

Protocol Title: A Double-blind, Randomized, Multicenter Study to Evaluate the Safety and Efficacy of Evolocumab, Compared With Ezetimibe, in Hypercholesterolemic Japanese Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor due to Muscle Related Side Effects

GAUSS-4: Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects

Evolocumab (AMG 145)

Amgen Protocol Number 20140234

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Signature

Name of Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: A Double-blind, Randomized, Multicenter Study to Evaluate the Safety and Efficacy of Evolocumab, Compared With Ezetimibe, in Hypercholesterolemic Japanese Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor Due to Muscle Related Side Effects (GAUSS-4: Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects)

Study Phase: Phase 3

Indication: Hypercholesterolemia

Primary Objective: To evaluate the effect of 12 weeks of subcutaneous evolocumab compared with ezetimibe, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in hypercholesterolemic subjects unable to tolerate an effective dose of a statin.

Secondary Objective(s):

- To evaluate the safety and tolerability of **subcutaneous (SC)** evolocumab, compared with ezetimibe, in hypercholesterolemic subjects unable to tolerate an effective dose of a statin
- To assess the effects of 12 weeks of evolocumab, compared with ezetimibe, on change from baseline in LDL-C, and percent change from baseline in non high density lipoprotein cholesterol (non HDL-C), total cholesterol (TC), apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, ApoB/Apolipoprotein A1 (ApoA1) ratio, lipoprotein(a) [Lp(a)], triglycerides, very low-density lipoprotein cholesterol (VLDL-C), and HDL-C in hypercholesterolemic subjects unable to tolerate an effective dose of a statin
- To assess the effects of 12 weeks SC evolocumab, compared with ezetimibe, on percent of subjects attaining LDL-C < 70 mg/dL (1.8 mmol/L) in hypercholesterolemic subjects unable to tolerate an effective dose of a statin

Hypotheses: The primary hypothesis is that evolocumab (AMG 145) SC will be well tolerated and will result in greater reduction of LDL-C than ezetimibe, defined by the mean percent change from baseline at week 10 and 12 and percent change from baseline at week 12.

Co-Primary Endpoints:

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

Secondary Endpoint(s):

- Co-secondary endpoints of the means at weeks 10 and 12 and at week 12 for:

Tier 1

- Change from baseline in LDL-C
- LDL-C response (LDL-C < 70 mg/dL [1.8 mmol/L])
- Percent change from baseline in total cholesterol
- Percent change from baseline in non-HDL-C
- Percent change from baseline in ApoB
- Percent change from baseline in the total cholesterol/HDL-C ratio
- Percent change from baseline in ApoB/ApoA1 ratio

Tier 2

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

Study Design: This is a phase 3, multicenter, double-blind, randomized, ezetimibe controlled, parallel group study for evolocumab in hypercholesterolemic Japanese subjects unable to tolerate an effective dose of a statin. Subjects who meet all inclusion/exclusion criteria will be randomized with an allocation ratio of 2:2:1:1 into 4 groups: evolocumab 420 mg SC QM + placebo PO QD, evolocumab 140 mg SC **every 2 weeks (Q2W)** + placebo PO QD, placebo QM SC + ezetimibe 10 mg PO QD, placebo SC Q2W + ezetimibe 10 mg PO QD. Randomization will be stratified by screening LDL-C level and baseline statin use. Randomization should occur within 5 – 10 days of the screening LDL-C evaluation used to determine eligibility. Subjects on low or atypical statin **therapy must be on a stable dose for at least 4 weeks prior to screening and throughout the blinded portion of the study; the dose cannot be adjusted during screening and for the duration of the study.**

To ensure tolerance of SC injections, patients will receive a 1-time placebo injection by AI/Pen prior to randomization.

For blinding purposes, every subject will receive investigational product (IP) SC and PO. Subjects will be provided with evolocumab or placebo through the use of a prefilled autoinjector/pen (AI/Pen) or Personal Injector (also known as the automated mini-doser [AMD]). Depending on availability either a single Personal Injector will be provided for monthly dosing (QM) or QM evolocumab may be provided by the use of 3 autoinjectors. Evolocumab and corresponding placebo will be administered at the study site or at an appropriate non-clinic setting per protocol Table 1 (Schedule of Assessment). PO placebo will be available to match PO ezetimibe through over-encapsulation. The SC IP dose frequencies of Q2W and QM will not be blinded. Evolocumab SC, ezetimibe PO, and placebo SC and PO will be blinded. Central laboratory results of the lipid panel, ApoA1, ApoB, lipoprotein(a), and high sensitivity C-reactive protein (hsCRP) will be blinded during double-blind treatment. Investigators will be provided lipid results starting at week 24 until the end of study for each subject. All lipid results from posttreatment to week 24 will remain blinded until the unblinding of the clinical database.

Subjects will self-administer IP in the non-clinic setting and return to the clinical site at W24, W36, W48 and W52 for subsequent visits. There will be an end of study phone call at W54 (**Q2W subjects only**) for any potential adverse events/serious adverse events/**adverse device effects.**

The study includes collection of biomarker samples, where approved by the institutional review board (IEC/IRB). Administration of non-Amgen IP: PO IP (ezetimibe or placebo) will end with the week 12 visit for all subjects. Following the week 12 visit subjects should be treated to standard of care in addition to receiving Amgen IP: open label evolocumab.

Subjects will be encouraged to complete all planned visits regardless of their adherence to investigational product (IP) administration. The study includes a formal review of the accumulating blinded data by an independent Data Monitoring Committee (DMC).

Sample Size: Approximately 60 subjects (approximately 40 evolocumab subjects) will be randomized. A subject will be considered enrolled upon randomization.

Investigational Product(s) Dosage, Administration, Protocol-required Therapies, and Standard of Care:

Amgen Investigational Product Dosage and Administration

Evolocumab will be administered using a spring-based prefilled autoinjector/pen (prefilled AI/Pen) or 3.5 mL Personal Injector.

Evolocumab will be administered at 1 of 2 regimens:

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

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

Non Amgen Investigational Product Dosage and Administration: Ezetimibe 10 mg (and placebo) will be provided by Amgen (or designee) and will be taken by the subject PO QD. Placebo will be matching ezetimibe by over-encapsulation.

Amgen will not provide Standard of Care (SOC) medication for the open label period.

Summary of Subject Eligibility Criteria: Males and females, ≥ 20 to ≤ 80 years of age, **Japanese by self-identification**, are eligible for this study. Subject must have tried and failed at least 2 statins with failure to at least 1 of the statins at an average daily dose at or below the following doses due to intolerable myopathy, ie, myalgia (muscle pain, ache, or weakness without CK elevation), myositis (muscle symptoms with increased CK levels), or rhabdomyolysis (muscle symptoms with marked CK elevation). For subjects that developed rhabdomyolysis, defined as CK $> 10 \times$ ULN, failure of only 1 statin at any dose is acceptable.

- Atorvastatin 10 mg
- Fluvastatin 20 mg
- Pravastatin 10 mg
- Rosuvastatin 2.5 mg
- Simvastatin 5 mg
- Pitavastatin 1 mg
- For unlisted statins, the average daily dose should not exceed the lowest available recommended starting dose approved by the Japanese Ministry of Health, Labour and Welfare.

Symptoms must have resolved **or improved** when statin was discontinued or the dose was reduced. Depending on a subject's management category per 2012 JAS guideline (see [Appendix D](#)) subjects must meet criteria provided. Fasting triglycerides must be ≤ 400 mg/dL (4.5 mmol/L) as determined by the central laboratory analysis at screening.

Major exclusion criteria include, but are not limited to moderate to severe heart failure, uncontrolled cardiac arrhythmia, symptomatic coronary artery disease within the last 3 months, recently diagnosed or poorly controlled diabetes, hypertension or hyper/hypothyroidism, known active infection or major hematologic, renal, hepatic, metabolic, gastrointestinal or endocrine dysfunction, systemic steroid use, pregnancy or lactation, previous exposure to evolocumab or other PCSK9 inhibitor.

Statistical Considerations:

General Considerations

When all the randomized subjects in the study have either completed the scheduled visits up to and including Week **24** or have early terminated from the study, a primary analysis will be performed. Efficacy and safety of 12 weeks of evolocumab compared with ezetimibe will be evaluated on the full analysis set (FAS) that includes all randomized subjects who received at least 1 dose of IP in the double blind treatment period. **In addition, the 12 weeks of data from the open-label extension (weeks 12 to 24) will also be summarized.** The **treatment effect of evolocumab compared to ezetimibe will be evaluated for all efficacy endpoints through the Week 12 visit. In addition, descriptive analyses from the open-label extension (weeks 12 to 24) will be performed on the open label extension analysis set (OLEAS).** Methods of adjusting for multiplicity are provided in [Section 10](#).

The final analysis will be conducted to evaluate the long-term efficacy and safety of evolocumab when all enrolled subjects have either completed the scheduled visits or have early terminated from the study.

Analyses of Co-primary Endpoints

To assess the co-primary endpoints of the mean percent change in LDL-C from baseline at weeks 10 and 12 and the percent change from baseline at week 12, a repeated measures linear effects model will be used to compare the efficacy of evolocumab (pooled Q2W and QM) with the pooled ezetimibe. Missing values will not be imputed when the repeated measures linear model is used.

Analyses of Co-Secondary Efficacy Endpoints

The statistical model for the co-secondary efficacy endpoints will be similar to the co-primary endpoints. However, the co-secondary efficacy endpoints of LDL-C response will be analyzed using the Cochran-Mantel Haenszel (CMH) test.

Safety analyses

Safety summaries will include the subject incidence of adverse events, summaries of laboratory parameters and anti-evolocumab **antibodies**.

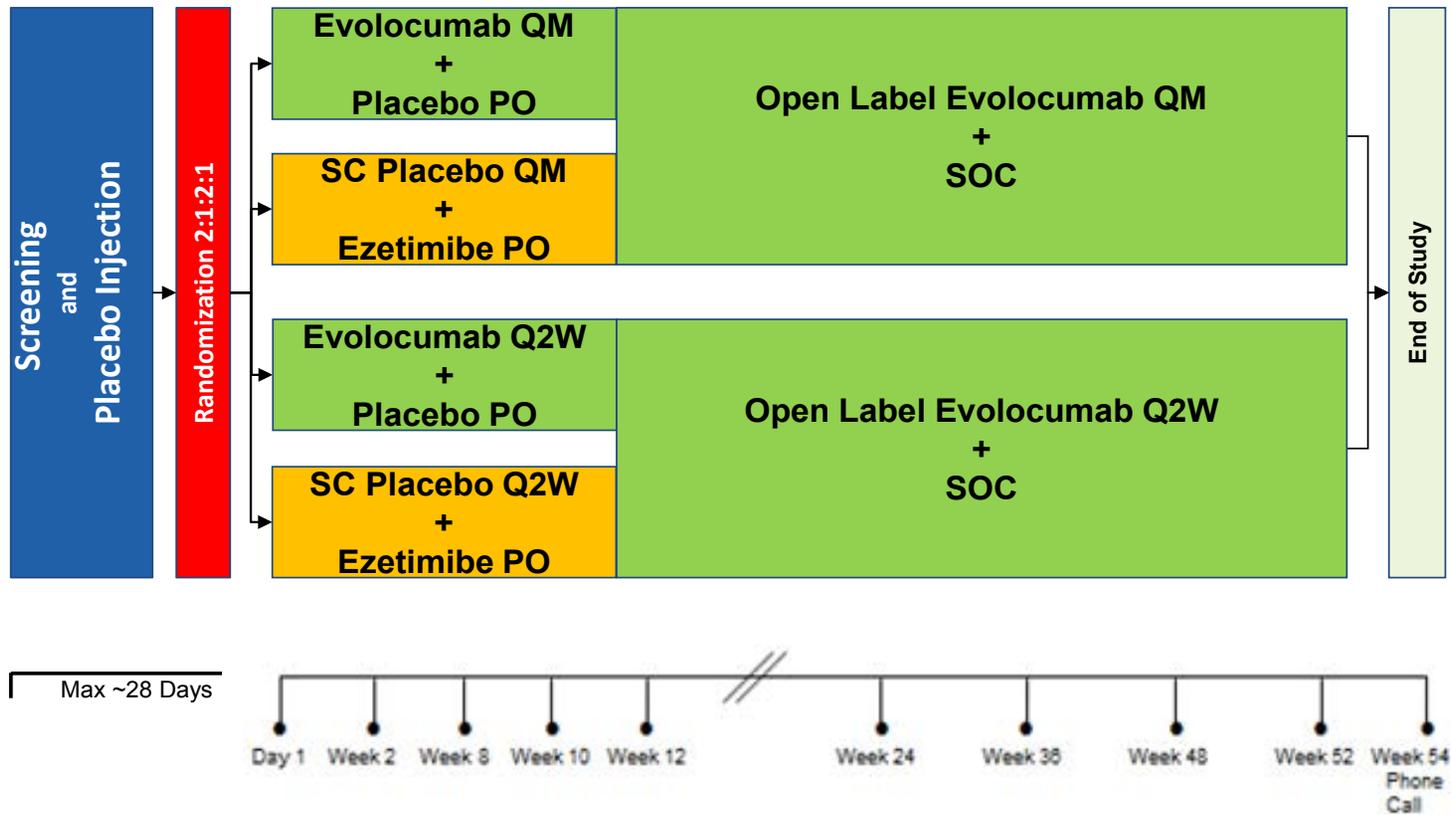
For a full description of statistical analysis methods, please refer to [Section 10](#).

Sponsor: Amgen Inc.

Data Element Standards
Version/Date:

Version 5/20 March 2015

Study 20140234 Treatment Schema



Study Glossary

Abbreviation or Term	Definition/Explanation
AHA	American Heart Association
AI/Pen	Autoinjector/pen
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase (serum glutamic-pyruvic transaminase)
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
AST (SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
AUC	Area under the curve
BP	Blood pressure
CABG	Coronary artery bypass graft
CAS	Completer analysis set
CBC	Complete blood count
CETP	Cholesterylester transfer protein
CHD	Coronary heart disease
CK	Creatine kinase
CRP	C-reactive protein
CTCAE	NCI Common Terminology Criteria for AEs
CV	Cardiovascular
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DILI	Drug-induced liver injury
DMC	Data monitoring committee
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate; eGFR will be calculated by the central laboratory and provided to the investigator.
End of study	The end of the study is defined as the last day on which a randomized subject completes the study or the day the subjects terminates the study early.
End of study for individual subject	Defined as the last day that protocol-specified procedures are conducted for an individual subject or the day the subject withdraws from study early.
End of treatment	Defined as the day a subject receives the last treatment with investigational product before the subject completes the study or ends the treatment early.
Enrollment	A subject is considered enrolled upon randomization

Abbreviation or Term	Definition/Explanation
EOS	End of study (for individual subject)
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HCV	Hepatitis C virus
HDL-C	High density lipoprotein cholesterol
HepG2 cells	Human hepatocellular carcinoma cell line
HR	Heart Rate
hsCRP	High sensitivity CRP
IBG	Independent Biostatistical Group
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC/IRB	Independent Ethics Committee / Institutional Review Board
IFU	Instructions for use
INR	International normalized ratio
IP	Investigational product
IPIM	Investigational Product Instruction Manual
IVRS/IWRS	Interactive Voice Response System / Interactive Web Response System
IV	Intravenous
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LDLR	LDL receptor
LLN	Lower limit of normal
LLOQ	Lower limit of quantitation
LOCF	Last observation carried forward
LOF	Loss of function
Lp(a)	Lipoprotein(a)
MedDRA	Medical dictionary for regulatory activities
Muscle Symptoms	Muscle pain, aches, weakness, cramps
NASH	Nonalcoholic steatohepatitis
NOAEL	No-observed-adverse-effect level
OLE	Open Label Extension

Abbreviation or Term	Definition/Explanation
OLEAS	Open Label Extension Analysis Set
PBO	Placebo
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
PKPD	Pharmacokinetic / pharmacodynamics
PO	Oral administration
Q2W	Q2W is defined as every 2 weeks with a window of \pm 3 days
Q4W	Every 4 weeks, (AMG 145 Background Section)
QD	Each day
QM	QM is defined as every 4 weeks with a window of \pm 7 days
QW	Every week
Randomized	Assignment to treatment group based on computer-generated randomization schedules prepared by Amgen before the start of the study
RAS	Rechallenge Analysis Set
RBC	Red blood cells
RR	Respiratory rate
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SF-36	Short Form (36) Health Survey
Source Data	Information from an original record or certified a copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline (E6)). Examples of source data include Subject ID, Randomization ID, and Stratification Value.
TBL	Total bilirubin
TIA	Transient ischemic attack
Tmax	Time to maximum concentration
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol
WBC	White blood cell

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1. OBJECTIVES

The main strategic objective of this study is to support the Japan LDL-C lowering submission for evolocumab in the setting of statin intolerance. The Pharmaceuticals Medical Devices Agency, Japan (PMDA) considers the Japanese (and East Asian) population to be distinct from the Caucasian population and requires additional data on the use of investigational drugs in their specific population. Further, PMDA has asked for a specific study in the statin intolerant Japanese population. This study will provide Amgen with additional data to support the use of evolocumab for treatment of Japanese hypercholesterolemic subjects that are unable to tolerate an effective dose of a HMG-CoA reductase inhibitor. Protocol 20140234 is a phase 3 study to be conducted in Japan to address the unmet medical need of statin intolerance in this country

Studies 20110116 (GAUSS-2) and 20130332 (GAUSS-3) are global phase 3 studies for statin intolerance that will be supplemented by this proposed protocol.

1.1 Primary

To evaluate the effect of 12 weeks of subcutaneous evolocumab compared with ezetimibe, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in hypercholesterolemic subjects unable to tolerate an effective dose of a statin.

1.2 Secondary

- To evaluate the safety and tolerability of **subcutaneous (SC)** evolocumab, compared with ezetimibe, in hypercholesterolemic subjects unable to tolerate an effective dose of a statin
- To assess the effects of 12 weeks of evolocumab, compared with ezetimibe, on change from baseline in LDL-C, and percent change from baseline in non high density lipoprotein cholesterol (non HDL-C), total cholesterol (TC), apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, ApoB/Apolipoprotein A1 (ApoA1) ratio, lipoprotein(a) [Lp(a)], triglycerides, very low-density lipoprotein cholesterol (VLDL-C), and HDL-C in hypercholesterolemic subjects unable to tolerate an effective dose of a statin
- To assess the effects of 12 weeks SC evolocumab, compared with ezetimibe, on percent of subjects attaining LDL-C < 70 mg/dL (1.8 mmol/L) in hypercholesterolemic subjects unable to tolerate an effective dose of a statin

2. BACKGROUND AND RATIONALE

2.1 Disease

Some individuals are intolerant to statin therapy due to muscle-related side effects ([Franc, Dejager et al, 2003](#), [Bruckert, Hayem et al, 2005](#)). In the literature, terminology used to describe muscle-related side effects can be confusing, therefore in this document the terms described by Pasternak in the ACC/AHA/NHLBI Clinical Advisory on

the Use and Safety of Statins ([Pasternak, Smith et al, 2002](#)) have been adopted: Myopathy - a general term referring to any disease of muscles; Myalgia - muscle ache or weakness without creatine kinase (CK) elevation. Myositis - muscle symptoms with increased CK levels. Rhabdomyolysis - muscle symptoms with marked CK elevation (typically substantially greater than 10 times the upper limit of normal [ULN]) and with creatinine elevation (usually with brown urine and urinary myoglobin).

The fact that statins are uncommonly associated with the development of myopathy is well accepted. The incidence of myopathy is increased under equally well-accepted conditions, such as when the statin is used in combination with drugs such as cyclosporine, fibrates, macrolide antibiotics, certain antifungal drugs, and niacin. Many of these associations relate to the use of drugs that antagonize metabolism through the cytochrome P-450 system, particularly the 3A4 isozyme. While myopathy is rare, a more common adverse event is the development of myalgia, described as non-specific muscle aches or perceptions of weakness that do not involve any increase in CK. In the placebo-controlled clinical trials with statins, the frequency of myalgia has been around 5% and has been very similar between drug and placebo. Nevertheless, many patients believe that their temporally associated myalgia is due to a statin, and it often returns on rechallenge. Other patients can have mild-to-moderate elevations of CK symptoms involving muscle complaints. Again, elevations may be non-specific, but a statin effect often cannot be ruled out.

The PRIMO Study was a French nationwide observational survey of the risk factors and management of muscular side effects in patients receiving high-dosage statin treatment in general practice in France ([Bruckert, Hayem et al, 2005](#)). A total of 7,924 hyperlipidemic patients with age 18 - 75 years who were seen by their general practitioners (GPs) in regular outpatient visits were entered in the study. GPs were asked to include the first three consecutive patients who satisfied the survey inclusion criteria during a period of up to 2 months following initiation of the study. Patients were included if they had been prescribed high-dosage statin treatment (fluvastatin 80 mg; atorvastatin 40 or 80 mg; pravastatin 40 mg; or simvastatin 40 or 80 mg) for at least 3 months prior to the study. Patients were also included if their regimen had been adjusted (statin withdrawal or dose reduction) within the last 3 months due to muscular pain. The risk factor analysis in PRIMO was consistent with the results of a preliminary study ([Franc, Dejager et al, 2003](#)), confirming that a personal or family history of

muscular symptoms, cramps, hypothyroidism and elevated CK levels were major risk factors for muscular symptoms during high-dosage statin therapy.

In the PRIMO study population, 10.5% of patients on high-dosage statin therapy complained of muscle pain, a figure which is considerably higher than that reported previously for clinical trials but which is consistent with anecdotal experiences of practicing physicians. The experience in PRIMO may be more representative than data from large scale placebo controlled studies where patients may have been excluded on the basis of age, diabetes, renal or hepatic impairment or a history of muscular symptoms or CK elevations.

The results of the PRIMO study indicate that muscular symptoms associated with high dosage statin therapy may have a greater impact on the everyday life of patients than was previously thought. Muscular pain was continuous in 25% of patients, while 39% of patients reported using an analgesic for pain relief of their muscular symptoms. Moreover, 38% of patients reported that their muscular symptoms prevented even moderate exertion during everyday activities, while 4% of patients suffered major disruption to their everyday life (being confined to bed or unable to work) due to muscular pain. These findings are of considerable importance, because patients who experience adverse events during statin treatment are more likely to discontinue therapy.

Asian patients frequently have heightened responses to therapeutic drugs, and statins in particular. As a consequence, the recommended drug doses are often lower in Asian countries than in Western countries. Studies have noted higher plasma levels of statins in Asians compared with Caucasians but not an increased safety risk (Wu, Sy et al, 2002). While the dosing of Japanese patients is different from the perspective of the highest dose used, only rosuvastatin is different when compared to American guidelines with respect to the lowest therapeutically effective dose. The below table recommended dose ranges for selected statins in the US and Japan (Saito, Hirata-Koizumi et al, 2005).

Recommended dose ranges for selected statins

Statin	Dose Range (mg/day)	
	Japan	United States
Atorvastatin	10–40	10–80
Fluvastatin	20–60	20–80
Pravastatin	10–20	10–80
Rosuvastatin	2.5–20	5–40
Simvastatin	5–20	5–80
Pitavastatin	1–4	1–4

In summary, while there are anecdotal reports of increased statin intolerance in Asian populations due to increased pharmacokinetic exposure, and Asians appear to display higher plasma levels of rosuvastatin in comparison with Whites ([Lee, Ryan et al, 2005](#)), it is expected that statin intolerance will occur at similar rates as in Caucasian patients. Further, there is an unmet medical need for an effective non-statin agent that will get a significant proportion of Japanese patients to LDL-C goal.

2.2 Amgen Investigational Product Background

Recycling of the hepatic cell surface LDL receptor (LDLR) plays a critical role in the maintenance of cellular and whole body cholesterol balance by regulating plasma LDL-C levels. Recently it has been shown that Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays an important role in the recycling and regulation of LDLR ([Horton et al, 2007](#); [Brown and Goldstein, 2006](#)). PCSK9 is a member of the subtilisin family of serine proteases and is expressed predominantly in the liver, kidney, and intestine ([Zaid et al, 2008](#)). Following secretion, it causes post-translational downregulation of hepatic cell surface LDLR by a mechanism that involves direct binding to the LDLR. Downregulation of hepatic LDLR in turn leads to increased levels of circulating LDL-C. Thus PCSK9 may represent a target for inhibition by novel therapeutics in the setting of dyslipidemia. The rationale for such an approach is available from studies in preclinical models, and from human genetic data that provide strong validation for the role of PCSK9 in modulating LDL-C levels and the incidence of CHD in man. These human studies have identified gain-of-function mutations in the PCSK9 gene that are associated with elevated serum LDL-C levels (> 300 mg/dL [approximately 7.8 mmol/L]) and premature CHD ([Abifadel et al, 2003](#)); and loss-of-function (LOF) mutations that are associated with low serum LDL-C levels (\leq 100 mg/dL [approximately 2.6 mmol/L]) ([Cohen et al, 2005](#)). Strikingly, subjects with

heterozygous LOF mutations exhibit lower serum PCSK9 levels and as much as 88% reduction in the incidence of CHD over a 15-year period compared with noncarriers of the mutations (Cohen et al, 2006). Moreover, despite complete loss of PCSK9 and associated very low serum LDL-C levels (< 20 mg/dL [approximately 0.5 mmol/L]), the 2 subjects who have been identified with compound heterozygote LOF mutations appear healthy (Hooper et al, 2007; Zhao et al, 2006).

Evolocumab is a fully human monoclonal immunoglobulin (Ig) G2 that binds specifically to human PCSK9 and prevents the interaction of PCSK9 with LDLR. Details of the biochemistry, nonclinical pharmacology, nonclinical pharmacokinetics (PK), and nonclinical toxicology with evolocumab are contained in the [Investigator's Brochure, 2016](#). Evolocumab binds to human, monkey, and hamster PCSK9 with high affinity ($K_d < 100$ pM). Evolocumab caused a dose-dependent inhibition of PCSK9 binding to the LDLR and of PCSK9-mediated reduction in low-density lipoprotein (LDL) uptake in HepG2 cells (human hepatocellular carcinoma cell line) in culture. In cynomolgus monkeys and in hamsters, in vivo administration of evolocumab resulted in reduced serum lipoprotein cholesterol levels in a dose-dependent manner. Based on a comprehensive package of PK, pharmacodynamics (PD), and toxicology studies ([Investigator's Brochure, 2016](#)), a program to develop evolocumab as a treatment for dyslipidemia was initiated.

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2.3 Non-Amgen Medicinal Product Background

Ezetimibe 10mg tablets will be provided during study participation. Ezetimibe will be over-encapsulated to maintain blinding.

Ezetimibe is in a class of lipid-lowering compounds that selectively inhibits the intestinal absorption of cholesterol and related phytosterols. Ezetimibe is approved in Japan for treatment of hypercholesterolemia, familial hypercholesterolemia, and homozygous

sitosterolemia. For patients with homozygous familial hypercholesterolemia, ezetimibe should be used as an adjunct to HMG-CoA reductase inhibitor and other lipid-lowering non-pharmacological treatments (eg, LDL apheresis) or when such treatments are unavailable.

In the double blind placebo-controlled study of 100 Japanese hypercholesterolemia patients described in the label with a treatment duration of 12 weeks, LDL-C, total cholesterol, TG were reduced by 18.1%, 12.8% and 2.2%, respectively. HDL-C was increased by 5.9%.

In the ezetimibe clinical studies of 504 Japanese patients described in the label, 18.8% of patients on ezetimibe reported adverse reactions. The most commonly reported adverse reactions were constipation (3.0%), erythema (2.4%), diarrhea (2.2%), abdominal pain (2.0%), abdominal distension (1.6%), and nausea and vomiting (1.6%).

Ezetimibe is contraindicated in the following circumstances: in combination with a statin in patients with severe liver dysfunction and in patients with a known hypersensitivity to ezetimibe.

The recommended dose of ezetimibe is 10 mg once daily, administered after meal.

2.4 Rationale

There is an established unmet medical need in Japan for patients with hypercholesterolemia who experience muscle-related side effects when using statins. Amgen is therefore seeking an indication for the use of evolocumab alone or in combination with a statin or other lipid-lowering therapies in patients with hypercholesterolemia who are statin-intolerant or unable to tolerate an effective dose of a statin.

Subjects on low or atypical statin therapy must be on a stable dose for at least 4 weeks prior to screening and throughout the blinded portion of the study; the dose cannot be adjusted during screening and for the duration of the study.

This design provides a scientifically rigorous study to show the superiority of evolocumab over ezetimibe in Japanese patients who are intolerant to statins. Identified patients will be randomized 2:2:1:1 to QM evolocumab + PO placebo **each day (QD), every 2 weeks (Q2W)** evolocumab + PO placebo QD, QM SC placebo + ezetimibe QD, or Q2W SC placebo + ezetimibe QD for a head to head comparison evolocumab versus ezetimibe.

Long term exposure data will be provided by a 9-month open label extension where all patients will receive evolocumab in the same SC regimen (QM or Q2W) they were randomized to on Day 1.

2.5 Clinical Hypotheses

The primary hypothesis is that evolocumab will be well tolerated and will result in greater reduction of LDL-C than ezetimibe, defined by the mean percent change from baseline at Weeks 10 and 12 and percent change from baseline at Week 12, in Japanese hypercholesterolemic subjects who are intolerant to statins or unable to tolerate an effective dose of a statin.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 3, multicenter, double-blind, randomized, ezetimibe controlled, parallel group study for evolocumab in hypercholesterolemic Japanese subjects unable to tolerate an effective dose of a statin. Subjects who meet all inclusion/exclusion criteria will be randomized with an allocation ratio of 2:2:1:1 into 4 groups: QM 420 mg SC evolocumab + QD PO placebo, Q2W 140 mg SC evolocumab + QD PO placebo, QM SC placebo + QD 10 mg PO ezetimibe, Q2W SC placebo + QD 10 mg PO ezetimibe. Randomization will be stratified by screening LDL-C level and baseline statin use. Randomization should occur within 5 – 10 days of the screening LDL-C evaluation used to determine eligibility. **Subjects on low or atypical statin therapy must be on a stable dose for at least 4 weeks prior to the screening and throughout the blinded portion of the study; the dose cannot be adjusted during screening and for the duration of the study.**

For blinding purposes, every subject will receive investigational product (IP) SC and PO. Patients will be provided with evolocumab or placebo through the use of an autoinjector (AI) or Personal Injector. Depending on availability either a single Personal Injector or 3 autoinjectors will be provided for monthly dosing. A single AI will be used for Q2W dosing. Evolocumab and corresponding placebo will be administered at the study site or at appropriate non-clinic setting per [Table 1](#) (Schedule of Assessments). PO placebo will be available to match PO ezetimibe through over-encapsulation. The SC IP dose frequencies of Q2W and QM will not be blinded.

Following the Week 12 visit, all subjects will self-administer IP in the non-clinic setting; subjects will return to the clinical site at W24, W36, W48 and W52 for subsequent visits.

There will be an end of study phone call at W54 (**Q2W subjects only**) for any potential adverse events, serious adverse events, or adverse device effects.

Central laboratory results of the lipid panel, ApoA1, ApoB, lipoprotein(a), and high sensitivity C-reactive protein (hsCRP) will be blinded during double-blind treatment. Investigators will be provided lipid results starting at week 24 until the end of study for each subject. All lipid results from posttreatment to week 24 will remain blinded until the unblinding of the clinical database.

The study includes collection of biomarker samples, where approved by the institutional review board (IEC/IRB). Administration of PO IP (ezetimibe or placebo) will end with the week 12 visit for all subjects. Following the week 12 visit, subjects should be treated to standard of care in addition to receiving open label evolocumab.

Subjects will be encouraged to complete all planned visits regardless of their adherence to investigational product (IP) administration. Formal review of the accumulating blinded data by an independent Data Monitoring Committee (DMC) **will occur**.

The study endpoints are defined in [Section 10.1.1](#).

3.2 Number of Sites

Approximately 40 sites in Japan will be selected to participate in this study. Additional centers may be added.

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

3.3 Number of Subjects

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

The number of subjects will fulfill the planned sample size of 60 subjects.

3.4 Replacement of Subjects

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

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

Subject participation is anticipated to continue for 12 months (excluding screening period). There will be a 3 month double blind, randomized period with a 9-month open label extension.

3.5.2 End of Study

Primary Completion: defined as the time when all the randomized subjects in the study have either completed the scheduled visits up to and including Week **24** or have early terminated from the study;

End of Trial: defined as the time when all enrolled subjects have either completed the scheduled visits or have early terminated from the study.

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening). Before any study-specific procedure, the appropriate written informed consent must be obtained. **Screening is initiated from the time of obtaining informed consent. The screening period must be completed within 28 days.**

For a full list of eligibility criteria, please refer to [Section 4.1](#).

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria

- 101 Subject who has provided informed consent/assent prior to initiation of any study-specific activities/procedures
- 102 Male or female ≥ 20 to ≤ 80 years of age, **Japanese by self-identification**, at signing of informed consent
- 103 Subject who is not at LDL-C goal as evidenced by the 2012 JAS management category and the following LDL-C levels by central laboratory at screening:
- a) Fasting LDL-C ≥ 100 mg/dL (2.59 mmol/L) for subjects with diagnosed CHD or are CHD risk equivalent or
 - b) Fasting LDL-C ≥ 120 mg/dL (3.37 mmol/L) for subjects without diagnosed CHD or risk equivalent and Management Category III
 - c) Fasting LDL-C ≥ 140 mg/dL (4.14 mmol/L) for subjects without diagnosed CHD or risk equivalent and Management Category II
 - d) Fasting LDL-C ≥ 160 mg/dL (4.9 mmol/L) for subjects without diagnosed CHD or risk equivalent and Management Category I
- 104 Subject must have tried and failed at least 2 statins with failure to at least 1 of the statins at an average daily dose at or below the following doses due to intolerable myopathy, ie, myalgia (muscle pain, ache, or weakness without CK elevation), myositis (muscle symptoms with increased CK levels), or rhabdomyolysis (muscle symptoms with marked CK elevation). For subjects that developed rhabdomyolysis, defined as CK $> 10 \times$ ULN, failure of only 1 statin at any dose is acceptable. **Symptoms must have resolved or improved when statin was discontinued or the dose was reduced.**

- Atorvastatin 10 mg
- Fluvastatin 20 mg
- Pravastatin 10 mg
- Rosuvastatin 2.5 mg
- Simvastatin 5 mg
- Pitavastatin 1 mg
- For unlisted statins, the average daily dose should not exceed the lowest available **recommended** starting dose approved by the **Japanese Ministry of Health, Labour and Welfare**.

105 **Subjects taking bile-acid sequestering resins and/or stanol, stanol esters, low (lowest available recommended starting dose approved by the Japanese Ministry of Health, Labour and Welfare) or atypical dose of statin must be on a stable dose for at least 4 weeks prior to screening. No adjustments to statin (or other lipid lowering therapy) dose are allowed during screening and throughout study.**

EXCEPTION: if subject is on ezetimibe at start of screening it must be discontinued for ≥ 1 week before LDL-C screening

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

4.1.2 Exclusion Criteria

201 History of hemorrhagic stroke

202 Personal or family history of hereditary muscular disorders

203 NYHA III or IV heart failure, or last known left ventricular ejection fraction (LVEF) $< 30\%$

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

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

206 Planned cardiac surgery or revascularization

207 Type 1 diabetes, poorly controlled type 2 diabetes (HbA1c $> 9.0\%$), newly diagnosed type 2 diabetes (within 6 months of randomization), or laboratory evidence of diabetes during screening (fasting serum glucose ≥ 126 mg/dL [7.0 mmol/L] or HbA1c $\geq 6.5\%$) without prior diagnosis of diabetes

208 Uncontrolled hypertension defined as sitting systolic blood pressure (SBP) > 160 mmHg or diastolic BP (DBP) > 100 mmHg

209 Subject has taken in the last 4 weeks prior to LDL-C screening red yeast rice, > 200 mg/day niacin, or prescription lipid-regulating drugs (eg, fibrates and derivatives) other than **low (lowest available recommended starting dose approved by the Japanese Ministry of Health, Labour and Welfare) or atypical dose of statins, ezetimibe, bile-acid sequestering resin, or stanols and stanol esters**

-
- 210 Subject who has taken a cholesterylester transfer protein (CETP) inhibitor in the last 12 months prior to LDL-C screening, such as: anacetrapib, dalcetrapib or evacetrapib
- 211 Treatment in the last 3 months prior to LDL-C screening with any of the following drugs: systemic cyclosporine, systemic steroids (eg, IV, intramuscular [IM], or PO) (Note: hormone replacement therapy is permitted), vitamin A derivatives and retinol derivatives for the treatment of dermatologic conditions (eg, Accutane); (Note: vitamin A in a multivitamin preparation is permitted)
- 212 Uncontrolled hypothyroidism or hyperthyroidism as defined by thyroid stimulating hormone (TSH) < 1.0 time the lower limit of normal or > 1.5 times the ULN, respectively, at screening. Potential subjects with TSH < 1.0 time the lower limit of normal due to thyroid replacement therapy is not considered an exclusion
- 213 Moderate to severe renal dysfunction, defined as an estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m² at screening
- 214 Active liver disease or hepatic dysfunction, defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 times the ULN as determined by central laboratory analysis at screening
- 215 CK > 3 times the ULN at screening
- 216 Known active infection or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction in the judgment of the investigator
- 217 Diagnosis of deep vein thrombosis or pulmonary embolism within 3 months prior to randomization
- 218 Unreliability as a study participant based on the investigator's (or designee's) knowledge of the subject (eg, alcohol or other drug abuse, inability or unwillingness to adhere to the protocol, or psychosis)
- 219 Female subject who has either (1) not used (an) acceptable method(s) of effective birth control (see below) for at least 1 month prior to screening and (2) is not willing to inform her partner of her participation in this clinical study and to use such (an) acceptable method(s) of effective birth control during treatment with SC IP (evolocumab/placebo) and for an additional 15 weeks after the end of treatment with SC IP (evolocumab/placebo), unless the female subject is sterilized or postmenopausal (see below);
- a. A female is considered of childbearing potential unless sterilized or postmenopausal with menopause defined as:
- i. 12 months of spontaneous and continuous amenorrhea in a female ≥ 55 years old, or
 - ii. 12 months of spontaneous and continuous amenorrhea with a follicle-stimulating hormone (FSH) level > 40 IU/L (or according to the definition of "postmenopausal range" for the laboratory involved) in a female < 55 years old, or
 - iii. The subject has undergone bilateral oophorectomy

- b. Acceptable methods of preventing pregnancy include not having intercourse (sexual abstinence), surgical contraceptive methods – (vasectomy of the male partner **[and testing shows there is no sperm in the semen]** or bilateral tubal ligation/occlusion), or use of hormonal birth control methods (pills, patches), intrauterine devices (IUDs), **intrauterine hormonal-releasing system (IUS), male partner uses a condom with or without spermicide, use of a cervical cap, diaphragm, or contraceptive sponge with spermicide**; or two (2) barrier methods (each partner must use one barrier method) with spermicide – males must use condom with spermicide; females must choose either diaphragm with spermicide, OR cervical cap with spermicide, OR contraceptive sponge with spermicide.
- c. Note: If additional medications are given during treatment which may alter the contraceptive requirements (these additional medications may require an increase in the number of contraceptive methods and/or length of time that contraception is to be utilized **and/or length of time breastfeeding is to be avoided** after the last dose of protocol-required therapies) the investigator is to discuss changes with the study subject.

- 220 Subject who is pregnant or breast feeding, or planning to become pregnant or breastfeed during treatment with SC IP (evolocumab/placebo) and/or within 15 weeks after the end of treatment with SC IP (evolocumab/placebo)
- 221 Subject who has previously received evolocumab or any other therapy to inhibit PCSK9
- 222 Subject who has any kind of disorder that, in the opinion of the investigator, may compromise the ability of the subject to give written informed consent and/or to comply with all required study procedures
- 223 Malignancy except non-melanoma skin cancers, cervical or breast ductal carcinoma in situ within the last 5 years
- 224 Subject who has known sensitivity **or intolerance** (eg, allergy or serious adverse reaction to ezetimibe) to any of the products or components to be administered during dosing
- 225 Subject who is likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, Patient Reported Outcomes [PROs]) to the best of the subject and investigator's knowledge
- 226 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion
- 227 Currently enrolled in another investigational device or drug study, or less than 30 days since ending investigational device or drug study(ies), or receiving other investigational agent(s) or procedures

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see [Section 11.2](#)). All subjects must personally sign and date the informed consent form before commencement of study-specific activities/procedures. **Screening is initiated from the time of obtaining informed consent. The screening period must be completed within 28 days.**

A subject is considered enrolled upon randomization. The investigator is to document and date this decision in the subject's medical record and on the enrollment **electronic case report form (eCRF)**.

Each subject who enters into the screening period for the study upon signing informed consent receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned through an interactive voice/web response system (IVRS/IWRS). This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. Subjects who do not meet LDL-C eligibility criteria cannot be rescreened.

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. PPD [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

5.1 Randomization/Treatment Assignment

Subjects will be randomized 2:2:1:1 assignment to 4 treatment groups and will be based on a computer-generated randomization schedule prepared by Amgen before the start of the study. Randomization will be stratified by screening LDL-C concentration (< 180 mg/dL [4.66 mmol/L] vs. ≥ 180 mg/dL) and baseline **statin use**.

The following are treatment groups (2:2:1:1 respectively):

- Evolocumab SC, 420mg QM (3 AI/Pen or one Personal Injector) and PO placebo 10mg QD
- Evolocumab SC, 140mg Q2W (1 AI/Pen) and PO placebo 10mg QD
- Placebo SC 420mg QM (3 AI/Pen or one Personal Injector) and PO ezetimibe 10mg QD
- Placebo SC 140mg Q2W (1 AI/Pen) and PO ezetimibe 10mg QD

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

Please refer to [Section 5.2](#) below for details on when and how the randomization code may be broken. The treatment assignment date is to be documented in the subject's medical record and on the enrollment eCRF.

5.2 Site Personnel Access to Individual Treatment Assignments

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

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

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

6. TREATMENT PROCEDURES

Evolocumab (AMG 145), placebo SC, ezetimibe PO, and placebo PO are IPs in this study. An Investigational Product Instruction Manual (IPIM) containing detailed information regarding the storage, preparation, **destruction**, and administration of IP will be provided separately.

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

The Amgen Investigational Product(s) and/or matched placebo (except if required by local regulation) used in this study include(s): SC evolocumab (AMG 145) and SC Placebo.

The Non-Amgen investigational product(s) used in this study include: PO Ezetimibe 10 mg, and PO Placebo.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, **destruction**, and administration of evolocumab, matched placebo, and over-encapsulated ezetimibe.

The medical device(s) used in this study include(s): Prefilled AI/Pen and Personal Injector.

6.2 Investigational Product

6.2.1 Amgen Investigational Product Evolocumab (AMG 145)

Evolocumab and respective placebo will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical IP distribution procedures.

Evolocumab will be presented as a sterile, preservative-free solution in a single use, disposable, handheld mechanical (spring-based) 1.0 mL prefilled autoinjector/pen (AI/Pen) or 3.5 mL Personal Injector for fixed dose, subcutaneous injection. The prefilled AI/Pen contains a 1.0 mL deliverable volume of 140 mg/mL evolocumab.

The Personal Injector with prefilled cartridge assembly is a single-use, disposable, on-body electro-mechanical injection device that is co-packaged with a prefilled Crystal Zenith (CZ) cartridge assembly containing 3.5 mL deliverable volume of 120 mg/mL evolocumab.

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

The box number of IP (active drug or placebo) is to be recorded on each subject's Drug Administration eCRF.

6.2.1.1 Dosage, Administration, and Schedule

IP will be administered SC (evolocumab or matched placebo) in accordance with instructions in the IPIM. **For visits with IP administration at the study site, administration should be the last procedure to be performed during each visit.** The date and time of evolocumab or placebo will be recorded on the individual subject's worksheet and eCRF. After **the first** IP administration at **the first** dosing visit, subjects should be observed for at least 30 minutes before being discharged.

Details of preparing and administering IP are included in the IPIM provided by Amgen at the start of the study. The dosing schedule is described by a [schema](#) in the protocol synopsis.

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

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

Subjects who are late for a Scheduled Dose of Investigational Product

Administration of IP should occur within the visit window for each scheduled visit. IP must never be administered within less than 7 days of a previous dose. If a subject arrives for a visit and IP was administered within less than 7 days prior the dose should not be administered, but all other study procedures should be conducted. These subjects will receive their next SC IP administration as previously scheduled.

Subjects who miss a Scheduled Dose of Investigational Product Completely

Subjects randomized to SC IP administration (evolocumab or placebo) who completely miss a scheduled visit or IP administration will continue in the study and receive scheduled study drug at the next scheduled visit.

6.2.2 Non-Amgen Investigational Product(s)

Non-Amgen investigational product(s) including ezetimibe 10mg PO and placebo PO will be used in this study.

6.2.2.1 Non-Amgen Investigational Product Ezetimibe

6.2.2.1.1 Dosage, Administration, and Schedule

Ezetimibe 10 mg tablets will be administered orally, once daily, with or without food, at a time convenient to the subject. To enable blinding of the PO IP, ezetimibe will be supplied as over-encapsulated 10 mg tablets.

Ezetimibe 10mg is an approved drug for the treatment of patients with hypercholesterolemia, familial hypercholesterolemia, and homozygous sitosterolemia (ZETIA® [ezetimibe]).

Subjects who miss a dose of ezetimibe will be advised to take the missed dose as soon as they can however subjects should not take more than one dose of ezetimibe per day; subsequent doses will be taken at the usual time. However, if the next scheduled dose would be due in less than 12 hours, the subject will be advised to omit the missed dose entirely and to take the next dose at the normal time. Consult the IPIM for additional information on ezetimibe.

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

No dosage adjustment is necessary in patients with mild hepatic or renal impairment. No dosage adjustment is necessary in geriatric patients. Additional details regarding ezetimibe are provided in the IPIM.

6.3 Hepatotoxicity Stopping and Rechallenge Rules

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

6.3.1 Criteria for Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Amgen investigational product and other protocol required therapies should be discontinued permanently and the subject should be followed according to the recommendations in [Appendix A](#) (Additional Safety Assessment Information) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:

- TBL > 2x upper limit of normal (ULN) or INR > 1.5
- AND increased AST or ALT from the relevant baseline value as specified below:

Baseline AST or ALT value	AST or ALT elevation
< ULN	> 3x ULN

- AND no other cause for the combination of the above laboratory abnormalities is immediately apparent; important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:
 - Hepatobiliary tract disease
 - Viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, toxoplasmosis, and Parvovirus)
 - Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia.
 - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
 - Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
 - Alpha-one antitrypsin deficiency
 - Alcoholic hepatitis
 - Autoimmune hepatitis
 - Wilson's disease and hemochromatosis
 - Nonalcoholic Fatty Liver Disease including Steatohepatitis (NASH)
 - Non-hepatic causes (eg, rhabdomyolysis, hemolysis)

6.3.2 Criteria for Conditional Withholding of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent discontinuation of Amgen investigational product outlined above and have no underlying liver disease, and eligibility criteria requiring normal transaminases and TBL at baseline or subjects with underlying liver disease and baseline abnormal transaminases, the following rules are recommended for withholding of Amgen investigational product and other protocol-required therapies:

- Elevation of either AST or ALT according to the following schedule:

Baseline AST or ALT value	AST or ALT elevation
Any	> 8x ULN at any time
Any	> 5x ULN but < 8x ULN for ≥ 2 weeks
Any	> 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule
Any	> 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice).

- OR: TBL > 3x ULN at any time
- OR: ALP > 8x ULN at any time>>

Evolocumab should be withheld pending investigation into alternative causes of DILI. If investigational product(s) is withheld, the subject is to be followed according to recommendations in [Appendix A](#) for possible DILI. Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline ([Section 6.3.3](#)).

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

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

If signs or symptoms recur with rechallenge, then evolocumab should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in [Section 6.3.1](#)) should never be rechallenged.

6.4 Concomitant Therapy, Diet, and Exercise

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

Subjects should maintain their current regimen of diet and exercise. Subjects will be required to refrain from unaccustomed intensive exercise (eg, heavy lifting or long runs) 48 hours prior to each visit.

6.5 Medical Devices

Amgen SC IP (evolocumab/placebo) will be administered per prefilled AI/Pen or 3.5 mL Personal Injector, provided by Amgen. Additional details regarding the use of the AI/Pen or Personal Injector is provided in the IPIM and in the Instructions for Use (IFU) brochure. **Other medical devices** (eg, syringes, sterile needles, alcohol prep pads), **which are not considered test articles, may be used in the conduct of this study as part of standard care. These devices** are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

6.6 Product Complaints, Including Device 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 or device after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. **This includes any drug(s), device(s), or combination product(s) provisioned and/or repackaged/modified by Amgen. Drugs or devices include evolocumab/placebo, prefilled AI/Pen, and Personal Injector.**

Concerns or irregularities about the packaging, appearance or usage of the prefilled AI/Pen or Personal Injector must be reported to Amgen within 24 hours of discovery or notification of the concern or irregularity. Should any such concerns or irregularities occur please do not use the prefilled AI/Pen or Personal Injector until Amgen confirms that it is permissible to use.

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

- broken container or cracked container,
- subject or healthcare provider cannot appropriately use the product despite training (eg, due to malfunction of the prefilled AI/Pen or Personal Injector),

- missing labels, illegible labels, incorrect labels, and/or suspect labels,
- change in IP appearance, for example color change or visible presence of foreign material,
- unexpected quantity or volume, for example amount of fluid in the prefilled AI/Pen or Personal Injector, or
- evidence of tampering or stolen material.

If possible, please have the prefilled AI/Pen or Personal Injector available for examination when making a product complaint. Maintain the prefilled AI/Pen or Personal Injector at appropriate storage conditions until further instructions are received from Amgen.

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

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

6.7 Excluded Treatments and/or Procedures During Study Period

The following treatments are not permitted during the study:

- Prescription lipid regulating medications (eg, non-study ezetimibe, or fibrates and derivatives)
- **However, the following agents are allowed:**
 - bile-acid sequestering resin
 - stanol and stanol esters
 - **Please note: subjects on a low (lowest available recommended starting dose approved by the Japanese Ministry of Health, Labour and Welfare) or atypical dose of statins may continue their current dose if the subject has taken it for at least 4 weeks prior to the screening; new statin initiations, and/or dose adjustments are not permitted during screening or the study itself.**
- Red yeast rice, niacin > 200 mg per day
- Any other drug that significantly affects lipid metabolism (eg, systemic cyclosporine, systemic steroids [IV, IM, or PO] (*Note: hormone replacement therapy is permitted, vitamin A derivatives and retinol derivatives for the treatment of dermatologic conditions [eg, Accutane]*). Vitamin A as part of a multivitamin preparation is permitted.

- Prescribed amphetamines, or amphetamine derivatives, and weight loss medications.

Should there be a clinical need to prescribe one of these treatments, the investigator should call the Amgen Medical Monitor to discuss.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Table 1. Schedule of Assessments

Study Day / Timepoint	Screening & Placebo Run-in	D1 Visit	W2 Visit	W4	W6	W8 Visit	W10 Visit	W12 Visit	W24 Visit	W36 Visit	W48 Visit	W52 Visit	W54 ⁱ EOS Phone Call
General Procedures													
Informed consent	X												
Medical history	X												
Vital Signs (sitting BP, HR, RR, Temp)	X	X				X	X	X	X	X	X	X	
Review for AE/SAE/ADE ^a	X	X	X			X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X			X	X	X	X	X	X	X	X
Dietary instruction	X	X	X			X	X	X					
Physical exam	X							X				X	
Body weight, waist circumference	X											X	
Body height	X												
SF-36		X						X					
Randomization		X											
Central Laboratory													
Fasting lipids ^b	X	X	X			X	X	X	X	X	X	X	
ApoA1, ApoB, Lp(a)		X					X	X	X	X	X	X	
PK, PCSK9		X	X				X	X				X	
Chemistry ^c Hematology ^d	X	X				X		X				X	
hsCRP		X						X				X	
HbA1c	X							X				X	
TSH	X												
Biomarkers (blood)		X						X				X	
Anti-evolocumab antibodies		X						X				X	
HCV antibodies	X												
HCV viral load (only HCV positive patients)		X						X				X	
Serum pregnancy; FSH	X							X				X	
Urine pregnancy^e		X	X			X	X	X					
Urinalysis ^f	X	X						X				X	
SC Placebo Run-in	X												
Q2W SC IP on-site		X	X			X	X	X					
Q2W SC IP non-clinic setting ^g				X	X				X	X	X		
Q2W IP Dispensation/Accountability		X	X			X	X	X	X	X	X	X	
QM SC IP on-site		X				X		X					
QM SC IP non-clinic setting ^h				X					X	X	X		
QM IP Dispensation/Accountability		X	X			X		X	X	X	X	X	
PO IP Dispensation/Accountability		X	X			X	X	X					

Footnotes defined on next page of the table

^a **Review for adverse events, serious adverse events, and adverse device effects. Adverse events possibly related to study procedures, adverse device effects, and serious adverse events** are collected **during the screening period** from signing of the ICF through 30 days post last dose of IP or EOS, whichever is later.

^b Fasting lipids: Total cholesterol, HDL-C, LDL-C, Triglycerides, VLDL-C, non-HDL-C.

^c Chemistry: Sodium, Potassium, Chloride, Bicarbonate, Total protein, Albumin, Calcium, Magnesium, Phosphorus, Fasting Glucose, BUN or Urea, Creatinine, Uric acid, Total bilirubin, Direct bilirubin, CK, Alk phos, LDH, AST (SGOT), ALT (SGPT).

^d Hematology: RBC, Hemoglobin, Hematocrit, MCV, MCH, MCHC, RDW, WBC, Platelets

^e Prior to on-site SC IP administration, **female** subjects of childbearing potential should have urine pregnancy test performed.

^f Urinalysis: Specific gravity, pH, Blood, Protein, Glucose, Bilirubin, WBC, RBC, Epithelial cells, Bacteria, Casts, Crystals.

^g Subjects on Q2W dosing will continue non-clinic setting injections after the Week 12 visit per dosing regimen.

^h Subjects on QM dosing will continue non-clinic setting injections after the Week 12 visit per dosing regimen.

ⁱ **For Q2W subjects only.**

7.2 General Study Procedures

Written informed consent must be obtained and will be implemented before protocol specific procedures are carried out. The risks and benefits of participating in the study will be verbally explained to each potential subject prior to entering into the study. The study includes collection of biomarker samples, where approved by the independent ethics committee and/or institutional review board (IEC/IRB) . If IP is administered during a study visit, administration should occur after completion of vital signs and blood draw procedures, as applicable.

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

The Analyte Listing below outlines the specific analytes for serum chemistry, hematology, urinalysis, and other testing to be conducted.

Analyte Listing

Chemistry

Sodium
Potassium
Chloride
Bicarbonate
Total protein
Albumin
Calcium
Magnesium
Phosphorus
Fasting Glucose
BUN or Urea
Creatinine
Uric acid
Total bilirubin
Direct bilirubin
CK
Alk phos
LDH
AST (SGOT)
ALT (SGPT)

Urinalysis

Specific gravity
pH
Blood
Protein
Glucose
Bilirubin
WBC
RBC
Epithelial cells
Bacteria
Casts
Crystals

Hematology

RBC
Hemoglobin
Hematocrit
MCV
MCH
MCHC
RDW
WBC
Platelets

Other Labs

Fasting lipids

- Total cholesterol
- HDL-C
- LDL-C
- Triglycerides
- VLDL-C
- non-HDL-C

ApoA1
ApoB
hsCRP
LP(a)
Anti-evolocumab antibodies
PCSK9
HbA1c
Pregnancy test (females of childbearing potential)
FSH (if needed per [exclusion 219](#))
TSH
PK & biomarkers
HCV antibody*
HCV viral load**

*HCV antibodies are measured before initiating treatment with investigational product in subjects at high risk for HCV infection and in subjects with ALT or AST > 2x ULN at any time during screening. **Conditions that may place subjects at high risk for HCV infection include the following:**

- Ever injected illegal drugs
- Received clotting factors made before 1987
- Received blood/organs before July 1992 or were exposed to blood known to be infected with HCV
- Were ever on chronic hemodialysis
- Are known to be infected with HIV
- Have a known HCV-infected sexual partner

**Viral load will be tested at the time points indicated in Schedule of Assessments, only in subjects who are positive for HCV.

Some laboratory results may inadvertently unblind investigators to treatment assignment to evolocumab. Central laboratory results of the lipid panel, ApoA1, ApoB, Lp(a), and hsCRP posttreatment to week 24 will not be reported to the investigator until the unblinding of the clinical database. Investigators should not perform non-protocol testing of these analytes during a subject's study participation from first administration of IP until at least 24 weeks after the subject's first blinded IP administration. Investigators will be informed if triglycerides are > 1000 mg/dL (11.3 mmol/L) so that appropriate subject follow-up can be initiated.

7.2.1 Placebo Run-in

In order to reduce the burden of unnecessary procedures on subjects who subsequently elect not to participate in the study or continue with study procedures, all subjects will enter a placebo run-in period to confirm tolerance of SC administration prior to randomization. This placebo run-in period can be started before or after venipuncture procedures for the study and will consist of SC administration of placebo consisting of the AI/Pen. This administration will follow the same procedures as injections of IP using the AI/Pen during the treatment period. Further details will be provided in the IPIM.

7.2.2 Screening Enrollment and/or Randomization

The following procedures are to be completed during the screening period of subjects at time points designated in the Schedule of Assessments:

- Informed Consent Form signed
- Medical history
- Vital signs (eg, sitting blood pressure, heart rate, respiratory rate, temperature)
- Review for **adverse events, serious adverse events, and adverse device effects**. **Adverse events** possibly related to study procedures, **adverse device effects**, and **serious adverse events** are collected during the screening period from signing of the ICF
- Documentation of concomitant medications
- Dietary instruction: subject will be counseled on the importance of maintaining a "heart-healthy" diet throughout the course of the study; medication compliance reminder
- Physical exam
- Body height
- Body weight and waist circumference
- Central Laboratory Assessments (**as per Schedule of Assessments**):
 - Blood draw for fasting lipids (≥ 9 hour fasting sample), chemistry (including fasting glucose), CK, hematology, HbA1c, TSH, (Note: eGFR will be calculated by the central laboratory and will be provided to the site for eligibility)

determination), blood draws for hepatitis C virus (HCV) antibodies in subjects at high risk for, or with history of, HCV infection and in subjects with AST or ALT > 2x ULN at any time during screening, serum FSH (only if required to ensure menopause in a female subject by central laboratory)

- Serum pregnancy (females of childbearing potential only)
- Urine sample for urinalysis
- **Subject instruction on self-administration of evolocumab for AI/Pen or Personal Injector**
- AI/Pen placebo injection (does not need to be repeated for rescreening)

7.2.3 Treatment

7.2.3.1 Visit Day 1 (Randomization)

The following procedures should be conducted at this visit for all subjects unless specified otherwise.

- Vital signs (eg, sitting blood pressure, heart rate, respiratory rate, temperature)
- Review for **adverse events, serious adverse events, and adverse device effects**
- Documentation of concomitant medications
- Provide dietary instruction: subject will be counseled on the importance of maintaining a “heart-healthy” diet throughout the course of the study; medication compliance reminder
- Randomization treatment assignment via IVR/IWR system
- Urine pregnancy test (for **female** subjects of childbearing potential only): **precedes on-site SC IP administration**
- SF-36
- Central Laboratory Assessments as Per Schedule of Assessments
- Anti-evolocumab Antibodies
- HCV viral load (only HCV positive individuals)
- **Subject instruction on self-administration of evolocumab for AI/Pen or Personal Injector**
- SC IP administration on-site under site staff supervision (all subjects)
- PO IP dispensing

7.2.3.2 Visit/Week 2

The following procedures should be conducted at this visit for all subjects unless specified otherwise (\pm 3 days).

- Review for **adverse events, serious adverse events, and adverse device effects**
- Documentation of concomitant medications
- Provide dietary instruction: subject will be counseled on the importance of maintaining a “heart-healthy” diet throughout the course of the study; medication compliance reminder

- Central Laboratory Assessments as Per Schedule of Assessments
- **Urine pregnancy test (for female subjects of childbearing potential only): precedes on-site SC IP administration**
- PO IP tablet count
- SC IP dispensing with instructions for use at week 4 (all subjects) and week 6 (Q2W subjects only)
- **Subject instruction on self-administration of evolocumab for AI/Pen or Personal Injector**
- SC IP administration on-site (Q2W subjects only)
- PO IP dispensing

7.2.3.3 Week 4

The following procedure will be performed in a non-clinic setting, eg, self-administration by the subject in the non-clinic setting (\pm 3 days):

- Administration of SC IP

7.2.3.4 Week 6 (Subjects on Q2W SC IP Only)

The following procedure will be performed in a non-clinic setting, eg, self-administration by the subject in the non-clinic setting (\pm 3 days):

- Administration of SC IP to subjects randomized to Q2W SC IP

7.2.3.5 Visit/Week 8

The following procedures will need to be conducted at this visit for all subjects unless specified otherwise (\pm 3 days).

- Vital signs (eg, sitting blood pressure, heart rate, respiratory rate, temperature)
- Review for **adverse events**, **serious adverse events**, **and adverse device effects**
- Documentation of concomitant medications
- Provide dietary instruction: subject will be counseled on the importance of maintaining a “heart-healthy” diet throughout the course of the study; medication compliance reminder
- Central Laboratory Assessments as Per Schedule of Assessments
- **Urine pregnancy test (for female subjects of childbearing potential only): precedes on-site SC IP administration**
- PO IP tablet count
- SC IP administration on-site (all subjects)
- PO IP dispensing

7.2.3.6 Visit/Week 10

The following procedures will need to be conducted at this visit for all subjects unless specified otherwise (\pm 3 days).

- Vital signs (eg, sitting blood pressure, heart rate, respiratory rate, temperature)
- Review for **adverse events**, **serious adverse events**, **and adverse device effects**
- Documentation of concomitant medications
- Provide dietary instruction: subject will be counseled on the importance of maintaining a “heart-healthy” diet throughout the course of the study; medication compliance reminder
- Central Laboratory Assessments as Per Schedule of Assessments
- **Urine pregnancy test (for female subjects of childbearing potential only): precedes on-site SC IP administration**
- PO IP tablet count
- SC IP administration on-site (Q2W subjects only)
- SC IP dispensing (if applicable)
- **PO IP dispensing**

7.2.3.7 Visit/Week 12

The following procedures will need to be conducted at this visit for all subjects unless specified otherwise (\pm 3 days).

- Vital signs (eg, sitting blood pressure, heart rate, respiratory rate, temperature)
- Review for **adverse events**, **serious adverse events**, **and adverse device effects**
- Documentation of concomitant medications
- Provide dietary instruction: subject will be counseled on the importance of maintaining a “heart-healthy” diet throughout the course of the study; medication compliance reminder
- Physical exam
- SF-36
- Central Laboratory Assessments as Per Schedule of Assessments
- **Urine pregnancy test (for female subjects of childbearing potential only): precedes on-site SC IP administration**
- PO IP tablet count
- SC IP dispensing (subjects will continue with the previously assigned dosing regimen of Q2W or QM)
- Remind patients to discontinue blinded oral IP
- SC IP administration on-site (all subjects)

7.2.3.8 Visit/Week 24

The following procedures will need to be conducted at this visit for all subjects unless specified otherwise (± 3 days).

- Vital signs (eg, sitting blood pressure, heart rate, respiratory rate, temperature)
- Review for **adverse events**, **serious adverse events**, **and adverse device effects**
- Documentation of concomitant medications
- Central Laboratory Assessments as Per Schedule of Assessments
- SC IP dispensing (subjects will continue with the previously assigned dosing regimen of Q2W or QM)

7.2.3.9 Visit/Week 36

The following procedures will need to be conducted at this visit for all subjects unless specified otherwise (± 3 days).

- Vital signs (eg, sitting blood pressure, heart rate, respiratory rate, temperature)
- Review for **adverse events**, **serious adverse events**, **and adverse device effects**
- Documentation of concomitant medications
- Central Laboratory Assessments as Per Schedule of Assessments
- SC IP dispensing (subjects will continue with the previously assigned dosing regimen of Q2W or QM)

7.2.3.10 Visit/Week 48

The following procedures will need to be conducted at this visit for all subjects unless specified otherwise (± 3 days).

- Vital signs (eg, sitting blood pressure, heart rate, respiratory rate, temperature)
- Review for **adverse events**, **serious adverse events**, **and adverse device effects**
- Documentation of concomitant medications
- Central Laboratory Assessments as Per Schedule of Assessments
- SC IP dispensing (subjects will continue with the previously assigned dosing regimen of Q2W or QM)

7.2.3.11 Visit/Week 52

The following procedures will need to be conducted at this visit for all subjects unless specified otherwise (± 3 days).

- Vital signs (eg, sitting blood pressure, heart rate, respiratory rate, temperature)
- Review for **adverse events**, **serious adverse events**, **and adverse device effects**
- Documentation of concomitant medications
- Physical exam

- Body weight and waist circumference
- Central Laboratory Assessments as Per Schedule of Assessments
- SC IP accountability

7.2.4 Safety Follow-up / End of Study Phone Call/Week 54 (\pm 3 days)

- Review for adverse events, serious adverse events, and adverse device effects (Q2W subjects only)
- Documentation of concomitant medications (Q2W subjects only)

7.2.5 Standardization of Study Procedures

7.2.5.1 Measurement of Vital Signs

The following measurements must be performed: Systolic/Diastolic Blood Pressure, Heart Rate, Respiratory Rate, and Temperature.

Subject must be in a seated and calm state for at least 5 minutes before blood pressure assessments are conducted. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign eCRF.

Record all measurements on the vital signs eCRF.

7.2.5.2 Waist Circumference

Subjects should wear minimal clothing to ensure that the measuring tape is correctly positioned. Subjects should stand erect with the abdomen relaxed, arms at the sides, feet together and with their weight equally divided over both legs. To perform the waist measurement, the lowest rib margin is first located and marked with a pen. The iliac crest is then palpated in the midaxillary line, and also marked. It is recommended to apply an elastic tape horizontally midway between the lowest rib margin and the iliac crest, and tie firmly so that it stays in position around the abdomen about the level of the umbilicus. The elastic tape thus defines the level of the waist circumference, which can then be measured by positioning the measuring tape over the elastic tape. Subjects are asked to breathe normally, and to breathe out gently at the time of the measurement to prevent them from contracting their muscles or from holding their breath. Measurements should be performed using the same procedure throughout the study. The reading is taken to the nearest centimeter or $\frac{1}{2}$ inch and entered in the source document.

7.2.5.3 Lipid Measurements

Only the screening LDL-C concentration will be reported to the site for the eligibility decision. For subjects who are rescreened, data from the first screening period will not be used for the analysis. Central laboratory results of the lipid panel, as well as ApoA1, ApoB, lipoprotein(a), and high sensitivity C-reactive protein (hsCRP) will be blinded

posttreatment to week 24 until unblinding of the clinical database. Investigators will be provided lipid results starting at week 24 until the end of study for each subject. If a lipid panel is drawn, all reasonable steps must be undertaken to avoid informing the subject and study personnel of the results.

7.3 Antibody Testing Procedures

All subjects who have received at least one administration of evolocumab will have samples assayed for binding antibodies. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity and presence of immune complexes. Additional blood samples may be obtained to rule out anti-evolocumab antibodies during the study.

Subjects who test positive for neutralizing antibodies to evolocumab at the final scheduled study visit will be asked to return for additional follow-up testing. This testing should occur approximately every 12 weeks starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable or (2) the subject has been followed for a period of at least 1 year (\pm 4 weeks). More frequent testing (eg, every 4 weeks), or testing for a longer period of time may be requested in the event of safety-related concerns. Follow-up testing will not be required where it is established that the subject did not receive evolocumab.

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

7.4 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Biomarker development can be useful in developing markers to identify disease subtypes, guide therapy, and/or predict disease severity.

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It is not possible at this stage to anticipate what these advances will be; however, considerable benefit could accrue to future sufferers of coronary artery disease if these markers can be correlated with the data from the study. It is also important to clarify any potential drug interactions in this population of subjects who will be on a number of other drugs.

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

Blood Samples

Blood samples are to be collected for biomarker development. CCI [REDACTED]

[REDACTED]

7.5 Sample Storage and Destruction

Samples and any other components from the cells may be stored for up to 20 years from the end of the study to research scientific questions related to hypercholesterolemia, metabolic disorders, and/or evolocumab. The subject retains the right to request that the sample material be destroyed at any time by contacting the principal investigator. The sponsor will be the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the principal investigator or at the end of the storage period or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample).

Following the request from the subject, the principal investigator will provide the sponsor with the required study and subject numbers so that any remaining plasma and blood samples and any other components from the cells can be located and destroyed. If a commercial product is developed from this research project, the sponsor will own the commercial product. The subject will have no commercial rights to such product and will have no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. Any blood (eg, biomarker) sample collected according to the Schedule of Assessments can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to

the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the PCSK9 inhibition, the dose response and/or prediction of response to evolocumab or anti-evolocumab antibodies, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of 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.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

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

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

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

8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with [Section 12.1](#).

8.3 Reasons for Removal From Treatment, or Study

8.3.1 Reasons for Removal From Treatment

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

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

- death
- lost to follow-up
- decision by Sponsor (other than subject request, safety concern, lost to follow-up)

8.3.2 Reasons for Removal From Study

- Reasons for removal of a subject from the study are:
 - decision by sponsor
 - withdrawal of consent from study
 - death
 - lost to follow-up

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of Adverse Events

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

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than would be expected, and/or has an association with a significantly worse outcome than expected. A pre-existing condition that has not worsened more than anticipated (ie, more than usual fluctuation of disease) during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study is not considered an adverse event.

Resolution of the adverse event will be captured using the applicable eCRF.

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

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies

or the study due to an adverse event, refer to [Section 8.1](#) for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

9.1.2 Definition of Serious Adverse Events

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

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

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

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

9.2 Reporting of Adverse Events

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

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after enrollment and all adverse events possibly related to study procedures **and all adverse device effects** from signing of the informed consent through the safety follow-up/end of study (End of Study Phone Call) are reported using the applicable eCRF (eg, Event **eCRF**).

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Severity [and/or toxicity per protocol],

- Assessment of relatedness to SC IP (evolocumab or placebo), PO IP (ezetimibe or placebo), Amgen medical device(s): prefilled Autoinjector/Pen (AI/Pen) or 3.5 mL Personal Injector and
- Action taken

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE). The grading scale used in this study is described in [Appendix A](#). The investigator must assess whether the adverse event is possibly related to SC IP (evolocumab or placebo) or PO IP (ezetimibe or placebo). This relationship is indicated by a “yes” or “no” response to the question: Is there a reasonable possibility that the event may have been caused by SC IP or PO IP? **Relatedness means that there are facts or reasons to support a relationship between IP and the event.**

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

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

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

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

9.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 days after the last day of the dosing interval of investigational product(s) or end of study, whichever is later, are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the applicable eCRF.

The serious adverse event must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the applicable eCRF (eg, the Safety Report Form). If the electronic data capture (EDC) system is unavailable to the site staff to report the Serious Adverse Event, the information is to be reported to Amgen via an electronic Serious Adverse Event (eSAE) Contingency Report Form within 24 hours of the investigator's knowledge of the event. See [Appendix B](#) for a sample of the electronic Serious Adverse Event Contingency Report Form. For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via the eSerious Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

The investigator must assess whether the serious adverse event is possibly related to SC IP (evolocumab or placebo) or PO IP (ezetimibe or placebo). This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by SC IP or PO IP? **Relatedness means that there are facts or reasons to support a relationship between IP and the event.**

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

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

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

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

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

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

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

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

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

After the protocol-required reporting period defined above **or after end of study**, the investigator does not need to actively monitor subjects for serious adverse events. However, if the investigator becomes aware of a serious adverse event after this protocol required reporting period **or after end of study**, the investigator will report the event to Amgen within 24 hours following the investigator's knowledge of the event.

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

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 (eSAE Contingency Report Form).

9.3 Pregnancy and Lactation Reporting

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

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

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

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

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

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of **evolocumab** through an additional 15 weeks after the end of treatment with **evolocumab**, report the lactation case to Amgen, as specified below.

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

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

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

Co-Primary Endpoints:

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

Co-Secondary Efficacy Endpoints:

Co-secondary endpoints of the means at weeks 10 and 12 and at week 12 for:

Tier 1

- Change from baseline in LDL-C
- LDL-C response (LDL-C < 70 mg/dL [1.8 mmol/L])
- Percent change from baseline in total cholesterol
- Percent change from baseline in non-HDL-C
- Percent change from baseline in ApoB
- Percent change from baseline in the total cholesterol/HDL-C ratio
- Percent change from baseline in ApoB/ApoA1 ratio

Tier 2

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

Tertiary Efficacy Endpoints

- Mean percent change from baseline in ApoA1 at weeks 10 and 12
- Percent change from baseline in ApoA1 at week 12

Exploratory Endpoints

- Subject incidence of non-coronary revascularization
- Observed values, change and percent change from baseline at each scheduled visit in each of the following parameters:
 - LDL-C
 - Total cholesterol
 - non-HDL-C
 - ApoB
 - Total cholesterol/HDL-C ratio

- ApoB/ApoA1 ratio
- VLDL-C
- HDL-C
- ApoA1
- Triglycerides
- Lp(a)
- hsCRP at each scheduled assessment
- PCSK9 change from baseline at each scheduled assessment

Safety Endpoints

- Subject incidence of adverse events
- Safety laboratory values at each scheduled visit
- Incidence of anti-evolocumab antibody (binding and neutralizing) formation

Pharmacokinetics Endpoints

- Serum concentration of evolocumab at selected time points

10.1.2 Analysis Sets

Full Analysis Set

The full analysis set (FAS) includes all randomized subjects who received at least 1 dose of IP in the double blind treatment period. This analysis set will be used in both efficacy and safety analyses for the double blind treatment period.

Generally, in efficacy analyses, subjects will be grouped according to their randomized treatment group assignment and by pooled treatment. In safety analyses, subjects will be grouped according to their randomized treatment group assignment with the exception: if a subject receives treatment throughout the study is different than the randomized treatment group assignment, then the subject will be grouped by the actual treatment group.

Completer Analysis Set

The completer analysis set (CAS) includes subjects in the FAS who adhered to the scheduled IP in the double blind treatment period and have observed values for the co-primary endpoints.

Open Label Extension Period Analysis Set

The open label extension period analysis set (OLEAS) includes subjects in the FAS who received at least 1 dose of evolocumab in the open label extension period. This analysis set will be used in both efficacy and safety analyses for the open label extension period.

10.1.3 Covariates and Subgroups

Baseline covariates include, but are not limited to:

- Stratification factors:
 - Screening LDL-C level: < 180 mg/dL [4.7 mmol/L] vs. ≥ 180 mg/dL
 - Baseline statin use: yes vs. no

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

- Age: < 65 years, ≥ 65 years; < 75 years, ≥ 75 years
- Sex
- LDL-C: < baseline median, ≥ baseline median
- PCSK9 level: < baseline median, ≥ baseline median
- Baseline lipid regulating medications use: yes vs. no

10.2 Sample Size Considerations

The planned sample size for the comparison between evolocumab and ezetimibe is 40 (20 in Q2W and QM each) and 20 subjects (10 in Q2W and QM each), respectively (60 total). The primary analysis will require the 2-sided tests of each co-primary endpoint to be significant at a level of 0.05. From the global phase 3 study 20110116, the treatment effect of evolocumab compared to ezetimibe for reduction from baseline in LDL-C at week 12 is at least 37.6% (32.9%, 42.2%) and for the mean of week 10 and 12, 36.9% (31.6%, 42.3%). Assuming 5% of randomized subjects do not receive any IP and with a common standard deviation (SD) of approximately 20%, this study has at least 93% power to detect a treatment effect of 20% or greater reduction for each of the co-primary endpoints in testing the superiority of evolocumab over ezetimibe, based on a two-sided t-test with significance level 0.05.

As the co-primary endpoints are correlated, there is at least 85% (93% x 93%) power to detect significant treatment effects of the co-primary endpoints. The power calculation is derived using nQuery version 7.01.

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Unblinding and potentially unblinding information should not be distributed to the study team, investigators or subjects prior to the study being formally unblinded except as specified (eg, [Section 5.2](#) and [Section 9.2.2](#)).

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

10.4 Planned Analyses

10.4.1 Data Monitoring Committee (DMC)

An external independent DMC has been established to formally review the accumulating data from this and other completed and ongoing studies with evolocumab to ensure there is no avoidable increased risk for harm to subjects. The independent DMC is chaired by an external academic cardiologist who is an expert in lipids and clinical trials. Analyses for the DMC are provided by the Independent Biostatistical Group (IBG), which is external to Amgen. Details are provided in the DMC charter.

10.4.2 Primary Analysis

To evaluate efficacy and safety of 12 weeks of evolocumab compared with ezetimibe **and summarize 12 weeks of data from the open-label extension (weeks 12 to 24)**, the primary analysis will be performed when all the randomized subjects in the study have either completed the scheduled visits up to and including Week **24** or have early terminated from the study. At that time, the database of the study will be cleaned, processed and a snapshot will be taken; the study will also be unblinded.

10.4.3 Final Analysis

The final analysis will be conducted when all enrolled subjects have either completed the scheduled visits or have early terminated from the study. At that time, the database of study will be cleaned, processed and a snapshot will be taken. The long-term safety and efficacy of evolocumab will be assessed.

10.5 Planned Methods of Analysis

10.5.1 General Considerations

Based on the snapshot for the primary analysis, efficacy and safety analyses will be performed on the FAS. Unless otherwise specified, the FAS will be the default analysis set for the primary analysis and data will be summarized by randomized treatment group assignment and by pooled frequency for evolocumab and pooled ezetimibe. The **treatment effect** of evolocumab **compared** to ezetimibe will be **evaluated** for all efficacy endpoints **through the Week 12 visit. In addition, descriptive analyses from the open-label extension (weeks 12 to 24) will be performed on OLEAS.**

Based on the snapshot for the final analysis, long-term efficacy and safety analyses will be performed on OLEAS and the analyses will be descriptive.

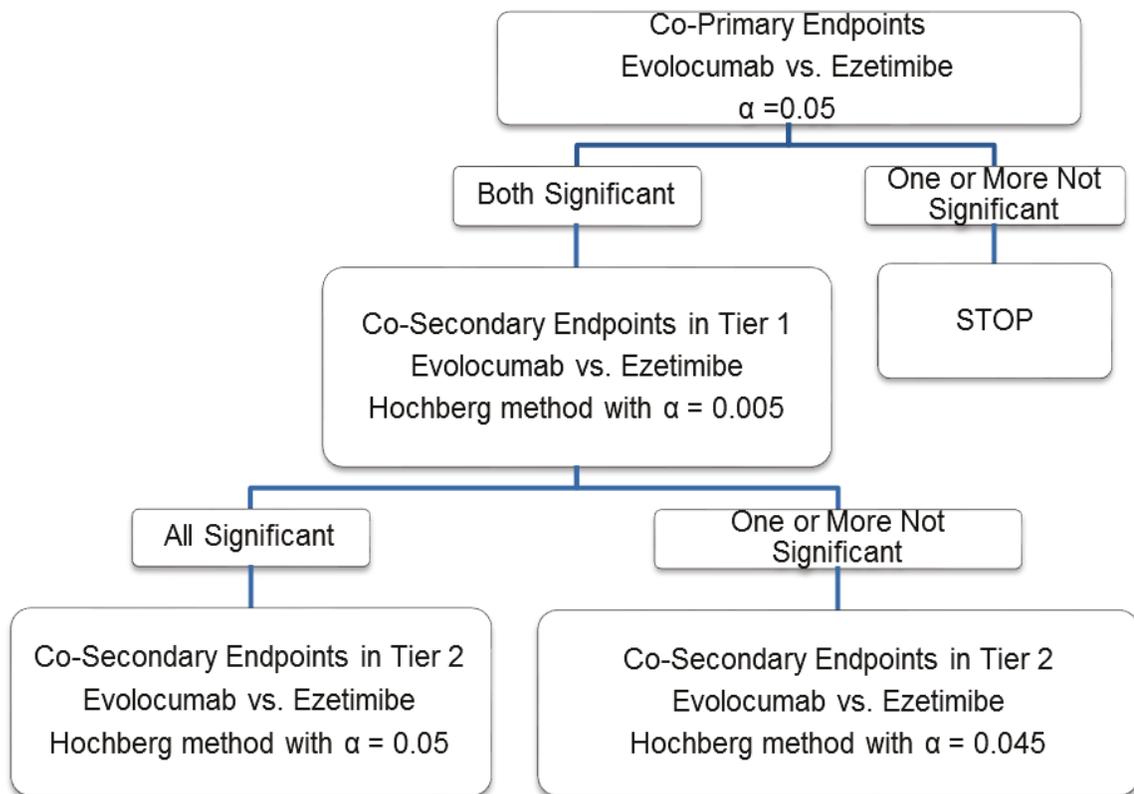
Subject disposition, demographics, baseline characteristics, and exposure to IP will be summarized.

Summary statistics for continuous variables will include the number of subjects, mean, median, Q1, Q3, standard deviation or standard error, minimum, and maximum. For categorical variables, the frequency and percentage will be given.

Missing data will not be imputed for safety endpoints.

Multiplicity Adjustment Method

Methods of adjusting for multiplicity due to multiple endpoints (co-primary and co-secondary efficacy endpoints) in order to preserve the familywise error rate at 0.05 are described in the diagram below.



Testing of each co-endpoint pair for the pooled evolocumab vs. pooled ezetimibe analysis will result in a single p-value, and for co-secondary endpoints these p-values will then be used in the Hochberg procedure. The following test procedure will be used to preserve the familywise error rate for the co-primary and co-secondary endpoints:

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

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

10.5.2 Primary Efficacy Endpoint

Primary Analysis

To assess the co-primary endpoints of the mean percent change from baseline at weeks 10 and 12 and the percent change from baseline at week 12 in LDL-C, a repeated measures linear effects model will be used to compare the efficacy of evolocumab (pooled Q2W and QM) with pooled ezetimibe. The repeated measures model will include terms of treatment group, stratification factor of screening LDL-C level, scheduled visit, and the interaction of treatment group with scheduled visit. Missing values will not be imputed when the repeated measures linear effects model is used.

Sensitivity Analysis

To evaluate the robustness of the primary analysis results, sensitivity analyses will be performed as follows:

- The primary analysis will be repeated using the CAS
- Non-parametric analyses ([Quade, 1979](#))

Additional Analyses

The co-primary endpoints will also be assessed within each dose frequency using dose frequency matched control (ie, evolocumab Q2W SC plus placebo PO QD vs. ezetimibe QD plus placebo Q2W SC; evolocumab QM SC **plus placebo PO QD** vs. ezetimibe QD plus placebo QM SC) and pooled ezetimibe (ie, evolocumab Q2W vs. pooled ezetimibe; evolocumab QM vs. pooled ezetimibe)

In addition, the difference between the evolocumab Q2W and evolocumab QM groups will be estimated.

10.5.3 Secondary Efficacy Endpoints

The statistical model and testing of the tier 1 co-secondary efficacy endpoints will be similar to the primary analysis of the co-primary endpoints. The co-secondary efficacy endpoints of LDL-C response will be analyzed using the Cochran-Mantel Haenszel (CMH) test adjusted by stratification factor.

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

Multiplicity adjustment procedures are defined in [Section 10.5.1](#).

10.5.4 Tertiary Efficacy Endpoints Analyses

Analysis of the tertiary efficacy endpoints will be similar to the primary analysis of the co-primary endpoints. No multiplicity adjustment will be applied.

10.5.5 Safety Endpoints

Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, treatment-related adverse events, adverse events leading to withdrawal from investigational product, and significant treatment-emergent adverse events will also be provided. Subject-level data may be provided instead of tables if the subject incidence is low.

Safety Laboratory Parameters

The analyses of key safety laboratory endpoints will include summary statistics at each scheduled visit by treatment group. Shifts in grades of safety laboratory values between the baseline and the maximum post-baseline grade will be tabulated by treatment group. Laboratory shift tables for certain analytes will be provided using the CTCAE v.4 toxicity criteria.

Vital Signs and Physical Measurement

The analyses of vital signs and physical measurement will include summary statistics at each scheduled visit by treatment group.

Concomitant Medications

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

Anti-AMG 145 antibodies

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

10.5.6 Exploratory Endpoint Analyses

Exploratory endpoints related to lipid parameters will be summarized by treatment group and by scheduled visit using descriptive statistics.

Non-coronary revascularizations will be collected on the eCRF. Subject incidence of exploratory endpoint events will be summarized for each treatment group.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

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

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational product(s) is/are administered.

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

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

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

11.2 Institutional Review Board/Independent Ethics Committee

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

written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

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

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

11.3 Subject Confidentiality

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

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the eCRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.
- For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

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

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

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

12.2 Study Documentation and Archive

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

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

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

Elements to include:

- Subject files containing completed eCRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen

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

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

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

12.3 Study Monitoring and Data Collection

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

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

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

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

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the eCRFs must be maintained and readily available.
- Updates to eCRFs will be automatically documented through the software's "audit trail".

- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications are created in the EDC system database for site resolution and closed by Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that investigator inspected or reviewed the data on the eCRF, the data queries, and the site notifications, and agrees with the content.

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

12.4 Investigator Responsibilities for Data Collection

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

12.5 Language

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood. eCRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

12.6 Publication Policy

To coordinate dissemination of data from this study, Amgen encourages the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to

collaborate with authors and Amgen staff as appropriate as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the **Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals** (International Committee of Medical Journal Editors, 2013, updated 2014), which states:

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

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

12.7 Compensation

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

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

Refer to the NCI Common Terminology Criteria for AEs (CTCAE) Version 4.0 for AE grading and information. The CTCAE is available at the following link:

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

Drug-induced Liver Injury Reporting & Additional Assessments Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation according to the criteria specified in [Section 6.3](#) 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 eCRF (eg, Event eCRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Amgen.
- Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in [Section 9.2.2](#).

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in [Section 6.3.1](#) and [Section 6.3.2](#) or who experience AST or ALT elevations >3 x ULN are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels. Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve
- Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic
- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL:
- Obtain complete blood count (CBC) with differential to assess for eosinophilia

- Obtain serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
- Obtain serum acetaminophen (paracetamol) levels
- Obtain a more detailed history of:
 - Prior and/or concurrent diseases or illness
 - Exposure to environmental and/or industrial chemical agents
 - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
 - Prior and/or concurrent use of alcohol, recreational drugs and special diets
 - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Obtain viral serologies
- Obtain CPK, haptoglobin, LDH, and peripheral blood smear
- Perform appropriate liver imaging if clinically indicated
- Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal. 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 corresponding eCRFs.

Appendix B. Sample Electronic Serious Adverse Event Contingency Reporting Form

AMGEN Study # 20140234 evolocumab (AMG 145)	Electronic Adverse Event Contingency Report Form <u>For Restricted Use</u>
----------------------------------------------------------	--------------------------------------------------------------------------------------

Reason for reporting this event via fax The Clinical Trial Database (eg. Rave): <input type="checkbox"/> Is not available due to internet outage at my site <input type="checkbox"/> Is not yet available for this study <input type="checkbox"/> Has been closed for this study																
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 <input type="checkbox"/> F <input type="checkbox"/> M	Race	If applicable, provide End of Study date												
If this is a follow-up to an event reported in the EDC system (eg. Rave), provide the adverse event term: _____ and _____																
3. ADVERSE EVENT																
Provide the date the investigator became aware of this information: Day Month Year																
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	Date Ended	Check only if event occurred before/first dose of (P)but under study	Is event serious?	Is event a potential endpoint?	Eventus enter Serious Critical Other (see code below)	Relationship Is there a reasonable possibility that the event may have been caused by (P)drug under study or an Amgen device used to administer the (P)drug under study?		Outcome of Event Resolved Not Resolved Unknown	Check only if event is related to study procedure No Yes						
Day Month Year	Day Month Year		<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="padding: 2px;">endocrine (AMG145)</td> <td style="padding: 2px;">Adolescent (P) (P) (P)</td> <td style="padding: 2px;">Percut (P) (P) (P) (P)</td> <td style="padding: 2px;">Other</td> </tr> <tr> <td style="padding: 2px;">Y/N</td> <td style="padding: 2px;">Y/N</td> <td style="padding: 2px;">Y/N</td> <td style="padding: 2px;">Y/N</td> </tr> </table>	endocrine (AMG145)	Adolescent (P) (P) (P)	Percut (P) (P) (P) (P)	Other	Y/N	Y/N	Y/N	Y/N		
endocrine (AMG145)	Adolescent (P) (P) (P)	Percut (P) (P) (P) (P)	Other													
Y/N	Y/N	Y/N	Y/N													
Serious: 01 Fatal Critical: 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? <input type="checkbox"/> No <input type="checkbox"/> Yes if yes, please complete all of Section 4																
Date Admitted					Date Discharged											
Day Month Year					Day Month Year											

AMGEN Study # 20140234 evolocumab (AMG 145)	Electronic Adverse Event Contingency Report Form <u>For Restricted Use</u>														
Site Number			Subject ID Number												
5. Was IP/Drug under study administered/taken prior to this event? <input type="checkbox"/> No <input type="checkbox"/> Yes if yes, please complete all of Section 5															
IP/Drug/Amgen Device:	Date of Initial Dose	Date of Dose			Prior to, or at time of Event		Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #				
	Day Month Year	Day Month Year	Day Month Year	Day Month Year											
evolocumab (AMG 145)	<input type="checkbox"/> blinded <input type="checkbox"/> open label										Lot # _____ <input type="checkbox"/> Unknown Serial # _____ <input type="checkbox"/> Unavailable / Unknown				
Pre-filled Auto-Injector/Pen (AI/Pen)	<input type="checkbox"/> open label										Lot # _____ <input type="checkbox"/> Unknown Serial # _____ <input type="checkbox"/> Unavailable / Unknown				
3.5 mL Personal Injector/Automated Mini-Coax (AMD)	<input type="checkbox"/> open label										Lot # _____ <input type="checkbox"/> Unknown Serial # _____ <input type="checkbox"/> Unavailable / Unknown				
ezetimibe	<input type="checkbox"/> blinded <input type="checkbox"/> open label										Lot # _____ <input type="checkbox"/> Unknown Serial # _____ <input type="checkbox"/> Unavailable / Unknown				
6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, please complete:															
Medication Name(s)	Start Date			Stop Date			Co-suspect		Continuing		Dose	Route	Freq.	Treatment Med	
	Day	Month	Year	Day	Month	Year	No	Yes	No	Yes				No	Yes
7. RELEVANT MEDICAL HISTORY (include dates, allergies and any relevant prior therapy)															
8. RELEVANT LABORATORY VALUES (include baseline values) Any Relevant Laboratory values? <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, please complete:															
Date	Test	Unit	Day	Month	Year										
	Day	Month	Year												

Appendix C. Pregnancy and Lactation Notification Worksheets



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: 20140234				
Study Design: <input type="checkbox"/> Interventional <input type="checkbox"/> Observational (If Observational: <input type="checkbox"/> Prospective <input type="checkbox"/> Retrospective)				
2. Contact Information				
Investigator Name		Site #		
Phone ()	Fax ()	Email		
Institution				
Address				
3. Subject Information				
Subject ID #		Subject Gender: <input type="checkbox"/> Female <input type="checkbox"/> Male		Subject DOB: mm / dd / yyyy
4. Amgen Product Exposure				
Amgen Product	Dose at time of conception	Frequency	Route	Start Date mm / dd / yyyy
Was the Amgen product (or study drug) discontinued? <input type="checkbox"/> Yes <input type="checkbox"/> No				
If yes, provide product (or study drug) stop date: mm / dd / yyyy				
Did the subject withdraw from the study? <input type="checkbox"/> Yes <input type="checkbox"/> No				
5. Pregnancy Information				
Pregnant female's LMP mm / dd / yyyy		<input type="checkbox"/> Unknown		
Estimated date of delivery mm / dd / yyyy		<input type="checkbox"/> Unknown <input type="checkbox"/> N/A		
If N/A, date of termination (actual or planned) mm / dd / yyyy				
Has the pregnant female already delivered? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> N/A				
If yes, provide date of delivery: mm / dd / yyyy				
Was the infant healthy? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> N/A				
If any Adverse Event was experienced by the infant, provide brief details:				
Form Completed by:				
Print Name:		Title:		
Signature:		Date:		

AMGEN Lactation 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: 20140234

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

2. Contact Information

Investigator Name _____ Site # _____
Phone (____) _____ Fax (____) _____ Email _____
Institution _____
Address _____

3. Subject Information

Subject ID # _____ Subject Date of Birth: mm ____ / dd ____ / yyyy ____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm ____ / dd ____ / yyyy ____

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

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

Did the subject withdraw from the study? Yes No

5. Breast Feeding Information

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

If No, provide stop date: mm ____ / dd ____ / yyyy ____

Infant date of birth: mm ____ / dd ____ / yyyy ____

Infant gender: Female Male

Is the infant healthy? Yes No Unknown N/A

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

Form Completed by:

Print Name: _____

Title: _____

Signature: _____

Date: _____

Appendix D. Japan Atherosclerosis Society (JAS) Guidelines for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases in Japan (2012)

From: https://www.jstage.jst.go.jp/article/jat/20/6/20_15792/_pdf

Journal of Atherosclerosis and Thrombosis Vol.20, No.6

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Committee Report 1

Executive Summary of the Japan Atherosclerosis Society (JAS) Guidelines for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases in Japan – 2012 Version

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Committee for Epidemiology and Clinical Management of Atherosclerosis

Among the various atherosclerotic cardiovascular diseases (CVDs), these guidelines primarily deal with cerebrovascular disease, peripheral arterial disease (PAD) and coronary artery disease (CAD), which occur in association with atherosclerosis and is closely related to dyslipidemia.

1. Comprehensive Risk Management for the Prevention of Atherosclerotic CVD

To prevent CVD, it is important to manage dyslipidemia in addition to other risk factors. For this purpose, we propose comprehensive risk management for the prevention of CVD. Risk factors that should be considered include dyslipidemia, hypertension, diabetes mellitus, smoking, chronic kidney disease (CKD), a family history of premature CAD, a history of CAD, noncardiogenic cerebral infarction, PAD, age and sex. In this article, we describe the comprehensive management of CVD.

2. Diagnostic Criteria for Dyslipidemia

It has been shown in epidemiological studies conducted in Japan, as well as in Western countries, that the incidence of CAD increases in association with increases in the levels of LDL-cholesterol (LDL-C)³¹ and triglycerides (TGs)^{2, 31} and decreases in the level of HDL cholesterol (HDL-C)⁴⁻⁷. Currently in Japan, the incidence of CAD is much lower than that observed in Western countries^{2, 3, 8, 9}; however, this incidence is anticipated to increase in the near future due to the recent Westernization of the Japanese lifestyle. Therefore, the current guidelines provide screening criteria for dyslipidemia to prevent CVD with a specific emphasis on the prevention of CAD, as shown in Table 1.

Regarding the diagnosis of dyslipidemia, the total cholesterol (TC), TG and HDL-C levels should be measured after an overnight fast. The LDL-C level is then calculated using the Friedewald formula (LDL-C = TC - HDL-C - TG/5).

This formula cannot be used if blood is collected without fasting or if the TG is ≥ 400 mg/dL. In such cases, using the non HDL-C level is recommended, which is calculated by subtracting the HDL-C level from the TC level. Data obtained in Japan indicate that the non HDL-C level is approximately 30 mg/dL higher than the LDL-C level. This view is shared by the National Cholesterol Education Program (NCEP). When lipids are evaluated based on the non HDL-C level, the target value of non HDL-C is determined by adding 30 mg/dL to the value of LDL-C (Table 2).

The incidence and mortality of CAD increase continuously in association with increases in the LDL-C level. At present, the incidence of CAD is lower in Japanese individuals than in Westerners. To maintain this low rate, efforts directed toward early prevention are required. Therefore, from the perspective of the prevention and treatment of CAD, the current guidelines propose an LDL-C level of 140 mg/dL as the reference value when screening Japanese individuals for hyper-LDL cholesterolemia. This value was selected because it corresponds to a TC level of 220 mg/dL, at which point the relative risk is approximately 1.5-fold higher than that observed at a TC level of < 180 mg/dL, according to the NIPPON DATA80¹⁰. Since the LDL-C goal may vary depending on concomitant risk factors, an LDL-C level between 120 and 139 mg/dL is defined as indicating borderline hyper-LDL cholesterolemia.

Hypo-HDL cholesterolemia has also been established to be a risk factor for CVD. The current guidelines define an HDL-C level of < 40 mg/dL as indicating hypo-HDL cholesterolemia, as determined in

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Table 1. Dyslipidemia: Diagnostic Criteria for Screening (Fasting*)

Low-density lipoprotein cholesterol (LDL-C)	≥ 140 mg/dL	Hyper-LDL cholesterolemia
	120-139 mg/dL	Borderline hyper-LDL cholesterolemia**
High-density lipoprotein cholesterol (HDL-C)	< 40 mg/dL	Hypo-HDL cholesterolemia
Triglycerides (TG)	≥ 150 mg/dL	Hypertriglyceridemia

- * The LDL-C level is calculated using the Friedewald formula (TC - HDL-C - TG/5) (for TG < 400 mg/dL).
- * If the TG level is ≥ 400 mg/dL or non-fasting blood is used, the non HDL-C (TC - HDL-C) level should be used with a cutoff value of LDL-C + 30 mg/dL.
- **Fasting is defined as deprivation of food for at least 10 to 12 hours; however, the ingestion of noncaloric beverages, such as water and tea, is allowed.
- **If a patient is found to have borderline hyper-LDL cholesterolemia during screening, he/she should be examined for any high-risk conditions and the need for treatment should be considered.

Table 2. Lipid Management Targets for Patients with Different Risk Levels

Therapeutic principle	Management category	Lipid management target (mg/dL)			
		LDL-C	HDL-C	TG	Non HDL-C
Primary prevention Drug therapy should be considered after lifestyle modification	Category I	< 160			< 190
	Category II	< 140			< 170
	Category III	< 120	≥ 40	< 150	< 150
Secondary prevention Drug therapy should be considered, together with lifestyle modification	History of CAD	< 100			< 130

- * For patients at low absolute risk, such as the young, the relative risk chart (Supplementary Table) should be used and changes in the absolute risk should be monitored carefully while encouraging the patient to modify their lifestyle.
- * These values should be considered general, not mandatory, goals.
- * A 20%-30% reduction in the level of LDL-C is considered to be a prime target for pharmacological intervention.
- * The management target for the non HDL-C level is the secondary target to be used after a patient with hypertriglyceridemia has achieved the management target for the LDL-C level. The non HDL-C level should be used if blood is collected after meals or if the TG level is ≥ 400 mg/dL.
- * For patients in any category, the management goals should generally be achieved via lifestyle modification.
- * For patients in category I, drug therapy should be considered if the LDL-C level is ≥ 180 mg/dL.

our previous guidelines. A number of studies have demonstrated sex differences in the HDL-C levels; however, it remains unclear whether these sex differences are reflected in the diagnosis of hypo-HDL cholesterolemia.

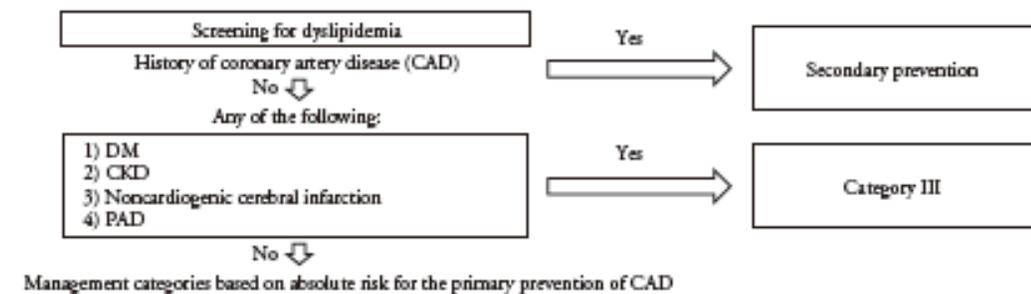
Hypertriglyceridemia has been found to occur in association with various conditions. Although some researchers insist that more intensive management is required in patients with certain diseases, such as diabetes mellitus, the current guidelines define a TG level of ≥ 150 mg/dL as indicating hypertriglyceridemia, based on epidemiological data obtained during screenings of the general population.

3. Risk Stratification Based on Absolute Risk

The current guidelines stratify the risk of CVD

for primary prevention according to the absolute risk calculated based on the results of the NIPPON DATA80¹¹⁾. This study identified age, sex, diabetes mellitus, current smoking, systolic blood pressure and the TC level as risk factors and determined the absolute risk of death from CAD depending on the degree or existence of these factors.

How absolute risk categories should be determined is based on clinical consensus and/or conventional wisdom. The U.S. NCEP Adult Treatment Panel III classifies a 10-year risk of death from CAD or the development of nonfatal myocardial infarction of ≥ 20% (based on the Framingham score) as high risk¹²⁾, whereas European guidelines classify a 10-year risk of death from CVD (including strokes and CAD) of ≥ 5% as high risk¹³⁾. The current guidelines classify



10-year probability (absolute risk) of CAD death derived from NIPPON DATA80	Additional risk factors	
	No additional risk factors	One or more of the following: (1) Hypo-HDL cholesterolemia (HDL-C <40 mg/dL) (2) Family history of premature CAD in first-degree relatives (a man aged <55 years or a women aged <65 years) (3) Impaired glucose tolerance
<0.5%	Category I	Category II
≥0.5%–<2.0%	Category II	Category III
≥2.0%	Category III	Category III

This flow chart is not applicable to patients with FH.

Fig. 1. Flow chart for setting management targets for LDL cholesterol

patients with a 10-year risk of death from CAD of $\geq 2\%$ as belonging to the high-risk group (category III), those with a risk of $\geq 0.5\%$ to $< 2\%$ as belonging to the intermediate-risk group (category II) and those with a risk of $< 0.5\%$ as belonging to the low-risk group (category I), considering that there is little evidence of an association between hypercholesterolemia and cerebrovascular diseases in Japanese individuals. Since diabetes mellitus, CKD and a history of noncardiogenic cerebral infarction or PAD are considered to be important risk factors, patients with any of these conditions are classified as belonging to the high-risk group (Fig. 1).

The 10-year absolute risk of CAD-related death should be determined based on the risk assessment chart provided in the NIPPON DATA80¹³⁾. However, since this chart does not include hypo-HDL cholesterolemia, a family history of premature CAD or impaired glucose tolerance, the category should be raised if the patient meets one or more of these criteria (Fig. 2).

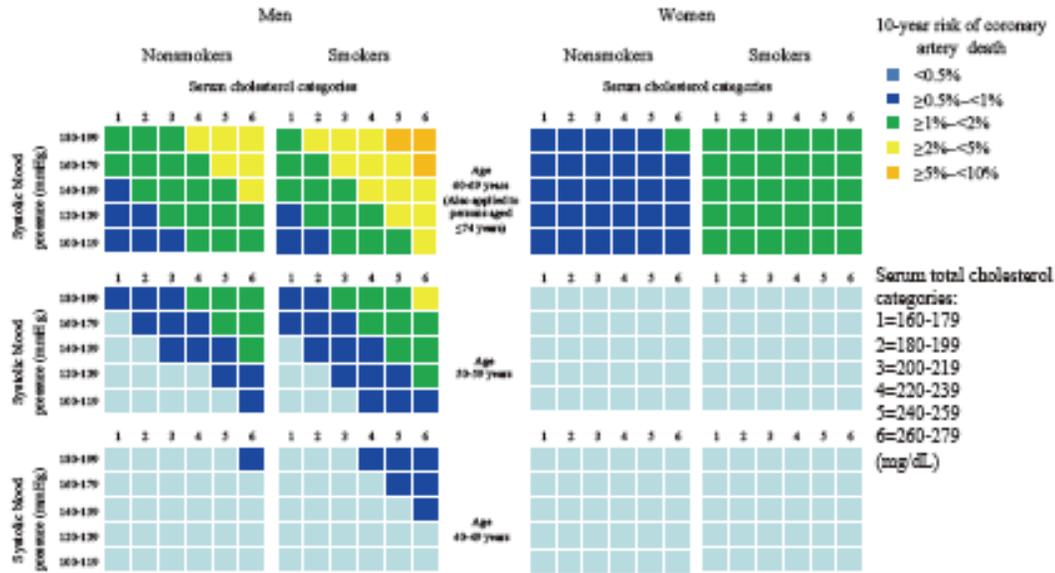
The chart obtained from the NIPPON DATA80 addresses the risk of CAD-related death in individuals

between 40 and 79 years of age. While the current guidelines are intended for adults younger than 65 years of age, they can also be applied to persons between 65 and 74 years of age. To calculate the absolute risk for individuals ≥ 70 and < 75 years of age, the table for individuals between 60 and 69 years of age should be used. For adults < 40 years of age, the table for individuals between 40 and 49 years of age should be used.

When assessing the absolute risk, it should be noted that the absolute risk greatly depends on age. If a low absolute risk is obtained for a young individual with a risk factor, such as hypertension or smoking, the risk factors should be managed appropriately. When secondary prevention is required, each risk factor should be dealt with separately, as outlined in the previous guidelines.

4. Management Targets for Dyslipidemic Patients

The management targets for dyslipidemic patients are presented by category in Table 2. For primary prevention, drug therapy should be considered after lifestyle factors have been improved for a certain



The section of hyperglycemia from the NIPPON DATA80 risk assessment chart is omitted here. These charts cannot be applied to high-risk patients, such as those with DM or CKD.

Fig. 2. Absolute risk assessment charts for death from coronary artery disease (primary prevention).

Absolute risk should be reassessed at least once a year since it may be affected by either risk factor or aging.

Step 1: The applicable portion of the above figures should be assessed based on gender, age, the present smoking status, systolic blood pressure (mmHg) and the TC level (mg/dL).

Absolute risk $\geq 2\%$ → Category III

Absolute risk $< 2\%$ → To Step 2

Step 2: Any of the following conditions: hypo-HDL-cholesterolemia (< 40 mg/dL), a family history of CAD and/or impaired glucose tolerance

Absolute risk $\geq 0.5\% < 2\%$ + Yes → Category III

Absolute risk $\geq 0.5\% < 2\%$ + No → Category II

Absolute risk $< 0.5\%$ + Yes → Category II

Absolute risk $< 0.5\%$ + No → Category I

Supplementary notes

(1) The TC category 160-179 mg/dL should be used in patients with a TC level of < 160 .

(2) The TC category 260-279 mg/dL should be used in patients with a TC level of ≥ 280 mg/dL.

(3) The systolic blood pressure category of 100-119 mmHg should be used in patients with a systolic blood pressure of < 100 mmHg, while the systolic blood pressure category of 180-199 mmHg should be used in patients with a systolic blood pressure of ≥ 200 mmHg.

(4) The guidelines cannot be applied to persons 75 years of age or older. "The Elderly." For patients < 40 years of age, the relative risk chart (Supplementary Table) should be used.

(5) Blood pressure should be managed according to the guidelines established by the Japanese Society of Hypertension, while diabetes mellitus should be managed according to the guidelines established by the Japan Diabetes Society.

(6) It is desirable to encourage smokers to stop smoking irrespective of the level of absolute risk.

period and the response has been evaluated. For individuals in category I (low absolute risk group), the management target for the LDL-C level is set at < 160 mg/dL. The target for individuals in category II is set at < 140 mg/dL, while that for individuals in category III (high absolute risk group) is set at < 120 mg/

dL. It should be noted that achieving these targets is recommended but not obligatory. A meta-analysis of preventive clinical trials demonstrated that a 20%-30% reduction in the LDL-C level results in a decrease in the incidence of CAD of approximately 30%. Based on this finding, a 20%-30% decrease in

the LDL-C level can be considered a target. For secondary prevention, since the patient has already been diagnosed with CAD, the administration of drug therapy targeting an LDL-C level of <100 mg/dL is recommended in addition to lifestyle modification.

For the management of hypertriglyceridemia and hypo-HDL cholesterolemia, targeting a TG level of <150 mg/dL and an HDL-C level of ≥ 40 mg/dL is recommended, as in the previous guidelines.

Some researchers have the opinion that stricter targets should be established for high-risk patients (such as those with diabetes mellitus or CKD) or those who require secondary prevention, depending on the patient's condition and severity of disease; however, there is insufficient evidence to support setting such goals. Nevertheless, the current guidelines also suggest that high-risk patients be stratified according to risk factors and that lower targets be established for such patients.

5. Treatment

Dyslipidemia should be treated with lifestyle modification, including smoking cessation and the administration of diet and/or exercise therapy. In primary prevention patients, drug therapy should only be considered when the lipid management targets are not achieved after sufficient effort has been made to improve lifestyle factors. In patients with a history of CAD, the use of drug therapy should be considered simultaneously with lifestyle modification.

When drug therapy is provided for patients with hyper-LDL cholesterolemia, statins are the first drug of choice. Resin, probucol and/or ezetimibe are used in combination with statins or selected when statins cannot be administered. The combination of statins and EPA is useful for treating high-risk patients with hyper-LDL cholesterolemia. For treating hypertriglyceridemia accompanied by hypo-HDL cholesterolemia, drugs such as fibrates and nicotinic acid derivatives should be considered.

6. High-Risk Conditions for CVD

The current guidelines include CKD in addition to a history of CAD (secondary prevention), diabetes mellitus, noncardiogenic cerebral infarction and PAD as high-risk conditions based on the findings of epidemiological studies, including evidence showing that the presence of CKD increases the incidence of CAD by at least two-fold. The previous guidelines classified a history of cerebral infarction as a high-risk condition, while the current guidelines classify a history of noncardiogenic cerebral infarction as a high-risk condition because cardiogenic cerebral infarctions are not

caused by atherosclerotic disease.

7. Familial Hypercholesterolemia

Familial hypercholesterolemia occurs in approximately one in 500 individuals and is associated with a high risk of CAD. The current guidelines reference the diagnostic criteria for FH reported by the 2011 Primary Hyperlipidemia Research Group and set a target of an LDL-C level of <100 mg/dL or a decrease in the LDL-C level of at least 50%.

8. Evaluation of CVD

To prevent CVD, the presence or absence and severity of atherosclerosis must be evaluated before symptoms occur and risk factors must be managed or treated with the objective of preventing progression or possibly achieving regression. For this purpose, correctly staging CVD is important. At present, the degree of atherosclerosis is primarily evaluated using imaging techniques. Invasive techniques include angiography (to assess the severity of stenosis) as well as angioscopy and intravascular ultrasonography (to qualitatively assess the vessel walls). Noninvasive techniques include transcutaneous ultrasonography of the arteries, such as the carotid artery, to qualitatively and quantitatively evaluate the degree of atherosclerosis. Carotid artery ultrasonography is often used in general practice because the extent of carotid sclerosis has been shown to be correlated with the risk of cerebrovascular disease and/or CAD. The development of multidetector CT (MDCT) has allowed for easier detection of coronary artery lesions. At present, carotid artery ultrasonography and MDCT are less invasive and easier to perform than other imaging modalities. In the near future, developing guidelines for the assessment of atherosclerosis that can be employed before the onset of symptoms is necessary. At present, however, assessing the degree of atherosclerotic lesions using the above-mentioned imaging techniques is associated with some limitations. CVD should be diagnosed based on a clear understanding of these limitations.

Footnotes

This is an English version of the guidelines of the Japan Atherosclerosis Society (Chapter 1) published in Japanese in June 2012.

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Disclosures

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Supplementary Table. Relative Risk Charts for the Young, etc. with a Low Absolute Risk (based on the risk charts of the NIPPON DATA80)

	Non-smoker					
Systolic blood pressure						
Second-degree or higher hypertension (≥160 mmHg)	2.2	2.8	3.6	4.6	5.8	7.4
First-degree hypertension (140-159 mmHg)	1.7	2.2	2.8	3.5	4.5	5.7
Normal (≤140)	1.0*	1.3	1.6	2.1	2.6	3.4
TC category (mg/dL)	160-179	180-199	200-219	220-239	240-259	260+
	Smoker					
Systolic blood pressure						
Second-degree or higher hypertension (≥160 mmHg)	3.2	4.1	5.2	6.6	8.4	10.7
First-degree hypertension (140-159 mmHg)	2.5	3.1	4.0	5.1	6.5	8.2
Normal (≤140 mmHg)	1.4	1.8	2.3	3.0	3.8	4.8
TC category (mg/dL)	160-179	180-199	200-219	220-239	240-259	260+

Amendment 3.0

Protocol Title: A Double-blind, Randomized, Multicenter Study to Evaluate the Safety and Efficacy of Evolocumab, Compared With Ezetimibe, in Hypercholesterolemic Japanese Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor due to Muscle Related Side Effects

GAUSS-4: Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects

Amgen Protocol Number Evolocumab 20140234

Amendment Date: 21 March 2017

Rationale:

This is Amendment 3 for Evolocumab Study 20140234. Amendment 2 for this protocol was not implemented and therefore, the changes captured in this document reflect changes made from Amendment 1 to Amendment 3.

The primary change to the protocol is to clarify the timing for the primary analysis from week 12 to week 24 per agreement with the Japanese Pharmaceuticals and Medical Devices Agency (PMDA). The analyses will include the

- Double-blind phase efficacy and safety evaluations (week 12 data)
- Open-label extension phase safety data (week 12 to week 24 data)
- Combined double-blind and open-label extension phase efficacy data

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

- Update acceptable methods of birth control that are now available in Japan
- Removal of Vitamin E from [Section 7.2](#) as this analyte is neither collected nor analyzed
- Removal of adjudication of events as CV events were never adjudicated in GAUSS 4 (a memo was distributed to the sites during startup activities, prior to any subjects being enrolled)
- Removal of collection of "CV events" as these are already captured as adverse events or serious adverse events
- Clarify that prior to on-site subcutaneous (SC) investigational product (IP) administration, female subjects of childbearing potential should have a urine pregnancy test performed
- Include information about providing subject instruction for self-administration of AI/Pen or Personal Injector
- Add low or atypical statin therapy that is ongoing at study entry can be continued throughout the study
- The screening period is initiated from the time of obtaining informed consent and must be completed within 28 days

- Observation is required only after first IP administration visit
- Align safety definitions and reporting procedures with current protocol template (including pregnancy and lactation notification worksheets)
- Administration, typographical, and formatting changes were made throughout the protocol

Description of Changes

Section: Global

Change: Updated document date from 09 September 2015 to **21 March 2017**.

Section: Global

Change: Updated International Conference of Harmonisation to International **Council** for Harmonisation.

Section: Global

Change: Updated Investigator's Brochure version from 2014 to 2016.

Section: Global

Change: Rearranged bullets for consistency in Sections 7.2.3.1 (Visit Day 1), 7.2.3.2 (Visit/Week 2), 7.2.3.5 (Visit/Week 8), and 7.2.3.7 (Visit/Week 12).

Section: Global

Change: Removed collection of CV Events from the entirety of Section 7 (Study Procedures).

Section: Global

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

Section: Title Page, Key Sponsor Contact(s)

Replace:

PPD

One Amgen Center Drive, MS 27-2-F
Thousand Oaks, CA 91320-1799, USA

Phone: PPD

Fax: PPD

Email: PPD

With:

PPD

One Amgen Center Drive, MS **38-2-C**
Thousand Oaks, CA 91320-1799, USA

Phone: PPD

Fax: PPD

Email: PPD

Section: Title page

Add:

Amendment 2: 11 April 2016 (not distributed)

Amendment 3: 21 March 2017

Section: Protocol Synopsis, Study Design, Paragraph 1

Replace:

Subjects on low or atypical statin dose will continue to take the statin without any dose adjustment for the duration of the blinded portion of the study.

With:

Subjects on low or atypical statin **therapy must be on a stable dose for at least 4 weeks prior to screening and throughout** the blinded portion of the study; **the dose cannot be adjusted during screening and for the duration of the study.**

Section: Protocol Synopsis, Study Design, Paragraph 4

Add:

There will be an end of study phone call at W54 (**Q2W subjects only**) for any potential adverse events/serious adverse events/**adverse device effects**.

Section: Protocol Synopsis, Study Design, Paragraph 5

Delete:

The study includes collection of biomarker samples, where approved by the institutional review board (IEC/IRB). ~~The last collection of lipids for the primary analysis will occur at week 12. End of study (EOS) for subjects is by contact (eg, phone call) from the site at week 54 for any potential Adverse Events or Serious Adverse Events.~~

Section: Protocol Synopsis, Study Design, Paragraph 6

Replace:

The study includes adjudication of deaths and specific cardiovascular (CV) events by an independent Clinical Events Committee (CEC) and formal review of the accumulating blinded data by an independent Data Monitoring Committee (DMC).

With:

The study includes a formal review of the accumulating blinded data by an independent Data Monitoring Committee (DMC).

Section: [Protocol Synopsis, Summary of Subject Eligibility Criteria](#), Paragraph 1

Add:

Males and females, ≥ 20 to ≤ 80 years of age, **Japanese by self-identification**, are eligible for this study.

Section: [Protocol Synopsis, Summary of Subject Eligibility Criteria](#), Paragraph 2

Add:

Symptoms must have resolved **or improved** when statin was discontinued or the dose was reduced.

Section: [Protocol Synopsis, Statistical Considerations, General Considerations](#), Paragraph 1

Replace:

When all the randomized subjects in the study have either completed the scheduled visits up to and including Week 12 or have early terminated from the study, a primary analysis will be performed, where efficacy and safety of 12 weeks of evolocumab compared with ezetimibe will be evaluated on the full analysis set (FAS) that includes all randomized subjects who received at least 1 dose of IP in the double blind treatment period. The superiority of evolocumab to ezetimibe will be assessed for all efficacy endpoints.

With:

When all the randomized subjects in the study have either completed the scheduled visits up to and including Week **24** or have early terminated from the study, a primary analysis will be performed. **Efficacy and safety of 12 weeks of evolocumab compared with ezetimibe will be evaluated on the full analysis set (FAS) that includes all randomized subjects who received at least 1 dose of IP in the double blind treatment period. In addition, the 12 weeks of data from the open-label extension (weeks 12 to 24) will also be summarized.** The **treatment effect** of evolocumab **compared** to ezetimibe will be **evaluated** for all efficacy endpoints **through the Week 12 visit. In addition, descriptive analyses from the open-label extension**

(weeks 12 to 24) will be performed on the open label extension analysis set (OLEAS).

Section: Protocol Synopsis, Statistical Considerations, Safety Analyses

Replace:

Safety summaries will include the subject incidence of adverse events, summaries of laboratory parameters and anti-evolocumab. Deaths and major CV events will be adjudicated by an independent CEC. Subject incidence of adjudicated events will be summarized for each treatment group.

With:

Safety summaries will include the subject incidence of adverse events, summaries of laboratory parameters and anti-evolocumab **antibodies**.

Section: Protocol Synopsis, End of section

Add:

Data Element Standards Version 5/20 March 2015
Version/Date:

Section: Study Glossary

Delete:

Abbreviation or Term	Definition/Explanation
ADE	Adverse device effect
AE	Adverse event
CEC	Clinical events committee
Q2W	Q2W is defined as every 2 weeks with a window of \pm 3 days for each visit
QM	QM is defined as every 4 weeks with a window of \pm 7 days for each visit
SAE	Serious adverse event

Section: 2.4 Rationale, Paragraph 2

Replace:

Patients on low or atypical statin dose will continue to take the statin without any dose adjustment for the duration of the study.

With:

Subjects on low or atypical statin therapy must be on a stable dose for at least 4 weeks prior to screening and throughout the blinded portion of the study; the dose cannot be adjusted during screening and for the duration of the study.

Section: [3.1 Study Design](#), Paragraph 1

Replace:

Patients on low or atypical statin dose will continue to take the statin without any dose adjustment for the duration of the blinded portion of the study.

With:

Subjects on low or atypical statin therapy must be on a stable dose for at least 4 weeks prior to the screening and throughout the blinded portion of the study; the dose cannot be adjusted during screening and for the duration of the study.

Section: [3.1 Study Design](#), Paragraph 3

Add:

There will be an end of study phone call at W54 (**Q2W subjects only**) for any potential **adverse events, serious adverse events, or adverse device effects.**

Section: [3.1 Study Design](#), Paragraph 5

Delete:

The study includes collection of biomarker samples, where approved by the institutional review board (IEC/IRB). ~~The last collection of lipids for the primary analysis will occur at week 12. EOS for subjects is by contact (eg, phone call) from the site at week 54 for any potential AEs or SAEs.~~

Section: [3.1 Study Design](#), Paragraph 6

Replace:

The study includes adjudication of deaths and specific cardiovascular (CV) events by an independent Clinical Events Committee (CEC) and formal review of the accumulating blinded data by an independent Data Monitoring Committee (DMC).

With:

Formal review of the accumulating blinded data by an independent Data Monitoring Committee (DMC) **will occur.**

Section: 3.5.2 End of Study

Replace:

Primary Completion: defined as the time when all the randomized subjects in the study have either completed the scheduled visits up to and including Week 12 or have early terminated from the study;

With:

Primary Completion: defined as the time when all the randomized subjects in the study have either completed the scheduled visits up to and including Week **24** or have early terminated from the study;

Section: 4 Subject Eligibility, Paragraph 1

Add:

Screening is initiated from the time of obtaining informed consent. The screening period must be completed within 28 days.

Section: 4 Subject Eligibility, Paragraph 2

Delete:

For a full list of eligibility criteria, please refer to Section 4.1. and ~~Section 4.1.2~~

Section: 4.1.1 Inclusion Criteria, Criterion 102

Add:

102 Male or female ≥ 20 to ≤ 80 years of age, **Japanese by self-identification**, at signing of informed consent

Section: 4.1.1 Inclusion Criteria, Criterion 104

Add:

104 Subject must have tried and failed at least 2 statins with failure to at least 1 of the statins at an average daily dose at or below the following doses due to intolerable myopathy, ie, myalgia (muscle pain, ache, or weakness without CK elevation), myositis (muscle symptoms with increased CK levels), or rhabdomyolysis (muscle symptoms with marked CK elevation). For subjects that developed rhabdomyolysis, defined as CK > 10 x ULN, failure of only 1 statin at any dose is acceptable. **Symptoms must have resolved or improved when statin was discontinued or the dose was reduced.**

Section: 4.1.1 Inclusion Criteria, Criterion 104, Bullet 7

Replace:

- For unlisted statins, the average daily dose should not exceed the lowest available starting dose approved by PMDA or applicable country regulatory authority.

With:

- For unlisted statins, the average daily dose should not exceed the lowest available **recommended** starting dose approved by **the Japanese Ministry of Health, Labour and Welfare**.

Section: 4.1.1 Inclusion Criteria, Criterion 105

Replace:

105 Lipid lowering therapy has been stable prior to LDL-C screening for at least 4 weeks if currently on a bile-acid sequestering resin and/or stanol; if subject is on ezetimibe at start of screening it must be discontinued for ≥ 1 week before LDL-C screening

With:

105 **Subjects taking** bile-acid sequestering resins and/or stanol, **stanol esters, low (lowest available recommended starting dose approved by the Japanese Ministry of Health, Labour and Welfare) or atypical dose of statin must be on a stable dose for at least 4 weeks prior to screening. No adjustments to statin (or other lipid lowering therapy) dose are allowed during screening and throughout study. EXCEPTION:** if subject is on ezetimibe at start of screening it must be discontinued for ≥ 1 week before LDL-C screening

Section: 4.1.2 Exclusion Criteria, Criterion 209

Add:

209 Subject has taken in the last 4 weeks prior to LDL-C screening red yeast rice, > 200 mg/day niacin, or prescription lipid-regulating drugs (eg, fibrates and derivatives) other than **low (lowest available recommended starting dose approved by the Japanese Ministry of Health, Labour and Welfare) or atypical dose of** statins, ezetimibe, bile-acid sequestering resin, or stanols and stanol esters

Section: 4.1.2 Exclusion Criteria, Criterion 219, Items b and c

Add:

- b. Acceptable methods of preventing pregnancy include not having intercourse (sexual abstinence), surgical contraceptive methods – (vasectomy of the male partner **[and testing shows there is no sperm in the semen]** or bilateral tubal ligation/occlusion), or use of hormonal birth control methods (pills, patches), intrauterine devices (IUDs), **intrauterine hormonal-releasing system (IUS), male partner uses a condom with or without spermicide, use of a cervical cap, diaphragm, or contraceptive sponge with spermicide;** or two (2) barrier methods (each partner must use one barrier method) with spermicide – males must use condom with spermicide; females must choose either diaphragm with spermicide, OR cervical cap with spermicide, OR contraceptive sponge with spermicide.
- c. Note: If additional medications are given during treatment which may alter the contraceptive requirements (these additional medications may require an increase in the number of contraceptive methods and/or length of time that contraception is to be utilized **and/or length of time breastfeeding is to be avoided** after the last dose of protocol-required therapies) the investigator is to discuss changes with the study subject.

Section: 4.1.2 Exclusion Criteria, Criterion 221

Delete:

- 221 Subject who has previously received evolocumab or any other ~~investigational~~ therapy to inhibit PCSK9

Section: 4.1.2 Exclusion Criteria, Criterion 224

Add:

- 224 Subject who has known sensitivity **or intolerance** (eg, allergy or serious adverse reaction to ezetimibe) to any of the products or components to be administered during dosing

Section: 5 Subject Enrollment, Paragraph 1

Add:

Screening is initiated from the time of obtaining informed consent. The screening period must be completed within 28 days.

Section: 5.1 Randomization/Treatment Assignment, Paragraph 1

Replace:

Randomization will be stratified by screening LDL-C concentration (< 180 mg/dL [4.66 mmol/L] vs. \geq 180 mg/dL) at baseline.

With:

Randomization will be stratified by screening LDL-C concentration (< 180 mg/dL [4.66 mmol/L] vs. \geq 180 mg/dL) **and** baseline **statin use**.

Section: 5.1 Randomization/Treatment Assignment, Paragraph 3

Replace:

A confirmation fax will be sent to the site to verify that the correct information has been entered and to confirm the assignment of a randomization number.

With:

A confirmation **email** will be sent to the site to verify that the correct information has been entered and to confirm the assignment of a randomization number.

Section: 6 Treatment Procedures

Add:

Evolocumab (AMG 145), placebo SC, ezetimibe PO, and placebo PO are IPs in this study. An Investigational Product Instruction Manual (IPIM) containing detailed information regarding the storage, preparation, **destruction**, and administration of IP will be provided separately.

Section: 6.1 Classification of Product(s) and/or Medical Device(s), Paragraph 3

Add:

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, **destruction**, and administration of evolocumab, matched placebo, and over-encapsulated ezetimibe.

[Section: 6.2.1.1 Dosage, Administration, and Schedule](#), Paragraph 1

Replace:

IP administration by SC injection at each visit must be done after vital signs and blood draw procedures, if applicable. The date and time of evolocumab or placebo will be recorded on the individual subject's worksheet and/or eCRF. After IP administration at each dosing visit, subjects should be observed for at least 30 minutes before being discharged.

With:

For visits with IP administration at the study site, administration should be the last procedure to be performed during each visit. The date and time of evolocumab or placebo will be recorded on the individual subject's worksheet and eCRF. After **the first** IP administration at **the first** dosing visit, subjects should be observed for at least 30 minutes before being discharged.

[Section: 6.5 Medical Devices](#), Paragraph 1

Add:

Amgen SC IP (evolocumab/placebo) will be administered per prefilled AI/Pen or 3.5 mL Personal Injector, provided by Amgen. Additional details regarding the use of the AI/Pen or Personal Injector is provided in the IPIM and in the Instructions for Use (IFU) brochure. **Other medical devices** (eg, syringes, sterile needles, alcohol prep pads), **which are not considered test articles, may be used in the conduct of this study as part of standard care.** These devices are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation).

[Section: 6.6 Product Complaints, Including Device Complaints](#), Paragraph 1

Add:

This includes any drug(s), device(s), or combination product(s) provisioned and/or repackaged/modified by Amgen. Drugs or devices include evolocumab/placebo, prefilled AI/Pen and Personal Injector.

[Section: 6.6 Product Complaints, Including Device Complaints](#), Paragraph 5

Add:

The investigator is responsible for ensuring that all product complaints, including device complaints, observed by the investigator or reported by the subject that occur after

signing of the **informed consent form (ICF)** through 30 days after the last dose of IP or EOS, whichever is later, are reported to Amgen within 24 hours of discovery or notification of the product **and/or device** complaint.

Section: 6.7 Excluded Treatments and/or Procedures During Study Period,
Paragraph 1, Bullet 1

Replace:

- Prescription lipid regulating medications (eg, non-study ezetimibe, or fibrates and derivatives), other than bile-acid sequestering resin, or stanol and stanol esters

With:

- Prescription lipid regulating medications (eg, non-study ezetimibe, or fibrates and derivatives)
- **However, the following agents are allowed:**
 - bile-acid sequestering resin
 - stanol and stanol esters
 - **Please note: subjects on a low (lowest available recommended starting dose approved by the Japanese Ministry of Health, Labour and Welfare) or atypical dose of statins may continue their current dose if the subject has taken it for at least 4 weeks prior to the screening; new statin initiations, and/or dose adjustments are not permitted during screening or the study itself.**

Section: 7.1 Schedule of Assessments, Table1

Replace:

Study Day / Timepoint	Screening & Placebo Run-in	D1 Visit	W2 Visit	W4	W6	W8 Visit	W10 Visit	W12 Visit	W24 Visit	W36 Visit	W48 Visit	W52 Visit	W54 EOS Phone Call
<i>General Procedures</i>													
Informed consent	X												
Medical history	X												
Vital Signs (sitting BP, HR, RR, Temp)	X	X				X	X	X	X	X	X	X	
Review for AEs/SAEs/ADEs/CV Events ^a	X	X	X			X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X			X	X	X	X	X	X	X	X
Dietary instruction	X	X	X			X	X	X					
Physical exam	X							X				X	
Body weight, waist circumference	X											X	
Body height	X												
SF-36		X						X					
Randomization		X											
<i>Central Laboratory</i>													
Fasting lipids ^b	X	X	X			X	X	X	X	X	X	X	
ApoA1, ApoB, Lp(a)		X					X	X	X	X	X	X	
PK, PCSK9		X	X				X	X				X	
Chemistry ^c Hematology ^d	X	X				X		X				X	
hsCRP		X						X				X	
HbA1c	X							X				X	
TSH	X												
Biomarkers (blood)		X						X				X	
Anti-evolocumab antibodies		X						X				X	
HCV antibodies	X												
HCV viral load (only HCV positive patients)		X						X				X	
Serum pregnancy; FSH	X							X				X	
Urinalysis ^e	X	X						X				X	
SC Placebo Run-in	X												
Q2W SC IP on-site		X	X			X	X	X					
Q2W SC IP non-clinic setting ^{f9}				X	X				X	X	X		
Q2W IP Dispensation/Accountability		X	X			X	X	X	X	X	X	X	
QM SC IP on-site		X				X		X					
QM SC IP non-clinic setting ^{gh}				X					X	X	X		
QM IP Dispensation/Accountability		X	X			X	X	X	X	X	X	X	
PO IP Dispensation/Accountability		X	X			X		X					

With:

Study Day / Timepoint	Screening & Placebo Run-in	D1 Visit	W2 Visit	W4	W6	W8 Visit	W10 Visit	W12 Visit	W24 Visit	W36 Visit	W48 Visit	W52 Visit	W54 ⁱ EOS Phone Call
<i>General Procedures</i>													
Informed consent	X												
Medical history	X												
Vital Signs (sitting BP, HR, RR, Temp)	X	X				X	X	X	X	X	X	X	
Review for AE/SAE/ADE ^a	X	X	X			X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X			X	X	X	X	X	X	X	X
Dietary instruction	X	X	X			X	X	X					
Physical exam	X							X				X	
Body weight, waist circumference	X											X	
Body height	X												
SF-36		X						X					
Randomization		X											
<i>Central Laboratory</i>													
Fasting lipids ^b	X	X	X			X	X	X	X	X	X	X	
ApoA1, ApoB, Lp(a)		X					X	X	X	X	X	X	
PK, PCSK9		X	X				X	X				X	
Chemistry ^c Hematology ^d	X	X				X		X				X	
hsCRP		X						X				X	
HbA1c	X							X				X	
TSH	X												
Biomarkers (blood)		X						X				X	
Anti-evolocumab antibodies		X						X				X	
HCV antibodies	X												
HCV viral load (only HCV positive patients)		X						X				X	
Serum pregnancy; FSH	X							X				X	
Urine pregnancy^e		X	X			X	X	X					
Urinalysis ^f	X	X						X				X	
SC Placebo Run-in	X												
Q2W SC IP on-site		X	X			X	X	X					
Q2W SC IP non-clinic setting ^g				X	X				X	X	X		
Q2W IP Dispensation/Accountability		X	X			X	X	X	X	X	X	X	
QM SC IP on-site		X				X		X					
QM SC IP non-clinic setting ^h				X					X	X	X		
QM IP Dispensation/Accountability		X	X			X		X	X	X	X	X	
PO IP Dispensation/Accountability		X	X			X	X	X					

Section: 7.1 Schedule of Assessments, Table1, Footnotes

Replace:

Footnotes defined on next page.

^a SAEs are collected from signing of the ICF through 30 days post last dose of IP or EOS, whichever is later (*only AEs possibly related to study procedures from signing of the ICF*)

^b Fasting lipids: Total cholesterol, HDL-C, LDL-C, Triglycerides, VLDL-C, non-HDL-C,

^c Chemistry: Sodium, Potassium, Chloride, Bicarbonate, Total protein, Albumin, Calcium, Magnesium, Phosphorus, Fasting Glucose, BUN or Urea, Creatinine, Uric acid, Total bilirubin, Direct bilirubin, CK, Alk phos, LDH, AST (SGOT), ALT (SGPT)

^d Hematology: RBC, Hemoglobin, Hematocrit, MCV, MCH, MCHC, RDW, WBC, Platelets

^e Urinalysis: Specific gravity, pH, Blood, Protein, Glucose, Bilirubin, WBC, RBC, Epithelial cells, Bacteria, Casts, Crystals

^f Subjects on Q2W dosing will continue non-clinic setting injections after the Week 12 visit per dosing regimen

^g Prior to on-site SC IP administration, women subjects of childbearing potential should have urine pregnancy test performed

^h Subjects on QM dosing will continue non-clinic setting injections after the Week 12 visit per dosing regimen

With:

^a **Review for adverse events, serious adverse events, and adverse device effects. Adverse events possibly related to study procedures, adverse device effects, and serious adverse events** are collected **during the screening period** from signing of the ICF through 30 days post last dose of IP or EOS, whichever is later.

^b Fasting lipids: Total cholesterol, HDL-C, LDL-C, Triglycerides, VLDL-C, non-HDL-C.

^c Chemistry: Sodium, Potassium, Chloride, Bicarbonate, Total protein, Albumin, Calcium, Magnesium, Phosphorus, Fasting Glucose, BUN or Urea, Creatinine, Uric acid, Total bilirubin, Direct bilirubin, CK, Alk phos, LDH, AST (SGOT), ALT (SGPT) .

^d Hematology: RBC, Hemoglobin, Hematocrit, MCV, MCH, MCHC, RDW, WBC, Platelets.

^e Prior to on-site SC IP administration, **female** subjects of childbearing potential should have urine pregnancy test performed.

^f Urinalysis: Specific gravity, pH, Blood, Protein, Glucose, Bilirubin, WBC, RBC, Epithelial cells, Bacteria, Casts, Crystals.

^g Subjects on Q2W dosing will continue non-clinic setting injections after the Week 12 visit per dosing regimen.

^h Subjects on QM dosing will continue non-clinic setting injections after the Week 12 visit per dosing regimen.

ⁱ **For Q2W subjects only.**

Section: 7.2 General Study Procedures, Analyte Listing Table, Footnote*

Replace:

HCV antibodies are measured before initiating treatment with investigational product in subjects at high risk for HCV infection and in subjects with ALT or AST > 2x ULN at any time during screening. Please note that subjects with ALT or AST > 2x ULN must be screen failed unless the elevation is transient as confirmed by retesting. High risk subjects for this protocol are those who meet any of the following conditions:

With:

HCV antibodies are measured before initiating treatment with investigational product in subjects at high risk for HCV infection and in subjects with ALT or AST > 2x ULN at any time during screening. **Conditions that may place subjects at high risk for HCV infection include the following:**

Section: 7.2 General Study Procedures, Paragraph 4

Delete:

Some laboratory results may inadvertently unblind investigators to treatment assignment to evolocumab. Central laboratory results of the lipid panel, ApoA1, ApoB, Lp(a), ~~Vitamin E~~ and hsCRP posttreatment to week 24 will not be reported to the investigator until the unblinding of the clinical database.

Section: 7.2.2 Screening Enrollment and/or Randomization, Paragraph 1, Bullet 4

Replace:

- Review for Adverse Events, Serious Adverse Events (only AEs possibly related to study procedures and SAEs are collected during the screening period from signing of informed consent [ICF]), Adverse Device Effects, and CV Events

With:

- Review for **adverse events, serious adverse events, and adverse device effects.** **Adverse events** possibly related to study procedures, **adverse device effects,** and **serious adverse events** are collected during the screening period from signing of the ICF

Section: 7.2.2 Screening Enrollment and/or Randomization, Paragraph 1, Bullets 10-12

Add:

- Central Laboratory Assessments (**as per Schedule of Assessments**):

- **Subject instruction on self-administration of evolocumab for AI/Pen or Personal Injector**
- AI/Pen placebo injection (does not need to be repeated for rescreening)

Section: 7.2.2 Screening Enrollment and/or Randomization, Paragraph 1, Bullet 10, Sub-bullet 1

Delete:

- Blood draw for fasting lipids (≥ 9 hour fasting sample), chemistry (including fasting glucose), CK, hematology, HbA1c, TSH, (Note: eGFR will be calculated by the central laboratory and will be provided to the site for eligibility determination), blood draws for hepatitis C virus (HCV) antibodies in subjects at high risk for, or with history of, HCV infection and in subjects with AST or ALT $> 2x$ ULN at any time during screening, ~~HCV viral load (only in subjects positive for HCV)~~, serum FSH (only if required to ensure menopause in a female subject by central laboratory)

Section: 7.2.3.1 Visit Day 1 (Randomization), first sentence

Delete:

The following procedures should be conducted at this visit for all subjects unless specified otherwise (~~± 3 days~~).

Section: 7.2.3.1 Visit Day 1 (Randomization), Paragraph 1, Bullet 6

Replace:

- Urine pregnancy test (for women subjects of childbearing potential only)

With:

- Urine pregnancy test (for **female** subjects of childbearing potential only): **precedes on-site SC IP administration**

Section: 7.2.3.1 Visit Day 1 (Randomization), Paragraph 1, Bullet 11

Replace:

- AI/Pen or Personal Injector subject instruction on self-administration of evolocumab

With:

- **Subject instruction on self-administration of evolocumab for AI/Pen or Personal Injector**

Section: 7.2.3.2 Visit/Week 2, Paragraph 1, Bullet 5

Add:

- **Urine pregnancy test (for female subjects of childbearing potential only): precedes on-site SC IP administration**

Section: 7.2.3.2 Visit/Week 2, Paragraph 1, Bullet 8

Replace:

- AI/Pen or Personal Injector subject instruction on self-administration of evolocumab

With:

- **Subject instruction on self-administration of evolocumab for AI/Pen or Personal Injector**

Section: 7.2.3.5 Visit/Week 8, Paragraph 1, Bullet 6

Add:

- **Urine pregnancy test (for female subjects of childbearing potential only): precedes on-site SC IP administration**

Section: 7.2.3.6 Visit/Week 10, Paragraph 1, Bullet 6

Add:

- **Urine pregnancy test (for female subjects of childbearing potential only): precedes on-site SC IP administration**

Section: 7.2.3.6 Visit/Week 10, Paragraph 1, Bullet 10

Add:

- **PO IP dispensing**

Section: 7.2.3.7 Visit/Week 12, Paragraph 1, Bullet 8

Add:

- **Urine pregnancy test (for female subjects of childbearing potential only): precedes on-site SC IP administration visits**

Section: 7.2.4 Safety Follow-up / End of Study Phone Call/Week 54 (\pm 3 days), heading

Add:

7.2.4 Safety Follow-up / End of Study Phone Call/Week 54 (\pm 3 days)

Section: 9.1.1 Definition of Adverse Events, Paragraph 4

Add:

An adverse device effect is any adverse event related to the use of a **combination product or a** medical device.

Section: 9.1.2 Definition of Serious Adverse Events, Paragraph 3

Add:

Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, DILI (**see Appendix A** for drug-induced liver injury reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

Section: 9.2.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria, Paragraph 1

Replace:

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after enrollment and all adverse events possibly related to study procedures from signing of the informed consent through the safety follow-up/end of study (End of Study Phone Call) are reported using the applicable eCRF (eg, Adverse Event Summary).

With:

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after enrollment and all adverse events possibly related to study procedures **and all adverse device effects** from signing of the informed consent through the safety follow-up/end of study (End of Study Phone Call) are reported using the applicable eCRF (eg, Event **eCRF**).

Section: 9.2.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria, Paragraph 3

Add:

Is there a reasonable possibility that the event may have been caused by SC IP or PO IP? **Relatedness means that there are facts or reasons to support a relationship between IP and the event.**

Section: 9.2.2 Reporting Procedures for Serious Adverse Events, Paragraph 3

Add:

Is there a reasonable possibility that the event may have been caused by SC IP or PO IP? **Relatedness means that there are facts or reasons to support a relationship between IP and the event.**

Section: 9.2.2 Reporting Procedures for Serious Adverse Events, Paragraph 7

Delete:

Information provided about the serious adverse event must be consistent with that recorded on the applicable eCRF (eg, ~~Adverse-Event Summary eCRF~~)

Section: 9.2.3 Reporting Serious Adverse Events After the Protocol-required Reporting Period, (Moved from Section 9.2.2, Paragraph 2)

Add:

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

After the protocol-required reporting period defined above **or after end of study**, the investigator does not need to actively monitor subjects for serious adverse events. However, if the investigator becomes aware of a serious adverse event after this protocol required reporting period **or after end of study**, the investigator will report the event to Amgen within 24 hours following the investigator's knowledge of the event.

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

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 (eSAE Contingency Report Form).

Section: 9.3 Pregnancy and Lactation Reporting, Paragraph 1

Replace:

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

With:

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

Section: 9.3 Pregnancy and Lactation Reporting, Paragraph 3

Replace:

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

With:

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

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

Section: 9.3 Pregnancy and Lactation Reporting, Paragraph 6

Replace:

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through an additional 15 weeks after the end of treatment with IP, report the lactation case to Amgen, as specified below.

With:

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of **evolocumab** through an additional 15 weeks after the end of treatment with **evolocumab**, report the lactation case to Amgen, as specified below.

Section: [9.3 Pregnancy and Lactation Reporting](#), Paragraph 7

Replace:

Any lactation case should be reported to Amgen's global Lactation Surveillance Program (LSP) within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C).

With:

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

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

Section: [10.1.1 Study Endpoints](#), Exploratory Endpoints, Bullet 1

Delete:

- ~~• Subject incidence of adjudicated events:~~
 - ~~○ Death by any cause~~
 - ~~○ Cardiovascular death~~
 - ~~○ Myocardial infarction~~
 - ~~○ Hospitalization for unstable angina~~
 - ~~○ Coronary revascularization~~
 - ~~○ Stroke~~
 - ~~○ Hospitalization for heart failure~~
 - ~~○ Transient ischemic attack (TIA)~~

Section: 10.4.2 Primary Analysis

Replace:

To evaluate efficacy and safety of 12 weeks of evolocumab compared with ezetimibe, the primary analysis will be performed when all the randomized subjects in the study have either completed the scheduled visits up to and including Week 12 or have early terminated from the study. At that time, the database of the study will be cleaned, processed and a snapshot will be taken; the study will also be unblinded.

With:

To evaluate efficacy and safety of 12 weeks of evolocumab compared with ezetimibe **and summarize 12 weeks of data from the open-label extension (weeks 12 to 24)**, the primary analysis will be performed when all the randomized subjects in the study have either completed the scheduled visits up to and including Week **24** or have early terminated from the study. At that time, the database of the study will be cleaned, processed and a snapshot will be taken; the study will also be unblinded.

Section: 10.5.1 General Considerations, Paragraph 1

Replace:

The superiority of evolocumab to ezetimibe will be assessed for all efficacy endpoints.

With:

The **treatment effect** of evolocumab **compared** to ezetimibe will be **evaluated** for all efficacy endpoints **through the Week 12 visit. In addition, descriptive analyses from the open-label extension (weeks 12 to 24) will be performed on OLEAS.**

Section: 10.5.2 Primary Efficacy Endpoint, Additional Analyses

Add:

The co-primary endpoints will also be assessed within each dose frequency using dose frequency matched control (ie, evolocumab Q2W SC plus placebo PO QD vs. ezetimibe QD plus placebo Q2W SC; evolocumab QM SC **plus placebo PO QD** vs. ezetimibe QD plus placebo QM SC) and pooled ezetimibe (ie, evolocumab Q2W vs. pooled ezetimibe; evolocumab QM vs. pooled ezetimibe).

Section: 10.5.5 Safety Endpoints, After Paragraph 1

Delete:

~~Subject incidence of all disease related events and fatal disease related events will be tabulated by system organ class and preferred term.~~

Section: 10.5.6 Exploratory Endpoint Analyses, Paragraph 2

Delete:

~~Death, myocardial infarction, hospitalization for unstable angina, coronary revascularization, stroke, TIA, and hospitalization for heart failure will be adjudicated by an independent CEC. Non-coronary revascularizations will be collected on the eCRF and will not be adjudicated. Subject incidence of exploratory endpoint events will be summarized for each treatment group.~~

Section: 12.6 Publication Policy, Paragraph 2 and bullet 1

Replace:

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

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

With:

Authorship of any publications resulting from this study will be determined on the basis of the **Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals** (International Committee of Medical Journal Editors, **2013, updated 2014**), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; **(4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.** Authors should meet conditions 1, 2, 3, and 4.

Section: [Appendix A](#), Drug-induced Liver Injury Reporting & Additional Assessments Reporting, Paragraph 1 Bullet 2

Delete:

- The appropriate eCRF (eg, ~~Adverse-Event~~ eCRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Amgen.

Section: Appendix C

Replace:

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: 20140234				
Study Design: <input checked="" type="checkbox"/> Interventional <input type="checkbox"/> Observational (If Observational: <input type="checkbox"/> Prospective <input type="checkbox"/> Retrospective)				
2. Contact Information				
Investigator Name _____		Site # _____		
Phone (____) _____		Fax (____) _____		Email _____
Institution _____				
Address _____				
3. Subject Information				
Subject ID # _____ Subject Gender: <input type="checkbox"/> Female <input type="checkbox"/> Male Subject DOB: mm ____/dd ____/yyyy ____				
4. Amgen Product Exposure				
Amgen Product	Dose at time of conception	Frequency	Route	Start Date mm ____/dd ____/yyyy ____
Was the Amgen product (or study drug) discontinued? <input type="checkbox"/> Yes <input type="checkbox"/> No				
If yes, provide product (or study drug) stop date: mm ____/dd ____/yyyy ____				
Did the subject withdraw from the study? <input type="checkbox"/> Yes <input type="checkbox"/> No				
5. Pregnancy Information				
Pregnant female's LMP mm ____/dd ____/yyyy ____ <input type="checkbox"/> Unknown				
Estimated date of delivery mm ____/dd ____/yyyy ____ <input type="checkbox"/> Unknown <input type="checkbox"/> N/A				
If N/A, date of termination (actual or planned) mm ____/dd ____/yyyy ____				
Has the pregnant female already delivered? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> N/A				
If yes, provide date of delivery: mm ____/dd ____/yyyy ____				
Was the infant healthy? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> N/A				
If any Adverse Event was experienced by the infant, provide brief details: _____				

Form Completed by:				
Print Name: _____		Title: _____		
Signature: _____		Date: _____		

Amgen maintains a Pregnancy Surveillance Program that collects data about pregnancy of women who have been exposed to an Amgen product directly or via male sexual partner. Information from this program and from other sources of information, will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during pregnancy.

AMGEN Lactation 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: 20140234				
Study Design: <input type="checkbox"/> Interventional <input type="checkbox"/> Observational (If Observational: <input type="checkbox"/> Prospective <input type="checkbox"/> Retrospective)				
2. Contact Information				
Investigator Name _____		Site # _____		
Phone (____) _____	Fax (____) _____	Email _____		
Institution _____				
Address _____				
3. Subject Information				
Subject ID # _____		Subject Date of Birth: mm____/dd____/yyyy____		
4. Amgen Product Exposure				
Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____
Was the Amgen product (or study drug) discontinued? <input type="checkbox"/> Yes <input type="checkbox"/> No				
If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____				
Did the subject withdraw from the study? <input type="checkbox"/> Yes <input type="checkbox"/> No				
5. Breast Feeding Information				
Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? <input type="checkbox"/> Yes <input type="checkbox"/> No				
If No, provide stop date: mm____/dd____/yyyy____				
Infant date of birth: mm____/dd____/yyyy____				
Infant gender: <input type="checkbox"/> Female <input type="checkbox"/> Male				
Is the infant healthy? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> 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: _____

Amgen maintains a Lactation Surveillance Program that collects data about women who have been exposed to an Amgen product while breastfeeding. Information from this program and from other sources of information will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during lactation.
 Effective Date: 03 April 2012, version 2. Page 1 of 1

With:

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: 20140234				
Study Design: <input type="checkbox"/> Interventional <input type="checkbox"/> Observational (If Observational: <input type="checkbox"/> Prospective <input type="checkbox"/> Retrospective)				
2. Contact Information				
Investigator Name		Site #		
Phone ()	Fax ()	Email		
Institution				
Address				
3. Subject Information				
Subject ID #		Subject Gender: <input type="checkbox"/> Female <input type="checkbox"/> Male	Subject DOB: mm / dd / yyyy	
4. Amgen Product Exposure				
Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm / dd / yyyy
Was the Amgen product (or study drug) discontinued? <input type="checkbox"/> Yes <input type="checkbox"/> No				
If yes, provide product (or study drug) stop date: mm / dd / yyyy				
Did the subject withdraw from the study? <input type="checkbox"/> Yes <input type="checkbox"/> No				
5. Pregnancy Information				
Pregnant female's LMP		mm / dd / yyyy <input type="checkbox"/> Unknown		
Estimated date of delivery		mm / dd / yyyy <input type="checkbox"/> Unknown <input type="checkbox"/> N/A		
If N/A, date of termination (actual or planned) mm / dd / yyyy				
Has the pregnant female already delivered? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> N/A				
If yes, provide date of delivery: mm / dd / yyyy				
Was the infant healthy? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> N/A				
If any Adverse Event was experienced by the infant, provide brief details:				

Form Completed by:	
Print Name:	Title:
Signature:	Date:

AMGEN Lactation 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: 20140234

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

2. Contact Information

Investigator Name _____ Site # _____
Phone (____) _____ Fax (____) _____ Email _____
Institution _____
Address _____

3. Subject Information

Subject ID # _____ Subject Date of Birth: mm ____ / dd ____ / yyyy ____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm ____ / dd ____ / yyyy ____

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

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

Did the subject withdraw from the study? Yes No

5. Breast Feeding Information

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

If No, provide stop date: mm ____ / dd ____ / yyyy ____

Infant date of birth: mm ____ / dd ____ / yyyy ____

Infant gender: Female Male

Is the infant healthy? Yes No Unknown N/A

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

Form Completed by:

Print Name: _____ Title: _____
Signature: _____ Date: _____

Amendment 1

Protocol Title: A Double-blind, Randomized, Multicenter Study to Evaluate the Safety and Efficacy of Evolocumab, Compared With Ezetimibe, in Hypercholesterolemic Japanese Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor Due to Muscle Related Side Effects

GAUSS-4: Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects

Amgen Protocol Number (Evolocumab) 20140234

Original Protocol: 20 January 2015
Amendment Date: 09 September 2015

Rationale:

The protocol is being amended for the following key reasons:

- To reduce the washout period for ezetimibe from 4 weeks to 1 week. In the initial protocol, a 4-week washout for ezetimibe was mandated in order to remain consistent with the other evolocumab protocols. Since ezetimibe half-life is 22 hours, a 1-week washout is sufficient to ensure adequate washout for accurate baseline lipid laboratories. Based on updated feedback from Japanese opinion leaders, the standard 4-week ezetimibe washout was expected to create a large hurdle for enrollment therefore reducing the washout time to 1-week is necessary.
- To reduce the approximate sample size from 100 to 60 subjects. In the initial protocol, a sample size of 100 subjects was selected because it provided a conservative number of subjects to evaluate safety in a high risk population. Based on feasibility results, it appears very unlikely that 100 subjects can be enrolled in a reasonable timeframe. Based on updated feedback from Japanese opinion leaders, a sample size of 60 is considered feasible and adequate to assess safety in this patient population. Study power has also been updated to reflect the change in sample size.
- Remove PO IP dispensing from week 10 as week 8 dispensing provides a sufficient supply of IP.
- Correct IP dispensation/accountability in schedule of events.
- Revise study schema to include all on-site visits.
- Revise exclusion criteria with updated contraception language.
- Clarify adverse event collection language and clarify adverse event definition.
- Add "Adverse Device Effects" review at each visit as per new protocol template.

- Add footnote to schedule of events on collection of SAEs to maintain consistency within the protocol.
- Add IP PO dispensation/accountability to schedule of events to maintain consistency within the protocol.
- Add SC IP accountability to study procedures at week 52 to maintain consistency with schedule of events.
- Additional additions and clarifications added throughout after PMDA review, including:
 - Addition of “GAUSS-4: Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects” to end of protocol title
 - Clarified laboratory results will remain blinded from posttreatment to week 24 until unblinding of the clinical database.
 - Clarified investigators will be provided laboratory results starting with week 24 until the end of study
 - Removed pharmacogenetic analysis from protocol
 - Changed number of sites from approximately 20 to approximately 40
- Make minor corrections and clarifications throughout, including administrative, typographical, and formatting changes.