Title Page

Protocol Title:		A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate the Impact of Evolocumab on Major Cardiovascular Events in Patients at High Cardiovascular Risk Without Prior Myocardial Infarction or Stroke
Short Protocol Title:		Effect of Evolocumab in Patients at High Cardiovascular Risk Without Prior Myocardial Infarction or Stroke
Protocol Number:		20170625
Investigational Product:		Evolocumab
Trade Name:		Repatha®
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Version:		**Data Element Standards Version** 6.0

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

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Investigator's Agreement:

I have read the attached protocol entitled A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate the Impact of Evolocumab on Major Cardiovascular Events in Patients at High Cardiovascular Risk Without Prior Myocardial Infarction or Stroke, dated **28 February 2020**, and agree to abide by all provisions set forth therein.

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

I agree to ensure that Financial Disclosure Statements will be completed by: me (including, if applicable, my spouse or legal partner and dependent children) and my subinvestigators (including, if applicable, their spouses or legal partners and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

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

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

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1. Protocol Synopsis

Protocol Title: A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate the Impact of Evolocumab on Major Cardiovascular Events in Patients at High Cardiovascular Risk Without Prior Myocardial Infarction or Stroke
Short Protocol Title: Effect of Evolocumab in Patients at High Cardiovascular Risk Without Prior Myocardial Infarction or Stroke

Study Phase: 3

Indication: Reduce the risk of coronary heart disease (CHD) death, myocardial infarction (MI), stroke, and ischemia-driven arterial revascularization in adults at high risk of cardiovascular events without prior MI or stroke.

Rationale

This study will assess the effect of lowering low-density lipoprotein cholesterol (LDL-C) with evolocumab on major cardiovascular events in subjects without a prior MI or stroke at high risk of a cardiovascular event.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for coronary heart disease (CHD) death, myocardial infarction (MI), or ischemic stroke, whichever occurs first, in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to CHD death, MI, or ischemic stroke, whichever occurs first
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization, whichever occurs first, in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization, whichever occurs first
Primary Estimands	
The primary estimands consist of: • The target population, which is adults at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy. • The primary variables, which are: – time to CHD death, MI, or ischemic stroke, whichever occurs first – time to CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization, whichever occurs first • The intercurrent events are discontinuation of investigational product or commencing commercial proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. For the primary estimand, the treatment effect will be estimated regardless of the occurrence of these events. • The summary measure, which is the hazard ratio (HR) comparing the hazard in the evolocumab group to the hazard in the placebo group.	

Objectives	Endpoints
Primary Estimands (Continued)	
The primary estimands are the HRs comparing evolocumab and placebo for time to CHD death, MI, ischemic stroke, whichever occurs first and time to CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization, whichever occurs first, for adults at high cardiovascular risk without past MI or stroke and receiving optimized lipid-lowering therapy, who are randomized, regardless of discontinuation of investigational product or commencing commercial PCSK9 inhibitors	
Secondary	
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for MI, ischemic stroke, or any ischemia-driven arterial revascularization in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to MI, ischemic stroke, or any ischemia-driven arterial revascularization
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for CHD death, MI, or any ischemia-driven arterial revascularization in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to CHD death, MI, or any ischemia-driven arterial revascularization
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for cardiovascular death, MI, or stroke in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to cardiovascular death, MI, or stroke
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for MI in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to MI
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for any ischemia-driven arterial revascularization in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to any ischemia-driven arterial revascularization
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for CHD death, in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to CHD death

Objectives	Endpoints
Secondary (Continued)	
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for cardiovascular death, in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to cardiovascular death
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for all cause of death, in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to all cause of death
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for ischemic stroke in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to ischemic stroke
Secondary Estimands	
The secondary estimands are the HRs comparing evolocumab and placebo for: • time to MI, ischemic stroke, or any ischemia-driven arterial revascularization • time to CHD death, MI, or any ischemia-driven arterial revascularization • time to cardiovascular death, MI, or stroke • time to MI • time to any ischemia-driven arterial revascularization • time to CHD death • time to cardiovascular death • time to all cause of death • time to ischemic stroke for adults at high cardiovascular risk without past MI or stroke and receiving optimized lipid-lowering therapy, who are randomized, regardless of discontinuation of investigational product or commencing commercial PCSK9 inhibitors.	

Hypotheses

The primary hypothesis is that additional LDL-C lowering with evolocumab when used in addition to optimized lipid-lowering therapy decreases:

- the risk of CHD death, MI, or ischemic stroke
- the risk of CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization in adults without a prior MI or stroke at high risk of major cardiovascular events.

Overall Design

This is a phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group, cardiovascular outcomes study for evolocumab in subjects at high cardiovascular risk without prior MI or stroke. **S**ubjects must be receiving stable, lipid-lowering background therapy **as per local guidelines, starting** at least **2** weeks

prior to the qualifying lipid panel. Such therapy must include optimized statin therapy, except in subjects with documented statin intolerance (see Section 12.8 for details regarding lipid-lowering therapy). Lipid-lowering background therapy should remain unchanged throughout the duration of the study.

Eligible subjects will be randomized with an allocation ratio of 1:1 to either receive evolocumab or placebo. Follow-up of all randomized subjects is planned to continue for a minimum of 4 years (anticipated median around 4.5 years) and until at least 751 subjects have experienced a primary triple component endpoint event (CHD death, MI, ischemic stroke) and 1254 subjects have experienced a primary quadruple component endpoint event (CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization). Subjects will be requested to complete all planned visits regardless of their adherence to investigational product.

Number of Subjects

At least **12 000** subjects will be enrolled in the study, with at least **6000** subjects per treatment group.

Summary of Subject Eligibility Criteria

Key inclusion criteria:

- Subjects must be ≥ 50 years (men) or ≥ 55 years (women) to < 80 years of age (either sex) and **meeting lipid criteria**
- **Lipid Criteria (see Appendix 8 for permissible concomitant lipid-lowering therapy):**
  - **Subjects must have an LDL-C ≥ 90 mg/dL (≥ 2.3 mmol/L) OR non-high density lipoprotein (HDL)-C ≥ 120 mg/dL (≥ 3.1 mmol/L) OR apolipoprotein B ≥ 80 mg/dL (≥ 1.56 μmol/L)**
- Diagnostic evidence of at least 1 of the following (A – D) at screening:
  - A. Significant coronary artery disease meeting at least 1 of the following criteria:
    - History of coronary revascularization with multi-vessel coronary disease as evidenced by any of the following:
      - (a) percutaneous coronary intervention (PCI) **of 2 or more vessels, including branch arteries**
      - (b) PCI or coronary artery bypass grafting (CABG) with residual ≥ 50% stenosis in a separate, unrevascularized vessel, or
      - (c) multi-vessel CABG 5 years **or more** prior to screening
    - Significant coronary disease without prior revascularization as evidenced by either a ≥ 70% stenosis of at least 1 coronary artery, ≥ 50% stenosis of 2 or more coronary arteries, or ≥ 50% stenosis of the left main coronary artery
    - known coronary artery calcium score ≥ 100 **in subjects without a coronary artery revascularization prior to randomization**
  - B. Significant atherosclerotic cerebrovascular disease meeting at least 1 of the following criteria:
    - prior transient ischemic attack with ≥ 50% carotid stenosis
    - **internal or external** carotid artery stenosis of ≥ 70% or 2 or more ≥ 50% stenos**e**s
    - prior **internal or external** carotid artery revascularization

C. Significant peripheral arterial disease meeting at least 1 of the following criteria:
   - ≥ 50% stenosis in a limb artery
   - history of abdominal aorta treatment (percutaneous and surgical) **due to atherosclerosic disease**
   - ankle brachial index (ABI) < 0.85

D. Diabetes mellitus with at least 1 of the following:
   - known microvascular disease, defined by diabetic nephropathy or treated retinopathy. Diabetic nephropathy defined as **persistent** microalbuminuria (urinary albumin to creatinine ratio ≥ 30mg/g) and/or **persistent** estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 **that is not reversible due to an acute illness**
   - chronic **daily** treatment with **an intermediate or long-acting** insulin
   - diabetes diagnosis ≥ 10 years ago

- At least 1 of the following high risk criteria (most recent lab values **within 6 months** prior to screening, as applicable):
   - polyvascular disease, defined as coronary, carotid, or peripheral artery stenosis ≥ 50% in a second distinct vascular location in a patient with coronary, cerebral or peripheral arterial disease (A, B, or C above)
   - **presence of either** diabetes **mellitus** or metabolic syndrome (Section 12.9) in a subject with coronary, cerebral, or peripheral artery disease (A, B, or C above)
   - at least 1 coronary, carotid, or peripheral artery **residual** stenosis of ≥ 50% in a patient with diabetes meeting inclusion criterion (D above)
   - LDL**-C** ≥ 130 mg/dL (≥ 3.**36** mmol/L)**, OR** non-HDL**-C** ≥ 160 mg/dL (≥ 4.**14** mmol/L)**, OR apolipoprotein B ≥ 120 mg/dL (2.3 μmol/L) if available**
   - lipoprotein (a) > 125 nmol/L (50 mg/dL)
   - known familial hypercholesterolemia
   - family history of premature coronary artery disease defined as an MI or CABG in the subject's father or brother at age < 55 years or an MI or CABG in the subject's mother or sister at age < 60 years
   - high sensitive c-reactive protein **(hsCRP)** ≥ 3.0 mg/L **in the absence of an acute illness**
   - current tobacco use
   - ≥ 65 years of age
   - menopause before 40 years of age
   - eGFR 15 to < 45 mL/min/1.73 m^2
   - **coronary artery calcification score ≥ 300 in a patient without a coronary revascularization prior to randomization**

Key exclusion criteria:

- MI or stroke prior to randomization
- CABG < 3 months prior to screening
- eGFR < 15 mL/min/1.73 m^2
- Uncontrolled or recurrent ventricular tachycardia **in the absence of an implantable-cardioverter defibrillator.**
- Atrial fibrillation not on anticoagulation therapy **(vitamin K antagonist, heparin, low-molecular weight heparin, fondaparinux, or non-Vitamin K antagonist oral anticoagulant)**
- Fasting triglycerides ≥ 500 mg/dL (5.7 mmol/L) at screening
- Last measured left-ventricular ejection fraction < 30% or New York Heart Association (NYHA) Functional Class III/IV
- **Planned arterial revascularization**

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

Treatments

Investigational product (evolocumab [140 mg] or placebo) will be self-administered every 2 weeks (Q2W) for a minimum of 4 years.

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. Prior to randomization, all subjects will receive a placebo injection to confirm tolerance of subcutaneous (SC) administration. At randomization, an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) will allocate subjects to receive either evolocumab SC Q2W or placebo SC Q2W. Day 1 of the treatment period (ie, first dose of investigational product) **will** happen within **21** days of the **screening or re-screening visit**.

After day 1, subjects will return to the study site every 16 weeks to review reportable adverse events, concomitant therapies, potential endpoints, vital status, and acquire another 4-month supply of investigational product. Fasting **or non-fasting** lipid panels **may** be collected at screening for **those subjects without lipid panels drawn in the last 3 months** (analyzed at local laboratory). In a subset of subjects (approximately 2000 subjects **from randomly selected sites and stratified by geographic region**), additional lipid panels (fasting **is not required**) will be collected on day 1, at the end of year 1 visit **(week 48)**, end of year 2 visit **(week 96)**, and at the end of study visit (analyzed at central laboratory).

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

Unless specified otherwise, efficacy analyses will be performed on the full analysis set by randomized treatment group; and safety analyses will be performed on the safety analysis set by actual treatment group.

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

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

All deaths and components of primary, secondary, and exploratory endpoints (MI, stroke, and ischemia-driven arterial revascularization) will be adjudicated by an independent external Clinical Events Committee (CEC), using standardized definitions.

In order to preserve the overall type I error rate at 0.05, a parallel gatekeeping strategy will be applied to the primary analysis of the primary and secondary estimands. The primary analysis of all time-to-event estimands will be the log-rank test stratified by the randomization stratification factors. Kaplan-Meier (K-M) time-to-event curves will be presented by randomized treatment and K-M estimates (95% CI) will be provided. In addition, a HR and 95% CI will be estimated from a Cox model stratified by the randomization stratification factors. All adjudicated events will be reported.

Treatment-emergent serious adverse events and adverse events leading to discontinuation of investigational product will be summarized by actual treatment group.

An external independent Data Monitoring Committee (DMC) has been established to formally review the accumulating data from this and other ongoing studies with evolocumab to ensure there is no avoidable increased risk for harm to subjects. Analyses for the DMC will be provided by the Independent Biostatistics Group (IBG), which is external to Amgen.

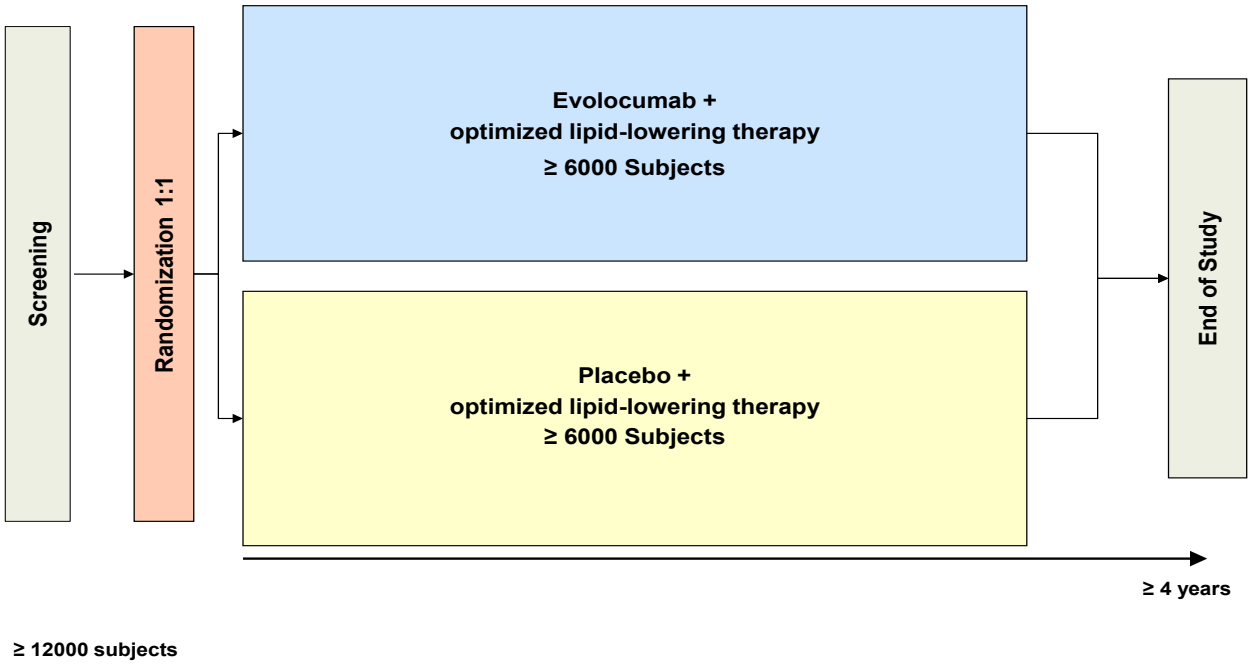
For a full description of statistical analysis methods, please refer to Section 10.

Sponsor Name: Amgen Inc.

2. Study Schema and Schedule of Activities

2.1 Study Schema

Figure 2-1. Study Schema



2.2 Schedule of Activities

Table 2-1. Schedule of Activities

Procedure	SCR[a]	Treatment Period (years)				EOS[b]	Notes
		Day 1	1 (week 48)	2 (week 96)	3+ (week 144+)		
			These visits will have a ± 7 day window				
General and Safety Assessments							
Informed consent	X						
Inclusion and exclusion criteria	X						
Demographics	X						
Physical examination	X						
Physical measurements	X						Height and weight only
Medical history	X						**NYHA Functional Classification at baseline only for subjects with a known history of heart failure. Rutherford classification will be collected for subjects with a known history of peripheral artery disease and symptoms of claudication.**
Substance use history	X						Substance: tobacco
Vital signs	X					X	Blood pressure and heart rate only
Treatment compliance			Q16W	Q16W	Q16W	X	
Adverse events	(X)	continually				X	(X): Serious adverse events only. See Section 9.2.3 for guidance on what adverse events are to be collected and reported.
Potential endpoint data collection		continually				X	
Concomitant therapies	X	X	Q16W	Q16W	Q16W	X	**Only cardiovascular and diabetes medications**
Vital status		X	Q16W	Q16W	Q16W	X	

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Abbreviations and footnotes defined on last page of table.

Table 2-1. Schedule of Activities

Procedure	SCR[a]	Treatment Period (years)				EOS[b]	Notes
			1 (week 48)	2 (week 96)	3+ (week 144+)		
		Day 1	These visits will have a ± 7 day window				
LOCAL Laboratory Assessments							
Serum or urine pregnancy test (FCBP)[c]	X	X				X	
Chemistry	X						
Fasting **or non-fasting** lipid panel	X						**If no changes in lipid-lowering medication, lipid values measured up to 3 months prior to screening are permitted.** **Use Martin-Hopkins estimate when calculating the LDL-C with TG over 400 mg/dL.**
CENTRAL Laboratory Assessments							
Lipid panel, non-fasting (see notes)		(X)	(X)	(X)		(X)	(X): Additional lipid panels for subset of subjects (approximately 2000 subjects **from randomly selected sites and stratified by geographic region**). Years 1 and 2 visits to be scheduled at the end of years 1 and 2, respectively.
Biomarker sample (optional)		(X)					(X): Collected as permissible by law, additional consent required
Pharmacogenetic sample (optional)		(X)					(X): Collected as permissible by law, additional consent required
Study Treatment							
Placebo injection	X						**Day 1 dose to be done in clinic**
Investigational product administration		X	Q2W	Q2W	Q2W		**Day 1 dose to be done in clinic**
Investigational product dispensation		X	Q16W	Q16W	Q16W		

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EOS = end of study; FCBP = female of childbearing potential; QXW = every X weeks; SCR = screening.

[a] The screening period will be up to **21** days before day 1 **of study treatment**. **Subjects should be randomized within 21 days of the screening visit. If the subject is not randomized within this period, the subject may be rescreened.**

[b] The EOS visit **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, safety or efficacy follow-up), as applicable**.

[c] Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or as required per local laws and regulations.

3. Introduction

3.1 Study Rationale

This study is being done in order to assess the effect of lowering low-density lipoprotein cholesterol (LDL-C) with evolocumab on major cardiovascular events in subjects without a prior myocardial infarction (MI) or stroke at high risk of a cardiovascular event.

3.2 Background

3.2.1 Cardiovascular Disease

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 MI or stroke (World Health Organization, 2014). The morbidity associated with MI 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 MI or coronary death, 155 000 have a silent first MI, 610 000 have a new stroke (ischemic or hemorrhagic), and 185 000 have a recurrent stroke (Mozaffarian et al, 2016).

Elevated cholesterol, in particular LDL-C, is a modifiable independent cardiovascular risk factor (Silverman et al, 2016).

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 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 (Silverman et al, 2016). 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 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. Evolocumab is a fully human monoclonal immunoglobulin (Ig)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.

A detailed description of the chemistry, pharmacology, efficacy, and safety of evolocumab is provided in the Evolocumab (AMG 145) Investigator's Brochure.

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

Evolocumab reduces LDL-C by approximately 60%, an effect maintained over 4 years.

3.3.1.2 Reduction in the Risk of Cardiovascular Events

In FOURIER (study 20110118), treatment with evolocumab as compared with placebo, in addition to stable lipid-lowering therapy, statistically significantly reduced the risk of cardiovascular events. With a median follow-up period of 26 months, evolocumab reduced the risk of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization, (primary component endpoint) by 15% (hazard ratio [HR] of 0.85, 95% CI: 0.79, 0.92; $p < 0.0001$) (Sabatine et al, 2017). Evolocumab reduced the risk of cardiovascular death, MI, or stroke, (key secondary component endpoint) by 20% (HR 0.80, 95% CI: 0.73, 0.88; $p < 0.0001$). 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 atherosclerotic cardiovascular disease and a prior MI, stroke, or symptomatic peripheral artery disease who cannot achieve LDL-C control with statins alone.

3.3.2 Risks of Evolocumab

The safety profile of evolocumab has been characterized in an estimated 29 788 subjects (57 632.1 subject years) who have been exposed to evolocumab in Amgen-sponsored clinical studies since the beginning of the development program.

There are no important identified or potential risks with evolocumab. Evolocumab had a very low rate of immunogenicity (0.1%) which did not affect pharmacokinetics, pharmacodynamics, efficacy, or safety. Common adverse reactions associated with evolocumab are described in the approved drug labeling.

A similar patient population has been studied as part of the evolocumab development program and no new risks are anticipated in the target patient population.

Detailed safety information for evolocumab including contraindications, warnings and precautions, adverse reactions, and overdose can be found in Appendix A of the Evolocumab (AMG 145) Investigator's Brochure.

3.3.3 Conclusion

Evolocumab has demonstrated a favorable benefit risk profile in patients with primary hyperlipidemia, mixed dyslipidemia, and familial hypercholesterolemia to reduce LDL-C, in patients with coronary artery disease for the regression of coronary atherosclerosis, and in patients with atherosclerotic cardiovascular disease to reduce the risk of cardiovascular events. It is anticipated that the well-established relationship between LDL-C reduction and cardiovascular risk reduction observed with evolocumab in patients with established cardiovascular disease, will be observed in this patient population at high risk of experiencing a first cardiovascular event.

There are no important identified or potential risks with evolocumab and the target patient population has been studied as part of the evolocumab development program, thus a similarly favorable benefit-risk profile is anticipated.

4. Objectives, Endpoints and Hypotheses

4.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for coronary heart disease (CHD) death, myocardial infarction (MI), or ischemic stroke, whichever occurs first, in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to CHD death, MI, or ischemic stroke, whichever occurs first
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization, whichever occurs first, in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization, whichever occurs first
Primary Estimands	
The primary estimands consist of: • The target population, which is adults at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy. • The primary variables, which are: – time to CHD death, MI, or ischemic stroke, whichever occurs first – time to CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization, whichever occurs first • The intercurrent events are discontinuation of investigational product or commencing commercial proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. For the primary estimand, the treatment effect will be estimated regardless of the occurrence of these events. • The summary measure, which is the hazard ratio (HR) comparing the hazard in the evolocumab group to the hazard in the placebo group. The primary estimands are the HRs comparing evolocumab and placebo for time to CHD death, MI, ischemic stroke, whichever occurs first and time to CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization, whichever occurs first, for adults at high cardiovascular risk without past MI or stroke and receiving optimized lipid-lowering therapy, who are randomized, regardless of discontinuation of investigational product or commencing commercial PCSK9 inhibitors	

Objectives	Endpoints
Secondary	
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for MI, ischemic stroke, or any ischemia-driven arterial revascularization in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to MI, ischemic stroke, or any ischemia-driven arterial revascularization
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for CHD death, MI, or any ischemia-driven arterial revascularization in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to CHD death, MI, or any ischemia-driven arterial revascularization
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for cardiovascular death, MI, or stroke in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to cardiovascular death, MI, or stroke
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for MI in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to MI
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for any ischemia-driven arterial revascularization in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to any ischemia-driven arterial revascularization
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for CHD death, in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to CHD death
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for cardiovascular death, in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to cardiovascular death

Objectives	Endpoints
Secondary (Continued)	
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for all cause of death, in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to all cause of death
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for ischemic stroke in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to ischemic stroke
Secondary Estimands	
The secondary estimands are the HRs comparing evolocumab and placebo for: • time to MI, ischemic stroke, or any ischemia-driven arterial revascularization • time to CHD death, MI, or any ischemia-driven arterial revascularization • time to cardiovascular death, MI, or stroke • time to MI • time to any ischemia-driven arterial revascularization • time to CHD death • time to cardiovascular death • time to all cause of death • time to ischemic stroke for adults at high cardiovascular risk without past MI or stroke and receiving optimized lipid-lowering therapy, who are randomized, regardless of discontinuation of investigational product or commencing commercial PCSK9 inhibitors.	
Safety	
• To evaluate the safety and tolerability of evolocumab treatment, compared with placebo, in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• **T**reatment-emergent adverse events leading to investigational product discontinuation • **T**reatment-emergent serious adverse events

Objectives	Endpoints
Exploratory	
• To evaluate the effect of treatment with evolocumab, compared with placebo, on change and percent change from baseline of low-density lipoprotein cholesterol (LDL-C), in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• LDL-C change and percent change from baseline
• **To evaluate the effect of treatment with evolocumab, compared with placebo, on the incidence of new or worsening aortic valve stenosis**	• **New or worsening aortic valve stenosis**
• **To evaluate the effect of treatment with evolocumab, compared with placebo, on the incidence of new or recurrent venous thromboembolism**	• **New or recurrent venous thromboembolism (pulmonary embolus and/or deep venous thrombosis)**

4.2 Hypotheses

The primary hypothesis is that additional LDL-C lowering with evolocumab when used in addition to optimized lipid-lowering therapy decreases:

- the risk of CHD death, MI, or ischemic stroke
- the risk of CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization

in adults without a prior MI or stroke at high risk of major cardiovascular events.

5. Study Design

5.1 Overall Design

This is a phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group, cardiovascular outcomes study for evolocumab in subjects at high cardiovascular risk without prior MI or stroke. **S**ubjects must be receiving stable, lipid-lowering background therapy **as per local guidelines, starting** at least **2** weeks **prior to the qualifying lipid panel**. Such therapy must include optimized statin therapy, except in subjects with documented statin intolerance (see Section 12.8 for details regarding lipid-lowering therapy). **Optimized lipid-lowering therapy could be high, moderate, or low dose.** Lipid-lowering background therapy should remain unchanged throughout the duration of the study.

Eligible subjects will be randomized with an allocation ratio of 1:1 to either receive evolocumab or placebo. Randomization will be stratified by the screening LDL-C level (< 160 mg/dL [4.**14** mmol/L] vs ≥ 160 mg/dL) and by geographical region **(North**

America, Europe, and others). Evolocumab and placebo will be blinded. Central laboratory results of the lipid panel (**fasting or** non-fasting; only collected in a subset of subjects) will be blinded on study and not reported to the investigator until unblinding of the clinical database. Investigators and staff involved with this trial should not perform non-protocol lipid panel testing during a subject's study participation and until at least 12 weeks after the subject's last administration of investigational product or the end of study, whichever is later (to avoid potential unblinding). The study includes collection of biomarker samples, unless prohibited by local law or regulations. Follow-up of all randomized subjects is planned to continue for a minimum of 4 years (anticipated median around 4.5 years) and until at least 751 subjects have experienced a primary triple component endpoint event (CHD death, MI, ischemic stroke) and 1254 subjects have experienced a primary quadruple component endpoint event (CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization). Subjects will be requested to complete all planned visits regardless of their adherence to investigational product. At minimum, vital status **must** be collected on day 1 and every 16 weeks and must be obtained at the end of the study for all subjects including those who withdraw consent, unless prohibited by local law.

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

At least **12 000** subjects will be enrolled in the study, with at least **6000** subjects per treatment group.

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

Up to approximately **900** investigative sites in North America, Europe, and **other regions** will be included in the study. Sites that do not enroll subjects 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), whether the study **is** concluded as planned in the protocol or was terminated early.

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

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

End of Study: The end of study 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, safety or efficacy follow-up), as applicable.

5.3.2 Study Duration for Subjects

Including the initial screening, study treatment period (double-blind), and the safety/end of study follow-up, the estimated study duration is a minimum of 4 years. Subjects should be randomized no more than **21** days after the signing of informed consent. **If the subject is not randomized within this period, the subject may be rescreened.**

5.4 Justification for Investigational Product Dose

Evolocumab will be administered as 140 mg SC every 2 weeks (Q2W) in a 1.0 mL prefilled autoinjector pen (AI/pen). The evolocumab dose being used in this study is consistent with the dose in its current marketing authorization and is broadly available worldwide.

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 Section 12.3).

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

The sponsor will monitor the study population baseline characteristics during enrollment. If necessary, the sponsor may restrict enrollment of certain populations in order to ensure the appropriate distributions of subject characteristics.

6.1 Inclusion Criteria

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

101 Subject has provided informed consent prior to initiation of any study specific activities/procedures

102 Adult subjects ≥ 50 years (men) or ≥ 55 years (women) to < 80 years of age (either sex) **and meeting lipid criteria**

107 Subjects must have an LDL-C ≥ **90** mg/dL (≥ 2.**3** mmol/L) **OR** non-HDL-C ≥ 1**2**0 mg/dL (≥ **3.1** mmol/L)**, OR apolipoprotein B ≥ 80 mg/dL (≥ 1.56 μmol/L)**

- **Lipid entry criteria can be measured up to 3 months prior to screening in the absence of changes to background therapy**
- **Lipid criteria should be assessed after ≥ 2 weeks of stable, optimized lipid-lowering therapy**

108 Diagnostic evidence of at least 1 of the following (A – D) at screening:

A. Significant coronary artery disease meeting at least 1 of the following criteria:
   - History of coronary revascularization with multi-vessel coronary disease as evidenced by any of the following:
     - (a) percutaneous coronary intervention (PCI) **of 2 or more vessels, including branch arteries**
     - (b) PCI or coronary artery bypass grafting (CABG) with residual ≥ 50% stenosis in a separate, unrevascularized vessel, or
     - (c) multi-vessel CABG 5 years **or more** prior to screening
   - Significant coronary disease without prior revascularization as evidenced by either a ≥ 70% stenosis of at least 1 coronary artery, ≥ 50% stenosis of 2 or more coronary arteries, or ≥ 50% stenosis of the left main coronary artery
   - known coronary artery calcium score ≥ 100 **in subjects without a coronary artery revascularization prior to randomization**

B. Significant atherosclerotic cerebrovascular disease meeting at least 1 of the following criteria:
   - prior transient ischemic attack with ≥ 50% carotid stenosis
   - **internal or external** carotid artery stenosis of ≥ 70% or 2 or more ≥ 50% stenos**e**s
   - prior **internal or external** carotid artery revascularization

C. Significant peripheral arterial disease meeting at least 1 of the following criteria:
   - ≥ 50% stenosis in a limb artery
   - history of abdominal aorta treatment (percutaneous and surgical) **due to atherosclerosic disease**
   - ankle brachial index (ABI) < 0.85

D. Diabetes mellitus with at least 1 of the following:
   - known microvascular disease, defined by diabetic nephropathy or treated retinopathy. Diabetic nephropathy defined as **persistent** microalbuminuria (urinary albumin to creatinine ratio ≥ 30 mg/g) and/or **persistent** estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 **that is not reversible due to an acute illness**
   - chronic **daily** treatment with **an intermediate or long-acting** insulin
   - diabetes diagnosis ≥ 10 years ago

109 At least 1 of the following high risk criteria (most recent lab values **within 6 months** prior to screening, as applicable):

- polyvascular disease, defined as coronary, carotid, or peripheral artery stenosis ≥ 50% in a second distinct vascular location in a patient with coronary, cerebral or peripheral arterial disease (inclusion criterion **108** A-C)
- **presence of either** diabetes **mellitus** or metabolic syndrome (Section 12.9) in a subject with coronary, cerebral, or peripheral artery disease (inclusion criterion **108** A-C)
- at least 1 coronary, carotid, or peripheral artery **residual** stenosis of ≥ 50% in a patient with diabetes meeting inclusion criterion **108** D
- LDL**-C** ≥ 130 mg/dL (≥ 3.**36** mmol/L)**, OR** non-HDL**-C** ≥ 160 mg/dL (≥ 4.**14** mmol/L)**, OR apolipoprotein B ≥ 120 mg/dL (2.3 μmol/L) if available**
- lipoprotein (a) > 125 nmol/L (50 mg/dL)
- known familial hypercholesterolemia
- family history of premature coronary artery disease defined as an MI or CABG in the subject's father or brother at age < 55 years or an MI or CABG in the subject's mother or sister at age < 60 years
- **hsCRP** ≥ 3.0 mg/L **in the absence of an acute illness**
- current tobacco use
- ≥ 65 years of age

- menopause before 40 years of age
- eGFR 15 to < 45 mL/min/1.73 m^2
- **coronary artery calcification score ≥ 300 in a patient without a coronary revascularization prior to randomization**

6.2 Exclusion Criteria

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

Disease Related

201 MI or stroke prior to randomization

202 CABG < 3 months prior to screening

203 Uncontrolled or recurrent ventricular tachycardia **in the absence of an implantable-cardioverter defibrillator.**

204 Atrial fibrillation not on anticoagulation therapy **(vitamin K antagonist, heparin, low-molecular weight heparin, fondaparinux, or non-vitamin K antagonist oral anticoagulant)**

206 Last measured left-ventricular ejection fraction < 30% or New York Heart Association (NYHA) Functional Class III/IV

219 Planned arterial revascularization

Diagnostic Assessments

207 Fasting triglycerides ≥ 500 mg/dL (5.7 mmol/L) at screening

208 End stage renal disease (ESRD), defined as an eGFR < 15 mL/min/1.73 m^2 or receiving dialysis at screening

Other Medical Conditions

209 Malignancy (except non-melanoma skin cancers, **cervica**l in situ **carcinoma, breast ductal carcinoma in situ, or stage 1** prostate **carcinoma)** within **the last** 5 years prior to **day 1**

210 History or evidence of clinically significant disease (eg, malignancy, respiratory, gastrointestinal, renal or psychiatric disease) or unstable disorder that, in the opinion of the investigator(s), Amgen physician or designee would pose a risk to the patient's safety or interfere with the study assessments, procedures, completion, or result in a life expectancy of less than 1 year

220 Persistent acute liver disease or hepatic dysfunction, defined as Child Pugh score of C (see Appendix 12.11)

Prior/Concomitant Therapy

212 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

221 Previously received or receiving any other therapy to inhibit PCSK9 **in the following timeframe prior to screening:**

- **bococizumab at any time**
- **evolocumab, alirocumab, or any other monoclonal antibody against PCSK9 within 3 months**
- **inclisiran within 12 months**

Prior/Concurrent Clinical Study Experience

213 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 Exclusions

215 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 Section 12.5 for additional contraceptive information.

216 Subject has known sensitivity to any of the products or components to be administered during dosing.

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

218 Subject is staff **personnel** directly involved with the study or is a family member of the investigational study staff

222 Female subject is pregnant, had a positive pregnancy test at screening (by a serum pregnancy test and/or urine pregnancy test), breastfeeding, or planning to become pregnant or breastfeed during treatment and for an additional 15 weeks after the last dose of investigational product.

6.3 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, ICF, and all other subject information and/or recruitment material, if applicable (see Section 12.3).

The subject or the subject's legally acceptable representative must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures.

Each subject who enters into the screening period for the study (defined as when the subject signs the IRB/IEC approved ICF) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by 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.

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).

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

6.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. Individuals who do not meet the criteria for participation in this study (screen failure) **can** be rescreened.

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.

Refer to Section 9.1.1.

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 Table 7-1 below.

7.1 Treatment Procedures

7.1.1 Investigational Products

Table 7-1. Investigational Products

Study Treatment Name	Amgen Investigational Product:[a] Evolocumab (Repatha, AMG 145)	Placebo
Dosage Formulation	Evolocumab will be presented as a sterile, preservative-free solution in a single-use, disposable, handheld mechanical (spring-based) prefilled AI/pen for fixed dose, SC injection. The prefilled AI/pen contains a 1-mL deliverable volume of 140 mg/mL evolocumab.	Placebo will be presented in identical containers, and stored/packaged the same as evolocumab.
Unit Dose Strength(s)/Dosage Level(s) and Dosage Frequency	140 mg/mL 140 mg Q2W	Q2W
Route of Administration	SC	SC
Accountability	The amount dispensed, amount returned, date dispensed, date returned, lot number, box number of investigational product are to be recorded on each subject's CRF(s).	
Dosing Instructions	Subjects may self-administer, defined as SC administration of IP by the subject, designee, or a qualified health care professional in a non-investigator site setting (eg, at home). If IP is administered on site, it must be performed after all scheduled assessments.	
Device	AI/pen	AI/pen

AI/pen = autoinjector pen; CRF = case report form; IP = investigational product; Q2W = every 2 weeks; SC = subcutaneous

[a] Evolocumab will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

7.1.2 Non-investigational Products

Not applicable in this study.

7.1.3 Medical Devices

The following medical device provided by Amgen for use in this study is the spring-based prefilled AI/pen (Table 7-1). AI/pen training by study site staff to each subject will occur at the day 1 visit and each visit thereafter, if necessary.

The AI/pen is a single use disposable, handheld mechanical “spring-based” device for fixed dose SC injection of 140 mg evolocumab in 1.0-mL deliverable volume or an identical volume of placebo.

Additional details are provided in the IPIM.

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 or the patient's primary care physician will be responsible for obtaining supplies of these devices.

7.1.4 Other Protocol-required Therapies

Background lipid-lowering therapies will not be provided or reimbursed by Amgen (except if required by local regulation). All such therapy needs to be unchanged during the entire time of screening and study participation unless a change is clinically necessary. If a change is made, the reason for the change must be provided in the CRF.

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

Any product complaint(s) associated with an investigational product(s), devices(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 (including commercially available PCSK9 inhibitors) not already taking at the time of screening and enrollment

Please contact the Amgen medical monitor or designee (Thrombolysis in Myocardial Infarction [TIMI] Study Group Hotline) 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.

7.2 Method of Treatment Assignment

Subjects will be randomized in 1:1 allocation ratio, to evolocumab and placebo, respectively, in 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 the screening LDL-C level ($<$ 160 mg/dL [4.**14** mmol/L] vs $\geq$ 160 mg/dL) and by geographical region **(North America, Europe, and others)**.

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 **and lipid levels after randomization** will be blinded to all subjects, site personnel, study committee members (excluding the Data Safety Monitoring Board), and Amgen as described below. **Refer to Section 12.2 for additional information.**

7.3.1 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment is to only be unblinded by the investigator when knowledge of the treatment is essential for the further management of the subject on this study or may potentially impact the safety of the subject. Unblinding at the study site for any other reason will be considered a protocol deviation. It is encouraged that the Amgen Trial Manager or Amgen designee be notified before the blind is broken unless the investigator believes that identification of the study treatment is required for a medical emergency. If this is not possible, the Amgen Trial Manager or Amgen

designee must be notified within 1 business day 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 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 and must be within ± 7 days of the originally scheduled dose. If the dose is not administered within ± 7 days, instruct the subject to wait until the next dose on the original schedule. 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.

7.4.2 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 12.7 for details regarding drug-induced liver injury guidelines, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

7.5 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product and/or device (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

Only cardiovascular and diabetes prior therapies that were being taken from 30 days prior to signing of the informed consent should be collected. For lipid-lowering therapies, collect therapy name, dose, unit, frequency, start and stop dates. For all other prior therapies, collect therapy name, start and stop dates.

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.

Only cardiovascular and diabetes concomitant therapies are to be collected from signing of the informed consent through the end of safety follow-up period.

For lipid-lowering therapies, collect therapy name, dose, unit, frequency, start and stop dates, reason for stop or change. For all other concomitant therapies, collect therapy name, start and stop dates.

8. Discontinuation Criteria

Subjects have the right to discontinue from investigational product and/or other protocol-required therapies, protocol procedures, or withdraw from 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 discontinue a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or withdraw from the study as a whole at any time prior to study completion for the reasons listed in Sections 8.1, 8.2.1, and 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 and reason(s) for discontinuation. 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 **continue to be followed** to ensure safety surveillance and/or collection of outcome data per the Schedule of Activities (see Table 2-1). If this is not possible or agreeable to a subject, different options of follow-up (eg, 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 must document this decision in the subject's medical records.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.3.

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

- adverse event
- subject request
- requirement for alternative therapy
- pregnancy (see Section 9.2.3.1.5 for details regarding evolocumab pregnancy registries)

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 (including blood, urine, and other specimens) collected up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data **(eg, vital status)** can be included after withdrawal of consent.

Discontinuation of investigational product (temporary or permanent) is not considered withdrawal of consent. Subjects who do not wish to attend regular site visits as per the schedule of activities after investigational product discontinuation should be offered alternative methods of follow up including periodic telephone follow up, contact at the end of study, or assessment of health status via treating physicians or medical records. Withdrawal of consent should only occur if the subject refuses all potential options of further follow up. 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 **and electronic data capture (EDC) CRF**. **For subjects who are confirmed to have fully withdrawn consent for all study procedures, only publicly available records (where permitted) may be searched after withdrawal.**

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 Section 12.6 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 Washout, Run-in, or Invasive Procedures

This is not applicable to this study.

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 prior to database lock.

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 potentially lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (including, but not limited to, telephone calls, certified letters to the subject's last known mailing address or local equivalent methods, contact of other individuals as identified by the subject at the start of the trial, contact of the subject's healthcare providers). These contact attempts are to be documented in the subject's medical record.
- For subjects who are potentially lost to follow-up, the investigator can search **all** available records (where permitted) to ascertain **efficacy and safety outcomes as well as** vital 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 or designee 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, is essential and required for study conduct.

9.1 General Study Periods

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 ICF, the site will register the subject in the IVRS/IWRS and screen the subject in order to confirm eligibility. The screening **period will be** up to **21 days before day 1 of study treatment**.

All screening evaluations (including the placebo injection; Section 9.2.1.7) must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. **L**ipid samples collected during screening (local laboratory), **may be fasting or non-fasting**. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure (see Section 6.4), as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects **are** eligible for rescreening.

Rescreen subjects must first be registered as screen failures in IVRS/IWRS and subsequently registered as rescreens. Once the subject is registered as rescreened, a new **21 day** screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 30 days after the original signing of the ICF, all screening procedures, including informed consent, must be repeated. **With the exception of the placebo run-in, rescreened subjects who are re-reconsented will repeat all screening procedures. Subjects may be rescreened more than once.**

9.1.2 Treatment Period

Day 1 of the treatment period (ie, first dose of investigational product) **will** happen within **21** daysof **the screening or re-screening visit**. Visits will occur per the Schedule of Activities (Table 2-1). On-study visits may be completed within ± 7 days. The date of the first dose of investigational product is defined as day 1**; day 1 dose will be performed in clinic**. 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.

If a subject discontinues study treatment but is not removed from the study, the subject will continue following the Schedule of Activities as discussed in Section 8.1.

9.1.3 Safety Follow-up

Upon discontinuation from the study treatment for any reason, a safety follow-up visit will be performed approximately 30 (+3) days after the last dose of investigational product unless the subject is lost to follow-up, has withdrawn consent from the study, or has died. The safety follow-up visit may coincide with the end of study visit.

9.1.4 End of Study

The end of study visit occurs once the specified number of events to support the primary endpoints has been reached. If the subject terminates early, all end of study visit assessments should be performed.

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. Additionally, demographic data will be used to study the impact on biomarkers variability of the protocol-required therapies.

9.2.1.3 Medical History

The investigator or designee will collect a targeted cardiovascular medical and surgical history that started prior to screening through the start of the adverse event reporting period. 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. Record NYHA Functional Classification at baseline on the medical history CRF **only for subjects with a known history of heart failure**.

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). The Modified Rankin Scale **will only** be used to measure disability **if a subject experiences a stroke event during the study**.

9.2.1.5 Physical Measurements

Height (in centimeters) and weight (in kilograms) should be measured without shoes. Subject's body mass index (BMI) will be derived in kg/m^2 in the clinical database.

9.2.1.6 Substance Abuse History

Obtain a detailed history of prior and/or concurrent use of tobacco.

9.2.1.7 Placebo Injection

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

9.2.2 Efficacy Assessments

At each scheduled visit, the survival status and non-fatal potential endpoint assessment will be recorded on the CRF, including the survival status date and non-fatal potential endpoint assessment date. Non-fatal potential endpoints are considered to be assessed if it is known that the subject has not experienced any potential endpoint since the last visit, or they have experienced an event (and event should be recorded within the EDC CRF).

Potential endpoint data will be collected **within the EDC** CRFs as detailed in the Endpoint Reporting Manual. All supporting documentation will be provided to Amgen or designee for each event as it occurs during the course of the study. Potential endpoints will be adjudicated by an independent external Clinical Events Committee (CEC), as defined in the CEC charter.

9.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see (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

This study follows a limited safety data collection approach. As such, the investigator is responsible for ensuring that only adverse events that lead to investigational product discontinuation that occur after first dose of investigational product(s) through the end of study/safety follow-up visit are reported using the Event CRF. While this is a limited safety data collection approach**,** unscheduled study visits, hospitalizations and accidental injuries should be recorded on the Event CRF. The adverse event grading scale to be used for this study will be the Amgen Adverse Event Grading Scale and is described in Section 12.4.

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 of the informed consent through the end of study/safety follow-up visit are reported using the Event CRF. **Occurrences of unscheduled study visits, hospitalization, and accidental injuries should be assessed for potential serious adverse events.**

All serious adverse events will be collected, recorded, and reported to the sponsor or designee within 24 hours, following the investigator's knowledge of the event, as indicated in Section 12.4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

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 end of study. 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 end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to investigational product.

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Section 12.4.

9.2.3.1.1.4 Reporting Study Endpoints

All potential endpoints (death, MI, ischemic stroke, ischemia-driven arterial revascularization) must be recorded on the Event CRF within 24 hours of knowledge of the event. **In addition, aortic valve stenosis and venous thromboembolic events (pulmonary embolism and/or deep vein thrombosis) should be recorded as potential endpoints on the Event CRF.** Information regarding dates of onset and resolution, severity, action taken, investigator assessment of relatedness, and assessment of seriousness must be collected as indicated in Section 12.4.

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 reportable adverse events and all 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 Section 12.4.

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 discontinued 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 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.

Potential endpoint events meeting seriousness criteria will be evaluated by Amgen for adverse event reporting requirements. Potential endpoints that are serious, unexpected, and for which there is evidence suggesting a causal relationship between the drug and the event will be expedited to Health Authorities, even if they are a component of one of the study endpoints.

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 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 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 Section 12.5. 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 Section 12.5.

Evolocumab Pregnancy Registries

Amgen is sponsoring 2 prospective, observational studies of pregnant women that have been exposed to evolocumab. One study registry is conducted in the United States and Canada, and enrolls any patient exposed to evolocumab at any point during pregnancy. The other registry is conducted in Europe, South Africa, and Australia, and enrolls patients diagnosed with familial hypercholesterolemia exposed to evolocumab at any point during pregnancy and/or breast-feeding. Participants are not asked to make any changes to their healthcare routine. If a site investigator/health care practitioner has a subject/patient that has, or may have, been exposed to evolocumab while pregnant or breast-feeding, they will be advised to refer the subject to Amgen's evolocumab pregnancy registry according to the place of residency. To learn more about the study in the United States and Canada, you can go to MotherToBaby.org or call at 877.311.8972. To learn more about the study in Europe, South Africa, and Australia you can contact medInfo@amgen.com or call 0800121 8703 (toll-free) or +44 1223 420305.

9.2.3.2 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure and heart rate. **It is recommended that the s**ubject 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. 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 Section 12.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Table 2-1) for the timing and frequency.

All protocol-required laboratory assessments, as defined in Section 12.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Table 2-1).

NOTE: Fasting **or non-fasting** lipid panels **may** be collected from subjects during screening and if so, will be analyzed at the local laboratory**. In the absence of changes in lipid-lowering therapy or significant changes in diet, the most recent lipid values obtained within 3 months prior to screening may be used to determine eligibility**. A subset of subjects (approximately 2000 subjects from randomly selected sites and stratified by geographic region) will have additional lipid panels collected during the study (Table 2-1) which will be analyzed at the central laboratory (fasting is not required).

9.2.4.1 Pregnancy Testing

A highly sensitive **(serum or** urine**)** pregnancy test should be completed at screening and prior to administration of investigational product on day 1 for females of childbearing potential (analyzed at local laboratory).

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 Section 12.5 for contraceptive requirements.

A pregnancy test should be performed after discontinuing investigational product (analyzed at local laboratory).

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations. See Section 9.2.3.1.5 for details regarding evolocumab pregnancy registries.

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 or designees 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).

9.2.6 Pharmacogenetic Assessments

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals include the use of genetic markers to help in the investigation of cardiovascular events and/or to identify subjects who may have more or less benefit to evolocumab. Additional samples are collected for this part of the study. For subjects who consent to this/these analysis/analyses, DNA may be extracted.

The final disposition of samples will be described in Section 12.6.

10. Statistical Considerations

10.1 Sample Size Determination

The calculation of sample size is based on the primary endpoints in this study (triple component of CHD death, MI, or ischemic stroke; quadruple component of CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization).

Based on the lipid entry criteria, it is anticipated that the median baseline LDL-C will be **approximately** 12**0** mg/dL. Taking into account premature discontinuation of study drug and **potential** use of commercially available PCSK9 inhibitors, it is anticipated that the LDL-C difference between the evolocumab and placebo arms will be **approximately** 1.7 mmol/L at the midpoint of the trial. After accounting for a 12-month treatment lag at the beginning of the trial, and assuming a median follow-up of at least 4.5 years, the anticipated HRs over the duration of this entire study for the primary endpoints will be 0.77 for primary triple component endpoint and 0.80 for primary quadruple component endpoint.

The annualized event rate of the primary triple endpoint and the primary quadruple endpoint in the placebo arm are estimated approximately 1.**63**% and 2.**72**%, respectively **(Bhatt et al, 2019; Steg et al, 2019)**.

The **2-sided** 0.025 significance level of type I error is used for each of the primary estimands.

Assuming a 15-month enrollment period, a 1% of loss to follow-up rate per year, and a total study duration of 63 months, a total sample size of at least **12 000** subjects, with approximately 751 subjects experiencing a primary triple component endpoint, is required to ensure approximately 90.5% power (Shih, 1995) based on a 2-sided log-rank

test of demonstrating the superiority of evolocumab over placebo. At the time of 751 subjects with the primary triple component endpoint observed, there will be approximately 1254 subjects with the primary quadruple component endpoint, which will ensure a power of 95.**6**% to demonstrate superiority for that component endpoint of evolocumab over placebo.

Based on the accumulating event rate in the pooled blinded treatment groups, the sample size and/or study duration may be altered in order to complete the trial with at least 751 subjects with the primary triple component events and at least approximately 1254 subjects with the primary quadruple observed in approximately 63 months.

10.2 Analysis Sets, Subgroups, and Covariates

10.2.1 Analysis Sets

Full Analysis Set: The primary efficacy analysis set is the full analysis set, which includes all randomized subjects. All subjects will be analyzed according to their randomized treatment assignment.

Safety Analysis Set: Safety analyses will be performed on the safety analysis set, which includes all randomized subjects who received at least 1 dose of investigational product. For safety analyses, subjects will be grouped according to their actual treatment group which is defined as the randomized treatment group assignment with the following exception: if a subject receives treatment throughout the study that is different than the randomized treatment group assignment, then the actual treatment group is the treatment received.

10.2.2 Covariates

Baseline covariates include, but are not limited to:

- stratification factors
  - geographical region **(North America, Europe, and others)**
  - screening LDL-C level **(< 160 mg/dL, ≥ 160 mg/dL)**
- age
- sex
- race
- baseline LDL-C

10.2.3 Subgroups

Subgroups include, but are not limited to the following:

- stratification factors
  - geographical region **(North America, Europe, and others)**
  - screening LDL-C level **(< 160 mg/dL, ≥ 160 mg/dL)**
- age (< 65 years, ≥ 65 years)
- sex (male, female)
- race (white, black, other)
- baseline LDL-C by quartiles

10.2.4 Handling of Missing and Incomplete Data

All attempts will be made to capture missing or partial data for this trial prior to the data lock.

The frequency and pattern of missing data for efficacy endpoints will be assessed through descriptive summaries of the measurements over time.

For all time-to-event endpoints, there will be no imputation of the data, except for incomplete dates of the events. Incomplete dates for adverse events, concomitant medication, and historical events will be imputed. Further details on the imputations rules are specified in the Statistical Analysis Plan. For all other efficacy and safety endpoints, unless specified otherwise, missing data will not be imputed.

10.3 Statistical Analyses

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

10.3.1 Planned Analyses

10.3.1.1 Interim Analysis

The DMC will review all available safety data periodically (approximately every 6 months) and will consider a recommendation for early termination of the study based on their review of the totality of evidence at 2 pre-specified interim analyses.

Further details regarding DMC analyses are provided in Appendix 12.3.

10.3.1.2 Primary Analysis

The primary objectives of the primary analysis will be to assess the study hypotheses that treatment with evolocumab when used in addition to stable optimized lipid-lowering background therapy, reduces the risk for CHD death, MI, ischemic stroke, whichever occurs first, and/or reduces the risk for CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization in subjects at high risk of major cardiovascular events (without prior MI or stroke). All secondary and exploratory objectives will also be assessed at the time of the primary analysis. The primary analysis will occur at the primary completion date, when at least 751 subjects have experienced the primary triple component event and at least 1254 subjects have experienced the primary quadruple component event. At this time, the data will be cleaned, processed, and locked; the study will then be unblinded. All primary and secondary endpoint events reported and adjudicated at the time of database lock will be included in the primary analysis.

10.3.2 Methods of Analyses

10.3.2.1 General Considerations

Unless specified otherwise, efficacy analyses will be performed on the full analysis set by randomized treatment group; and safety analyses will be performed on the safety analysis set by actual treatment group.

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

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

All deaths and components of primary, secondary, and exploratory endpoints (MI, stroke, and ischemia-driven arterial revascularization) will be adjudicated by an independent external CEC, using standardized definitions. The CEC is external to Amgen and primarily comprises both academic clinical physicians (to include cardiologists) and medical reviewers trained on the clinical trial protocol, the CEC charter, and CEC processes. The chairman of the CEC is responsible for overseeing the operations in conformance with the CEC charter and for supervising the flow of data between the sponsor/data management and the CEC. Committee members are qualified in the appropriate subspecialty and free of conflict of interest. The CEC is

blinded to treatment allocation and reviews events according to pre-specified criteria defined in the CEC charter.

In order to preserve the overall type I error rate at 0.05 in the primary analysis of the primary estimands in the primary endpoint family and secondary estimands in the secondary endpoint family, a parallel gatekeeping strategy will be applied. The primary endpoint family includes the primary triple component (CHD death, MI, or ischemic stroke) and the primary quadruple component (CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization); the secondary endpoint family includes all secondary endpoints described in Section 4.1.

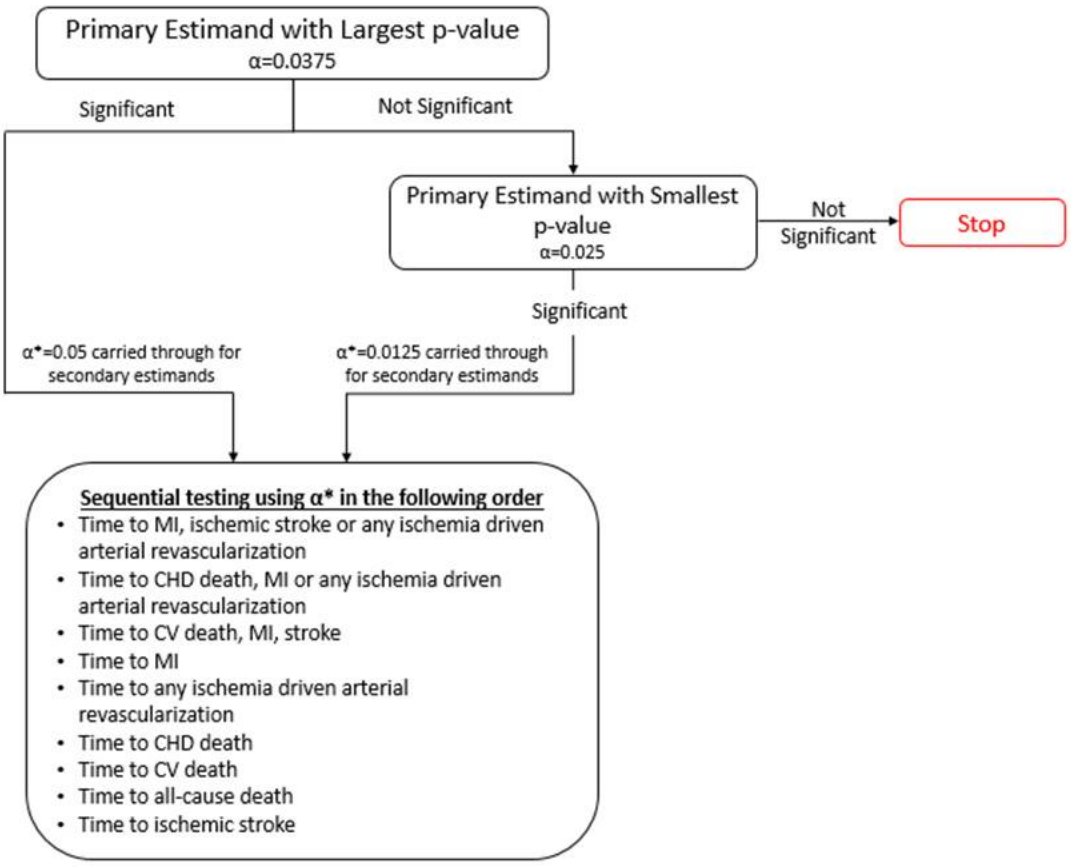
The multiplicity adjustment procedure used within the primary estimands is truncated Hochberg procedure (US FDA, 2017). The truncated Hochberg procedure is based on the 2-sided alpha level of 0.05. Truncated Hochberg procedure can pass the unused alpha from the primary estimands to the secondary estimands if at least 1 of the primary estimands is successful (Figure 10-1). The following estimands-specific alpha levels for the truncated Hochberg are constructed by combining the estimands-specific alpha levels of the conventional Hochberg method with the pre-specified truncation fraction of 0.5.

- The first test from the primary estimands (ie, the larger p-value for the primary estimands) for the truncated Hochberg test is performed at alpha level of 0.0375. If the first test is successful, then the remaining test is also considered successful.
- The remaining test from the primary estimands, after the first test is not successful, is performed at alpha level of 0.025.

The multiplicity adjustment procedure used within the secondary estimands is fixed sequence testing procedure. The specific 2-sided alpha level (α^*) is used for the secondary estimands depending on the statistically significant results of the primary estimands and the details are described below.

Figure 10-1 illustrates the parallel gatekeeping procedure.

Figure 10-1. Parallel Gatekeeping Procedure



CHD = coronary heart disease; CVD = cardiovascular disease; MI = myocardial infarction.

- $\alpha^* = 0.05$, if the first test from the primary estimands (ie, the larger p-value for the primary estimands) is successful. Note: If the first test is successful, then the remaining test is also considered successful. In this case, each of the secondary estimands are tested at an alpha level of 0.05 in the fixed sequential order the secondary endpoints are listed in Figure 10-1.
- $\alpha^* = 0.0125$, if the first test from the primary estimands is not successful (ie, the larger p-value for the primary estimands > 0.0375) and the remaining test from the primary estimands is successful (ie, the smaller p-value in the primary estimands ≤ 0.025). In this case, each of the secondary estimands are tested at an alpha level of 0.0125 in the fixed sequential order the secondary endpoints are listed in Figure 10-1.
- $\alpha^* = 0$, if both tests from the primary estimands are not successful.

10.3.2.2 Efficacy Analyses

Estimand	Statistical Analysis Methods
Primary	Intent-to-treat (ITT) principle: The following analyses will be performed for each primary estimands. Kaplan-Meier (K-M) curves will be estimated and graphically displayed for each randomized treatment group. The **primary test comparing the** 2 survival functions will be **performed** using a 2-sided log-rank test stratified by randomization stratification factors. Yearly K-M estimates and 95% CIs will be calculated by each randomized treatment group. The HR and its corresponding 95% CI will be estimated from a stratified Cox model, stratified by the randomization stratification factors. Sensitivity analysis: The following sensitivity analyses for the primary estimands will be performed: • Analyses using start date of **primary completion** visit period and subject last confirmed survival status date instead of the subject last non-fatal potential endpoint collection date. • Tipping point analysis to assess the impact of missing follow-up data. • **Multiple imputation analysis based on retrieved drop outs for subjects who are lost to follow-up prior to EOS** • Analyses using eCRF stratification factor instead of IVRS if there is a discrepancy in > 5% subjects. Subgroup analyses: Subgroup analyses on the primary estimands will be conducted using the stratification factors and baseline covariates.
Secondary	The analysis of the secondary estimands will be similar to the primary analysis of the primary estimands. Kaplan-Meier curves will be estimated and graphically displayed. The 2 survival functions will be compared using a 2-sided log-rank test stratified by randomization stratification factors. Yearly K-M estimates and 95% CIs will be calculated by each randomized treatment group. The HR and its corresponding 95% CI will be estimated from a stratified Cox model, stratified by the randomization stratification factors.
Exploratory	Will be described in the statistical analysis plan.

In addition to primary estimands, the supplemental estimands will be included that consider intercurrent events. On-treatment estimands will be defined as follows:

- the HR comparing evolocumab and placebo for time to CHD death, MI, ischemic stroke which occur on treatment and prior to discontinuation of investigational product or prior to first initiation of commercial PCSK9 inhibitors, whichever occurs first, for randomized patients who are adults and at high cardiovascular risk without past MI or stroke and receiving optimized lipid-lowering treatment indicated by their physician per local guidelines.
- the HR comparing evolocumab and placebo for time to CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization, whichever occurs first for randomized patients while on treatment and prior to discontinuation of investigational product or prior to first initiation of commercial PCSK9 inhibitors, for adults at high cardiovascular risk without past MI or stroke and receiving optimized lipid-lowering treatment indicated by their physician per local guidelines.

The proposed on-treatment estimands are similar to the 'while on treatment' strategy described in ICH E9(R1).

Additional estimands will be pre-specified in the Statistical Analysis Plan.

10.3.2.3 Safety Analyses

10.3.2.3.1 Adverse Events

Subject incidence of all treatment-emergent serious adverse events and adverse events leading to withdrawal from investigational product will be tabulated by system organ class, high level group (HLGT), high level term (HLT), and preferred term. Adverse events will be coded using version 21.1 or later of the Medical Dictionary for Regulatory Activities (MedDRA).

10.3.2.3.2 Exposure to Investigational Product

The exposure to investigational product will be summarized using descriptive statistics by treatment group.

10.3.2.3.3 Exposure to Concomitant Medication

Number and proportion of subjects receiving therapies of interest, including lipid-lowering therapy, will be summarized for each treatment group.

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12. Appendices

12.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
ABI	ankle brachial index
AI/pen	autoinjector pen
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body-mass index
CABG	coronary artery bypass grafting
CEC	Clinical Events Committee
CETP	cholesterol ester transfer protein
CFR	Code of Federal Regulations
CHD	coronary heart disease
CIF	cumulative incidence function
Cr	creatinine
CRF	case report form
CTT	Cholesterol Treatment Trialists'
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
e-mail	electronic mail
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) primary completion	defined as the primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), whether the study concluded as planned in the protocol or was terminated early.
End of Study (EOS) (end of trial)	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, safety or efficacy follow-up), as applicable
ESRD	end stage renal disease
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol

Abbreviation or Term	Definition/Explanation
HLGT	high level group term
HLT	high level term
HR	hazard ratio
HRT	hormonal replacement therapy
IBG	Independent Biostatistics Group
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	identification
IEC	Independent Ethics Committee
Ig	immunoglobulin
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
ITT	intent-to-treat
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
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
K-M	Kaplan-Meier
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LDLR	low-density lipoprotein receptor
MedDRA	Medical Dictionary for Regulatory Activities
MDRD	Modification of Diet in Renal Disease
MI	myocardial infarction
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
Q2W	every 2 weeks
SC	subcutaneous

Abbreviation or Term	Definition/Explanation
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study Day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
TBL	total bilirubin
TIMI	Thrombolysis in Myocardial Infarction
TIMI Study Group Hotline	**Communication system at the Thrombolysis in Myocardial Infarction Study Group of Brigham and Women's Hospital, Boston, Massachusetts, USA, that is providing protocol support to all participating active trial sites worldwide**
TMF	trial master folder
ULN	upper limit of normal

12.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 12-1 will be performed by the local laboratory. The tests details in Table 12-2 will be performed by the central laboratory.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 6.1 to 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. Local Laboratory Analyte Listing

Local Laboratory: Chemistry	Local Laboratory: Other	Fasting lipid panel (screening):
Creatinine eGFR[a]	**Serum or u**rine pregnancy	• total cholesterol • LDL-C[b] • HDL-C • non-HDL-C • triglycerides

C = cholesterol; eGFR = estimated glomerular filtration rate; HDL = high density lipoprotein; LDL = low-density lipoprotein; MDRD = Modification of Diet in Renal Disease
[a] Preference is to use MDRD equation as shown below (Levey et al, 1999).
[b] **Use the Martin-Hopkins formula (Martin et al, 2013) when calculation of LDL-C not possible due to TG > 400 mg/dL.**

Table 12-2. Central Laboratory Analyte Listing

Lipid panel[a] (only collected for subset of subjects)
• total cholesterol • LDL-C • HDL-C • VLDL-C • non-HDL-C • triglycerides • apoB • Lp(a)

apoB = apolipoprotein B; C = cholesterol; HDL = high density lipoprotein; LDL = low-density lipoprotein; Lp(a) = lipoprotein a; VLDL = very low-density lipoprotein
[a] The central laboratory will use the Martin-Hopkins formula (Martin et al, 2013), therefore, fasting is not necessary before sample collection.

Modification of Diet in Renal Disease (MDRD) Equation

- eGFR = 186 x (Serum Cr-1.154) x (age-0.203) x 1.212 (if subject is black) x 0.742 (if subject is female)
- Use serum creatinine (Cr) in mg/dL for this formula.

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 panel (**fasting or** non-fasting; only collected in a subset of subjects) will be blinded on study

and not reported to the investigator until unblinding of the clinical database. In addition, investigators and staff involved with this trial should not perform non-protocol lipid panel testing during a subject's study participation and until at least 12 weeks after the last administration of investigational product or the end of study, whichever is later (to avoid potential unblinding).

12.3 Appendix 3. Study Governance Considerations

Data Monitoring Committee, Executive Committee, and Clinical Events Committee

Details for each committee will be provided in a committee charter.

Data Monitoring Committee

An Independent Biostatistics Group (IBG) will perform the interim analysis and provide the interim report to an independent Data Monitoring Committee (DMC). The DMC will review all available safety data periodically (approximately every 6 months) **and will consider a recommendation for early termination of the study based on their review of the totality of evidence at 2 pre-specified interim analyses**. The IBG and DMC will have access to subjects' individual treatment assignments. To minimize the potential introduction of bias to the conduct of the study, members of the DMC and Data Monitoring Group will not have any direct contact with study site personnel or subjects. The DMC will communicate major safety concerns and recommendations regarding study modification or termination based on the safety and efficacy parameters to Amgen in accordance with the DMC charter.

Records of all meetings will be maintained by the DMC for the duration of the study. Records of all meetings will be transferred and stored in the trial master folder (TMF) at the conclusion of the study.

The independent DMC will not review the unblinded CV endpoints prior to the 2 pre-specified interim analyses and consider a recommendation for early termination of the study based on efficacy at 2 pre-specified interim analyses:

- **the first interim analysis (IA#1) for the DMC reviewing the unblinding CV endpoints will occur when the numbers of subjects who have experienced both of the primary triple and quadruple endpoints is 80% of the final targeted numbers and the median study duration is at least approximately 3.5 years.**
- **the second interim analysis (IA#2) for the DMC reviewing the unblinding CV endpoints will occur when the numbers of subjects who have experienced both of the primary triple and quadruple endpoints is 90% of the final targeted numbers and the median study duration is at least approximately 4.0 years.**

A summary of the timing and corresponding 2-sided alpha level for each interim analysis is detailed below.

Timing of IA: % of endpoints (# of endpoints)	Estimated median study duration	Haybittle-Peto alpha spending approach	
		Test statistics (Z) for log-rank test	Corresponding 2-sided alpha level
IA#1: 80% of targeted # of endpoints for the primary triple component endpoint and the primary quadruple endpoint	~3.5 years	3.291	0.001
IA#2: 90% of targeted # of endpoints for the primary triple component endpoint and the primary quadruple endpoint	~4.0 years	3.291	0.001

CHD = coronary heart disease; IA = interim analysis.

The DMC will recommend alteration or early termination based on a totality of evidence that will include proof beyond a reasonable doubt that is likely to influence clinical practice. Additional specific factors to be considered by the DMC will include:

(1) no major safety concerns

AND

(2) there is sufficient follow-up time to adequately characterize the long-term efficacy profile of evolocumab in this patient population studied (ie, median duration of at least 3.5 years)

AND

(3) A 2-sided $p < 0.001$ in both primary pre-specified endpoints with consistency in major subgroups and a definite reduction in coronary, cardiovascular, and total mortality.

The overall alpha left used for the primary analyses will be 0.05 based on Haybittle-Peto spending approach spent on the 2 pre-specified interim analyses by the DMC.

Executive Committee

An Executive Committee will be formed to advise Amgen on trial design and implementation, to conduct independent data analysis, and for assistance in the communication of trial results.

Clinical Events Committee

All deaths and components of primary and secondary endpoints will be adjudicated by an independent external Clinical Events Committee, using standardized definitions. Instructions regarding submission of potential endpoints will be provided.

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

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 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Informed Consent Process

An initial sample ICF is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the sample ICF are to be communicated formally in writing from the Amgen Trial Manager to the investigator. The written ICF 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 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 ICF.

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 ICF is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. 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 ICF(s) during their participation in the study.

The original signed ICF is to be retained in accordance with institutional policy, and a copy of the ICF(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 ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)

A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional future research. The investigator or authorized designee will explain to each subject the objectives of the future 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 future 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 case report form (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 ICFs) 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 will facilitate the formation of a publication committee consisting of the Executive Committee 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 (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 (ICMJE, 2013). 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 and 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.

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 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).

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, ICFs, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the (IRB/IEC) and Amgen
- Investigational product-related correspondence including Proof of Receipts, 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, 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 hospitalization but may jeopardize the subject or may require medical or surgical

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) 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.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording
• When a reportable adverse event (Section 9.2.3.1) or any 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. • The investigator must assign the following adverse event attributes: – adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms); – dates of onset and resolution (if resolved); – severity (or toxicity defined below); – assessment of relatedness to investigational product, device, or other protocol-required therapies; 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 reportable adverse event and any serious adverse event reported during the study. The assessment of severity will be based on:

The Amgen Standard Grading Scale as shown 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, device, and/or protocol-required therapies and each occurrence of each reportable adverse event and any 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 reportable 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 Contingency Report 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 a paper Serious Adverse Event Report Form (see Figure 12-1).

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

AMGEN
Study # 20170625
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

IP/Amgen Device:		Date of Initial Dose (Day Month Year)	Prior to, or at time of Event: Date of Dose (Day Month Year)	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
evolucumab	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

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

AMGEN
Study # 20170625
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

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

AMGEN Study # 20170625 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.		

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

Study-specific contraception requirements for female 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/or 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 postmenopausal 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)
- withdrawal (coitus interruptus)
- spermicides only

Collection of Pregnancy Information

See Section 9.2.3.1.5 for details regarding evolocumab pregnancy registries.

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 last dose of investigational product.
- 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 investigational product. 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 Section 12.4. 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 investigational product, 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 after last dose of investigational product.
- 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 **222**.
- 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 investigational product.

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: 20170625

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

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Figure 12-2. Pregnancy and Lactation Notification Worksheet

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: 20170625

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, pharmacogenetic, or biomarker samples 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 or designees can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand cardiovascular disease, 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 **or per local regulations**.

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 blood samples 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 Section 12.3 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 glucuronidation (eg, indinavir, atazanavir)
- alpha-one antitrypsin deficiency
- alcoholic hepatitis
- autoimmune hepatitis
- Wilson's disease and hemochromatosis
- nonalcoholic fatty liver disease including steatohepatitis
- 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 12-3. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

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

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

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 Amgen investigational product is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 12-3) 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 Section 12.4.

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 12-3 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, bilirubin (BIL) (total and direct), and INR within 24 hours
- In cases of TBL $>$ 2x ULN or INR $>$ 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve

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

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:

- complete blood count with differential to assess for eosinophilia
- serum total immunoglobulin (Ig)G, anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- serum acetaminophen (paracetamol) levels

- a more detailed history of:
  - prior and/or concurrent diseases or illness
  - exposure to environmental and/or industrial chemical agents
  - symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - prior and/or concurrent use of alcohol, recreational drugs and special diets
  - concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- viral serologies
- creatine phosphokinase, haptoglobin, lactate dehydrogenase 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, 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.

12.8 Appendix 8. Background Lipid-lowering Therapy

Background lipid-lowering therapy should be established jointly by the subject and their health care providers and be consistent with local professional society guidelines. By study design, subjects eligible for this study are at high risk for cardiovascular events. Thus, it is anticipated that the majority of subjects in this trial will be treated with a high intensity background lipid-lowering regimen that would be anticipated to reduce the LDL-C by ≥ 50% from the untreated baseline level. Either a high intensity statin (**eg**, atorvastatin ≥ 40 mg daily, rosuvastatin ≥ 20 mg daily, or **simvastatin 80 mg daily**) or a combination of **any** statin **at any approved daily dose** and ezetimibe **10 mg daily should** achieve this goal. (**Note: Simvastatin 80 mg is not available in all countries participating in this study. Use of simvastatin 80 mg applies to countries where its use has been approved by local regulatory authority.)**

Subjects on any statin intensity with or without ezetimibe are eligible for the trial. However, we encourage, as per local guidelines and standard of care, to have the subject on maximally tolerated dose and/or add ezetimibe prior to screening. If the subject does not tolerate higher doses of statin, then the subject may be enrolled on a lower statin intensity, provided they have been on stable regimen starting at least 2 weeks prior to the qualifying lipid panel. In subjects not able to tolerate high intensity statin, the addition of ezetimibe should be encouraged. Up to approximately 15% of subjects may be enrolled who are documented to have **complete** "statin intolerance" (defined as the inability to tolerate at least 2 different statins, including at least 1 statin at the lowest approved dose). The sponsor may limit or close enrollment of statin intolerant subjects if this threshold is exceeded.

12.9 Appendix 9. Criteria for Clinical Diagnosis of Metabolic Syndrome

Metabolic syndrome is defined by at least 3 of the 5 below:

- elevated waist circumferences, defined as ≥ 102 cm (40.1 inches) (or 90 cm [35.4 inches]) in males and ≥ 88 cm (34.6 inches) (or 80 cm [31.4 inches]) in females*
- elevated triglycerides ≥ 175 mg/dL (2.0 mmol/L[†]) or treatment for elevated triglycerides
- reduced HDL-C < 40 mg/dL (< 1.0 mmol/L) in men, < 50 mg/dl (< 1.3 mmol/L) in women, or drug treatment for low HDL-C
- hypertension defined a systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg or antihypertensive drug treatment in a patient with a history of hypertension
- elevated fasting glucose ≥ 100 mg/dL or hemoglobin A1c above the upper limit of normal, or drug treatment of elevated glucose

* Waist circumference cut points generally recommended for the United States are ≥ 102 cm in males and ≥ 88 cm in females, but lower cut points (≥ 90 cm in males and ≥ 80 cm in females) are commonly recommended for other populations.

† Categorical cut point for triglycerides incorporates both fasting and non-fasting triglycerides.

Source: Grundy et al, 2018.

12.10 Appendix 10. NYHA Classification and Rutherford Classification

New York Heart Association Functional Classification

Class I	**No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea.**
Class II	**Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.**
Class III	**Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation or dyspnea.**
Class IV	**Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency may be present even at rest. If any physical activity is undertaken, discomfort is increased.**

Source: American Heart Association, 2017.

Rutherford Classification for Chronic Limb Ischemia

Grade	Category	Clinical Description	Objective criteria
0	0	Asymptomatic – no hemodynamically significant occlusive disease	Normal treadmill or reactive hyperemia test
	1	Mild claudication	Completes treadmill exercise; AP after exercise > 50 mm Hg, but at least 20 mm Hg lower than resting value
I	2	Moderate claudication	Between categories 1 and 3
	3	Severe claudication	Cannot complete standard treadmill exercise, and AP after exercise < 50 mm Hg
II	4	Ischemic rest pain	Resting AP < 40 mm Hg, flat or barely pulsatile ankle or metatarsal PVR; TP < 30 mm Hg
III	5	Minor tissue loss – non-healing ulcer, focal gangrene with diffuse pedal ischemia	Resting AP < 60 mm Hg, ankle or metatarsal PVR flat or barely pulsatile; TP < 40 mm Hg
	6	Major tissue loss – extending above TM level, functional foot no longer salvageable	Same as category 5

AP = ankle pressure; PVR = pulse volume recording; TM = transmetatarsal; TP = toe pressure.
Source: Rutherford et al, 1997.

Rutherford Classification for Acute Limb Ischemia

		Findings		Doppler signal	
Category	**Description/prognosis**	**Sensory loss**	**Muscle weakness**	**Arterial**	**Venous**
I. Viable	**Not immediately threatened**	**None**	**None**	**Audible**	**Audible**
II. Threatened					
a. Marginally	**Salvageable if promptly treated**	**Minimal (toes) or none**		**Inaudible**	**Audible**
b. Immediately	**Salvageable with immediate revascularization**	**More than toes, associated rest pain**		**Inaudible**	**Audible**
III. Irreversible	**Major tissue loss or permanent nerve damage inevitable**	**Profound, anesthetic**		**Inaudible**	**Audible**

Source: Rutherford et al, 1997.

12.11 Appendix 11. Child-Pugh Score[a]

Measure	1 point	2 points	3 points
Bilirubin (mg/dL)	< 2	2 to 3	> 3
Albumin (g/dL)	> 3.5	2.8 to 3.5	< 2.8
Prothrombin time (seconds)	1 to 3	4 to 6	> 6
Ascites	None	Slight	Moderate
Encephalopathy	None	I to II	III to IV

[a] Defines 3 classes of liver function; grade A = 5 to 6 points; grade B = 7 to 9 points; grade C = 10 to 15 points.
Source: Schwartz et al, 2007.

Amendment 2

Protocol Title: A Double-blind, Randomized, Placebo controlled, Multicenter Study to Evaluate the Impact of Evolocumab on Major Cardiovascular Events in Patients at High Cardiovascular Risk Without Prior Myocardial Infarction or Stroke

Amgen Protocol Number (Evolocumab) 20170625

EudraCT number 2018-004565-14

NCT number 03872401

Amendment Date: 28 February 2020

Rationale:

This protocol is being amended to:

- Update the number of subjects in the study
- Clarify key inclusion criteria
  - Update subjects must be ≥ 50 years (men) or ≥ 55 years (women) to < 80 years of age (either sex) and have an LDL-C ≥ 100 mg/dL (≥ 2.6 mmol/L) or non-high density lipoprotein (HDL)-C ≥ 130 mg/dL (≥ 3.4 mmol/L) at screening (with allowed LDL-C and non-HDL-C values measured ≤ 4 weeks prior to informed consent)
  - Update diagnostic evidence for coronary artery disease criteria at screening and high risk criteria up to 6 months prior to screening
  - Clarify coronary artery calcification score ≥ 300 if subjects have diabetes mellitus, peripheral artery disease, or cardiovascular disease
  - Include intracranial disease and ≥ 4 weeks of optimized lipid-lowering therapy prior to informed consent as an inclusion criteria
- Clarify key exclusion criteria
  - Update that uncontrolled, persistent, severe hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg) at screening on more than 1 reading
  - Update that a subject that has any future, planned arterial revascularization cannot be enrolled in the trial
- Clarify other exclusion criteria
  - Update malignancy (including cervical in situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma) within the last 5 years prior to day 1 and persistent acute liver disease or hepatic dysfunction (with Child-Pugh score of C) as exclusion criteria

- Clarify that day 1 of the treatment period (ie, first dose of investigational product) will happen within 14 (± 7) days of the screening or re-screening visit
- Specify subjects from the lipid substudy are from randomly selected sites stratified by geographical region (defined as North American, Europe, and others)
- Schedule of assessments
    - Clarify that there are no separate yearly visits and that samples will be taken at nearest visit (week 48, week 96 and week 144)
    - Add ± 7 days to visit window for study visits
    - Remove Modified Rankin Scale to measure disability from screening period
    - Specify that New York Heart Association (NYHA) Functional Classification (from subjects with a known history of heart failure) and Rutherford Classification are to be collected for subjects with a known history of peripheral artery disease and symptoms of claudication
    - Define screening period and end of study visit definitions
- Update that pregnancy testing includes serum and urine testing
- Remove ineligibility determined, protocol deviation,and non-compliance from reasons for removal from protocol-required investigational product(s) or procedural assessments
- Clarify language for discontinuation from the study and lost to follow-up
- Clarify blood pressure should be taken from a supine position
- Update language for interim and efficacy analyses
- Update language for background lipid-lowering therapy
- Clarify that samples collected for the lipid substudy (from 2000 subjects in the lipid substudy) will be stored for 1 year after which the lipid sample panels will be destroyed
- Add NYHA Functional Classification, Rutherford Classification, and Child-Pugh score guidelines
- Administrative, typographical, and formatting changes were made throughout the protocol

Description of Changes:

Section: Global

Change: Updated version date throughout document from 29 March 2019 to **28 February 2020**

Section: Global

Change: Editorial changes (including typographical, grammatical, and formatting) have been made throughout the document.

Section: Title page

Add:

Original:	20 December 2018
Amendment 1:	29 March 2019
Amendment 2:	**28 February 2020**

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

Section: 1, Protocol Synopsis, Overall Design, Paragraph 1

Replace:

This is a phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group, cardiovascular outcomes study for evolocumab in subjects at high cardiovascular risk without prior MI or stroke. At screening, subjects must be receiving stable, lipid-lowering background therapy for at least 4 weeks, as per local guidelines. Such therapy must include optimized statin therapy, except in subjects with documented statin intolerance (see Section 12.8 for details regarding lipid-lowering therapy).

With

This is a phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group, cardiovascular outcomes study for evolocumab in subjects at high cardiovascular risk without prior MI or stroke. **S**ubjects must be receiving stable, lipid-lowering background therapy **as per local guidelines, starting** at least **2** weeks **prior to the qualifying lipid panel.** Such therapy must include optimized statin therapy, except in subjects with documented statin intolerance (see Section 12.8 for details regarding lipid-lowering therapy). **Optimized lipid-lowering therapy could be high, moderate, or low dose.**

Section: 1, Protocol Synopsis, Number of Subjects

Replace:

At least 13 000 subjects will be enrolled in the study, with at least 6500 subjects per treatment group.

With:

At least **12 000** subjects will be enrolled in the study, with at least **6000** subjects per treatment group.

Section: Protocol Synopsis, Summary of Subject Eligibility Criteria, Key Inclusion Criteria

Replace:

Key inclusion criteria:

- Subjects must be ≥ 50 years (men) or ≥ 55 years (women) to < 80 years of age (either sex) and
- Diagnostic evidence of at least 1 of the following (A – D) at screening:

A. Significant coronary artery disease meeting at least 1 of the following criteria:
   - History of coronary revascularization with multi-vessel coronary disease as evidenced by any of the following:
     - multi-vessel percutaneous coronary intervention (PCI)
     - PCI or coronary artery bypass grafting (CABG) with residual ≥ 50% stenosis in a separate, unrevascularized segment or vessel, or
     - multi-vessel CABG at least 5 years prior to screening
   - Significant coronary disease without prior revascularization as evidenced by either a ≥ 70% stenosis of at least 1 coronary artery, ≥ 50% stenosis of 2 or more coronary arteries, or ≥ 50% stenosis of the left main coronary artery
   - known coronary artery calcium score ≥ 100

B. Significant atherosclerotic cerebrovascular disease meeting at least 1 of the following criteria:
   - prior transient ischemic attack with ≥ 50% carotid stenosis
   - carotid artery stenosis of ≥ 70% or 2 or more ≥ 50% stenosis
   - prior carotid artery revascularization

C. Significant peripheral arterial disease meeting at least 1 of the following criteria:
   - ≥ 50% stenosis in a limb artery
   - history of abdominal aorta treatment (percutaneous and surgical)
   - ankle brachial index (ABI) < 0.85

D. Diabetes mellitus with at least 1 of the following:

- known microvascular disease, defined by diabetic nephropathy or treated retinopathy. Diabetic nephropathy defined as microalbuminuria (urinary albumin to creatinine ratio ≥ 30mg/g) and/or estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2
- chronic treatment with insulin
- diabetes diagnosis ≥ 10 years ago

- At least 1 of the following high risk criteria at screening (most recent lab values prior to screening, as applicable):
  - polyvascular disease, defined as coronary, carotid, or peripheral artery stenosis ≥ 50% in a second distinct vascular location in a patient with coronary, cerebral or peripheral arterial disease (A, B, or C above)
  - diabetes or known evidence of metabolic syndrome (Section 12.9) in a subject with coronary, cerebral, or peripheral artery disease (A, B, or C above)
  - at least 1 coronary, carotid, or peripheral artery stenosis of ≥ 50% in a patient with diabetes meeting inclusion criterion (D above)
  - LDL ≥ 130 mg/dL (≥ 3.4 mmol/L) or non-HDL ≥ 160 mg/dL (> 4.2 mmol/L)
  - lipoprotein (a) > 125 nmol/L (50 mg/dL)
  - known familial hypercholesterolemia
  - family history of premature coronary artery disease defined as an MI or CABG in the subject's father or brother at age < 55 years or an MI or CABG in the subject's mother or sister at age < 60 years
  - high sensitive c-reactive protein ≥ 3.0 mg/L
  - current tobacco use
  - ≥ 65 years of age
  - menopause before 40 years of age
  - eGFR 15 to < 45 mL/min/1.73 m^2

With:

Key inclusion criteria:

- Subjects must be ≥ 50 years (men) or ≥ 55 years (women) to < 80 years of age (either sex) and **meeting lipid criteria**
- **Lipid Criteria (see Appendix 8 for permissible concomitant lipid-lower therapy):**
  - **Subjects must have an LDL-C ≥ 90 mg/dL (≥ 2.3 mmol/L) OR non-high density lipoprotein (HDL)-C ≥ 120 mg/dL (≥ 3.1 mmol/L) OR apolipoprotein B ≥ 80 mg/dL (≥ 1.56 μmol/L)**
  - Diagnostic evidence of at least 1 of the following (A – D) at screening:

A. Significant coronary artery disease meeting at least 1 of the following criteria:
   - History of coronary revascularization with multi-vessel coronary disease as evidenced by any of the following:
     - percutaneous coronary intervention (PCI) **of 2 or more vessels, including branch arteries**
     - PCI or coronary artery bypass grafting (CABG) with residual ≥ 50% stenosis in a separate, unrevascularized vessel, or
     - multi-vessel CABG 5 years **or more** prior to screening
   - Significant coronary disease without prior revascularization as evidenced by either a ≥ 70% stenosis of at least 1 coronary artery, ≥ 50% stenosis of 2 or more coronary arteries, or ≥ 50% stenosis of the left main coronary artery
   - known coronary artery calcium score ≥ 100 **in subjects without a coronary artery revascularization prior to randomization**

B. Significant atherosclerotic cerebrovascular disease meeting at least 1 of the following criteria:
   - prior transient ischemic attack with ≥ 50% carotid stenosis
   - **internal or external** carotid artery stenosis of ≥ 70% or 2 or more ≥ 50% stenos**e**s
   - prior **internal or external** carotid artery revascularization

C. Significant peripheral arterial disease meeting at least 1 of the following criteria:
   - ≥ 50% stenosis in a limb artery
   - history of abdominal aorta treatment (percutaneous and surgical) **due to atherosclerosic disease**
   - ankle brachial index (ABI) < 0.85

D. Diabetes mellitus with at least 1 of the following:
   - known microvascular disease, defined by diabetic nephropathy or treated retinopathy. Diabetic nephropathy defined as **persistent** microalbuminuria (urinary albumin to creatinine ratio ≥ 30mg/g) and/or **persistent** estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 **that is not reversible due to an acute illness**

  - chronic **daily** treatment with **an intermediate or long-acting** insulin
  - diabetes diagnosis ≥ 10 years ago

- At least 1 of the following high risk criteria (most recent lab values **within 6 months** prior to screening, as applicable):
  - polyvascular disease, defined as coronary, carotid, or peripheral artery stenosis ≥ 50% in a second distinct vascular location in a patient with coronary, cerebral or peripheral arterial disease (A, B, or C above)
  - **presence of either** diabetes **mellitus** or metabolic syndrome (Section 12.9) in a subject with coronary, cerebral, or peripheral artery disease (A, B, or C above)
  - at least 1 coronary, carotid, or peripheral artery **residual** stenosis of ≥ 50% in a patient with diabetes meeting inclusion criterion (D above)
  - LDL**-C** ≥ 130 mg/dL (≥ 3.**36** mmol/L)**,** non-HDL**-C** ≥ 160 mg/dL (≥ 4.**14** mmol/L)**, or apolipoprotein B ≥ 120 mg/dL (2.3 μmol/L) if available**
  - lipoprotein (a) > 125 nmol/L (50 mg/dL)
  - known familial hypercholesterolemia
  - family history of premature coronary artery disease defined as an MI or CABG in the subject's father or brother at age < 55 years or an MI or CABG in the subject's mother or sister at age < 60 years
  - high sensitive c-reactive protein **(hsCRP)** ≥ 3.0 mg/L **in the absence of an acute illness**
  - current tobacco use
  - ≥ 65 years of age
  - menopause before 40 years of age
  - eGFR 15 to < 45 mL/min/1.73 m^2
  - **coronary artery calcification score ≥ 300 in a patient without a coronary revascularization prior to randomization**

Section: Protocol Synopsis, Summary of Subject Eligibility Criteria, Key Exclusion Criteria

Replace:

Key exclusion criteria:

- MI or stroke prior to randomization
- CABG < 3 months prior to screening
- eGFR < 15 mL/min/1.73 m^2
- Uncontrolled or recurrent ventricular tachycardia
- Atrial fibrillation not on anticoagulation therapy
- Uncontrolled hypertension (sitting systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg) at screening

- Fasting triglycerides ≥ 500 mg/dL (5.7 mmol/L) at screening
- Last measured left-ventricular ejection fraction < 30% or New York Heart Association (NYHA) Functional Class III/IV

With:

Key exclusion criteria:

- MI or stroke prior to randomization
- CABG < 3 months prior to screening
- eGFR <15 mL/min/1.73 m^2
- Uncontrolled or recurrent ventricular tachycardia **in the absence of an implantable-cardioverter defibrillator.**
- Atrial fibrillation not on anticoagulation therapy **(vitamin K antagonist, heparin, low molecular weight heparin, fondaparinux,or non-Vitamin K antagonist oral anticoagulant)**
- Fasting triglycerides ≥ 500 mg/dL (5.7 mmol/L) at screening
- Last measured left-ventricular ejection fraction < 30% or New York Heart Association (NYHA) Functional Class III/IV
- **Planned arterial revascularization**

Section: 1, Protocol Synopsis, Procedures, Paragraph 1 and 2

Replace:

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. Prior to randomization, all subjects will receive a placebo injection to confirm tolerance of subcutaneous (SC) administration. At randomization, an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) will allocate subjects to receive either evolocumab SC Q2W or placebo SC Q2W. Day 1 of the treatment period (ie, first dose of investigational product) must happen within 2 weeks (14 days) of the signing of the informed consent form (ICF).

After day 1, subjects will return to the study site every 16 weeks to review reportable adverse events, concomitant therapies, potential endpoints, vital status, and acquire another 4-month supply of investigational product. Fasting lipid panels will be collected at screening for all subjects (analyzed at local laboratory). In a subset of subjects (approximately 2000 subjects), additional lipid panels (non-fasting) will be collected on day 1, at the end of year 1 visit, end of year 2 visit, and at the end of study visit (analyzed at central laboratory).

With:

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. Prior to randomization, all subjects will receive a placebo injection to confirm tolerance of subcutaneous (SC) administration. At randomization, an Interactive Voice Response

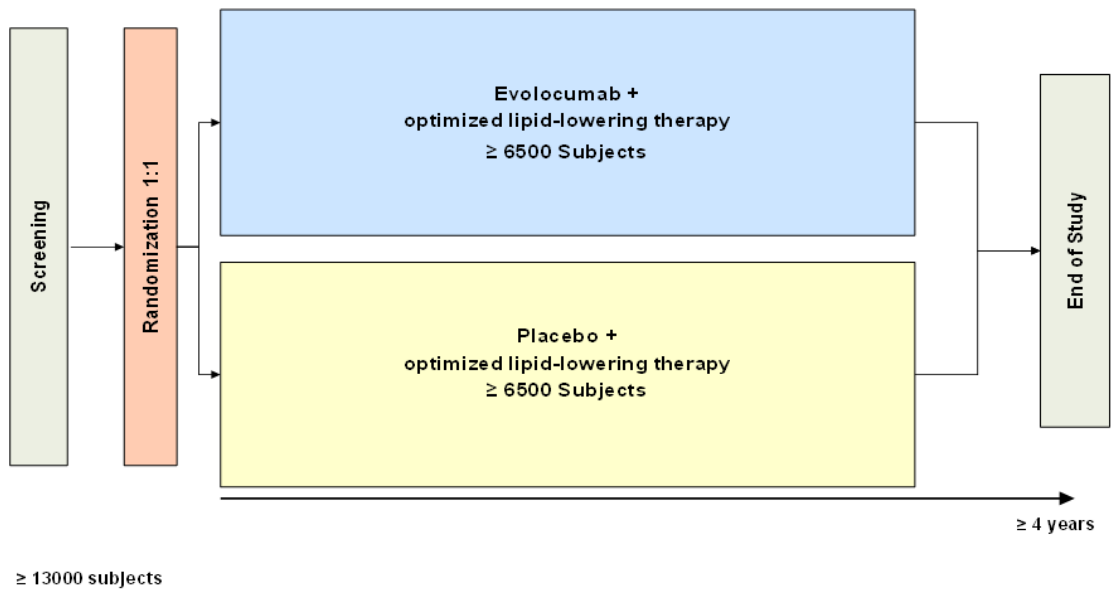
System/Interactive Web Response System (IVRS/IWRS) will allocate subjects to receive either evolocumab SC Q2W or placebo SC Q2W. Day 1 of the treatment period (ie, first dose of investigational product) **will** happen within **21** days of the **screening or re-screening visit**.

After day 1, subjects will return to the study site every 16 weeks to review reportable adverse events, concomitant therapies, potential endpoints, vital status, and acquire another 4-month supply of investigational product. Fasting **or non-fasting** lipid panels **may** be collected at screening for **those subjects without lipid panels drawn in the last 3 months** (analyzed at local laboratory). In a subset of subjects (approximately 2000 subjects **from randomly selected sites and stratified by geographic region**), additional lipid panels (fasting **is not required**) will be collected on day 1, at the end of year 1 visit **(week 48)**, end of year 2 visit **(week 96)**, and at the end of study visit (analyzed at central laboratory).

Section: 2.1, Study Schema

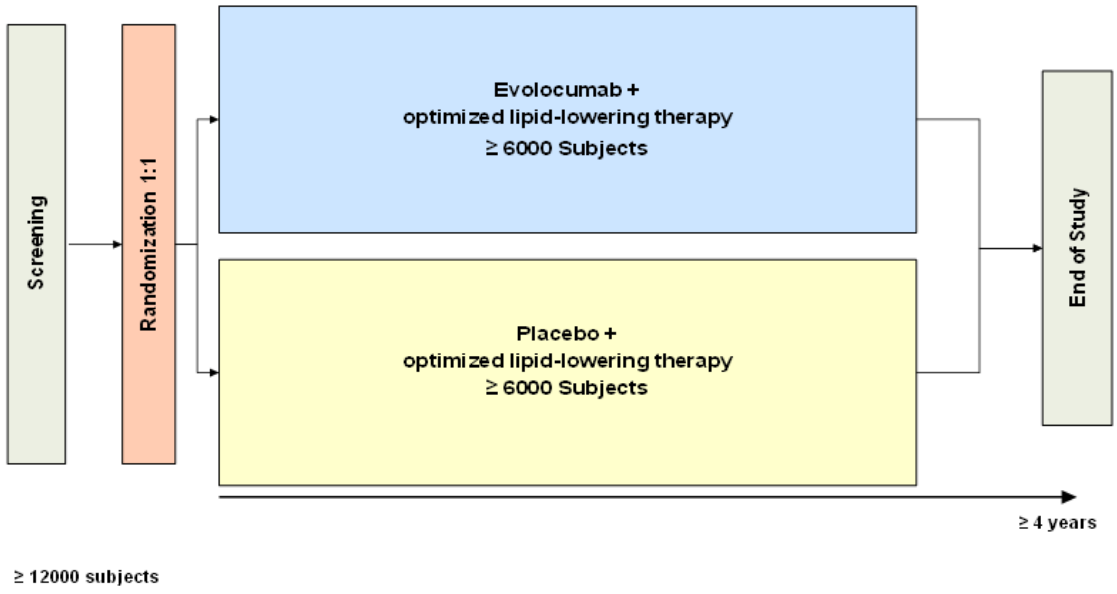
Replace:

Figure·2-1.··Study·Schema¶



With:

Figure·2-1.··Study·Schema¶



Section: 2.2, Schedule of Activities, Table 2-1

Replace:

Procedure	SCR[a]	Treatment Period (years) Day 1	1	2	3+	EOS[b]	Notes
General and Safety Assessments							
Informed consent	X						
Inclusion and exclusion criteria	X						
Demographics	X						
Physical examination	X						Includes Modified Rankin Scale to measure disability
Physical measurements	X						Height and weight only
Medical history	X						
Substance use history	X						Substance: tobacco
Vital signs	X					X	Blood pressure and heart rate only
Treatment compliance			Q16W	Q16W	Q16W	X	
Adverse events	(X)	continually				X	(X): Serious adverse events only. See Section 9.2.3 for guidance on what adverse events are to be collected and reported.
Potential endpoint data collection		continually				X	
Concomitant therapies review	X	X	Q16W	Q16W	Q16W	X	Targeted
Vital status		X	Q16W	Q16W	Q16W	X	
LOCAL Laboratory Assessments							
Urine pregnancy test (FCBP)[c]	X	X				X	
Chemistry	X						
Fasting lipid panel	X						

Abbreviations and footnotes defined on last page of table.

Procedure	SCR[a]	Treatment Period (years) Day 1	1	2	3+	EOS[b]	Notes
CENTRAL Laboratory Assessments							
Lipid panel, non-fasting (see notes)		(X)	(X)	(X)		(X)	(X): Additional lipid panels for subset of subjects (approximately 2000 subjects). Years 1 and 2 visits to be scheduled at the end of years 1 and 2, respectively.
Biomarker sample (optional)		(X)					(X): Collected as permissible by law, additional consent required
Pharmacogenetic sample (optional)		(X)					(X): Collected as permissible by law, additional consent required
Study Treatment							
Placebo injection	X						
Investigational product administration		X	Q2W	Q2W	Q2W		
Investigational product dispensation		X	Q16W	Q16W	Q16W		

EOS = end of study; FCBP = female of childbearing potential; QXW = every X weeks; SCR = screening.

[a] The screening period will be up to 2 weeks (14 days) before day 1.

[b] The EOS visit occurs once the specified number of events to support the primary endpoints has been reached. Upon permanent discontinuation of investigational product for any reason, a safety follow-up visit is to be scheduled 30 (+3) days after the last dose of investigational product (which may or may not coincide with the EOS visit).

[c] Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or as required per local laws and regulations.

With:

Procedure	SCR[a]	Treatment Period (years)				EOS[b]	Notes
		Day 1	1 **(week 48)**	2 **(week 96)**	3+ **(week 144+)**		
			These visits will have a ± 7 day window				
General and Safety Assessments							
Informed consent	X						
Inclusion and exclusion criteria	X						
Demographics	X						
Physical examination	X						
Physical measurements	X						Height and weight only
Medical history	X						**NYHA Functional Classification at baseline only for subjects with a known history of heart failure. Rutherford classification will be collected for subjects with a known history of peripheral artery disease and symptoms of claudication.**
Substance use history	X						Substance: tobacco
Vital signs	X					X	Blood pressure and heart rate only
Treatment compliance			Q16W	Q16W	Q16W	X	
Adverse events	(X)	continually				X	(X): Serious adverse events only . See Section 9.2.3 for guidance on what adverse events are to be collected and reported.
Potential endpoint data collection		continually				X	
Concomitant therapies review	X	X	Q16W	Q16W	Q16W	X	**Only cardiovascular and diabetes medications**
Vital status		X	Q16W	Q16W	Q16W	X	

Abbreviations and footnotes defined on last page of table.

Procedure	SCR[a]	Treatment Period (years)				EOS[b]	Notes
			1 **(week 48)**	2 **(week 96)**	3+ **(week 144+)**		
		Day 1	**These visits will have a ± 7 day window**				
LOCAL Laboratory Assessments							
Serum or urine pregnancy test (FCBP)[c]	X	X				X	
Chemistry	X						
Fasting **or non-fasting** lipid panel	X						**If no changes in lipid-lowering medication, lipid values measured up to 3 months prior to screening are permitted.** **Use Martin-Hopkins estimate when calculating the LDL-C with TG over 400 mg/dL.**
CENTRAL Laboratory Assessments							
Lipid panel, non-fasting (see notes)		(X)	(X)	(X)		(X)	(X): Additional lipid panels for subset of subjects (approximately 2000 subjects **from randomly selected sites and stratified by geographic region**). Years 1 and 2 visits to be scheduled at the end of years 1 and 2, respectively.
Biomarker sample (optional)		(X)					(X): Collected as permissible by law, additional consent required
Pharmacogenetic sample (optional)		(X)					(X): Collected as permissible by law, additional consent required
Study Treatment							
Placebo injection	X						**Day 1 dose to be done in clinic**
Investigational product administration		X	Q2W	Q2W	Q2W		**Day 1 dose to be done in clinic**
Investigational product dispensation		X	Q16W	Q16W	Q16W		

EOS = end of study; FCBP = female of childbearing potential; QXW = every X weeks; SCR = screening.

[a] The screening period will be up to **21** days before day 1 **of study treatment**. **Subjects should be randomized within 21 days of the screening visit. If the subject is not randomized within this period, the subject may be rescreened.**

[b] The EOS visit **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, safety or efficacy follow-up), as applicable**.

[c] Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or as required per local laws and regulations.

Section: 4.1, Objectives and Endpoints, Exploratory Objectives and Endpoints

Add:

Exploratory	
• To evaluate the effect of treatment with evolocumab, compared with placebo, on change and percent change from baseline of low-density lipoprotein cholesterol (LDL-C), in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• LDL-C change and percent change from baseline
• **To evaluate the effect of treatment with evolocumab, compared with placebo, on the incidence of new or worsening aortic valve stenosis**	• **New or worsening aortic valvestenosis**
• **To evaluate the effect of treatment with evolocumab, compared with placebo, on the incidence of new or recurrent venous thromboembolism**	• **New or recurrent venous thromboembolism (pulmonary embolus and/or deep venous thrombosis)**

Section: 5.1, Overall Design, Paragraph 1 and 2

Replace:

This is a phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group, cardiovascular outcomes study for evolocumab in subjects at high cardiovascular risk without prior MI or stroke. At screening, subjects must be receiving stable, lipid-lowering background therapy for at least 4 weeks, as per local guidelines. Such therapy must include optimized statin therapy, except in subjects with documented statin intolerance (see Section 12.8 for details regarding lipid-lowering therapy). Lipid-lowering background therapy should remain unchanged throughout the duration of the study.

Eligible subjects will be randomized with an allocation ratio of 1:1 to either receive evolocumab or placebo. Randomization will be stratified by the screening LDL-C level ($<$ 160 mg/dL [4.2 mmol/L] vs $\geq$ 160 mg/dL) and by geographical region. Evolocumab and placebo will be blinded. Central laboratory results of the lipid panel (non-fasting; only collected in a subset of subjects) will be blinded on study and not reported to the investigator until unblinding of the clinical database. Investigators and staff involved with this trial should not perform non-protocol lipid panel testing during a subject's study participation and until at least 12 weeks after the subject's last administration of investigational product or the end of study, whichever is later (to avoid potential

unblinding). The study includes collection of biomarker samples, unless prohibited by local law or regulations. Follow-up of all randomized subjects is planned to continue for a minimum of 4 years (anticipated median around 4.5 years) and until at least 751 subjects have experienced a primary triple component endpoint event (CHD death, MI, ischemic stroke) and 1254 subjects have experienced a primary quadruple component endpoint event (CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization). Subjects will be requested to complete all planned visits regardless of their adherence to investigational product. At minimum, vital status should be collected on day 1 and every 16 weeks and must be obtained at the end of the study for all subjects including those who withdraw consent, unless prohibited by local law.

With:

This is a phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group, cardiovascular outcomes study for evolocumab in subjects at high cardiovascular risk without prior MI or stroke. **S**ubjects must be receiving stable, lipid-lowering background therapy **as per local guidelines, starting** at least **2** weeks **prior to the qualifying lipid panel**. Such therapy must include optimized statin therapy, except in subjects with documented statin intolerance (see Section 12.8 for details regarding lipid-lowering therapy). **Optimized lipid-lowering therapy could be high, moderate, or low dose.** Lipid-lowering background therapy should remain unchanged throughout the duration of the study.

Eligible subjects will be randomized with an allocation ratio of 1:1 to either receive evolocumab or placebo. Randomization will be stratified by the screening LDL-C level ($<$ 160 mg/dL [4.**14** mmol/L] vs $\geq$ 160 mg/dL) and by geographical region **(North America, Europe, and others)**. Evolocumab and placebo will be blinded. Central laboratory results of the lipid panel (**fasting or** non-fasting; only collected in a subset of subjects) will be blinded on study and not reported to the investigator until unblinding of the clinical database. Investigators and staff involved with this trial should not perform non-protocol lipid panel testing during a subject's study participation and until at least 12 weeks after the subject's last administration of investigational product or the end of study, whichever is later (to avoid potential unblinding). The study includes collection of biomarker samples, unless prohibited by local law or regulations. Follow-up of all randomized subjects is planned to continue for a minimum of 4 years (anticipated median around 4.5 years) and until at least 751 subjects have experienced a primary triple component endpoint event (CHD death, MI, ischemic stroke) and 1254 subjects

have experienced a primary quadruple component endpoint event (CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization). Subjects will be requested to complete all planned visits regardless of their adherence to investigational product. At minimum, vital status **must** be collected on day 1 and every 16 weeks and must be obtained at the end of the study for all subjects including those who withdraw consent, unless prohibited by local law

Section: 5.2, Number of Subjects, Paragraph 1

Replace:

At least 13 000 subjects will be enrolled in the study, with at least 6500 subjects per treatment group.

With:

At least **12 000** subjects will be enrolled in the study, with at least **6000** subjects per treatment group.

Section: 5.2.2, Number of Sites

Replace:

Approximately 600 investigative sites in North America, South America, Europe, and Asia will be included in the study. Sites that do not enroll subjects within 3 months of site initiation may be closed.

With:

Up to approximately **900** investigative sites in North America, Europe, and **other regions** will be included in the study. Sites that do not enroll subjects within 3 months of site initiation may be closed.

Section: 5.3.1, End of Study Definition, paragraph 1

Add:

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

Section: 5.3.2, Study Duration for Subjects

Replace:

Including the initial screening, study treatment period (double-blind), and the safety/end of study follow-up, the estimated study duration is a minimum of 4 years. Subjects should be randomized no more than 2 weeks (14 days) after the signing of informed consent.

With:

Including the initial screening, study treatment period (double-blind), and the safety/end of study follow-up, the estimated study duration is a minimum of 4 years. Subjects should be randomized no more than **21** days after the signing of informed consent. **If the subject is not randomized within this period, the subject may be rescreened.**

Section: 6.1, Inclusion Criteria

Replace:

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

101 Subject has provided informed consent prior to initiation of any study specific activities/procedures

102 Adult subjects ≥ 50 years (men) or ≥ 55 years (women) to < 80 years of age (either sex)

107 Subjects must have an LDL-C ≥ 100 mg/dL (≥ 2.6 mmol/L) or non-HDL-C ≥ 130 mg/dL (≥ 3.4 mmol/L) at screening, after ≥ 4 weeks of optimized lipid-lowering therapy (see Section 12.8)

108 Diagnostic evidence of at least 1 of the following (A – D) at screening:

A. Significant coronary artery disease meeting at least 1of the following criteria:

- History of coronary revascularization with multi-vessel coronary disease as evidenced by any of the following:
  - (a) multi-vessel percutaneous coronary intervention (PCI)
  - (b) PCI or coronary artery bypass grafting (CABG) with residual ≥ 50% stenosis in a separate, unrevascularized segment or vessel, or
  - (c) multi-vessel CABG at least 5 years prior to screening
- Significant coronary disease without prior revascularization as evidenced by either a ≥ 70% stenosis of at least 1 coronary artery, ≥ 50% stenosis of 2 or more coronary arteries, or ≥ 50% stenosis of the left main coronary artery
- known coronary artery calcium score ≥ 100

B. Significant atherosclerotic cerebrovascular disease meeting at least 1 of the following criteria:
   - prior transient ischemic attack with ≥ 50% carotid stenosis
   - carotid artery stenosis of ≥ 70% or 2 or more ≥ 50% stenosis
   - prior carotid artery revascularization

C. Significant peripheral arterial disease meeting at least 1 of the following criteria:
   - ≥ 50% stenosis in a limb artery
   - history of abdominal aorta treatment (percutaneous and surgical)
   - ankle brachial index (ABI) < 0.85

D. Diabetes mellitus with at least 1 of the following:
   - known microvascular disease, defined by diabetic nephropathy or treated retinopathy. Diabetic nephropathy defined as microalbuminuria (urinary albumin to creatinine ratio ≥ 30mg/g) and/or estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2
   - chronic treatment with insulin
   - diabetes diagnosis ≥ 10 years ago

109 At least 1 of the following high risk criteria at screening (most recent lab values prior to screening, as applicable):

- polyvascular disease, defined as coronary, carotid, or peripheral artery stenosis ≥ 50% in a second distinct vascular location in a patient with coronary, cerebral or peripheral arterial disease (inclusion criterion 104 A-C)
- diabetes or known evidence of metabolic syndrome (Section 12.9) in a subject with coronary, cerebral, or peripheral artery disease (inclusion criterion 104 A-C)
- at least 1 coronary, carotid, or peripheral artery stenosis of ≥ 50% in a patient with diabetes meeting inclusion criterion 104 D
- LDL ≥ 130 mg/dL (≥ 3.4 mmol/L) or non-HDL ≥ 160 mg/dL (> 4.2 mmol/L)
- lipoprotein (a) > 125 nmol/L (50 mg/dL)
- known familial hypercholesterolemia
- family history of premature coronary artery disease defined as an MI or CABG in the subject's father or brother at age < 55 years or an MI or CABG in the subject's mother or sister at age < 60 years
- high sensitive c-reactive protein ≥ 3.0 mg/L
- current tobacco use
- ≥ 65 years of age
- menopause before 40 years of age
- eGFR 15 to < 45 mL/min/1.73 m^2

With:

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

101 Subject has provided informed consent prior to initiation of any study specific activities/procedures

102 Adult subjects ≥ 50 years (men) or ≥ 55 years (women) to < 80 years of age (either sex) **and meeting lipid criteria**

107 Subjects must have an LDL-C ≥ **90** mg/dL (≥ 2.**3** mmol/L) **OR** non-HDL-C ≥ 1**2**0 mg/dL (≥**3.1** mmol/L)**, OR apolipoprotein B ≥ 80 mg/dL (≥ 1.56 μmol/L)**

- **Lipid entry criteria can be measured up to 3 months prior to screening in the absence of changes to background therapy**
- **Lipid criteria should be assessed after ≥ 2 weeks of stable, optimized lipid-lowering therapy**

108 Diagnostic evidence of at least 1 of the following (A – D) at screening:

A. Significant coronary artery disease meeting at least 1 of the following criteria:
   - History of coronary revascularization with multi-vessel coronary disease as evidenced by any of the following:
     - (a) percutaneous coronary intervention (PCI) **of 2 or more vessels, including branch arteries**
     - (b) PCI or coronary artery bypass grafting (CABG) with residual ≥ 50% stenosis in a separate, unrevascularized vessel, or
     - (c) multi-vessel CABG 5 years **or more** prior to screening
   - Significant coronary disease without prior revascularization as evidenced by either a ≥ 70% stenosis of at least 1 coronary artery, ≥ 50% stenosis of 2 or more coronary arteries, or ≥ 50% stenosis of the left main coronary artery
   - known coronary artery calcium score ≥ 100 **in subjects without a coronary artery revascularization prior to randomization**

B. Significant atherosclerotic cerebrovascular disease meeting at least 1 of the following criteria:
   - prior transient ischemic attack with ≥ 50% carotid stenosis
   - **internal or external** carotid artery stenosis of ≥ 70% or 2 or more ≥ 50% stenos**e**s
   - prior **internal or external** carotid artery revascularization

C. Significant peripheral arterial disease meeting at least 1 of the following criteria:
   - ≥ 50% stenosis in a limb artery
   - history of abdominal aorta treatment (percutaneous and surgical) **due to atherosclerosic disease**
   - ankle brachial index (ABI) < 0.85

D. Diabetes mellitus with at least 1 of the following:

- known microvascular disease, defined by diabetic nephropathy or treated retinopathy. Diabetic nephropathy defined as **persistent** microalbuminuria (urinary albumin to creatinine ratio ≥ 30mg/g) and/or **persistent** estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 **that is not reversible due to an acute illness**
- chronic **daily** treatment with **an intermediate or long-acting** insulin
- diabetes diagnosis ≥ 10 years ago

109 At least 1 of the following high risk criteria (most recent lab values **within 6 months** prior to screening, as applicable):

- polyvascular disease, defined as coronary, carotid, or peripheral artery stenosis ≥ 50% in a second distinct vascular location in a patient with coronary, cerebral or peripheral arterial disease (inclusion criterion **108** A-C)
- **presence of either** diabetes **mellitus** or metabolic syndrome (Section 12.9) in a subject with coronary, cerebral, or peripheral artery disease (inclusion criterion **108** A-C)
- at least 1 coronary, carotid, or peripheral artery **residual** stenosis of ≥ 50% in a patient with diabetes meeting inclusion criterion **108** D
- LDL**-C** ≥ 130 mg/dL (≥ 3.**36** mmol/L)**,** non-HDL**-C** ≥ 160 mg/dL (≥ 4.**14** mmol/L)**, or apolipoprotein B ≥ 120 mg/dL (2.3 μmol/L) if available**
- lipoprotein (a) > 125 nmol/L (50 mg/dL)
- known familial hypercholesterolemia
- family history of premature coronary artery disease defined as an MI or CABG in the subject's father or brother at age < 55 years or an MI or CABG in the subject's mother or sister at age < 60 years
- **hsCRP** ≥ 3.0 mg/L **in the absence of an acute illness**
- current tobacco use
- ≥ 65 years of age
- menopause before 40 years of age
- eGFR 15 to < 45 mL/min/1.73 m^2
- **coronary artery calcification score ≥ 300 in a patient without a coronary revascularization prior to randomization**

Section: 6.2, Exclusion Criteria

Replace:

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

Disease Related

201 MI or stroke prior to randomization

202 CABG < 3 months prior to screening

203 Uncontrolled or recurrent ventricular tachycardia

204 Atrial fibrillation not on anticoagulation therapy

205 Uncontrolled hypertension (sitting systolic blood pressure $>$ 180 mmHg or diastolic blood pressure $>$ 110 mmHg) at screening

206 Last measured left-ventricular ejection fraction $<$ 30% or New York Heart Association (NYHA) Functional Class III/IV

Diagnostic Assessments

207 Fasting triglycerides $\geq$ 500 mg/dL (5.7 mmol/L) at screening

208 End stage renal disease (ESRD), defined as an eGFR $<$ 15 mL/min/1.73 m^2 or receiving dialysis at screening

Other Medical Conditions

209 Malignancy, except non-melanoma skin cancers, or in situ cancers of the cervix, prostate, or breast duct within 5 years prior to screening

210 History or evidence of clinically significant disease (eg, malignancy, respiratory, gastrointestinal, renal or psychiatric disease) or unstable disorder that, in the opinion of the investigator(s), Amgen physician or designee would pose a risk to the patient's safety or interfere with the study assessments, procedures, completion, or result in a life expectancy of less than 1 year

Prior/Concomitant Therapy

211 Previously received or receiving evolocumab or any other therapy to inhibit PCSK9

212 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

213 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 Exclusions

214 Female subject is pregnant, had a positive pregnancy test at screening, breastfeeding, or planning to become pregnant or breastfeed during treatment and for an additional 15 weeks after the last dose of investigational product.

215 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 Section 12.5 for additional contraceptive information.

216 Subject has known sensitivity to any of the products or components to be administered during dosing.

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

218 Subject is staff personal directly involved with the study or is a family member of the investigational study staff

With:

Disease Related

201 MI or stroke prior to randomization

202 CABG < 3 months prior to screening

203 Uncontrolled or recurrent ventricular tachycardia **in the absence of an implantable-cardioverter defibrillator.**

204 Atrial fibrillation not on anticoagulation therapy **(vitamin K antagonist, heparin, low molecular weight heparin, fondaparinux, or non-vitamin K antagonist oral anticoagulant)**

206 Last measured left-ventricular ejection fraction < 30% or New York Heart Association (NYHA) Functional Class III/IV

219 Planned arterial revascularization

Diagnostic Assessments

207 Fasting triglycerides ≥ 500 mg/dL (5.7 mmol/L) at screening

208 End stage renal disease (ESRD), defined as an eGFR < 15 mL/min/1.73 m^2 or receiving dialysis at screening

Other Medical Conditions

209 Malignancy (except non-melanoma skin cancers, **cervica**l in situ **carcinoma, breast ductal carcinoma in situ, or stage 1** prostate **carcinoma)** within **the last** 5 years prior to **day 1**

210 History or evidence of clinically significant disease (eg, malignancy, respiratory, gastrointestinal, renal or psychiatric disease) or unstable disorder that, in the opinion of the investigator(s), Amgen physician or designee would pose a risk to the patient's safety or interfere with the study assessments, procedures, completion, or result in a life expectancy of less than 1 year

220 Persistent acute liver disease or hepatic dysfunction, defined as Child Pugh score of C (see Appendix 12.11)

Prior/Concomitant Therapy

212 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

221 Previously received or receiving any other therapy to inhibit PCSK9 **in the following timeframe prior to screening:**

- **bococizumab at any time**
- **evolocumab, alirocumab, or any other monoclonal antibody against PCSK9 within 3 months**
- **inclisiran within 12 months**

Prior/Concurrent Clinical Study Experience

213 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 Exclusions

215 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 Section 12.5 for additional contraceptive information.

216 Subject has known sensitivity to any of the products or components to be administered during dosing.

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

218 Subject is staff **personnel** directly involved with the study or is a family member of the investigational study staff

222 **Female subject is pregnant, had a positive pregnancy test at screening (by a serum pregnancy test and/or urine pregnancy test), breastfeeding, or planning to become pregnant or breastfeed during treatment and for an additional 15 weeks after the last dose of investigational product**

Section: 6.4, Screening Failures, Paragraph 1, move text from paragraph 3

Replace:

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 be rescreened (subjects that screen fail inclusion criteria 103 cannot be rescreened). Refer to Section 9.1.1.

Individuals who do not meet the criteria for participation in this study (screen failure) can be rescreened.

With:

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in he study. Individuals who do not meet the criteria for participation in this study (screen failure) **can** be rescreened.

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.

Refer to Section 9.1.1.

Section: 7.1.3, Medical Devices, Paragraph 1

Delete:

The following ~~investigational~~ medical device provided by Amgen for use in this study is the spring-based prefilled AI/pen (Table 7-1). AI/pen training by study site staff to each subject will occur at the day 1 visit and each visit thereafter, if necessary.

Section: 7.1.4 Other Protocol-required Therapies

Delete:

Background lipid-lowering therapies will not be provided or reimbursed by Amgen (except if required by local regulation). ~~The investigator or the patient's primary care physician will be responsible for obtaining supplies of these protocol-required therapies.~~ All such therapy needs to be unchanged during the entire time of screening and study participation unless a change is clinically necessary. If a change is made, the reason for the change must be provided in the CRF.

Section: 7.2, Method of Treatment Assignment, Paragraph 4

Replace:

The randomization will be stratified by the screening LDL-C level ($<$ 160 mg/dL [4.2 mmol/L] vs $\geq$ 160 mg/dL) and by geographical region.

With:

The randomization will be stratified by the screening LDL-C level ($<$ 160 mg/dL [4.**14** mmol/L] vs $\geq$ 160 mg/dL) and by geographical region **(North America, Europe, and others)**.

Section: 7.3, Blinding

Add:

This is a double-blind study. Treatment assignment **and lipid levels after randomization** will be blinded to all subjects, site personnel, study committee members (excluding the Data Safety Monitoring Board), and Amgen as described below. **Refer to Section 12.2 for additional information.**

Section: 7.4.1.1, Amgen Investigational Product: Evolocumab, Paragraph 2

Add:

If a subject is late for administration of investigational product, administration should occur as soon as possible and must be within ± 7 days of the originally scheduled dose. If the dose is not administered within ± 7 days, instruct the subject to wait until the next dose on the original schedule. 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.

Section: 7.8.1, Prior Treatment

Replace:

Prior therapies that were being taken from 30 days prior to signing of the informed consent should be collected. For lipid-lowering therapies, collect therapy name, dose, unit, frequency, start and stop dates. For all other prior therapies, collect therapy name, start and stop dates.

With:

Only cardiovascular and diabetes prior therapies that were being taken from 30 days prior to signing of the informed consent should be collected. For lipid-lowering therapies, collect therapy name, dose, unit, frequency, start and stop dates. For all other prior therapies, collect therapy name, start and stop dates.

Section: 7.8.2, Concomitant Treatment, Paragraph 2

Replace:

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

With:

Only cardiovascular and diabetes concomitant therapies are to be collected from signing of the informed consent through the end of safety follow-up period.

Section: 8.1, Discontinuation from Study Treatment, Paragraph 1

Replace:

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 and reason(s) for discontinuation. 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 per the Schedule of Activities (see Table 2-1). If this is not possible or agreeable to a subject, different options of follow-up (eg, 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 must document this decision in the subject's medical records.

With:

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 and reason(s) for discontinuation. 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 **continue to be followed** to ensure safety surveillance and/or collection of outcome data per the Schedule of Activities (see Table 2-1). If this is not possible or agreeable to a subject, different options of follow-up (eg, 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 must document this decision in the subject's medical records.

Section: 8.1, Discontinuation from Study Treatment, Paragraph 3

Delete:

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
- pregnancy (see Section 9.2.3.1.5 for details regarding evolocumab pregnancy registries

Section: 8.2, Discontinuation from the Study, Paragraph 1 and 2

Replace:

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 (including blood, urine, and other specimens) collected 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.

With:

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 (including blood, urine, and other specimens) collected up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data **(eg, vital status)** can be included after withdrawal of consent.

Discontinuation of investigational product (temporary or permanent) is not considered withdrawal of consent. Subjects who do not wish to attend regular site visits as per the schedule of activities after investigational product discontinuation should be offered alternative methods of follow up including periodic telephone follow up, contact at the end of study, or assessment of health status via treating physicians or medical records. Withdrawal of consent should only occur if the subject refuses all potential options of further follow up. 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 **and electronic data capture (EDC) CRF**. **For subjects who are confirmed to have fully withdrawn consent for all study procedures, only publicly available records (where permitted) may be searched after withdrawal.**

Section: 8.3, Lost to Follow-up, Paragraph 2, Bullet 3

Delete:

- ~~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.~~

Section: 8.3, Lost to Follow-up, Paragraph 2, Bullet 4

Replace:

- For subjects who are potentially lost to follow-up, the investigator can search publicly available records (where permitted) to ascertain vital status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

With:

- For subjects who are potentially lost to follow-up, the investigator can search **all** available records (where permitted) to ascertain **efficacy and safety outcomes as well as** vital status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

Section: 9.1.1, Screening, Enrollment and/or Randomization

Replace:

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 ICF, the site will register the subject in the IVRS/IWRS and screen the subject in order to confirm eligibility. The screening window is up to 2 weeks.

All screening evaluations (including the placebo injection; Section 9.2.1.7) must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. Fasting lipid samples must be collected during screening (local laboratory), subjects must be fasting overnight. If the subject did not fast, another screening visit must be scheduled to collect these samples. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure (see Section 6.4), as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for rescreening 1 time (except those that screen fail inclusion criteria 103).

Rescreen subjects must first be registered as screen failures in IVRS/IWRS and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 2-week screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 30 days after the original signing of the ICF, all screening procedures, including informed consent, must be repeated.

With:

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 ICF, the site will register the subject in the IVRS/IWRS and screen the subject in order to confirm eligibility. The screening **period will be** up to **21 days before day 1 of study treatment**.

All screening evaluations (including the placebo injection; Section 9.2.1.7) must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. **L**ipid samples collected during screening (local laboratory), **may be fasting or non-fasting**. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure (see Section 6.4), as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects **are** eligible for rescreening.

Rescreen subjects must first be registered as screen failures in IVRS/IWRS and subsequently registered as rescreens. Once the subject is registered as rescreened, a

new **21 days** screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 30 days after the original signing of the ICF, all screening procedures, including informed consent, must be repeated. **With the exception of the placebo run-in, rescreened subjects who are re-reconsented will repeat all screening procedures. Subjects may be rescreened more than once.**

Section: 9.1.2, Treatment Period, Paragraph 1

Replace:

Day 1 of the treatment period (ie, first dose of investigational product) must happen within 2 weeks (14 days) of the signing of the informed consent. Visits will occur per the Schedule of Activities (Table 2-1). On-study visits may be completed within 7 days. 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.

With:

Day 1 of the treatment period (ie, first dose of investigational product) **will** happen within **21** days of **the screening or re-screening visit**. Visits will occur per the Schedule of Activities (Table 2-1). On-study visits may be completed within ± 7 days. The date of the first dose of investigational product is defined as day 1**; day 1 dose will be performed in clinic**. 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.

Section: 9.2.1.3, Medical History

Add:

The investigator or designee will collect a targeted cardiovascular medical and surgical history that started prior to screening through the start of the adverse event reporting period. 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. Record NYHA Functional Classification at baseline on the medical history CRF **only for subjects with a known history of heart failure**.

Section: 9.2.1.4, Physical Examination

Replace:

Physical examination will be performed as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event). The Modified Rankin Scale should be used to measure disability resulting from a stroke.

With:

Physical examination will be performed as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event). The Modified Rankin Scale **will only** be used to measure disability **if a subject experiences a stroke event during the study.**

Section: 9.2.2, Efficacy Assessments

Replace:

Potential endpoint data will be collected on Event CRFs as detailed in the Endpoint Reporting Manual. All supporting documentation will be provided to Amgen or designee for each event as it occurs during the course of the study. Potential endpoints will be adjudicated by an independent external Clinical Events Committee (CEC), as defined in the CEC charter.

With:

At each scheduled visit, the survival status and non-fatal potential endpoint assessment will be recorded on the CRF, including the survival status date and non-fatal potential endpoint assessment date. Non-fatal potential endpoints are considered to be assessed if it is known that the subject has not experienced any potential endpoint since the last visit, or they have experienced an event (and event should be recorded within the EDC CRF).

Potential endpoint data will be collected **within the EDC** CRFs as detailed in the Endpoint Reporting Manual. All supporting documentation will be provided to Amgen or designee for each event as it occurs during the course of the study. Potential endpoints will be adjudicated by an independent external Clinical Events Committee (CEC), as defined in the CEC charter.

Section: 9.2.3.1.1.2, Serious Adverse Events, Paragraph 1

Add:

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through the end of study/safety follow-up visit are reported using the Event CRF. **Occurrences of unscheduled study visits, hospitalization, and accidental injuries should be assessed for potential serious adverse events.**

Section: 9.2.3.1.1.4, Reporting Study Endpoints

Add:

All potential endpoints (death, MI, ischemic stroke, ischemia-driven arterial revascularization) must be recorded on the Event CRF within 24 hours of knowledge of the event. **In addition, aortic valve stenosis and venous thromboembolic events (pulmonary embolism and/or deep vein thrombosis) should be recorded as potential endpoints on the Event CRF.** Information regarding dates of onset and resolution, severity, action taken, investigator assessment of relatedness, and assessment of seriousness must be collected as indicated in Section 12.4.

Section: 9.2.3.2, Vital Signs

Replace:

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.

With:

The following measurements must be performed: systolic/diastolic blood pressure and heart rate. **It is recommended that the s**ubject 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. Record all measurements on the vital signs CRF.

Section: 9.2.4, Clinical Laboratory Assessments, Paragraph 3

Replace:

NOTE: Fasting lipid panels will be collected from ALL subjects during screening and will be analyzed at the local laboratory. A subset of subjects (approximately 2000 subjects) will have additional lipid panels collected during the study (Table 2-1) which will be analyzed at the central laboratory (fasting is not required).

With:

NOTE: Fasting **or non-fasting** lipid panels **may** be collected from subjects during screening**,** and **if so,** will be analyzed at the local laboratory**. In the absence of changes in lipid-lowering therapy or significant changes in diet, the most recent lipid values obtained within 3 months prior to screening may be used used to determine eligibility**. A subset of subjects (approximately 2000 subjects **from randomly selected sites and stratified by geographic region**) will have additional lipid panels collected during the study (Table 2-1) which will be analyzed at the central laboratory (fasting is not required).

Section: 9.2.4.1, Pregnancy Testing, Paragraph 1

Add:

A highly sensitive **(serum or** urine**)** pregnancy test should be completed at screening and prior to administration of investigational product on day 1 for females of childbearing potential (analyzed at local laboratory).

Section: 10.1, Sample Size Determination, Paragraphs 2, 3, and 5

Replace:

Based on the lipid entry criteria, it is anticipated that the median baseline LDL-C will be at least 125 mg/dL. Taking into account premature discontinuation of study drug and use of commercially available PCSK9 inhibitors, it is anticipated that the LDL-C difference between the evolocumab and placebo arms will be at least 1.7 mmol/L at the midpoint of the trial. After accounting for a 12-month treatment lag at the beginning of the trial, and assuming a median follow-up of at least 4.5 years, the anticipated HRs over the duration of this entire study for the primary endpoints will be 0.77 for primary triple component endpoint and 0.80 for primary quadruple component endpoint.

The annualized event rate of the primary triple endpoint and the primary quadruple endpoint in the placebo arm are estimated approximately 1.5% and 2.5%, respectively.

The 0.025 significance level of type I error is used for each of the primary estimands.

Assuming a 15-month enrollment period, a 1% of loss to follow-up rate per year, and a total study duration of 63 months, a total sample size of at least 13 000 subjects, with

approximately 751 subjects experiencing a primary triple component endpoint, is required to ensure approximately 90.5% power (Shih, 1995) based on a 2-sided log-rank test of demonstrating the superiority of evolocumab over placebo. At the time of 751 subjects with the primary triple component endpoint observed, there will be approximately 1254 subjects with the primary quadruple component endpoint, which will ensure a power of 95.7% to demonstrate superiority for that component endpoint of evolocumab over placebo.

With:

Based on the lipid entry criteria, it is anticipated that the median baseline LDL-C will be at least **approximately** 12**0** mg/dL. Taking into account premature discontinuation of study drug and **potential** use of commercially available PCSK9 inhibitors, it is anticipated that the LDL-C difference between the evolocumab and placebo arms will be **approximately** 1.7 mmol/L at the midpoint of the trial. After accounting for a 12-month treatment lag at the beginning of the trial, and assuming a median follow-up of at least 4.5 years, the anticipated HRs over the duration of this entire study for the primary endpoints will be 0.77 for primary triple component endpoint and 0.80 for primary quadruple component endpoint.

The annualized event rate of the primary triple endpoint and the primary quadruple endpoint in the placebo arm are estimated approximately 1.**63**% and 2.**72**%, respectively **(Bhat et al, 2019; Steg et al, 2019)**.

The **2-sided** 0.025 significance level of type I error is used for each of the primary estimands.

Assuming a 15-month enrollment period, a 1% of loss to follow-up rate per year, and a total study duration of 63 months, a total sample size of at least **12 000** subjects, with approximately 751 subjects experiencing a primary triple component endpoint, is required to ensure approximately 90.5**%** power (Shih, 1995) based on a 2-sided log-rank test of demonstrating the superiority of evolocumab over placebo. At the time of 751 subjects with the primary triple component endpoint observed, there will be approximately 1254 subjects with the primary quadruple component endpoint, which will ensure a power of **95.6%** to demonstrate superiority for that component endpoint of evolocumab over placebo.

Section: 10.2.2, Covariates, Paragraph 1, Bullet 1, Sub bullet 1 and 2

Add:

- geographical region **(North America, Europe, and others)**
- screening LDL-C level **(< 160 mg/dL, ≥ 160 mg/dL)**

Section: 10.2.3, Subgroups, Paragraph 1, Bullet 1, Sub bullet 1 and 2

Add:

- geographical region **(North America, Europe, and others)**
- screening LDL-C level **(< 160 mg/dL, ≥ 160 mg/dL)**

Section: 10.3, Statistical Analyses

Replace:

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

With:

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

Section: 10.3.1.1, Interim Analyses

Add:

10.3.1.1 Interim Analysis

The DMC will review all available safety data periodically (approximately every 6 months) and will consider a recommendation for early termination of the study based on their review of the totality of evidence at 2 pre-specified interim analyses.

Further details regarding DMC analyses are provided in Appendix 12.3.

Section: 10.3.2.2, Efficacy Analyses

Replace:

Estimand	Statistical Analysis Methods
Primary	Intent-to-treat (ITT) principle: The following analyses will be performed for each primary estimands. Kaplan-Meier (K-M) curves will be estimated and graphically displayed for each randomized treatment group. The 2 survival functions will be compared using a 2-sided log-rank test stratified by randomization stratification factors. Yearly K-M estimates and 95% CIs will be calculated by each randomized treatment group. The HR and its corresponding 95% CI will be estimated from a stratified Cox model, stratified by the randomization stratification factors. Sensitivity analysis: The following sensitivity analyses for the primary estimands will be performed: • Analyses using start date of end of study visit period and subject last confirmed survival status date instead of the subject last non-fatal potential endpoint collection date. • Tipping point analysis to assess the impact of missing follow-up data. • Analyses using eCRF stratification factor instead of IVRS if there is a discrepancy in > 5% subjects. • The Cumulative Incidence Function (CIF) will be used for estimation of the incidence of the primary estimands while taking competing risk of non-CHD deaths into account. Subgroup analyses: Subgroup analyses on the primary estimands will be conducted using the stratification factors and baseline covariates.

With:

Estimand	Statistical Analysis Methods
Primary	Intent-to-treat (ITT) principle: The following analyses will be performed for each primary estimands. Kaplan-Meier (K-M) curves will be estimated and graphically displayed for each randomized treatment group. The **primary test comparing the** 2 survival functions will be **performed** using a 2-sided log-rank test stratified by randomization stratification factors. Yearly K-M estimates and 95% CIs will be calculated by each randomized treatment group. The HR and its corresponding 95% CI will be estimated from a stratified Cox model, stratified by the randomization stratification factors. Sensitivity analysis: The following sensitivity analyses for the primary estimands will be performed: • Analyses using start date of **primary completion** visit period and subject last confirmed survival status date instead of the subject last non-fatal potential endpoint collection date. • Tipping point analysis to assess the impact of missing follow-up data. • **Multiple imputation analysis based on retrieved drop outs for subjects who are lost to follow-up prior to EOS.** • Analyses using eCRF stratification factor instead of IVRS if there is a discrepancy in > 5% subjects. Subgroup analyses: Subgroup analyses on the primary estimands will be conducted using the stratification factors and baseline covariates.

Section: 10.3.2.2, Efficacy Analyses, Paragraph 3

Add:

Additional estimands will be pre-specified in the Statistical Analysis Plan.

Section: 11, References

Add:

Bhatt DL, Steg G, Miller M, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N Eng J Med.* 2019;380:11-22.

Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg*. 1997;26(3):517-538.

Schwartz M, Roayaie S, Konstadoulakis M. Strategies for the management of heptatocellular carcinoma. *Nat Clin Pract Oncol*. 2007;4(7):424-432.

Steg PG, Bhatt DL, Simon T, et al. Ticagrelor in Patients with Stable Coronary Disease and Diabetes. *N Engl J Med*. 2019;381:1309-1320.

Section: 12.1, Appendix 1. List of Abreviations and Definition of Terms

Delete:

Abbreviation or Term	Definition/Explanation
~~CTCAE~~	~~Common Terminology Criteria for Adverse Events~~

Section: 12.1, Appendix 1. List of Abreviations and Definition of Terms

Add:

Abbreviation or Term	Definition/Explanation
TIMI Study Group Hotline	**Communication system at the Thrombolysis in Myocardial Infarction Study Group of Brigham and Women's Hospital, Boston, Massachusetts, USA, that is providing protocol support to all participating active trial sites worldwide**

Section: 12.2, Appendix 2. Clinical Laboratory Tests, Table 12-1. Local Laboratory Analyte Listing

Replace:

Local Laboratory: Chemistry	Local Laboratory: Other	Fasting lipid panel (screening):
Creatinine eGFR[a]	Urine pregnancy	• total cholesterol • LDL-C • HDL-C • non-HDL-C • triglycerides

C = cholesterol; eGFR = estimated glomerular filtration rate; HDL = high density lipoprotein; LDL = low-density lipoprotein; MDRD = Modification of Diet in Renal Disease
[a] Preference is to use MDRD equation as shown below (Levey et al, 1999).

With:

Local Laboratory: Chemistry	Local Laboratory: Other	Fasting lipid panel (screening):
Creatinine eGFR[a]	**Serum or u**rine pregnancy	• total cholesterol • LDL-C[b] • HDL-C • non-HDL-C • triglycerides

C = cholesterol; eGFR = estimated glomerular filtration rate; HDL = high density lipoprotein; LDL = low-density lipoprotein; MDRD = Modification of Diet in Renal Disease
[a] Preference is to use MDRD equation as shown below (Levey et al, 1999).
[b] **Use the Martin-Hopkins formula (Martin et al, 2013) when calculation of LDL-C not possible due to TG > 400 mg/dL.**

Section: 12.3, Appendix 3. Study Governance Considerations, Data Monitoring Committee, Executive Committee, and Clinical Events Committee, Data Monitoring Committee, Paragraph 1

Replace:

An Independent Biostatistics Group (IBG) will perform the interim analysis and provide the interim report to an independent Data Monitoring Committee (DMC). The DMC will review all available safety and efficacy data periodically (approximately every 6 months). The IBG and DMC will have access to subjects' individual treatment assignments. To minimize the potential introduction of bias to the conduct of the study, members of the DMC and Data Monitoring Group will not have any direct contact with study site personnel or subjects. The DMC will communicate major safety concerns and recommendations regarding study modification or termination based on the safety and efficacy parameters to Amgen in accordance with the DMC charter.

With:

An Independent Biostatistics Group (IBG) will perform the interim analysis and provide the interim report to an independent Data Monitoring Committee (DMC). The DMC will review all available safety data periodically (approximately every 6 months) **and will consider a recommendation for early termination of the study based on their review of the totality of evidence at 2 pre-specified interim analyses**. The IBG and DMC will have access to subjects' individual treatment assignments. To minimize the potential introduction of bias to the conduct of the study, members of the DMC and Data Monitoring Group will not have any direct contact with study site personnel or subjects. The DMC will communicate major safety concerns and recommendations regarding study modification or termination based on the safety and efficacy parameters to Amgen in accordance with the DMC charter.

Section: 12.3, Appendix 3. Study Governance Considerations, Data Monitoring Committee, Executive Committee, and Clinical Events Committee, Data Monitoring Committee, Paragraph 3(new)

Add:

The independent DMC (IDMC), will not review the unblinded CV endpoints prior to the 2 pre-specified interim analyses and consider a recommendation for early termination of the study based on efficacy at 2 pre-specified interim analyses:

- **the first interim analysis (IA#1) for the DMC reviewing the unblinding CV endpoints will occur when the numbers of subjects who have experienced both of the primary triple and quadruple endpoints is 80% of the final targeted numbers and the median study duration is at least approximately 3.5 years.**
- **the second interim analysis (IA#2) for the DMC reviewing the unblinding CV endpoints will occur when the numbers of subjects who have experienced both of the primary triple and quadruple endpoints is 90% of the final targeted numbers and the median study duration is at least approximately 4.0 years.**

A summary of the timing and corresponding 2-sided alpha level for each interim analysis is detailed below.

Timing of IA: % of endpoints (# of endpoints)	Estimated median study duration	Haybittle-Peto alpha spending approach	
		Test statistics (Z) for log-rank test	Corresponding 2-sided alpha level
IA#1: 80% of targeted # of endpoints for the primary triple component endpoint and the primary quadruple endpoint	~3.5 years	3.291	0.001
IA#2: 90% of targeted # of endpoints for the primary triple component endpoint and the primary quadruple endpoint; 182 subjects with CHD deaths	~4.0 years	3.291	0.001

CHD = coronary heart disease; IA = interim analysis.

The DMC will recommend alteration or early termination based on a totality of evidence that will include proof beyond a reasonable doubt that is likely to influence clinical practice. Additional specific factors to be considered by the DMC will include:

(1) no major safety concerns

AND

(2) there is sufficient follow-up time to adequately characterize the long-term efficacy profile of evolocumab in this patient population studied (ie, median duration of at least 3.5 years)

AND

(3) A 2-sided $p < 0.001$ in both primary pre-specified endpoints with consistency in major subgroups and a definite reduction in coronary, cardiovascular, and total mortality.

The overall alpha left used for the primary analyses will be 0.05 based on Haybittle-Peto spending approach spent on the 2 pre-specified interim analyses by the DMC.

Section: 12.5, Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information, Collection of Lactation Information, Bullet #3

Replace:

- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 214.

With:

- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion **221.**

Section: 12.6, Appendix 6. Sample Storage and Destruction, Paragraph 3

Replace:

If informed consent is provided by the subject, Amgen or designees can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand cardiovascular disease, 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**.**

With:

If informed consent is provided by the subject, Amgen or designees can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand cardiovascular disease, 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 **or per local regulations.**

Section: 12.8, Appendix 8. Background Lipid-lowering Therapy

Replace:

Background lipid-lowering therapy should be established jointly by the subject and their health care providers and be consistent with local professional society guidelines. By study design, subjects eligible for this study are at high risk for cardiovascular events.

Thus, it is anticipated that the majority of subjects in this trial will be treated with ahigh intensity background lipid-lowering regimen that would be anticipated to reduce the LDL-C by ≥ 50% from the untreated baseline level. Either a high intensity statin (ie, 1 that is at least as potent as atorvastatin 40 mg daily, rosuvastatin 20 mg daily, or equivalent) or a combination of statin and ezetimibe would achieve this goal. Up to approximately 15% of subjects may be enrolled who are documented to have "statin intolerance" per local guidelines (defined as the inability to tolerate at least 2 different statins, including at least 1 statin at the lowest approved dose). The sponsor may limit or close enrollment of statin intolerant subjects if this threshold is exceeded.

With:

Background lipid-lowering therapy should be established jointly by the subject and their health care providers and be consistent with local professional society guidelines. By study design, subjects eligible for this study are at high risk for cardiovascular events. Thus, it is anticipated that the majority of subjects in this trial will be treated with a high intensity background lipid-lowering regimen that would be anticipated to reduce the LDL-C by ≥ 50% from the untreated baseline level. Either a high intensity statin (**eg**, atorvastatin ≥ 40 mg daily, rosuvastatin ≥ 20 mg daily, or **simvastatin 80 mg daily**) or a combination of **any** statin **at any approved daily dose** and ezetimibe **10 mg daily should** achieve this goal.

Subjects on any statin intensity with or without ezetimibe are eligible for the trial. However, we encourage, as per local guidelines and standard of care, to have the subject on maximally tolerated dose and/or add ezetimibe prior to screening. If the subject does not tolerate higher doses of statin, then the subject may be enrolled on a lower statin intensity, provided they have been on stable regimen starting at least 2 weeks prior to the qualifying lipid panel. In subjects not able to tolerate high intensity statin, the addition of ezetimibe should be encouraged. Up to approximately 15% of subjects may be enrolled who are documented to have **complete** "statin intolerance" (defined as the inability to tolerate at least 2 different statins, including at least 1 statin at the lowest approved dose). The sponsor may limit or close enrollment of statin intolerant subjects if this threshold is exceeded.

Note: Simvastatin 80 mg is not available in all countries participating in this study. Use of simvastatin 80 mg applies to countries where its use has been approved by local regulatory authority.

Section: 12.10, Appendix 10. NYHA Classfication and Rutherford Classification,

(New Appendix)

Add:

12.10 Appendix 10. NYHA Classification and Rutherford Classification

New York Heart Association Functional Classification

Class I	**No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea.**
Class II	**Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.**
Class III	**Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation or dyspnea.**
Class IV	**Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency may be present even at rest. If any physical activity is undertaken, discomfort is increased.**

Source: American Heart Association, 2017.

Rutherford Classification for Chronic Limb Ischemia

Grade	Category	Clinical Description	Objective criteria
0	0	Asymptomatic – no hemodynamically significant occlusive disease	Normal treadmill or reactive hyperemia test
	1	Mild claudication	Completes treadmill exercise; AP after exercise > 50 mm Hg, but at least 20 mm Hg lower than resting value
I	2	Moderate claudication	Between categories 1 and 3
	3	Severe claudication	Cannot complete standard treadmill exercise, and AP after exercise < 50 mm Hg
II	4	Ischemic rest pain	Resting AP < 40 mm Hg, flat or barely pulsatile ankle or metatarsal PVR; TP < 30 mm Hg
III	5	Minor tissue loss – non-healing ulcer, focal gangrene with diffuse pedal ischemia	Resting AP < 60 mm Hg, ankle or metatarsal PVR flat or barely pulsatile; TP < 40 mm Hg
	6	Major tissue loss – extending above TM level, functional foot no longer salvageable	Same as category 5

AP = ankle pressure; PVR = pulse volume recording; TM = transmetatarsal; TP = toe pressure.
Source: Rutherford et al, 1997.

Rutherford Classification for Acute Limb Ischemia

		Findings		Doppler signal	
Category	**Description/prognosis**	**Sensory loss**	**Muscle weakness**	**Arterial**	**Venous**
I. Viable	**Not immediately threatened**	**None**	**None**	**Audible**	**Audible**
II. Threatened					
a. Marginally	**Salvageable if promptly treated**	**Minimal (toes) or none**		**Inaudible**	**Audible**
b. Immediately	**Salvageable with immediate revascularization**	**More than toes, associated rest pain**		**Inaudible**	**Audible**
III. Irreversible	**Major tissue loss or permanent nerve damage inevitable**	**Profound, anesthetic**		**Inaudible**	**Audible**

Source: Rutherford et al, 1997.

Section: 12.11, Appendix 11. Child-Pugh Score[a] (New Appendix)

Add:

Measure	1 point	2 points	3 points
Bilirubin (mg/dL)	< 2	2 to 3	> 3
Albumin (g/dL)	> 3.5	2.8 to 3.5	< 2.8
Prothrombin time (seconds)	1 to 3	4 to 6	> 6
Ascites	None	Slight	Moderate
Encephalopathy	None	I to II	III to IV

[a] Defines 3 classes of liver function; grade A = 5 to 6 points; grade B = 7 to 9 points; grade C = 10 to 15 points.
Source: Schwartz et al, 2007.