Antibodies
LDH			TSH
AST (SGOT)			
ALT (SGPT)			
eGFR			

Hepatitis C virus (HCV):

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:

- Intravenous usage of illegal drugs
- History of needle stick injuries as part of career or other reasons (tattoo, punch, acupuncture, etc)
- History of iatrogenic exposure
- History of high risk sexual behavior eg multiple sex partners, male homosexual
- Have a known HCV infected sexual partner or family member
- Are known to be infected with HIV or sexual partner of HIV infected person
- Wounded skin or mucosa contaminated with the blood of HCV infected person
- History of blood transfusion or use of blood product before 1993

Viral load will be tested in subjects who are positive for HCV antibody.

Blinding:

In order to protect the blinding of the double-blind treatment period the following labs will be blinded post-investigational product treatment until unblinding of the clinical database and not reported to sites as noted below:

- Blinded to the Amgen study team and site staff: lipid panel, ApoA1,ApoB, lipoprotein(a), hsCRP, and PCSK9

Investigators should not perform non-protocol testing of these analytes during a subject's study participation and until at least 12 weeks after last investigational product administration, or the subject's EOS, whichever is later.

Refer to the IPIM for a description regarding how responsible pharmacists and investigators will access treatment information via the IVR/IWR system, in the event that there is a need to break the blind. The investigator is strongly encouraged to contact the Clinical Trial Manager before unblinding any subject's treatment assignment, but must do so within 1 working day after the event.

7.2.3 Screening Enrollment and/or Randomization

The following procedures are to be completed during the screening period at time points designated in the Schedule of Assessments (Table 2)*:*

- Confirmation that the ICF has been signed
- Demographic data including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.
- Physical Examination as per standard of care
- Medical/surgical history
- Height, weight, and waist circumference
- Serum pregnancy test (for with childbearing potential)
- Vital signs (eg, BP, HR, respiration rate, temperature)
- Laboratory Assessments (Chemistry, Hematology, and Urinalysis), as applicable
- Assessment of HCV, HbA1c, Thyroid Stimulating Hormone, Fasting Lipids, ApoA1, ApoB and Lp(a)
- Serious Adverse Event reporting (AEs possibly related to study procedures, ADEs and SAEs are collected during the screening period, from signing of the ICF).
- Adverse Event reporting
- Disease Related Event Reporting
- Adverse Device Effect Reporting

- Documentation of concomitant medications
- Registration in IVRS/IWRS, as applicable
- Randomization via IVRS/IWRS, as applicable

ICF must be obtained before completing any other screening procedures.

The screening period is up to 4 weeks. If a subject has not met all eligibility criteria at the end of the 4-week window, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening once as described in Section 7.2.3.1.

Subjects will undergo SC placebo injection prior to randomization with a device to be used during the study (AI/pen). Subjects who tolerate the placebo injection, complete all screening procedures, and successfully meet all eligibility criteria at the end of screening will be randomized via IVRS/IWRS and will return to the study site for day 1 procedures while continuing their background lipid lowering treatment (if applicable). Subjects can only be randomized 1 time for this study. Subjects should be randomized before or on the day 1 visit, and initiate their first dose of investigational product within 5 days of randomization.

7.2.3.1 Rescreening

Subjects who screen fail due to the LDL-C below the limit for eligibility during final screening cannot be rescreened for this study.

Suitable subjects who are ineligible at the initial screening for other reasons and have not been randomized can be re-consented and rescreened once at a later time unless they withdraw from screening, provided the study is still enrolling subjects. For subjects who are rescreened, data from the first screening period will not be used for the analysis.

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

7.2.4 Treatment

7.2.4.1 Baseline (Day 1): All Subjects

The following procedures will be completed on Day 1 as indicated in the Schedule of Assessments (Table 2).

- Vital Signs
- Physical Examination
- Weight and waist circumference

- Urine pregnancy test (for females with childbearing potential, prior to administration of investigational product/placebo if the serum pregnancy test was performed over 7 days prior to initiation of IP/placebo)
- Laboratory Assessments (Chemistry, Hematology, and Urinalysis), as applicable
- Hepatitis C viral load
- hsCRP
- Antibody testing
- Fasting Lipids, ApoA1, ApoB, Lp(a)
- PCSK9 testing
- Serious Adverse Event reporting
- Adverse Event reporting
- Disease Related Event Reporting
- Adverse Device Effect Reporting
- Documentation of concomitant medications
- Investigational product dispensation to subject for non-clinic administration
- Investigational product administration
- Investigational product reconciliation

7.2.4.2 Week 8: All Subjects

The following procedures will be completed at Week 8 (± 3 days) as indicated in the Schedule of Assessments (Table 2).

- Vital Signs
- Laboratory Assessments (Chemistry, Hematology, and Urinalysis), as applicable
- Fasting Lipids, ApoA1, ApoB, Lp(a)
- PCSK9 testing
- Serious Adverse Event reporting
- Adverse Event reporting
- Disease Related Event Reporting
- Adverse Device Effect Reporting
- Documentation of concomitant medications
- Investigational product administration
- Investigational product reconciliation

7.2.4.3 Week 10: All Subjects

The following procedures will be completed at Week 10 (± 3 days) as indicated in the Schedule of Assessments (Table 2).

- Vital Signs
- Fasting Lipids, ApoA1, ApoB, Lp(a)
- PCSK9 testing
- Serious Adverse Event reporting
- Adverse Event reporting
- Disease Related Event Reporting
- Adverse Device Effect Reporting
- Documentation of concomitant medications
- Investigational product administration for Q2W subjects

7.2.4.4 Week 12: All Subjects

The following procedures will be completed at Week 12 (± 3 days) as indicated in the Schedule of Assessments (Table 2).

- Vital Signs
- Physical Examination
- Weight and waist circumference
- Laboratory Assessments including local and central laboratories, as applicable
- HbA1C
- HCV
- Hepatitis C viral load
- hsCRP
- Antibody testing
- Fasting Lipids, ApoA1, ApoB, Lp(a)
- PCSK9 testing
- Serious Adverse Event reporting
- Adverse Event reporting
- Disease Related Event Reporting
- Adverse Device Effect Reporting
- Documentation of concomitant medications

7.2.4.5 Week 14: Q2W Subjects Only

The following procedures will be completed at Week 14 (± 3 days) as indicated in the Schedule of Assessments (Table 2).

- Serious Adverse Event reporting
- Adverse Event reporting
- Disease Related Event Reporting
- Adverse Device Effect Reporting
- Documentation of concomitant medications

7.2.5 Early Termination Visit

The following procedures will be completed at the early termination visit as indicated in the Schedule of Assessments (Table 2).

- Vital Signs
- Physical Examination
- Weight and waist circumference
- Laboratory Assessments including local and central laboratories, as applicable
- HbA1C
- HCV
- Hepatitis C viral load
- hsCRP
- Antibody testing
- Fasting Lipids, ApoA1, ApoB, Lp(a)
- PCSK9 testing
- Serious Adverse Event reporting
- Adverse Event reporting
- Disease Related Event Reporting
- Adverse Device Effect Reporting
- Documentation of concomitant medications

7.3 Antibody Testing Procedures

Blood sample(s) for Antibody testing are to be collected at baseline, Week 12, and during the early termination visit for the measurement of anti-evolocumab binding antibodies. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity and presence of immune complexes. Additional blood samples may be obtained to rule out anti-evolocumab antibodies during the study.

Sites will be notified of any positive neutralizing antibody results to evolocumab for individual subjects at the end of the study for each subject. If results are not provided, no neutralizing antibodies to evolocumab have been detected.

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 is to 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) post administration of evolocumab. All follow-up results, both positive and negative will be communicated to the sites. 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 is not required where it is established that the subject did not receive evolocumab.

Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-evolocumab antibody response may also be asked to return for additional follow-up testing.

7.4 Sample Storage and Destruction

Any blood sample collected according to the Schedule of Assessments (Table 2) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the scientific questions related to hyperlipidemia and mixed dyslipidemia, metabolic disorders, the dose response and/or prediction of response to evolocumab, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

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

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

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

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

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

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product, device or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 2) and collection of data, including endpoints, adverse events, disease related events, and device related events, as applicable. The investigator must document the change to the Schedule of Assessments (Table 2) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in

correspondence/communication with other physicians, from review of the medical records).

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

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, device, 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

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, including pregnancy in a female subject)
- 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

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Disease Related Events

Disease Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. In this study, subjects are at risk or are known to have cardiovascular disease. Therefore, disease-related events potentially include manifestations and complications of atherosclerotic vascular disease such as coronary artery disease, angina, myocardial infarction, ischemic stroke, transient ischemic attack, carotid artery disease, peripheral vascular disease (including complications such as claudication), and testing suggesting progression of atherosclerotic vascular disease. Such events do not meet the definition of an adverse event unless assessed to be more severe than expected for the subject's condition.

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

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

Disease Related Events that would qualify as an Adverse Event or Serious Adverse Event:

- An event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition; or
- If the investigator believes there is a causal relationship between the investigational product(s)/study treatment/protocol-required therapies and disease worsening, this must be reported as an Adverse Event or Serious Adverse Event.

9.1.2 Adverse Events

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

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or

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

Resolution of the adverse event will be recorded on the event CRF.

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

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

9.1.3 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria (unless it meets the definition of a Disease Related Event as defined in Section 9.1.1):

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

A disease related event (eg, angina*)* is to be reported as a serious adverse event if:

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

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

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

9.2 Safety Event Reporting Procedures

9.2.1 Reporting Procedures for Disease Related Events

The investigator is responsible for ensuring that all Disease Related Events observed by the investigator or reported by the subject that occur from the time of randomization/ after the first dose of investigational medicinal product(s)/study treatment/protocol-required therapies through 30 days after the last administration of investigational product or the EOS visit/safetyfollow-up visit whichever is later, are recorded on the Event CRF as a Disease Related Event.

Disease Related Events assessed by the investigator to be more severe than expected and/or related to the investigational medicinal product(s)/study treatment/protocol-required therapies, and determined to be serious, must be recorded on the Event CRF as Serious Adverse Events.

Additionally, the investigator is required to report a fatal Disease Related Event on the Event CRF.

9.2.2 Adverse Events

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

Adverse events possibly related to study procedures, adverse device effects and serious adverse events are reported from signing of the ICF. All other adverse events are reported from the time of randomization/first dose of investigational product/study treatment/protocol-required therapies. The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur from signing of the ICF or from the time of randomization/first dose of investigational product/study treatment/protocol-required therapies through 30 days after the last administration of investigational product or the EOS visit/safety follow-up visit or whichever is later, are reported using the Event CRF.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Severity [and/or toxicity per protocol],
- Assessment of relatedness to investigational product (evolocumab/placebo and/or the device (the prefilled Autoinjector/Pen), (AI/Pen) or other protocol-required therapies or study mandated procedures or activity
- Action taken.

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

The investigator must assess whether the adverse event is possibly related to investigational medicinal product (IMP) (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 evolocumab or placebo (investigational medicinal product)?

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

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

If the severity of an adverse event changes from the date of onset to the date of resolution, record a single event for each level of severity on the Event CRF.

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be

recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

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

9.2.2.2 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 ICF through 30 days after the last administration of investigational product or the EOS/ safety follow-up visit, whichever is later, are recorded in the subject's medical record and are submitted to Amgen. This study will be utilizing electronic data capture for serious adverse events. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the Event CRF.

If the electronic data capture (EDC) system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen via an electronic serious adverse event Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix B for a sample of the electronic Serious Adverse Event Contingency Report Form. For EDC studies where 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 investigational medicinal product (IMP) (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 evolocumab or placebo (investigational medicinal product)?

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

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

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

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

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

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.

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

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

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

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen. In some countries (eg, European Union [EU]

member states), investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

9.2.2.4 Reporting a Safety Endpoint as a Study Endpoint

Safety endpoints (eg, treatment emergent adverse events) that are study endpoints are reported on an Event CRF.

9.3 Pregnancy and Lactation Reporting

If a female subject becomes pregnant, or a male subject fathers a child, while the subject is taking evolocumab, report the pregnancy to Amgen Global Patient Safety as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of protocol-required therapies and for an additional 15 weeks after the end of treatment with investigational product, report the pregnancy to Amgen as specified below.

The pregnancy should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

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

If the outcome of the pregnancy meets a criterion for immediate classification as a Serious Adverse Event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a Serious Adverse Event.

If a female breastfeeds while taking protocol-required therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should report lactation cases that occur 15 weeks after the last dose of protocol-required therapies.

Any lactation case should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Co-Primary Endpoints

- Mean percent change from baseline in LDL-C at weeks 10 and 12
- Percent change from baseline in LDL-C at week 12

10.1.1.2 Secondary Endpoints

- The mean of weeks 10 and 12 and for week 12 for the following:

Tier 1:

- Change from baseline in LDL-C
- Percent change from baseline in non-HDL-C
- Percent change from baseline in ApoB
- Percent change from baseline in total cholesterol
- Achievement of target LDL-C < 70 mg/dL (1.8 mmol/L)
- LDL-C response (50% reduction of LDL-C from baseline)

Tier 2:

- Percent change from baseline in Lp(a)
- Percent change from baseline in triglycerides
- Percent change from baseline in HDL-C
- Percent change from baseline in VLDL-C

10.1.1.3 Safety Endpoints

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

10.1.1.4 Exploratory Endpoint(s)

- Mean percent change from baseline in ApoA1 at weeks 10 and 12
- Percent change from baseline in ApoA1 at week 12
- Change from baseline in hsCRP
- PCSK9 change from baseline 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
  - VLDL-C
  - HDL-C
  - ApoA1
  - triglycerides
  - Lp(a)

10.1.2 Analysis Sets

The full analysis set (FAS) includes all randomized subjects who received at least 1 dose of investigational product. This analysis set will be used in both efficacy and safety analyses. In efficacy analyses, subjects will be grouped according to their randomized treatment group assignment. For safety analyses, subjects will be grouped according to their randomized treatment group assignment with the following exception: if a subject receives treatment throughout the study that is different than the randomized treatment group assignment, then the subject will be grouped by the actual treatment group.

The completer analysis set (CAS) includes subjects in the FAS who adhered to the scheduled investigational product regimen and have observed values for the co-primary endpoints.

10.1.3 Covariates and Sub-groups

Baseline covariates and sub-groups include, but are not limited to:

- Stratification factors:
  - entry CV risk (high/very high CV risk vs not high/very high CV risk).
- Age: < 65 year, ≥ 65 years
- Sex

- Medical history of Diabetes (yes/no)
- Study baseline LDL-C: < median / ≥ median
- Family history of premature coronary heart disease (yes/no)
- Baseline PCSK9
- Diagnosis of HeFH according to protocol defined criteria

Missing data will not be imputed for safety endpoints.

10.2 Sample Size Considerations

The sample size for this study has been considered to meet the requirement from regulatory authority (Drug Registration Regulation No 28; Oct 2007).

The planned total sample size is 450 subjects (150 randomized to evolocumab SC 140 mg Q2W, 150 randomized to evolocumab SC 420 mg QM, 75 randomized to placebo Q2W and 75 randomized to placebo QM). The primary analysis will require the tests of each co-primary endpoint to be significant at level of 0.05. The sample size should provide adequate power to determine the superiority of evolocumab (either Q2W or QM) relative to respective placebo (Q2W or QM) as measured by the co-primary endpoints.

From the phase 3 study 20120122 and phase 2 study 20110155, the mean treatment effect of evolocumab 140 mg Q2W and 420 mg QM compared to placebo in percent change from baseline in LDL-C at week 12 was at least -50.3%, with the smallest treatment effect of -44.6% estimated from 95% confidence intervals. For the co-primary endpoint of mean percent change from baseline in LDL-C at weeks 10 and 12, the mean treatment effect of evolocumab 140 mg Q2W and 420 mg QM compared to placebo was at least -62.4%, with the smallest treatment effect of -57.2% estimated from 95% confidence intervals.

The assumed treatment effect of evolocumab in LDL-C reduction is 40%, with a common SD of 25%. As the co-primary endpoints are correlated, the planned sample size will provide approximately at least 98% (99% x 99%) power in testing the superiority of each evolocumab dosing regimen over placebo on the co-primary endpoints, assuming a 10% drop out rate.

Since the testing statistics from Q2W and QM groups are independent, there is a 96% chance (98% x 98%) to show the superiority of both evolocumab dosing regimens over placebo.

The power calculation is derived using SAS Enterprise Guide version 6.1.

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Unblinding and potentially unblinding information should not be distributed to the study team, investigators or subjects prior to the study being formally unblinded (eg, the formal unblinding may occur at the final analysis rather than during the primary analysis) except as specified (eg, Section 5.2 and Section 9.2.2.2).

Amgen staff members who are involved in randomization, biological sample management, performing PK, and anti-evolocumab assay analysis will have treatment assignment information, but will not have access to subject level data from the clinical trial database.

10.4 Planned Analyses

10.4.1 Primary Analysis

The primary analysis will be performed when all subjects have either completed all scheduled study visits or have early terminated from the study. At that time, the database will be cleaned, processed and locked; the study will also be unblinded.

10.5 Planned Methods of Analysis

10.5.1 General Considerations

Efficacy and safety analyses will be performed on the FAS. Unless specified otherwise, the FAS will be the default analysis set in this study and data will be summarized by randomized treatment group. Analyses will be performed separately by each dose frequency (Q2W and QM) unless specified otherwise. The superiority of evolocumab to placebo will be assessed for all efficacy endpoints.

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

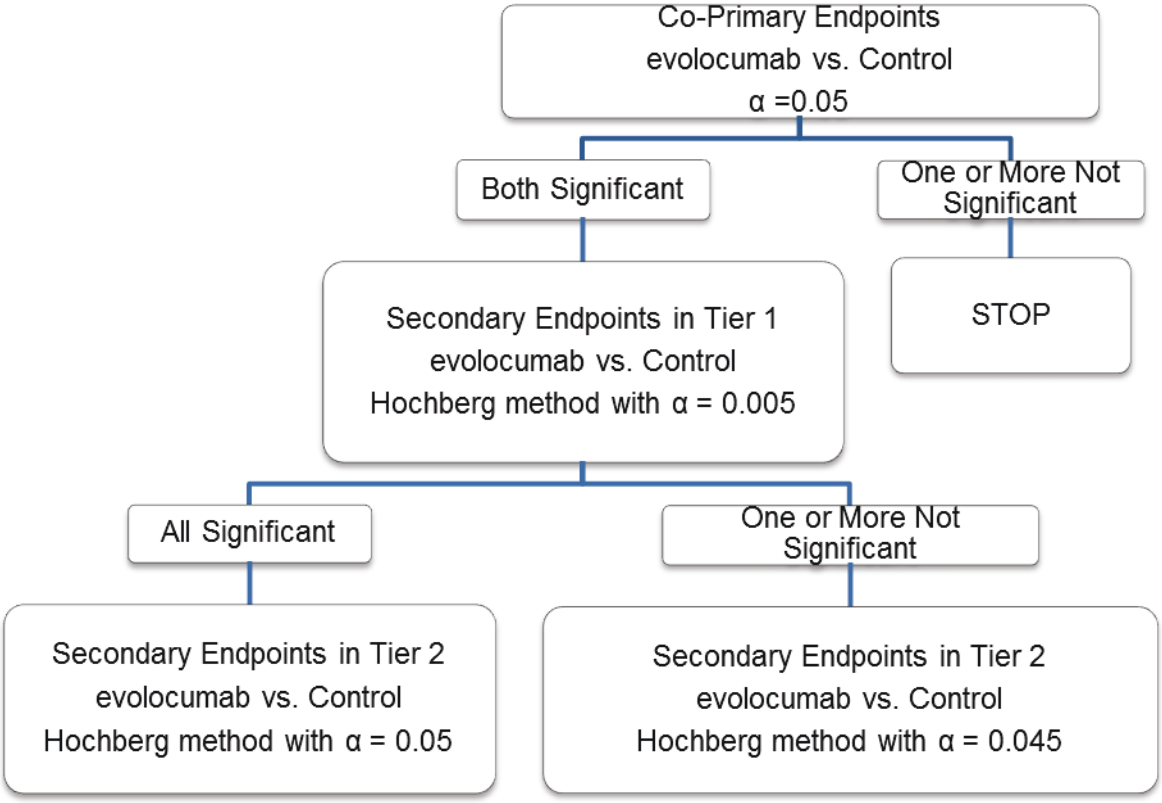
Summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation, or standard error, minimum, and maximum. For categorical variables, the frequency and percentage will be given.

Missing data will not be imputed for safety endpoints.

Multiplicity Adjustment Method

The analyses of Q2W and QM will be performed as 2 independent experiments. In order to preserve the familywise error rate at 0.05 within each independent experiment (Q2W and QM), methods of adjusting for multiplicity due to multiple endpoints

(co-primary and secondary efficacy endpoints) within each dose frequency are described in the diagram below.



Testing of each endpoint pair will result in a single p-value, and for secondary endpoints these p-values will then be used in the Hochberg procedure. The following method will be used to preserve the family wise error rate for the co-primary and secondary endpoints for testing within each dose frequency:

1. If the treatment effect from the primary analysis of the co-primary endpoints are both significant at a significance level of 0.05, statistical testing of the tier 1 secondary efficacy endpoints (as defined in Section 10.5.3) will follow the Hochberg procedure at a significance level of 0.005 (Hochberg, 1988)
2. If all tier 1 secondary efficacy endpoints are significant, the tier 2 secondary efficacy endpoints will be tested using the Hochberg procedure at a significance level of 0.05.
3. If not all tier 1 secondary efficacy endpoints are significant, the tier 2 secondary efficacy endpoints will be tested using the Hochberg procedure at a significance level of 0.045 (Wiens, 2003)

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

10.5.2 Co-Primary Efficacy Endpoints

10.5.2.1 Primary Analysis

To assess the co-primary endpoints of the mean percent change from baseline in LDL-C at weeks 10 and 12 and the percent change in LDL-C from baseline at week 12, a repeated measures linear effects model will be used on the FAS in each dose frequency to compare the efficacy of evolocumab with placebo. The repeated measures model will include terms for treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjustment procedures are defined in Section 10.5.1.

10.5.2.2 Subgroup Analysis

If applicable, subgroup analyses on the co-primary efficacy endpoints will be conducted using the stratification factor and baseline covariates.

10.5.3 Secondary Efficacy Endpoint(s)

The statistical model and testing of the tier 1 secondary efficacy endpoints will be similar to the primary analysis of the co-primary endpoints. The secondary efficacy endpoints of LDL-C response (achievement of LDL-C < 70 mg/dL and achievement of > 50% LDL-C reduction from baseline) will be analyzed using the Cochran-Mantel Haenszel (CMH) test adjusted by the stratification factor.

Analyses of the tier 2 secondary efficacy endpoints will use the same analysis model as the tier 1 endpoints, and testing will use a union-intersection test.

Multiplicity adjustment procedures are defined in Section 10.5.1.

10.5.4 Safety Endpoints

10.5.4.1 Treatment Emergent Adverse Events

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

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

10.5.4.2 Laboratory Parameters

Selected safety laboratory parameters will be summarized using descriptive statistics.

10.5.4.3 Vital Signs

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

10.5.4.4 Concomitant Medications

Concomitant Medications of interest will be summarized for each treatment group

10.5.4.5 Anti-evolocumab antibody

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

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

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

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

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

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

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

11.2 Institutional Review Board/Independent Ethics Committee

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

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

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

11.3 Subject Confidentiality

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

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

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

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

11.4 Investigator Signatory Obligations

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

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. After Amgen amends the protocol, Investigator is to return the signed Investigator's Signature page confirming agreement to continue participation in the study according to the amendment. The <<*IRB/IEC*>> must be informed of all amendments and give approval. The investigator **must** send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

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 Clinical Trial Agreement. The investigator is to notify the <<*IRB/IEC*>>

in writing of the study's completion or early termination and send a copy of the notification to Amgen.

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

12.2 Study Documentation and Archive

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

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

In this study, the IVR/IWR system captures the following data points and these are considered source data: protocol number, site number, subject ID, gender, date of birth, date informed consent was signed, treatment group assignment, screen failure reason, randomization date, randomization number and investigational product box ID assignment.

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 CRFs, 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 <<IRB/IEC>> and Amgen.
- Investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.
- Non-investigational product(s) and or medical device(s) documentation, as applicable.

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

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

12.3 Study Monitoring and Data Collection

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

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

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

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

Data capture for this study is planned to be electronic:

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

the study is set up to accept an electronic signature. This signature indicates that investigator inspected or reviewed the data on the CRF, the data queries, and agrees with the content.

Amgen (or designee) will perform Self-Evident Corrections (SEC) to obvious data errors in the clinical trial database. SECs will be documented in the eCRF instructions available in the EDC system. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (ie, the same results sent twice with the same date with different visit, [eg, week 4 and early termination]) and updating a specific response if the confirming datum is provided in the "other,specify" field (eg, for race, reason for ending study).

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 2), the investigator can search publically available records [where permitted] to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

CRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

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

12.6 Publication Policy

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

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors [ICMJE] Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states:

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

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

12.7 Compensation

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

13. REFERENCES

Bi Y, Gao R, Patel A, et al. Evidence-based medication use among Chinese patients with acute coronary syndromes at the time of hospital discharge and 1 year after hospitalization: results from the Clinical Pathways for Acute Coronary Syndromes in China (CPACS) study. *Am Heart J.* 2009;157:509-516.

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.

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.

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.

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

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

HPS2-THRIVE Collaborative Group. HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. *Eur Heart J.* 2013;34:1279–1291

Hu D, Li J, Li X. Investigation of blood lipid levels and statin interventions in outpatients with coronary artery disease in China: The China Cholesterol Education Program (CCEP). *Circ J.* 2008;72:2040-2045.

Knopp RH. Drug treatment of lipid disorders. *N Engl J Med.* 1999;341:498-511.

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. *Circ.* 2002;106:3143-3421.

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

Silva M, Matthews ML, Jarvis C, et al. Meta-analysis of drug induced adverse events associated with intensive-dose statin therapy. *Clin Thera.* 2007;29:253-260.

Wiens BL. A fixed sequence bonferroni procedure for testing multiple endpoints. *Pharmaceut Statist.* 2003;2:211-215.

Zhao S, Wang Y, Mu Y, et al; DYSIS-China Study Investigators. Prevalence of dyslipidaemia in patients treated with lipid-lowering agents in China: results of the DYSlipidemia International Study (DYSIS). *Atherosclerosis*. 2014;235:463-469

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

14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The Common Terminology Criteria for Adverse Events (CTCAE) is available at the following location:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm]

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation according to the criteria specified in Section 6.5 require the following:

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

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.2.2.2.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 1 or who experience AST or ALT elevations > 3 x ULN or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels.

Assessments that are to be performed during this period include:

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

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

- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:
  - Complete blood count (CBC) with differential to assess for eosinophilia
  - Serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
  - Serum acetaminophen (paracetamol) levels
  - A more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents
    - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
    - Prior and/or concurrent use of alcohol, recreational drugs and special diets
    - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
  - Viral serologies
  - Creatinine phosphokinase, haptoglobin, lactate dehydrogenase (LDH), and peripheral blood smear
  - Appropriate liver imaging if clinically indicated
    - Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
    - Hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
    - Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

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

Appendix B. Sample eSerious Event Contingency Form

AMGEN
Study # 20150172
Evolocumab (AMG 145)

Electronic Serious Adverse Event Contingency Report Form

For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

<< For competion by COM prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____

and start date: Day ____ Month ____ Year _____

3. SERIOUS ADVERSE EVENT

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

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report. List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.	Date Started (Day Month Year)	Date Ended (Day Month Year)	Check only if event occurred before first dose of IP	Is event serious?	Is event a potential endpoint?	If serious, enter Serious Criteria code (see codes below)	Relationship: Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? Evolocumab (AMG 145) No / Yes	Relationship: Prefilled autoinjector/ pen (Aipen) No / Yes	Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No	☐Yes ☐No					
				☐Yes ☐No	☐Yes ☐No					
				☐Yes ☐No	☐Yes ☐No					

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

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

Date Admitted (Day Month Year)	Date Discharged (Day Month Year)

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

IP/Amgen Device:		Date of Initial Dose (Day Month Year)	Prior to, or at time of Event: Date of Dose (Day Month Year)	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
Evolocumab (AMG 145)	☒ *Evolocumab (AMG 145) is blinded*							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Prefilled Autoinjector/Pen (AIPen) (*Amgen medical device*)	☒ *Device is open label*							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

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AMGEN
Study # 20150172
Evolocumab (AMG 145)

Electronic Serious Adverse Event Contingency Report Form

For Restricted Use

Site Number	Subject ID Number

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

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

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Test											
	Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

Approved

AMGEN Study # 20150172 Evolocumab (AMG 145)	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

	Site Number	Subject ID Number	

10. CASE DESCRIPTION *(Provide narrative details of events listed in section 3)* Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

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

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20150172

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

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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: 20150172

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.

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