Title Page

Protocol Title:		High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study (HUYGENS)
Short Protocol Title:		Imaging of Coronary Plaques in Subjects Treated With Evolocumab
Protocol Number:		20160184
Investigational Product:		Evolocumab
Trade Name:		Repatha®
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Investigator's Agreement:

I have read the attached protocol entitled High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study (HUYGENS), dated 19 April 2018, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or local regulations/guidelines.

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.

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Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

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1. Protocol Synopsis

Protocol Title: High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study (HUYGENS)

Short Protocol Title: Imaging of Coronary Plaques in Subjects Treated With Evolocumab

Study Phase: 3

Indication: Coronary Artery Disease (CAD)

Rationale

Plaque morphology plays pivotal role for the development of acute coronary syndromes (ACS). Lipid-lowering therapy with statins has proven to have beneficial effects on plaque morphology in patients suffering from coronary artery disease (CAD). Treatment with evolocumab in addition to optimal statin therapy has been shown to result in a regression of atherosclerotic plaque burden. While treatment with evolocumab is associated with a reduction in cardiovascular events, it is uncertain whether additional effects on plaque, beyond regression, may contribute to this benefit. The development of advanced imaging techniques permits evaluation of the effect of treatment on plaque phenotype features consistent with plaque instability. This study seeks to identify morphologic changes, such as increase in fibrous cap thickness (FCT), in atherosclerotic plaques associated with treatment with evolocumab and maximally tolerated statin therapy with or without additional lipid-modifying medication in patients presenting with non-ST-segment elevation (NSTE)-ACS using optical coherence tomography (OCT; primary, secondary, and exploratory endpoints) and intravascular ultrasound (IVUS; exploratory endpoints only - see Section 4.1 of the protocol).

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To evaluate the effect of evolocumab on fibrous cap thickness (FCT) in subjects with non-ST-elevation acute coronary syndrome (NSTE-ACS) who are taking maximally tolerated statin therapy.	• Absolute change in minimum FCT in a matched segment of artery as determined by optical coherence tomography (OCT) from baseline to week 50.
Secondary	

• To evaluate the effects of evolocumab on coronary plaque morphology in subjects with NSTE-ACS who are taking maximally tolerated statin therapy.	• Coronary artery segment-based:
	  • Percent change in minimum FCT in a matched segment of artery as determined by OCT from baseline to week 50.
	  • Absolute change in mean minimum FCT for all images assessed in an individual subject as determined by OCT from baseline to week 50.
	  • Absolute change in the maximum lipid arc in a matched segment of artery as determined by OCT from baseline to week 50.
	• Plaque-based:
	  • Absolute change in minimum FCT, maximum lipid arc, and lipid core length in lipid rich plaques defined as minimum FCT < 120 μm and lipid arc > 90° in at least 3 consecutive images as determined by OCT from baseline to week 50.

Safety	
• To evaluate the safety and tolerability of evolocumab treatment in subjects with NSTE-ACS who are taking maximally tolerated statin therapy.	• Subject incidence of treatment-emergent adverse events and serious adverse events.

Hypotheses

The primary hypothesis is that low-density lipoprotein cholesterol (LDL-C) lowering with evolocumab 420 mg monthly (QM) will result in a greater increase from baseline in

minimum FCT at week 50 than placebo in subjects taking maximally tolerated statin therapy.

Overall Design

This is a phase 3, double-blind, placebo-controlled, randomized study evaluating the effect of evolocumab on coronary atherosclerotic plaques as assessed by OCT at baseline and at week 50 in subjects with an NSTE-ACS. The trial duration of 1 year was chosen based on the results of several historical trials. Subjects will be randomized 1:1 into 2 treatment groups no more than 7 days after the signing of the informed consent: evolocumab 420 mg subcutaneously (SC) QM or placebo SC QM. The randomization will be stratified by current statin use (> 4 weeks or ≤ 4 weeks duration) at screening. Investigators will up-titrate statin therapy to the maximally tolerated dose, in accordance with local guidelines, for subjects prior to randomization.

Number of Subjects

Approximately 150 subjects will be enrolled in the study.

Summary of Subject Eligibility Criteria

Key Inclusion Criteria

- Age ≥ 18 years at screening.
- Clinical indication for coronary angiography during admission due to NSTE-ACS with interventional treatment of culprit plaque.
- LDL-C level via local lab assessment based on statin use at screening:
  - No statin use: ≥ 130 mg/dL
  - Low- or moderate-intensity statin use: ≥ 80 mg/dL
  - High-intensity statin use: ≥ 60 mg/dL
- On maximally tolerated statin therapy in accordance with standard of care per local guidelines prior to randomization.
- Tolerates placebo run-in injection at screening.
- Meet all the following criteria at the qualifying coronary angiogram:
  - Angiographic evidence of coronary artery disease (CAD) with ≥ 20% reduction of lumen diameter by angiographic visual estimation, in addition to the culprit plaque.
  - Left main coronary artery must not have a > 50% reduction in lumen diameter by visual angiographic estimation.
  - Targeted vessel:
    - may not be the culprit vessel for the current or a previous myocardial infarction (MI).
    - has not undergone prior percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), and may not be a bypass graft.

  - may not be a candidate for PCI or CABG currently or over the next 12 months, in the opinion of the investigator.
  - must be accessible by the OCT catheter.
- Targeted segment:
  - must have up to 50% but not > 50% reduction in lumen diameter by visual angiographic estimation and must be at least 40 mm in length.
  - must contain at least 1 image with an FCT of ≤ 120 µm and at least 1 image with a lipid arc of > 90° as determined by the imaging core laboratory.
  - distal plaques of up to 50% stenosis by visual angiographic estimation are permitted, provided that such stenosis is not a target for PCI or CABG.

For a full list of eligibility criteria, please refer to Section 6.1 to Section 6.2.

Treatments

Evolocumab QM will be administered on day 1 through week 48 with a personal injector or prefilled autoinjector/pens (AI/Pens).

Subcutaneous evolocumab and placebo will be administered at the study site or in an appropriate non-clinic setting (eg, at home). Observed, in-clinic dosing must occur at day 1 and should occur at week 4, and week 24. At home dosing by the subject should occur for all remaining dose administrations. Subjects who do not wish to self-inject at home may return to the clinic for injection.

Evolocumab or matching placebo will be administered in accordance with instructions in the IPIM and the Information for Use (IFU). The subject (or designee) must have demonstrated competency, as per site judgment, at administration of SC injections before self-administration is permitted. The first self-administered dose by the subject (or designee) must be administered at the site under the supervision of a healthcare provider.

It is suggested that the evolocumab administration is done by the subject under site staff supervision at each of the regular study visits (except day 1) to reinforce proper use of the injection device. If evolocumab or matching placebo is to be administered during the study visit, administration must occur after all other procedures have been completed.

Procedures

Written informed consent must be obtained from all subjects or legally acceptable representatives before any study-specific procedures are performed. Subjects will be assessed for eligibility and medical as well as medication history will be obtained. Subjects will undergo clinically-indicated coronary angiography for further clinical evaluation. Subjects who require a PCI because of qualifying angiography will have

baseline OCT and IVUS performed following the PCI. OCT and IVUS must not be performed in vessels that underwent an intervention. Prior to performing the baseline OCT and IVUS examinations, investigators should ensure that subjects' initial screening LDL-C results are available. If angiographic criteria are met, the subject will have baseline OCT and IVUS completed. Subjects should undergo all labs and receive a 3.5 mL placebo injection by SC administration to assess SC injection tolerability, at screening.

At randomization, an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) will allocate subjects to receive either evolocumab SC QM or placebo SC QM. Day 1 of the treatment period (ie, first dose of investigational product) must happen within 7 days of the signing of the informed consent. Investigational product will be administered monthly (every 4 weeks ± 3 days). Final administration of evolocumab or placebo will occur at week 48.

Subjects must fast overnight when fasting lipid samples are to be obtained (ie, day 1, week 24, and week 50). If the subject is not fasting for the day 1 visit, no visit procedures are performed and the visit should be rescheduled within the applicable protocol window. 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 for fasting labs and investigational product administration.

During the week 4, 12, 24, 36, and 50 visits, adverse events, serious adverse events, and concomitant medications will be recorded. Physical exams, laboratory tests and other procedures will be performed at the time points indicated in the Schedule of Activities (Table 2-1).

Final follow-up OCT and IVUS should take place at 50 ± 2 weeks (ie, 48 to 52 weeks) after initial baseline image acquisition. In any case, it is critical that the follow-up OCT and IVUS be obtained for all subjects, regardless of whether they discontinued study drug prematurely or are outside the 50 ± 2 weeks window.

End of study (EOS) for all subjects is by contact (eg, phone call) from the site at week 52 for any potential adverse events or serious adverse events. End of study phone call must be ≥ 2 weeks after the follow-up OCT and IVUS or ≥ 4 weeks after the last dose of treatment period investigational product administration, whichever is later.

For a full list of study procedures, including the timing of each procedure, please refer to Section 9.2 and the Schedule of Activities in Table 2-1.

Statistical Considerations

The planned total sample size is 150 subjects (75 randomized to evolocumab 420 mg SC QM and 75 randomized to placebo SC QM). This sample size will provide sufficient power (90%) to determine whether there is a treatment effect of evolocumab relative to placebo in the primary endpoint. The primary endpoint for the study is the absolute change in minimum fibrous cap thickness (FCT) from baseline to week 50 in a matched segment of artery as determined by optical coherence tomography (OCT). Hypothesis testing of the primary endpoint will be the primary objective of the final analysis. There will be no interim analysis for this study. The final analysis will be conducted after all subjects have either completed all the scheduled study visits or have early terminated from the study. At that time, the database will be cleaned and locked followed by unblinding of the study.

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

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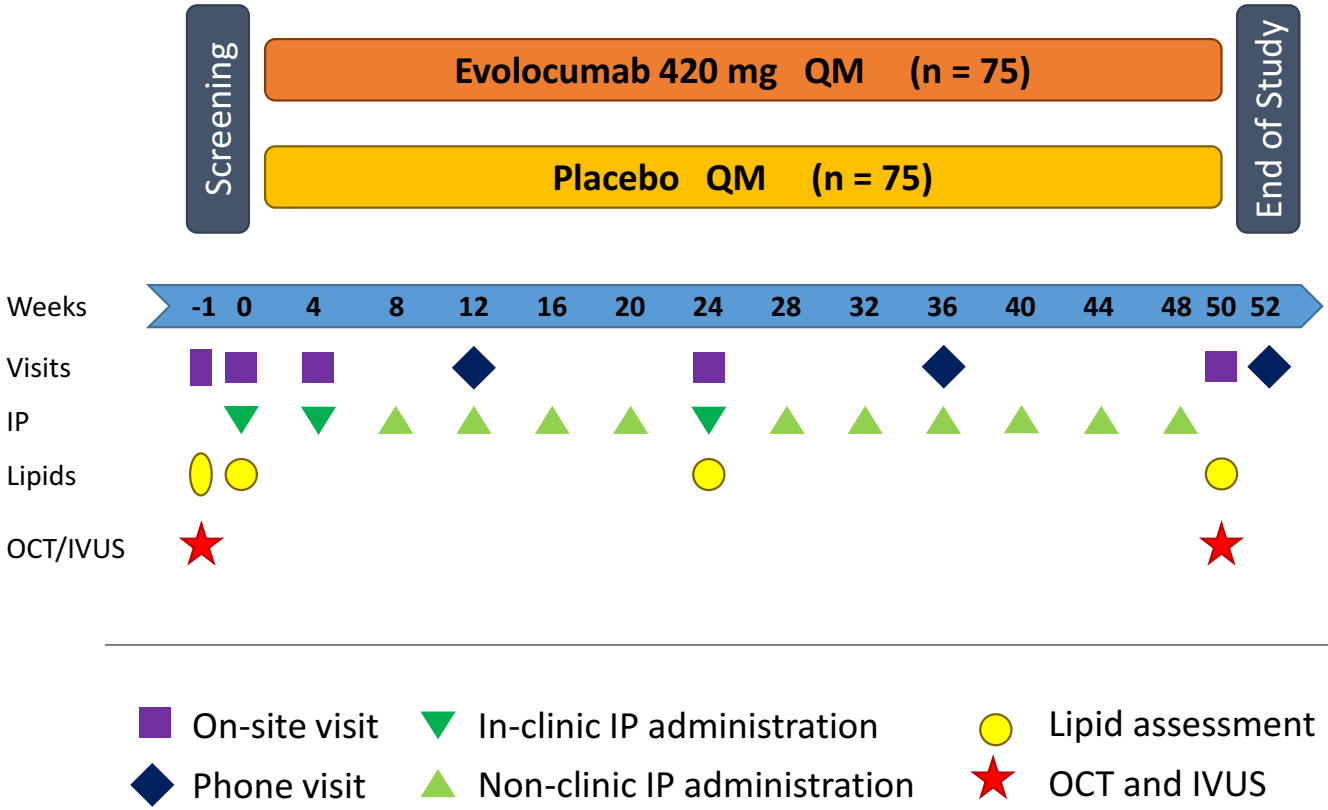
2.1



IP = investigational product; IVUS = intravascular ultrasound; OCT = optical coherence tomography; QM = every 4 weeks ± 3 days for each visit/dose

Note: To minimize the chances of performing unnecessary invasive procedures, investigators should ensure that initial screening lipid results are available prior to performing the baseline OCT and IVUS examination.
Note: Subjects may administer study drug at the clinic on non-visit days if preferred.

2.2 Schedule of Activities

Table 2-1. Schedule of Activities

PROCEDURE	Screening	Treatment Period (± 7 days)						End of Study[b] (+ 7 days)
		Day 1[a]	Week 4	Week 12[b] (Phone Visit)	Week 24	Week 36[b] (Phone Visit)	Week 50	Week 52 (Phone Visit)
GENERAL AND SAFETY ASSESSMENTS								
Informed consent	X							
Inclusion and exclusion criteria	X							
Demographics	X							
Physical examination	X	X					X	
Medical history	X							
Vital signs	X	X					X	
Personal injector or AI/Pen instructions and training		X						
Adverse events	X	X	X	X	X	X	X	X
Serious adverse events	X	X	X	X	X	X	X	X
Adverse device effects	X	X	X	X	X	X	X	X
Concomitant therapies review	X	X	X	X	X	X	X	X
LABORATORY ASSESSMENTS								
Urine/Serum pregnancy test (females of childbearing potential only)[c]	X	X			X		X	

Abbreviations and footnotes are defined on last page of table.

Table 2-1. Schedule of Activities

PROCEDURE	Screening	Treatment Period (± 7 days)						End of Study[b] (+ 7 days)
		Day 1[a]	Week 4	Week 12[b] (Phone Visit)	Week 24	Week 36[b] (Phone Visit)	Week 50	Week 52 (Phone Visit)
Chemistry	X							
Lipid testing[d]	X							
Fasting lipid testing[e]		X			X		X	
STUDY-SPECIFIC ASSESSMENTS (eg, DISEASE-SPECIFIC ASSESSMENTS, RADIOLOGICAL ASSESSMENTS)								
OCT	X						X[f]	
IVUS	X						X[f]	
BIOMARKER ASSESSMENTS								
Biomarker collection (blood/plasma)		X					X	
STUDY TREATMENT								
Placebo run-in[g]	X							
Statin optimization[h]	X							
Amgen investigational product dispensation			X		X			
Observe investigational product self-administration at hospital/clinic (retraining, if applicable)[i]		X	X		X			
Amgen investigational product administration		Investigational product administered once every 4 weeks (QM) beginning day 1 and ending week 48[j]						

AI = autoinjector; ApoA1 = apolipoprotein A1; ApoB = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; IVUS = intravascular ultrasound; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); OCT = optical coherence tomography; QM = every 4 weeks ± 3 days; TC = total cholesterol; TG = triglyceride; VLDL-C = very low-density lipoprotein cholesterol

[a] Day 1 is the first administration day of investigational product. Must be within 7 days the signing of informed consent.

[b] Subjects to participate in a phone visit. End of study phone call must be ≥ 2 weeks after the follow-up OCT and IVUS or ≥ 4 weeks after the last dose of treatment period investigational product administration, whichever is later.

[c] Urine/serum pregnancy test for females of childbearing potential is assessed by local lab, prior to coronary catherization (as applicable).

[d] Local laboratory is used during screening period for TG and LDL-C measurements. To minimize the chances of performing unnecessary invasive procedures, investigators should ensure that subjects' initial screening LDL-C results are available prior to performing the baseline OCT examination.
[e] Lipid measurements during treatment period must be performed via central lab. Collected lipids will consist of TC, HDL-C, VLDL-C, LDL-C, ApoA1, ApoB, TG, and Lp(a). If subject is not fasting on day 1, reschedule; if subject is not fasting after day 1, do all procedures except fasting labs and investigational product administration, if applicable; schedule another visit, if possible within the visit window for fasting labs and investigational product administration.
[f] Final, follow-up OCT and IVUS should take place 50 ± 2 weeks (ie, 48 to 52 weeks) after initial baseline image acquisition. End of study phone call must be ≥ 2 weeks after the follow-up OCT and IVUS or ≥ 4 weeks after the last dose of treatment period investigational product administration, whichever is later.
[g] Healthcare professional will deliver the placebo run-in at screening.
[h] Statin optimization occurs prior to randomization for all subjects.
[i] Personal injector or AI/Pen training will occur at the day 1 visit and each visit thereafter if necessary. First investigational product administration will be either in hospital or in clinic by subject after self-administration training.
[j] Investigational product administered QM beginning day 1 and ending week 48. Week 48 investigational product administration must occur prior to OCT and IVUS at week 50.

3. Introduction

3.1 Study Rationale

Plaque morphology plays pivotal role for the development of acute coronary syndromes (ACS) (Toutouzas et al, 2011; Ino et al, 2011). Lipid-lowering therapy with statins has proven to have beneficial effects on plaque morphology in patients suffering from coronary artery disease (CAD) (Takarada et al, 2009). Treatment with evolocumab in addition to optimal statin therapy has been shown to result in a regression of atherosclerotic plaque burden (Nicholls et al, 2016). While treatment with evolocumab is associated with a reduction in cardiovascular events (Sabatine et al, 2017), it is uncertain whether additional effects on plaque, beyond regression, may contribute to this benefit. The development of advanced imaging techniques permits evaluation of the effect of treatment on plaque phenotype features consistent with plaque instability. This study seeks to identify morphologic changes, such as increase in fibrous cap thickness (FCT), in atherosclerotic plaques associated with treatment with evolocumab and maximally tolerated statin therapy with or without additional lipid-modifying medication in patients presenting with non-ST-segment elevation (NSTE)-ACS using optical coherence tomography (OCT; primary, secondary, and exploratory endpoints) and intravascular ultrasound (IVUS; exploratory endpoints only - see Section 4.1).

3.2 Background

3.2.1 Cardiovascular Disease

According to the World Health Organization, cardiovascular disease is the leading cause of death and disability, accounting for approximately 31% of all deaths and 46% of deaths from noncommunicable diseases worldwide (World Health Organization, 2014). Of deaths related to cardiovascular disease, approximately 80% are from myocardial infarction or stroke (World Health Organization, 2014). The morbidity associated with myocardial infarction and stroke continues to be serious and multifaceted, the reduction of which is an important treatment goal. Each year, it is estimated that 935 000 Americans have myocardial infarction or coronary death, 155 000 have a silent first myocardial infarction, 610 000 have a new stroke (ischemic or hemorrhagic), and 185 000 have a recurrent stroke (Mozaffarian et al, 2016).

Elevated cholesterol, in particular low-density lipoprotein cholesterol (LDL-C), is a modifiable independent cardiovascular risk factor (Silverman et al, 2016). The effects of LDL-C on cardiovascular risk likely begin at the level of the arterial wall since low-density lipoprotein particles drive atheroma formation and progression

(Moore and Tabas, 2011). The formation of flow obstructing lesions and/or acute plaque rupture with subsequent thrombogenesis result in clinical sequelae including coronary heart, cerebrovascular, and peripheral arterial diseases. Results from imaging studies demonstrated that reductions in LDL-C can slow or halt coronary atheroma progression or even reduce their volume (Räber et al, 2015; Nicholls et al, 2016; Nicholls et al, 2011; Nissen et al, 2006; Nissen et al, 2004). These data illustrate important biologic effects of LDL-C reduction and support a potential mechanism by which lowering LDL-C reduces risk of cardiovascular events.

Many interventional studies evaluated the impact of therapeutic reductions in LDL-C on cardiovascular outcomes (Silverman et al, 2016; Cholesterol Treatment Trialists' [CTT] Collaboration et al, 2010). A meta-analysis (Silverman et al, 2016) included 49 randomized, controlled, cardiovascular outcomes studies and over 312 000 subjects to analyze the effects of therapies that act primarily via low-density lipoprotein receptor (LDLR) upregulation. Results from these studies show a strong relationship between LDL-C lowering and cardiovascular event reduction for drugs such as statins (Cannon et al, 2004; Sacks et al, 1996; Scandinavian Simvastatin Survival Study Group, 1994) and ezetimibe (Cannon et al, 2015).

3.2.2 Intracoronary Imaging

Several intracoronary imaging techniques exist to visualize coronary anatomy and assess the presence and extent of CAD. Fluoroscopic angiography allows a 2-dimensional depiction of the coronary arterial vasculature by delineating the vascular lumen. However, it is limited by its inability to provide detailed assessments of the vessel wall, particularly the intima and media, where coronary plaque formation takes place. In addition to fluoroscopy, IVUS and OCT are well-established imaging modalities frequently used in clinical practice (Matthews and Frishman, 2017).

Intravascular ultrasound uses an ultrasound transducer mounted on a coronary catheter. It provides cross-sectional, grey-scale images and can cover the entire circumference of the coronary artery wall from the inner border to the outer layer, thereby visualizing the extent of coronary plaque burden. With IVUS, large coronary segments can be visualized in a standardized and reproducible manner using automated pullback of the ultrasound probe (Nair et al, 2002; Nissen et al, 1991). In addition, IVUS has proven to be a valuable tool in clinical trials (Nicholls et al, 2016); however, IVUS image acquisition can be limited or impaired due to transducer rotation, guide wires and other mechanical hindrances, as well as anatomical and physiological aspects such as the heartbeat,

tortuous arteries, and bifurcations of side branches (ten Hoff et al, 1989). While IVUS is reproducible for quantitative serial plaque volume measurements, it cannot elucidate all features of plaque morphology due to insufficient spatial resolution. Virtual histology data acquired using specialized IVUS catheters may have the ability to provide additional information on plaque composition (eg, visualizing calcifications and quantification of the necrotic core). However, IVUS-virtual histology has limited ability to assess incremental changes in FCT over time (Puri et al, 2014).

Optical coherence tomography is based on coherent light; hence, it does not penetrate as deeply into the tissue and may therefore not always be able to visualize the entire arterial wall, but it provides a higher spatial resolution compared to IVUS. In addition, OCT is not limited by near-field artifacts, a feature commonly seen with ultrasound-based imaging techniques. The practical approach to OCT shares many similarities with IVUS, including some of the mechanical challenges regarding image acquisition. Similar to IVUS, coronary catheters carrying the imaging probe are used to acquire cross-sectional images, which are usually color-coded in sepia. These catheters can be operated manually or via automated pullback (Bezerra et al, 2009; Kume et al, 2005) allowing for a high degree of standardization and reliable reproducibility even when imaging large coronary segments (Kini et al, 2017; Jamil et al, 2013; Gonzalo et al, 2010). Optical coherence tomography's high-resolution images enable clear delineation and exact measurements of individual layers of the vessel wall, including the thin intima. Thus, a strength of OCT lies in its ability to assess intimal disease (Kubo et al, 2007; Yabushita et al, 2002).

All imaging techniques have their respective characteristics; they complement each other and provide interventional cardiologists with a solid armamentarium to assess coronary artery disease. Thus, it is possible to reveal morphologic differences of culprit lesion in STEMI and NSTEMI patients, such as the incidence of plaque rupture as well as the length, size, and location of the aperture in those ruptured plaques (Ino et al, 2011; Toutouzas et al, 2011). It is likely that such refined diagnostic tools will help physicians select the most appropriate treatment for patients (Bezerra et al, 2013). Moreover, the individual cardiovascular risk can be assessed in more detail and addressed accordingly (Tanaka et al, 2008).

In recent years, different features of plaque morphology such as FCT, calcifications, and size of necrotic core have been recognized as determining factors for the risk of acute coronary syndromes, with FCT being the most important predicting factor

(Stone et al, 2011; Virmani et al, 2006). Some publications suggest that FCT < 65 µm is associated with a high risk for future cardiovascular events (Stefanadis et al, 2017; Burke et al, 1997).

3.2.3 Amgen Investigational Product Background: Evolocumab

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

Refer to the Evolocumab (AMG 145) Investigator's Brochure for more information on evolocumab.

3.3 Benefit/Risk Assessment

The following benefit risk assessment supports the conduct of this clinical trial. Reference should be made to the Evolocumab (AMG 145) Investigator's Brochure for further data on evolocumab.

3.3.1 Benefits of Evolocumab

3.3.1.1 Reduction in Low-density Lipoprotein Cholesterol (LDL-C)

In the original marketing application, placebo-adjusted reductions in LDL-C of approximately 55% to 75% were consistently observed with evolocumab in subjects with primary hyperlipidemia (familial or non-familial) or mixed dyslipidemia. Evolocumab was also superior to ezetimibe in these subjects, comparatively reducing LDL-C by approximately 35% to 45%. LDL-C reductions with evolocumab treatment occurred regardless of cardiovascular risk level, statin use (none, low, moderate, or high intensity) or baseline LDL-C. The approved evolocumab dosing regimens of 140 mg every 2 weeks (Q2W) and 420 mg monthly were clinically equivalent. Effects of evolocumab were reversible upon cessation of treatment, with no evidence of rebound. Reductions in LDL-C were maintained during long-term use, without attenuation of effect; to date, results from long-term studies show LDL-C reductions of approximately 60% maintained over 4 years.

Data on reduction in LDL-C from both Study 20120153 (a 78-week, phase 3 study in subjects with clinical signs or symptoms of coronary artery disease [n = 968]) and Study 20110118 (a phase 3 study in subjects with or at risk for atherosclerotic cardiovascular disease [n = 27 564]), were consistent with that reported in the original evolocumab marketing application in subjects with hypercholesterolemia. In Study 20120153, mean reductions from baseline in LDL-C were approximately 60% in the evolocumab group and were maintained through end of study (week 78). In Study 20110118, median reductions in LDL-C of 64% to 70% were observed during evolocumab treatment and these reductions were maintained over the duration of the study (> 36 months) without attenuation of effect. Of note, Study 20110118 represents the lowest on-treatment LDL-C concentrations achieved to date in any cardiovascular outcomes study involving a lipid lowering agent, with 25% of subjects achieving LDL-C concentrations < 20 mg/dL.

3.3.1.2 Regression of Coronary Atherosclerosis

In Study 20120153, statistically significant regression in coronary atherosclerosis was observed at week 78 in comparison with placebo. Evolocumab, when added to statin therapy, reduced percent atheroma volume (PAV) by -1.01% (-1.38%, -0.64%), compared with placebo at week 78 ($p < 0.0001$). Evolocumab also reduced total atheroma volume (TAV) by -4.89% (-7.25%, -2.53%), compared with placebo, at week 78 ($p < 0.0001$). Evolocumab resulted in more regression in coronary atherosclerosis at week 78, compared with placebo, as measured by PAV and TAV; atherosclerosis regression was achieved by 17.0% (95% CI: 10.3, 23.5 [$p < 0.0001$]) and 12.5% (95% CI: 5.8, 19.1 [$p = 0.0002$]) more subjects, respectively, in the evolocumab group compared with the placebo group. In subjects with baseline LDL-C ≥ 70 mg/dL, a total of 61.0% (95% CI: 55.9, 66.1) of evolocumab-treated subjects experienced atherosclerosis regression, as measured by reduction in PAV, compared with 47.1% (95% CI: 41.9, 52.4) in the placebo group. Reducing LDL-C had favorable effects on coronary atherosclerosis even at very low concentrations of LDL-C. Adding evolocumab to statin therapy reduced LDL-C from baseline by 60% (at the end of the dosing interval) to 68% (2 weeks post-dose), and LDL C reductions were maintained through end of study at week 78. Subjects with baseline LDL-C levels below the lowest global targets in use at the time of the study also experienced plaque regression while receiving evolocumab. In addition, post-hoc analysis suggested a continuous relationship between achieved LDL-C and reductions in PAV, with evidence of regression in PAV extending to on-treatment LDL C levels as low as 7 mg/dL. In

conclusion, data from this study show a positive, measurable and statistically significant effect of evolocumab on coronary atherosclerosis, beyond what is achievable with statins alone.

3.3.1.3 Reduction in the Risk of Cardiovascular Events

In Study 20110118, treatment with evolocumab statistically significantly reduced the risk of cardiovascular events. With a median follow-up period of 26 months, evolocumab reduced the risk of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization, whichever occurred first (primary composite endpoint) by 15%, compared with placebo with a hazard ratio (HR) of 0.85 (95% CI: 0.79, 0.92; $p < 0.0001$). Evolocumab reduced the risk of cardiovascular death, myocardial infarction, or stroke, whichever occurred first (key secondary composite endpoint) by 20%, compared with placebo with a HR of 0.80 (95% CI: 0.73, 0.88; $p < 0.0001$). The treatment effect was driven by reductions in myocardial infarction, stroke, and coronary revascularization (primary composite endpoint); and by reductions in myocardial infarction and stroke (secondary composite endpoint), without a detectable effect on cardiovascular death. The primary and key secondary treatment effects were directionally consistent across subgroups. There was a clear relationship between reductions in LDL-C and lower rates of cardiovascular events. This relationship was observed across the spectrum of post baseline LDL-C levels, and no lower LDL-C threshold for this relationship was identified for post-baseline LDL-C levels (mean of lowest decile, 16.2 mg/dL [0.42 mmol/L]). Overall, results from this study provide compelling evidence that evolocumab, through effects on lowering LDL-C, reduces the risk for cardiovascular events in patients with or at risk of atherosclerotic cardiovascular disease who cannot achieve LDL-C control with statins alone.

3.3.2 Risks of Evolocumab

The safety profile provided in the original evolocumab application includes more than 6800 subjects in > 25 clinical studies with evolocumab. The adverse drug reactions consist of nausea, injection site reactions, influenza, nasopharyngitis, upper respiratory tract infection, arthralgia, back pain, rash, and urticaria. There were no important identified risks. Hypersensitivity was determined to be an important potential risk based on the adverse events of rash and urticaria; most events were mild to moderate and non-serious. Evolocumab had a very low rate of immunogenicity (0.1%) which did not affect pharmacokinetics, pharmacodynamics, efficacy, or safety.

Study 20110118 was a large clinical outcomes study of 27 564 subjects. The incidences of adverse events of interest were balanced between treatment groups, with the exception of injection site reactions and hypersensitivity events (rash and urticaria), which are known adverse drug reactions with evolocumab. These events occurred in a slightly higher percentage of evolocumab subjects than placebo subjects, were generally mild to moderate, nonserious, and did not lead to treatment discontinuation. The development of anti-evolocumab antibodies post-baseline was infrequent (0.3%). Anti-evolocumab antibodies were non-neutralizing and not associated with loss of efficacy or any safety concerns. In addition, there were no trends indicative of clinically important treatment-related laboratory abnormalities. No safety risk of very low LDL-C during treatment with evolocumab was identified. Among the evolocumab-treated subjects with post-baseline LDL-C measurements during evolocumab treatment and within 30 days after the last dose, who achieved a minimum LDL-C < 40 mg/dL (88.4%) and a minimum LDL-C < 25 mg/dL (69.9%), overall incidences of adverse events were similar between the evolocumab and placebo groups regardless of achieved LDL-C concentrations. In subjects not known to have pre-existing diabetes mellitus at baseline, a comparable proportion in each treatment group (8.1% evolocumab, 7.7% placebo) developed positively adjudicated new onset diabetes mellitus. No evidence of neurocognitive safety risk was observed based on review of adverse events from Study 20110118 and objective data from its neurocognitive sub-study (Study 20130385). Study 20130385 used a validated, objective assessment of higher-level executive function (Cambridge Neuropsychological Text Automated Battery [CANTAB]) and demonstrated non-inferiority of evolocumab compared with placebo. Neither analysis showed evidence for concern in subjects who achieved LDL-C levels < 40 mg/dL and < 25 mg/dL at least once.

Study 20120153 included a total of 968 subjects (484 evolocumab, 484 placebo) in the safety analysis set. The overall adverse event incidences were similar to those reported in the original evolocumab application and no new safety risks were identified. The incidence, type and severity of events were comparable between the evolocumab and placebo groups.

In the integrated safety set (which included Study 20110118 and Study 20120153), a slightly higher incidence of potential events of hypersensitivity were observed in the evolocumab group compared to the control group. Most of the adverse events were non-serious, reported as grade 1 and 2, and none were fatal. Within the potential

hypersensitivity events, events of rash and urticaria were considered adverse drug reactions for evolocumab and part of the safety profile. Overall, no new risks or change in the nature of the risk have been identified from the combined 28 532 evolocumab subjects in the integrated analysis set.

3.3.3 Conclusion

Overall, this structured benefit-risk assessment provides compelling evidence of the benefit of evolocumab, with minimal evidence of any significant hazard, even in patients that achieved at least one LDL-C value < 40 mg/dL. Adding evolocumab to high- to moderate-intensity statin therapy significantly reduced cardiovascular events. Evolocumab provided robust, consistent, and predictable LDL-C reduction across all populations and patient subgroups studied, regardless of cardiovascular risk, statin use (none, low, moderate, or high intensity), or baseline LDL-C. In addition, these analyses suggest a consistent relationship between lower achieved LDL-C and lower cardiovascular event rates to LDL-C levels as low as 16.2 mg/dL (mean LDL-C in lowest decile).

The safety data for evolocumab to date indicated no important identified risks. Hypersensitivity is an important potential risk; the incidence of hypersensitivity events is low and adverse events are mild to moderate in severity.

Based on the above evidence, the benefit-risk profile of evolocumab is favorable for use in:

- adults with hyperlipidemia, alone or in combination with other lipid-lowering therapies, as an adjunct to diet to reduce LDL-C.
- adults and adolescents aged 12 years and over with HoFH to reduce LDL-C, TC, ApoB, and non-HDL-C in combination with other lipid-lowering therapies (eg, statins, low-density lipoprotein [LDL] apheresis).
- adults with coronary artery disease for regression of coronary atherosclerosis.
- patients with established atherosclerotic cardiovascular disease to reduce the risk of cardiovascular events.

4. Objectives, Endpoints, and Hypotheses

4.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of evolocumab on fibrous cap thickness (FCT) in subjects with non-ST-elevation acute coronary syndrome (NSTE-ACS) who are taking maximally tolerated statin therapy.	• Absolute change in minimum FCT in a matched segment of artery as determined by optical coherence tomography (OCT) from baseline to week 50.
Secondary	

• To evaluate the effects of evolocumab on coronary plaque morphology in subjects with NSTE-ACS who are taking maximally tolerated statin therapy.	• Coronary artery segment-based:
	  • Percent change in minimum FCT in a matched segment of artery as determined by OCT from baseline to week 50.
	  • Absolute change in mean minimum FCT for all images assessed in an individual subject as determined by OCT from baseline to week 50.
	  • Absolute change in the maximum lipid arc in a matched segment of artery as determined by OCT from baseline to week 50.
	• Plaque-based:
	  • Absolute change in minimum FCT, maximum lipid arc, and lipid core length in lipid rich plaques defined as minimum FCT < 120 μm and lipid arc > 90° in at least 3 consecutive images as determined by OCT from baseline to week 50.

Safety	
• To evaluate the safety and tolerability of evolocumab treatment in subjects with NSTE-ACS who are taking maximally tolerated statin therapy.	• Subject incidence of treatment-emergent adverse events and serious adverse events.

Objectives	Endpoints
Exploratory	
• To evaluate the effects of evolocumab on lipid parameters in subjects with NSTE-ACS who are taking maximally tolerated statin therapy. • To evaluate the effects of evolocumab on features of coronary plaques in subjects with NSTE-ACS who are taking maximally tolerated statin therapy using different imaging techniques.	• Absolute and percent changes in lipid parameters by visit from baseline. • Absolute change in number of microchannels in matched segments of all lesions assessed in an individual subject as determined by OCT from baseline to week 50. • Absolute change in macrophage composition in matched segments of all lesions assessed in an individual subject as determined by OCT from baseline to week 50. • Absolute change in lipid content in matched segments of all lesions assessed in an individual subject as determined by IVUS from baseline to week 50.

The primary estimand consists of:

- The target population, which is the adult subjects with NSTE-ACS who are taking maximally tolerated statin therapy with or without additional lipid-modifying medication.
- The primary variable, which is the absolute change in minimum FCT in a matched segment of artery as determined by OCT from baseline to week 50.
- The summary measure, which is the mean treatment difference of the primary variable means between evolocumab and placebo.
- The intercurrent events, all randomized subjects who receive at least 1 dose of investigational product regardless of adherence to treatment.

4.2 Hypothesis

The primary hypothesis is that low-density lipoprotein cholesterol (LDL-C) lowering with evolocumab 420 mg monthly (QM) will result in a greater increase from baseline in minimum FCT at week 50 than placebo in subjects taking maximally tolerated statin therapy.

5. Study Design

5.1 Overall Design

This is a phase 3, double-blind, placebo-controlled, randomized study evaluating the effect of evolocumab on coronary atherosclerotic plaques as assessed by OCT at baseline and at week 50 in subjects with NSTE-ACS. The trial duration of 1 year was chosen based on the results of several historical trials (Dai et al, 2017; Hou et al, 2016;

Kataoka et al, 2014; Komukai et al, 2014; Nishio et al, 2014; Hattori et al, 2012; Takarada et al, 2009). Subjects will be randomized 1:1 into 2 treatment groups no more than 7 days after the signing of the informed consent: evolocumab 420 mg subcutaneously (SC) QM or placebo SC QM. The randomization will be stratified by current statin use (> 4 weeks or ≤ 4 weeks duration) at screening. Investigators will up-titrate statin therapy to the maximally tolerated dose, in accordance with local guidelines, for subjects prior to randomization.

The overall study design is described by a study schema in Section 2.1. The endpoints are defined in Section 4.1.

5.2 Number of Subjects

Approximately 150 subjects will be enrolled in the study, with 75 subjects randomized to receive evolocumab 420 mg SC QM and 75 subjects randomized to receive matching placebo SC QM.

Subjects in this clinical investigation shall be referred to as "subjects". For the sample size justification, see Section 10.1.

5.2.1 Replacement of Subjects

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

5.2.2 Number of Sites

Approximately 37 investigative sites globally will be included in the study. Sites that do not enroll a subject within 3 months of site initiation may be closed.

5.3 End of Study

5.3.1 End of Study Definition

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

The primary completion date is the date when all randomized subjects have either completed the assessments at week 50 or have early terminated from the study.

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

End of Study: The end of study (EOS) date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable.

5.3.2 Study Duration for Subjects

Including the initial screening, study treatment period (double-blind), and the safety/EOS follow-up, the maximum planned length of participation in the study for an individual subject is 53 weeks. Subjects should be randomized no more than 1 week after the signing of informed consent.

5.4 Justification for Investigational Product Dose

Selection of the proposed dose regimen (420 mg SC QM) was based on analysis of pharmacokinetic and pharmacodynamic data obtained from our interim phase 2 analysis (Studies 20110109, 20110110, 20110231, 20110233, and 20110271), bolstered by a single dose study of evolocumab in healthy volunteers (Study 20080397), and confirmed in phase 3 and registrational studies.

The no-observed-adverse-effect level (NOAEL) observed in a 6-month cynomolgus monkey toxicology study (300 mg/kg weekly SC) provides significant exposure multiples (86 x for exposure [area under the curve] and 254 x for maximum concentration) over the anticipated human exposures.

5.5 Patient Input on Study Design

Patient input on study design was not obtained.

6. Study Population

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

Eligibility criteria will be evaluated during screening.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Appendix 3).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions will not be provided.

6.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

101 Provided informed consent prior to initiation of any study-specific activities/procedures.

102 Age ≥ 18 years at screening.

103 Clinical indication for coronary angiography during admission due to non-ST-segment elevation acute coronary syndrome (NSTE-ACS) with interventional treatment of culprit plaque.

104 An eligible LDL-C level via local lab assessment based on statin use at screening (see Section 9.1.1):

- No statin use: ≥ 130 mg/dL
- Low- or moderate-intensity statin use (see Table 7-1): ≥ 80 mg/dL
- High-intensity statin use (see Table 7-1): ≥ 60 mg/dL

105 On maximally tolerated statin therapy in accordance with standard of care per local guidelines prior to randomization. See Section 7.1.4 for details.

106 Tolerates placebo run-in injection at screening.

107 Meets all the following criteria at the qualifying coronary angiogram:

- Angiographic evidence of coronary artery disease (CAD) with ≥ 20% reduction of lumen diameter by angiographic visual estimation, in addition to the culprit plaque.
- Left main coronary artery must not have a > 50% reduction in lumen diameter by visual angiographic estimation.
- Targeted vessel:
  - may not be the culprit vessel for the current or a previous myocardial infarction (MI).
  - has not undergone prior percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), and may not be a bypass graft.
  - may not be a candidate for PCI or CABG currently or over the next 12 months, in the opinion of the investigator.
  - must be accessible by the OCT catheter.
- Targeted segment:
  - must have up to 50% but not > 50% reduction in lumen diameter by visual angiographic estimation and must be at least 40 mm in length.
  - must contain at least 1 image with a FCT of ≤ 120 µm and at least 1 image with a lipid arc of > 90° as determined by the imaging core laboratory
  - distal plaques of up to 50% stenosis by visual angiographic estimation are permitted, provided that such stenosis is not a target for PCI or CABG.

6.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply.

Disease Related

201 ST-segment elevation myocardial infarction (STEMI) or left bundle branch block (LBBB).

202 ACS likely to be caused by a non-atherosclerotic process, in the opinion of the investigator (ie, type 2 myocardial infarction, which is characterized by an imbalance between myocardial oxygen demand and supply).

203 Clinically significant heart disease which in the opinion of the investigator is likely to require coronary bypass surgery, PCI (does not apply to PCI of non-STEMI (NSTEMI) during initial screening angiogram), surgical or percutaneous valve repair and/or replacement during the course of the study.

204 Any cardiac surgery within 6 weeks prior to screening.

Diagnostic Assessments

205 Triglycerides ≥ 400 mg/dL (4.5 mmol/L) at screening.

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

Other Medical Conditions

207 Malignancy except non-melanoma skin cancers, cervical, or breast ductal carcinoma in situ within the last 5 years.

208 Intolerant to statins as determined by principal investigator.

Prior/Concomitant Therapy

209 Previously received or receiving evolocumab or any other therapy to inhibit PCSK9.

210 Previously received a cholesterol ester transfer protein (CETP) inhibitor (ie, anacetrapib, dalcetrapib, evacetrapib), mipomersen, lomitapide, or has undergone LDL-apheresis in the last 12 months prior to LDL-C screening.

Prior/Concurrent Clinical Study Experience

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

Other Exclusions

212 Baseline OCT does not meet OCT imaging criteria as determined by the imagine core laboratory technical standards.

213 Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 15 weeks after the last dose of investigational product. (Females of childbearing potential should only be included in the study after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test.)

214 Female subjects of childbearing potential unwilling to use 1 acceptable method of effective contraception during treatment and for an additional 15 weeks after the last dose of investigational product. Refer to Appendix 5 for additional contraceptive information.

215 Female subject who has not used an acceptable method(s) of birth control for at least 1 month prior to screening, unless the female subject is sterilized or postmenopausal.

216 Known sensitivity to any of the products or components (eg, carboxymethylcellulose) to be administered during dosing.

217 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's and investigator's knowledge.

218 Unreliability based on the investigator's (or designee's) knowledge (eg, alcohol or other drug abuse, inability or unwillingness to adhere to the protocol, or psychosis).

219 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.

6.3 Lifestyle Restrictions

6.3.1 Meals and Dietary Restrictions

Subjects should adhere to the National Cholesterol Education Program Adult Treatment Panel 3, therapeutic lifestyles changes diet or an equivalent diet.

6.4 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, informed consent form, and all other subject information and/or recruitment material, if applicable (see Appendix 3).

All subjects must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures.

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

Each subject who enters into the screening period for the study (defined as when the subject signs the IRB/IEC approved informed consent form) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by the IVRS/IWRS. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

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

6.5 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, medical history, prior therapies, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened during the same index or NSTE-ACS admission period.

7. Treatments

Study treatment is defined as any investigational product(s), non-investigational product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

Note that in several countries, investigational product and non-investigational product are referred to as investigational medicinal product and non-investigational medicinal product, respectively.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment shown in Section 7.1 below.

7.1 Treatment Procedures

7.1.1 Investigational Products

7.1.1.1 Dosage Formulation: Evolocumab

Evolocumab and matching placebo will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical investigational product distributions procedures.

Evolocumab and placebo SC will be supplied as 1 personal injector or 3 AI/Pens. Evolocumab will be presented as follows:

- A personal injector as a single use, disposable, on-body electro-mechanical injection device that is co-packaged with a prefilled Crystal Zenith cartridge containing 3.5 mL deliverable volume of 120 mg/mL evolocumab or an identical volume of placebo
- An AI/Pen as a single use, disposable, handheld mechanical (spring-based) for fixed dose, subcutaneous injection of 140 mg evolocumab in 1.0 mL deliverable volume or an identical volume of placebo

Evolocumab and placebo should be stored refrigerated and protected from light according to the storage and expiration information provided on the label (where required). Evolocumab should be handled per the instructions provided in the IPIM and the clinical instructions for use (IFU) for the personal injector and AI/Pens.

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

The investigator may be required to record the box number of evolocumab on the subject's Drug Administration CRF.

7.1.1.2 Evolocumab: Dosage, Administration, and Schedule

Evolocumab or matching placebo will be administered SC on day 1 through week 48. Investigational product will be administered monthly (QM defined as every 4 weeks ± 3 days).

Subcutaneous evolocumab and placebo will be administered at the study site (ie, in-clinic) or in an appropriate non-clinic setting (eg, at home). Observed, in-clinic dosing must occur at day 1 and should occur at week 4, and week 24. At home dosing by the subject should occur for all remaining dose administrations. Subjects who do not wish to self-inject at home may return to the clinic for injection.

Evolocumab or matching placebo will be administered in accordance with instructions in the IPIM and the IFU. The subject (or designee) must have demonstrated competency, as per site judgment, at administration of SC injections before self-administration is permitted. The first self-administered dose by the subject (or designee) at day 1 must be administered at the site under the supervision of a healthcare provider. If evolocumab or matching placebo is to be administered during the study visit, administration must occur after all other procedures have been completed.

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

When evolocumab is administered at a non-investigator site location (eg, at home), at a minimum, the dates the devices were dispensed and the used devices returned, the number of devices returned, box numbers, and for each device whether it was returned fully or partially used are to be recorded on each subject's CRF.

It is suggested that the investigational product administration is done by the subject under site staff supervision at each of the regular study visits (except day 1) to ensure continued proper use of the injection device. Investigational product administration at a scheduled visit (eg, day 1, week 4, and week 24), if applicable, is to be performed after all study-related procedures.

Details of preparing evolocumab, the injection procedures, and device disposal are included in the IPIM and IFU provided by Amgen before the start of the study.

The effects of overdose of this product are not known.

7.1.2 Non-investigational Products

Not applicable for this study.

7.1.3 Medical Devices

The investigational medical devices provided by Amgen for use in this study are the personal injector, or the spring based prefilled AI/pen. Personal injector or AI/Pen training by study site staff to each subject will occur at the day 1 visit and each visit thereafter if necessary.

The personal injector with prefilled cartridge assembly is a single-use, disposable, on-body electro-mechanical injection device that is co-packaged with a prefilled Crystal Zenith cartridge assembly containing 3.5 mL deliverable volume of 120 mg/mL evolocumab. Additional details are provided in the IPIM.

An AI/Pen is a single use, disposable, handheld mechanical (spring-based) for fixed dose, SC injection of 140 mg evolocumab in 1.0 mL deliverable volume or an identical volume of placebo.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care.

Non-investigational medical devices (eg, syringes, sterile needles), 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.

7.1.4 Other Protocol-required Therapies

All other protocol-required therapies including, background lipid-lowering therapy, that are commercially available are not provided or reimbursed by Amgen (except if required

by local regulation). The investigator will be responsible for obtaining supplies of these protocol-required therapies.

Subjects must receive maximally tolerated statin therapy with or without additional lipid-modifying medication during the study. Statin therapy must be initiated or up-titrated to the maximally tolerated dose prior to randomization for all subjects; local guidelines should be taken into consideration when determining optimal treatment. All lipid therapies (doses and regimen) should remain unchanged for the duration of study participation (up to 52 weeks). All subjects should receive high-intensity statin therapy with atorvastatin ≥ 40 mg daily or equivalent (Table 7-1; criteria modified from American College of Cardiology/American Heart Association [ACC/AHA] guidelines), in accordance with local guidelines. If not receiving atorvastatin ≥ 40 mg or equivalent, the investigator must attest in eCRF that higher dose statin therapy has been considered but is not appropriate for this subject (eg, dose not tolerated, dose not available in that country, other significant concern).

If making any changes to this therapy after randomization, the reason for the change must be provided in the CRF and the Amgen medical monitor or designee should be consulted before making the change.

Other regulatory-approved lipid regulating therapies (eg, ezetimibe) used at screening should remain unchanged for the duration of study participation (up to 52 weeks).

Beyond the week 52 assessment, use of statins and other lipid regulating therapies will be at the discretion of the investigator.

Table 7-1. Acceptable Background Statin Therapy

	High-intensity Statin Therapy	Moderate-intensity Statin Therapy	Low-intensity Statin Therapy
Atorvastatin	≥ 40 mg QD	10 mg to < 40 mg QD	< 10 mg QD
Rosuvastatin	≥ 20 mg QD	5 mg to < 20 mg QD	< 5 mg QD
Simvastatin[a]	≥ 80 mg QD	20 mg to < 80 mg QD	< 20 mg QD
Pravastatin	-	≥ 40 mg QD	< 40 mg QD
Lovastatin	-	≥ 40 mg QD	< 40 mg QD
Fluvastatin	-	80 mg QD	< 80 mg QD
Pitavastatin	-	≥ 2 mg QD	< 2 mg QD

QD = once daily

[a] Use of simvastatin 80 mg was associated with myopathy and is not commonly recommended for use. Simvastatin 80 mg is not available in all countries participating in this study. Approval of simvastatin 80 mg by the local regulatory authority is required for subjects using simvastatin 80 mg in this study.

Statins are not provided or reimbursed by Amgen (except if required by local regulation).

Additional details regarding these protocol-required therapies are provided in the IPIM.

7.1.5 Other Treatment Procedures

There are no other treatment procedures for this study.

7.1.6 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
- Misuse of the personal injector (or AI/Pen) due to misunderstanding of the clinical IFU or error on part of the user, or other inability to appropriately use the product (eg, due to malfunction of the personal injector [or AI/Pen])
- Missing, illegible, incorrect, and/or suspect labels
- Change in investigational product appearance (eg, color change or visible presence of foreign material)
- Unexpected quantity or volume (eg, number of tablets or amount of fluid in the personal injector [or AI/Pen]), or evidence of tampering or stolen material

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

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

The following treatments are not permitted during the study:

- Non-study investigational therapies
- 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 study. Note that a change in background lipid-lowering therapy (including statins), does not necessarily require ending investigational product.

The following treatments are not recommended in subjects treated with statins metabolized by cytochrome P450 (CYP) 3A4 (eg, simvastatin or atorvastatin) because of their potential impact on metabolism of certain statins:

- Medications or foods that are known potent inhibitors of CYP 3A4 (eg, itraconazole, ketoconazole, and other antifungal azoles, macrolide antibiotics erythromycin, clarithromycin, and the ketolide antibiotic telithromycin, human immunodeficiency virus or hepatitis C virus (HCV) protease inhibitors, antidepressant nefazodone and grapefruit juice in large quantities (> 1 quart daily [approximately 1 L]) should not be used during the study.

7.2 Method of Treatment Assignment

Subjects will be randomized in a 1:1 allocation ratio, evolocumab to placebo, respectively, in a double-blind manner.

The randomization will be performed by IVRS/IWRS.

The randomization number will be provided once eligibility into the study has been confirmed. A site representative will make the randomization call to the IVRS/IWRS to assign a randomization number to the subject. The randomization call to the IVRS is accomplished by entering the pertinent information detailed in the IVRS/IWRS user manual. A confirmation fax/electronic-mail (e-mail) will be sent to the site to verify that the correct information has been entered and confirm the randomization number assigned.

The randomization will be stratified by current statin use (> 4 weeks or ≤ 4 weeks) at screening.

The randomization date is to be documented in the subject's medical record and on the enrollment CRF.

7.3 Blinding

This is a double-blind study. Treatment assignment will be blinded to all subjects, site personnel, and Amgen as described below.

7.3.1 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment is to only be unblinded when knowledge of the treatment is essential for further clinical management of the subject on this study. Unblinding at the study site for any other reason will be considered a protocol deviation. The Amgen Trial Manager must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management

of the subject's condition. In this case, the Amgen Trial Manager must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF, as applicable.

7.3.2 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 is not to 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 7.3.1).

7.4 Dose Modification

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

7.4.1.1 Amgen Investigational Product: Evolocumab

There will be no investigational product dose adjustments in this study. If, in the opinion of the investigator, a subject is unable to tolerate 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 subject arrives for a visit and investigational product was administered within less than 7 days prior, the dose should not be administered but all other study procedures should be conducted and administration of investigational product should occur as soon as possible at least 7 days after the previous administration.

If a subject completely misses a dose of SC investigational product, the subject should continue in the study and the next dose of investigational product should be administered per their schedule of administration.

7.4.1.2 Non-Amgen Non-Investigational Product: Background Lipid-lowering Therapy

The reason for dose change of non-Amgen non-investigational product (background lipid-lowering therapy) is to be recorded on each subject's CRF(s).

Subjects who miss a dose of background lipid-lowering therapy will be advised to refer to the product information of that drug and proceed according to the directions in the label.

If stopping or altering dosing of statin therapy (or allowable non-statin therapy) is medically warranted during the trial, the subject should continue to receive investigational product. These situations should be discussed with the Amgen medical monitor as soon as possible. In addition, if a medical decision is made to withhold investigational product during the study, subjects should continue to receive statin (and allowable non-statin) background therapy. The medical monitor should be contacted prior to stopping investigational product.

7.4.2 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Appendix 7 for details regarding drug-induced liver injury (DILI) guidelines, as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

If a possible DILI is suspected, investigational product, statin therapy, and other applicable lipid-regulating background therapy must be discontinued and the subject should be followed according to the recommendations in Appendix 7.

7.5 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product other protocol-required therapies and/or device (personal injector or AI/Pen) during the study are provided in the IPIM.

7.6 Treatment Compliance

Medication will be dispensed for self-administration at home. Subjects are to report all administered doses and missed doses for all study-required medication taken at home to their study physician upon collection of adverse events and product/device complaints. Non-compliance is to be documented in the medical file and will be reflected in the CRF. Non-compliant subjects are to be re-educated on the importance of adhering to the study drug administration schedule and reminded that repeated cycles of non-compliance could be a reason for discontinuation of study treatment.

7.7 Treatment of Overdose

There is no specific treatment for evolocumab overdose. In the event of an overdose, the patient should be treated symptomatically and supportive measures instituted as required.

7.8 Prior and Concomitant Treatment

7.8.1 Prior Treatment

Prior therapies that were being taken/used from 30 days prior to enrollment through the signing of the informed consent will be collected.

7.8.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 7.1.7.

Concomitant therapies are to be collected from informed consent through the end of safety follow-up period.

It is anticipated that subjects will remain on a stable dose of statin therapy and other allowed lipid-regulating therapies from randomization until the EOS.

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

8. Discontinuation Criteria

Subjects have the right to withdraw from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

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 for the reasons listed in Section 8.1, Section 8.2.1, and Section 8.2.2.

8.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Table 2-1) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events,

and device-related events, as applicable and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

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 Appendix 3.

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

- Decision by Sponsor
- Lost to follow-up
- Death
- Ineligibility determined
- Protocol deviation
- Non-compliance
- Adverse event
- Subject request
- Requirement for alternative therapy not allowed by protocol
- Pregnancy

8.2 Discontinuation From the Study

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, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study, and must document the subject's decision to withdraw in the subject's medical records.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Appendix 6 for further details). Refer to the Schedule of Activities (Table 2-1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.2.1 Reasons for Removal From Invasive Procedures

Reasons for removal from the invasive procedures include any of the following:

- Decision by Sponsor
- Lost to follow-up
- Death
- Ineligibility determined
- Protocol deviation
- Non-compliance
- Adverse event
- Subject request
- Requirement for alternative therapy not allowed by protocol
- Pregnancy

8.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- Decision by sponsor
- Withdrawal of consent from study
- Death
- Lost to follow-up

8.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.
- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For subjects who are lost to follow-up, the investigator can search publicly 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.

9. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Table 2-1).

As protocol waivers or exemptions are not allowed if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities (Table 2-1), is essential and required for study conduct.

9.1 General Study Periods

This will be a multi-center, double-blind, randomized, placebo-controlled trial. The study consists of:

- Screening
- Double-blind treatment period
- EOS visit

Written informed consent must be obtained and will be implemented before protocol-specific procedures are carried out. The risks and benefits of participating in the study will be verbally explained to each potential subject prior to entering the study. The procedures to be performed during the study are described below and are summarized in the Schedule of Activities (Table 2-1).

9.1.1 Screening, Enrollment and/or Randomization

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the informed consent form, the site will register the subject in the IVRS/IWRS and screen the subject in order to assess eligibility for participation. The screening window is up to 1 week.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria, including acceptability of OCT data set as determined by the imaging core laboratory. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

If a subject has not met all eligibility criteria at the time of randomization, the subject will be registered as a screen fail IVRS/IWRS. Subjects cannot undergo rescreening during the same admission, (ie, index date [admission]). Rescreening is only permitted if a subject is re-admitted for new occurrence of NSTE-ACS that is not related to the NSTE-ACS at index admission. Screen fail subjects may be eligible for rescreening 2 times.

All rescreened subjects must reconsent. Rescreen subjects must be registered as rescreens in IVRS/IWRS. Once the subject is registered as rescreened, a new 7-day screening window will begin. With the exception of the screening placebo injection, rescreened subjects will repeat all screening procedures. Rescreened subjects will maintain the originally assigned subject identification number.

For procedures regarding LDL-C assessments during screening, these should occur between admission for NSTE-ACS and the coronary angiogram. Subject eligibility (Section 6.1; inclusion criterion 104) based on subjects' statin dose at the time of LDL-C blood sample measurement is as follows:

No statin use

- LDL-C: ≥ 130 mg/dL

Low- or Moderate-intensity statin dose (see Table 7-1)

- LDL-C: ≥ 80 mg/dL

High-intensity statin dose (see Table 7-1)

- LDL-C: ≥ 60 mg/dL

Day 1 of the treatment period (ie, first dose of investigational product) must happen within 7 days of the signing of the informed consent.

9.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Table 2-1). On-study visits may be completed within 50 weeks and must occur within ± 7 days of their specified date (with the exception of the week 50 OCT and IVUS). The date of the first dose of investigational product is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. Administration of investigational product is to be administered last during each visit that it is required.

Before each study visit where fasting lipid samples are obtained, subjects must be fasting overnight. If the subject is not fasting for 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.

The study includes collection of biomarker samples.

Final, follow-up OCT and IVUS should take place 50 ± 2 weeks (ie, 48 to 52 weeks) after initial baseline image acquisition. It is critical that the follow-up OCT and IVUS be obtained for all subjects, regardless of whether they discontinued study drug prematurely or are outside the 50 ± 2 weeks window.

9.1.2.1 Clinically Indicated Catherization Prior to Week 40

For subjects requiring coronary angiography prior to week 40, the final OCT and IVUS examination should not be performed in these subjects at the time of clinically indicated catherization. Subjects will remain on study drug and complete all required visits and procedures, including the week 50 OCT and IVUS.

For subjects requiring coronary angiography with intervention of the targeted vessel prior to week 40, these subjects will continue investigational product and complete all study visits and procedures with the exception of the week 50 OCT and IVUS.

9.1.2.2 Clinically Indicated Catherization at Week 40 Prior to Week 50

Any subjects who require cardiac catherization for clinically indicated reasons at week 40 or later must have OCT and IVUS examination of the target vessel performed at that time. The week 50 OCT and IVUS will not be required for these subjects. If PCI of a non-target vessel is required, subjects will undergo the final OCT and IVUS after PCI is completed. If PCI of the target vessel is required, the final OCT and IVUS should be completed prior to PCI if clinically appropriate. These subjects will continue investigational product and complete all study visits and procedures with the exception of the week 50 OCT and IVUS.

9.1.3 End of Study

Subjects will end the study once contacted by the site by phone call at week 52.

Completion of the study is defined as the last day that protocol-specified procedures are conducted for an individual subject. Subjects who are not deceased, have not

withdrawn consent, or are not lost to follow-up, should have at minimum an EOS assessment for vital status (alive or deceased) and adverse events.

9.2 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required time points.

9.2.1 General Assessments

9.2.1.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the IRB/IEC approved informed consent before any study-specific procedures are performed.

9.2.1.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.

9.2.1.3 Medical History

The investigator or designee will collect a targeted medical and surgical history on the following conditions or indications that started prior to study entry/screening through the start of the adverse event reporting period: cardiovascular disease. Record all findings on the medical history CRF. The current severity will be collected for each condition that has not resolved. Additionally, patient reported cardiovascular risk factors will be collected at the time of randomization.

9.2.1.4 Physical Examination

Physical examination will be performed as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event).

9.2.1.5 Physical Measurements

9.2.1.5.1 Height

Height in centimeters should be measured without shoes.

9.2.1.5.2 Weight

Weight in kilograms should be measured without shoes.

9.2.2 Efficacy Assessments

Disease assessments will be based on intracoronary imaging (OCT and IVUS) and LDL-C assessments at scheduled timepoints in the Schedule of Activities (Table 2-1).

9.2.2.1 Intracoronary Imaging (OCT and IVUS)

In order to minimize the chances of performing unnecessary invasive procedures, investigators should ensure that subjects' initial screening LDL-C results are available prior to performing the baseline OCT and IVUS examination. Thereafter, subjects will undergo clinically-indicated coronary angiography for further clinical evaluation following their hospitalization for NSTE-ACS. If angiographic criteria are met, the subject will have baseline OCT and IVUS completed. Subjects who require a PCI deemed necessary by the qualifying angiogram will have baseline OCT and IVUS imaging performed immediately following the PCI. OCT and IVUS must not be performed in vessels that underwent an intervention.

The accuracy and reproducibility of the imaging endpoints of the study are dependent upon Investigator's commitment to rigorous image acquisition techniques. The central imaging core laboratory will provide a separate imaging guidance document to all participating sites. Adherence to these guidelines will ensure low inter- and intra-observer variability and high image quality.

For each patient, all imaging conditions at baseline must be duplicated at follow-up utilizing the same imaging system. The OCT and IVUS systems must not be changed between the baseline and follow-up examinations. All baseline studies (angiography, OCT, IVUS) must be forwarded to the imaging core laboratory for informational review. OCT images must be reviewed and approved by the imaging core laboratory before subjects return for randomization visit.

9.2.2.2 LDL-C

Low-density lipoprotein cholesterol analysis will be performed by local laboratory assessments during the Screening period. The results will have to be recorded in CRF. Treatment period LDL-C analysis will be performed by the central laboratory. The blood samples will be drawn at the time points indicated in the Schedule of Activities (Table 2-1).

9.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities (Table 2-1).

9.2.3.1 Adverse Events

9.2.3.1.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

9.2.3.1.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE) or the Amgen Adverse Event Grading Scale and is described in Appendix 4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after signing the informed consent through the EOS are reported using the Event CRF.

9.2.3.1.1.2 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 the informed consent through 30 days after the last dose of investigational product or EOS (whichever is later) are reported using the Event CRF.

All serious adverse events will be collected, recorded, and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

The criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events.

9.2.3.1.1.3 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 EOS. However, these serious adverse events can be reported to Amgen. Per local requirements in some countries, investigators are required to report serious adverse events that they become aware of after EOS. 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 and handled accordingly based on relationship to investigational product.

The method of recording, evaluating, and assessing causality of adverse events, adverse device effects, and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 4.

9.2.3.1.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

9.2.3.1.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

All new information for previously reported 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.

9.2.3.1.4 Regulatory Reporting Requirements for Serious Adverse Events

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

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

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. Aggregate analyses may also be unblinded by the Safety Assessment Team (SAT) as appropriate. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

9.2.3.1.5 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and, if indicated, female partners of male subjects will be collected after the start of study treatment and until 15 weeks after the last dose of investigational product.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Appendix 5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Appendix 5.

9.2.3.1.6 Adverse Device Effects

In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of any adverse device effects that occur during the study with such devices.

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

All adverse device effects are to be reported as adverse events following the same reporting periods and procedures.

Product complaints are described in Section 7.1.6.

Further details regarding adverse device effects can be found in Appendix 4.

9.2.3.2 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure and heart rate. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. Record all measurements on the vital signs CRF.

9.2.3.3 Vital Status

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

9.2.4 Clinical Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Table 2-1) for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event CRF. The investigator must determine 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.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Table 2-1).

Laboratory/analyte results that could unblind the study should not be performed during the subject's participation in the study. Central laboratory results of the lipid testing will be blinded post-treatment until unblinding of the clinical database and will not be

reported to the investigator post-screening. In addition, investigators and staff involved with this trial and all medical staff involved in the subject's medical care should refrain from obtaining lipid panels between randomization and at least 12 weeks after the subject ends the study (to avoid potential unblinding).

9.2.4.1 Pregnancy Testing

A high sensitive (urine or serum) pregnancy test should be completed at screening and within 7 days of initiation of investigational product for females of childbearing potential.

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Worksheet, see Figure 12-2). Refer to Appendix 5 for contraceptive requirements.

An additional pregnancy test should be performed also at week 24 and week 50.

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

9.2.5 Biomarker Development

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

Biomarker development can be useful in developing markers to identify disease subtypes, guide therapy, and/or predict disease severity.

Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to evolocumab to investigate and further understand cardiovascular disease.

Blood samples are to be collected for biomarker development at the time points specified in the Schedule of Activities (Table 2-1).

10. Statistical Considerations

10.1 Sample Size Determination

The planned total sample size is 150 subjects (75 randomized to evolocumab 420 mg SC QM and 75 randomized to placebo SC QM). This sample size will provide sufficient power (90%) to determine whether there is a treatment effect of evolocumab relative to placebo in the primary endpoint.

The assumptions in the sample size calculation are based on a linear regression meta-analysis of 7 historical trials (Dai et al, 2017; Hou et al, 2016; Kataoka et al, 2014; Komukai et al, 2014; Nishio et al, 2014; Hattori et al, 2012; Takarada et al, 2009) weighted by sample sizes.

The analysis result indicates that every 1 mg/dL reduction in LDL-C is estimated to be associated with 1.4785 µm increase in FCT in 12-month follow-up. Assuming a 50 mg/dL reduction in LDL-C, the predicted mean increase (95% CI) in FCT from the meta-analysis was 73.92 (50.97, 96.88) µm. For this study, the assumed treatment effect is at least 50.97 µm increase in FCT, which is approximated from the lower bound 95% CI of the expected change in FCT from the regression model, based on a conservative assumption of 50 mg/dL reduction in LDL-C from baseline to week 50.

The SD of FCT measurement at baseline or at the end of various length of follow-up was reported in a wide range (10.6 to 124 µm) based on 15 to 134 subjects per arm in the historical trials. The SD of change in FCT was only reported in 2 of the 7 trials, ranging from 22 to 86 µm. The assumed common SD for this study is 86 µm to be conservative.

Assuming 1 out of 6 subjects will not complete both baseline and week 50 OCT assessments, and therefore be excluded in the primary analysis, the sample size of 150 subjects will provide approximately 125 subjects in the primary analysis to ensure 90% power to test the study hypothesis.

The sample size calculation was performed using a 2-sided t-test with a 0.05 significance level. The sample size calculation was derived using East® software (version 6.4).

10.2 Analysis Sets, Subgroups, and Covariates

10.2.1 Analysis Sets

Full Analysis Set: The full analysis set (FAS) includes all randomized subjects who received at least 1 dose of investigational product.

10.2.2 Covariates

Baseline covariates will include, but are not limited to the following:

- Age
- Sex
- Baseline LDL-C

10.2.3 Subgroups

Subgroup analysis of the primary endpoint will be conducted for, but not limited to the following variables:

- Age (< median, ≥ median; < 65 years of age, ≥ 65 years of age)
- Sex
- Baseline LDL-C (< median, ≥ median)

10.2.4 Handling of Missing and Incomplete Data

Subjects may be missing specific data points for various reasons. In general, data may be missing due to a subject's early withdrawal from study, a missed visit, or non-evaluability of a data point or endpoint at a particular time. The frequency and pattern of missing data for efficacy endpoints will be assessed through descriptive summaries of the measurements over time. The reason of missing the final OCT measurement will be tabulated. For subjects with missing post-baseline FCT, the missing primary endpoint will be imputed using multiple imputation (see Section 10.3.2.2).

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the EOS, as defined in Section 5.3.1.

10.3.1 Planned Analyses

10.3.1.1 Final Analysis

There will be no interim analysis for this study. The final analysis will be conducted after all subjects have either completed all the scheduled study visits or have early terminated from the study. At that time, the database will be cleaned, processed, locked, and a snapshot will be taken; the study will also be unblinded. Based on the snapshot, efficacy and safety analyses will be performed.

10.3.2 Methods of Analyses

10.3.2.1 General Considerations

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

Statistical inferences will be provided for analyses of primary and secondary efficacy endpoints. Unless specified otherwise, all statistical tests are 2-sided with a significance

level of 0.05; no statistical inference and imputation will be conducted for analyses of safety of exploratory endpoints.

Multiplicity Adjustment Method

In order to preserve the family wise type 1 error rate at 0.05 for testing the primary and secondary endpoints, the primary analysis of primary endpoint will be tested first. If the treatment effect from the primary analysis of the primary endpoint is significant at a significance level of 0.05, the secondary endpoints will be tested with significance level of 0.05 using the Hochberg method

10.3.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary analysis method of the primary endpoint is to use the analysis of covariance (ANCOVA) model, including terms for treatment group, stratification factor (current statin use [> 4 weeks or ≤ 4 weeks] at randomization), and baseline FCT as covariates. Least square means and corresponding 95% confidence intervals will be calculated for each treatment group and for the difference between the treatment groups. For subjects with missing post-baseline FCT, the missing primary endpoint will be imputed using multiple imputation (details provided in SAP). FAS will be used. A sensitivity analysis of the primary endpoint will be conducted using nonparametric method and FAS.
Secondary	ANCOVA model including terms for treatment group, stratification factor (current statin use [> 4 weeks or ≤ 4 weeks] at randomization), and respective baseline value as covariates.
Exploratory	Will be described in the statistical analysis plan finalized before database lock

10.3.2.3 Safety Analyses

10.3.2.3.1 Adverse Events

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

10.3.2.3.2 Laboratory Test Results

The analyses of safety laboratory endpoints will include summary statistics at each scheduled visit for each treatment group. Shifts in grades of safety laboratory values between the worst on-study value from baseline to the EOS will be tabulated for each treatment group.

10.3.2.3.3 Vital Signs

The analyses of vital signs will include summary statistics at each measurement time point for each treatment group.

10.3.2.3.4 Physical Measurements

The analyses of physical measurements will include summary statistics at each measurement time point for each treatment group.

10.3.2.3.5 Exposure to Investigational Product

The patient-month exposure to investigational product, the categorical representation of dose received, and the total quantity of investigational product used by treatment group will be summarized using descriptive statistics.

10.3.2.3.6 Exposure to Concomitant Medication

Number and proportion of subjects receiving therapies of interest including statins will be summarized for each treatment group as coded by the World Health Organization Drug (WHODRUG) dictionary.

11. References

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12. Appendices

12.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
ACC	American College of Cardiology
AHA	American Heart Association
AI	autoinjector
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	anti-nuclear antibody
ANCOVA	analysis of covariance
ApoA1	apolipoprotein A1
ApoB	apolipoprotein B
AST	aspartate aminotransferase
BIL	bilirubin
CAD	coronary artery disease
CABG	coronary artery bypass grafting
CANTAB	Cambridge Neuropsychological Text Automated Battery
CBC	complete blood count
CETP	cholesterol ester transfer protein
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COA	clinical outcome assessment
CPK	creatine phosphokinase
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTT	Cholesterol Treatment Trialists'
CYP	cytochrome P450
DILI	drug-induced liver injury
EC	Executive Committee
ECG	electrocardiogram
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
e-mail	electronic mail
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
End of Follow-up	defined as when the last subject completes the last protocol-specified assessment in the study

Abbreviation or Term	Definition/Explanation
End of Study (EOS) for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Study (EOS) (end of trial)	defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
FAS	full analysis set
FCT	fibrous cap thickness
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
HIPAA	Health Insurance Portability and Accountability Act
HoFH	homozygous familial hypercholesterolemia
HR	hazard ratio
HRT	hormonal replacement therapy
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	identification
IEC	Independent Ethics Committee
IFU	instructions for use
index date	date subject is admitted to a hospital for a specific condition
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
Interactive Voice Response System (IVRS)	telecommunication technology that is linked to a central computer in real time as an interface to collect and process information
IVUS	intravascular ultrasound
Interactive Web Response System (IWRS)	web based technology that is linked to a central computer in real time as an interface to collect and process information
LBBB	left bundle branch block
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol

Abbreviation or Term	Definition/Explanation
LDLR	low-density lipoprotein receptor
LKM1	liver kidney microsomal antibody-1
Lp(a)	lipoprotein(a)
MI	myocardial infarction
NASH	nonalcoholic fatty liver disease including steatohepatitis
NOAEL	no-observed-adverse-effect level
NSTE-ACS	non-ST-segment elevation acute coronary syndrome
NSTEMI	non-ST-segment elevation myocardial infarction
OCT	optical coherence tomography
PAV	percent atheroma volume
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
POR	Proof of Receipts
Q2W	every 2 weeks
QM	monthly (every 4 weeks with a window of ± 3 days for each visit or dose)
SAT	Safety Assessment Team
SEC	Self-Evident Corrections
SC	subcutaneous
SD	standard deviation
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
SUSAR	suspected unexpected serious adverse reactions
STEMI	ST-segment elevation myocardial infarction
Study Day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
TAV	total atheroma volume
TC	total cholesterol
TBL	total bilirubin
ULN	upper limit of normal
US	United States
VLDL-C	very low-density lipoprotein cholesterol

Abbreviation or Term	Definition/Explanation
WHODRUG	World Health Organization Drug

12.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 12-1 will be performed by the local laboratory, or the central laboratory.

Whenever the local laboratory is used to make either a study treatment decision or response evaluation, the results must be entered into the case report form (CRF).

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 6.1 to Section 6.2 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 12-1. Analyte Listing

Laboratory: Chemistry	Laboratory: Coagulation	Laboratory: Hematology	Other Labs
Creatinine hs-Troponin (I/T)	-	-	Serum or Urine Pregnancy Lipid Testing • Total cholesterol • HDL-C • LDL-C • Triglycerides • VLDL-C • Non-HDL-C • ApoA1 • ApoB • ApoB/ApoA1 ratio • Total Cholesterol/HDL-C ratio • Lp(a) Biomarkers

Apo = apolipoprotein; HDL-C = high-density lipoprotein cholesterol; hs = high sensitive; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); VLDL-C = very low-density lipoprotein cholesterol

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded. Central laboratory results of the lipid testing will be blinded post-treatment until unblinding of the clinical database and will not be reported to the investigator post-screening. In addition, investigators and staff involved with this trial and all medical staff involved in the subject's medical care should refrain from obtaining lipid panels between randomization and at least 12 weeks after the subject ends the study (to avoid potential unblinding).

12.3 Appendix 3. Study Governance Considerations

Executive Committee

An Executive Committee (EC) has been formed to advise Amgen on trial design and for assistance in the communication of trial results. The EC will be blinded. Details will be provided in a committee charter.

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable ICH laws and regulations

The protocol, protocol amendments, informed consent form, Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an Institutional Review Board/Independent Ethics Committee (IRB/IEC) by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. 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 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.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- 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
- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the United States (US) Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Informed Consent Process

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

The investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered, and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative defined as 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 will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form.

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 unless it is a local requirement. The investigator shall then inform the primary care physician. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the

subject or a legally acceptable representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 8.

Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the study.

The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the subject or the subject's legally authorized representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9).

Subjects who are rescreened are required to sign a new informed consent form.

The informed consent form will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate will not provide this separate signature.

Data Protection/Subject Confidentiality

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

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

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 age (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 regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the 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.

Publication Policy

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

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors, 2013 (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states:

Authorship credit is to be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in

ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above.

Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

All persons designated as authors must qualify for authorship, and all those who qualify are to be listed.

Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter 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

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

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.

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.

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.

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

Amgen (or designee) will perform Self-Evident Corrections (SEC) to obvious data errors in the clinical trial database. SECs will be documented in the CRF Standard Instructions and the CRF Specific Instructions, both of these will be available through the electronic data capture (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), and updating a specific response if the confirming datum is provided in the "other, specify" field (eg, for race, reason for ending study).

Case report forms 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.

Source Documents

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 provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

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. Source documents may also include data captured in the Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) system (if used, such as subject identification [ID] and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment [COA]).

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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 to 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 pre-study 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) or combination product(s) documentation, as applicable

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

Study and Site Closure

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

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.

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.

12.4 Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure.
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.
Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other medically important serious event Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Other medically important serious event (continued)
hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Definition of Adverse Device Effect

The detection and documentation procedures for adverse device effects described in this protocol apply to all Amgen medical devices provided for use in the study (see Section 7.1.3 for the list of Amgen medical devices).

Adverse Device Effect Definition
An adverse device effect is any adverse event related to the use of a combination product or 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.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

• When an adverse event, or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
• The investigator will then record all relevant adverse event/serious adverse event information in the Event CRF.
  ○ Additionally, the investigator is required to report a fatal disease-related event on 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);

Adverse Event and Serious Adverse Event Recording

- Severity (or toxicity defined below);
- Assessment of relatedness to evolocumab/placebo, or devices; and
- Action taken.

- If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Event CRF.
- It is not acceptable for the investigator to send photocopies of the subject's medical records to Amgen in lieu of completion of the Event CRF page.
- 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. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity

The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on:

The **Common Terminology Criteria for Adverse Events (CTCAE)**, version 4.0 which is available at the following location:

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

When an adverse event cannot be graded by CTCAE version 4.0, the following severity grade may be used:

The Amgen Standard Grading Scale as show below:

Grade	Definition
MILD	Aware of sign or symptom, but easily tolerated
MODERATE	Discomfort enough to cause interference with usual activity
SEVERE[a]	Incapacitating with inability to work or do usual activity

[a] An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of a serious adverse event, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between investigational product, protocol-required therapies, device(s), and/or study-mandated procedure and each occurrence of each adverse event/serious adverse event.
- Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality.
- There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.
- The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.
    - If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed Event CRF.
- The investigator will submit any updated serious adverse event data to Amgen within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool
• The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system via the Safety Report Form. • If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using an Electronic Serious Adverse Event Contingency Form (paper form; see Figure 12-1) within 24 hours of the investigator's knowledge of the event. • The site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the site can report this information on an Electronic Serious Adverse Event Contingency Form (paper form; see Figure 12-1).

Adverse Device Effects: Recording, Evaluating and Reporting

- Any adverse event resulting from an adverse device effect that occur during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the Event CRF page.
- It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by Amgen) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident.

Figure 12-1. Sample Electronic Serious Adverse Event Contingency Form

AMGEN Study # 20160184 evolocumab	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day ____ Month ____ Year ____

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	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? <Device> No ✓ Yes ✓	<Device> No ✓ Yes ✓	<Device> No ✓ Yes ✓	<Device> 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							

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

		Prior to, or at time of Event: Date of Initial Dose Day Month Year	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 #
IP/Amgen Device:								
<<IP/Device>>	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

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AMGEN Study # 20160184 evolocumab	**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

AMGEN Study # 20160184 evolocumab	**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 -	Title	Date
I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.		

12.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for females of childbearing potential are outlined in Section 6.2.

Female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant during treatment and for 15 weeks after the last dose of protocol-required therapies.

Additional medications given during the study may alter the contraceptive requirements. These additional medications may require female subjects to use highly effective methods of contraception and for an increased length of time. In addition, male subjects may also be required to use contraception. The investigator must discuss these contraceptive changes with the subject.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered female of childbearing potential:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy;
  - Documented bilateral salpingectomy; or
  - Documented bilateral oophorectomy.

Note: Site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.

- Premenarchal female
- Postmenopausal female
  - 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.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 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

Contraception Methods for Female Subjects

Acceptable Methods of Effective Contraception

- Combined (estrogen and progestogen containing) or progestogen-only hormonal methods given via oral, intravaginal, transdermal, injectable, or implantable route
- Intrauterine device (IUD)
- Intrauterine hormonal-releasing system (IUS)
- 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)
- 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)
- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide
- Double barrier method: the male uses a condom and the female may choose either a cap, diaphragm, or sponge with spermicide (a female condom is not an option due to the risk of tearing when both partners use a condom)

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
- Lactational amenorrhea method

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 15 weeks after the end of treatment with evolocumab.
- Information will be recorded on the Pregnancy Notification Worksheet (see Figure 12-2). The worksheet must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws.)
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 15 weeks

after the last dose of the study drug. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- 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.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 8.1 for details).

Male Subjects With Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- In the event a male subject fathers a child during treatment, and for an additional 15 weeks after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Worksheet. The worksheet (see Figure 12-2) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws.)
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.

- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 15 weeks following end of treatment with evolocumab or placebo.
- Information will be recorded on the Lactation Notification Worksheet (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 213.
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 15 weeks after discontinuing protocol-required therapies.

Figure 12-2. Pregnancy and Lactation Notification Worksheet

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: 20160184

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
evolocumab				mm___/dd___/yyyy____

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

If yes, provide product (or study drug) stop date: mm___/dd___/yyyy____

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

5. Pregnancy Information

Pregnant female's LMP mm___/ dd___/ yyyy____ ☐ Unknown

Estimated date of delivery mm___/ dd___/ yyyy____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm___/ dd___/ yyyy____

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

If yes, provide date of delivery: mm___/ dd___/ yyyy____

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

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

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Effective Date: March 27, 2011 Page 1 of 1

Print Form

AMGEN Lactation Notification Worksheet

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

1. Case Administrative Information

Protocol/Study Number: 20160184

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
evolocumab				mm____/dd____/yyyy____

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

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

12.6 Appendix 6. Sample Storage and Destruction

Any blood sample collected according to the Schedule of Activities (Table 2-1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

If 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 cardiovascular disease, hyperlipidemia and other 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, biomarker development, 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 sample types (eg, blood, tumor) and any other components from the cells 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 Appendix 3 for subject confidentiality.

12.7 Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments

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

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 (BIL) glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis (NASH)
- Non-hepatic causes (eg, rhabdomyolysis, hemolysis)

If investigational product(s) is/are withheld, the subject is to be followed for possible drug-induced liver injury (DILI) according to recommendations in the last section of this appendix.

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 (see next section in this appendix).

Table 12-2. 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	> 3 x ULN at any time	> 2 x ULN
		OR
INR	--	> 1.5 x ULN (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8 x ULN at any time > 5 x ULN but < 8 x ULN for ≥ 2 weeks > 5 x ULN but < 8 x ULN and unable to adhere to enhanced monitoring schedule > 3 x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values > 3 x ULN (when baseline was < ULN)
	OR	
ALP	> 8 x ULN at any time	--

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

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

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

If signs or symptoms recur with rechallenge, then evolocumab is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 12-2) are never to be rechallenged.

Drug-induced Liver Injury Reporting and 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 the above, 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 Appendix 4.

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 12-2 or who experience AST or ALT elevations > 3 x upper limit of normal (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, BIL (total and direct), and INR within 24 hours
- In cases of TBL > 2 x 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 G, 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
- Creatine phosphokinase (CPK), 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 a hepatologist)

Follow the subject and the laboratory tests (ALT, AST, TBL, and 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.