

Title: A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability, and Efficacy of Evolocumab (AMG 145) on LDL-C in Subjects With Type 2 Diabetes Mellitus and Hypercholesterolemia/Mixed Dyslipidemia

Amgen Protocol Number (AMG 145/Evolocumab) 20130287

EudraCT Number 2015-004711-21

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Amendment 1 Date 06 January 2016

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I have read the attached protocol entitled "A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability, and Efficacy of Evolocumab (**AMG 145**) on LDL-C in Subjects With Type 2 Diabetes Mellitus and Hypercholesterolemia/Mixed Dyslipidemia", dated **06 January 2016**, and agree to abide by all provisions set forth therein.

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Signature

Name of Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability, and Efficacy of Evolocumab (AMG 145) on LDL-C in Subjects With Type 2 Diabetes Mellitus and Hypercholesterolemia/Mixed Dyslipidemia

Study Phase: 3b

Indication: Hypercholesterolemia/Mixed Dyslipidemia

Primary Objective: To evaluate the effect of 12 weeks of subcutaneous (SC) evolocumab monthly (QM) compared with placebo QM on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in subjects with type 2 diabetes mellitus and hypercholesterolemia or mixed dyslipidemia on maximally tolerated **dose of** statin of at least moderate-intensity oral daily.

Secondary Objective(s): To assess the effects of 12 weeks of SC evolocumab QM compared with placebo QM, in subjects with type 2 diabetes mellitus and hypercholesterolemia or mixed dyslipidemia in combination with maximally tolerated **dose of** statin of at least moderate-intensity oral daily on the following:

- Change from baseline in LDL-C, and percent change from baseline in non-high-density lipoprotein cholesterol (HDL-C), apolipoprotein B (ApoB), total cholesterol (TC), lipoprotein(a) (Lp[a]), triglycerides, HDL-C, and very low-density lipoprotein cholesterol (VLDL-C)
- Percent of subjects attaining LDL-C < 70 mg/dL (1.8 mmol/L)
- Percent of subjects attaining a 50% reduction in LDL-C from baseline

Safety Objective: To evaluate the safety and tolerability of SC evolocumab QM compared with placebo QM in subjects with type 2 diabetes mellitus and hypercholesterolemia or mixed dyslipidemia in combination with maximally tolerated **dose of** statin of at least moderate-intensity oral daily.

Hypotheses: Subcutaneous evolocumab 420 mg QM in combination with statin once daily will be well tolerated and will result in greater reduction of LDL-C, defined as mean percent change from baseline at weeks 10 and 12 and percent change from baseline at week 12, compared with placebo QM in subjects with type 2 diabetes mellitus and hypercholesterolemia or mixed dyslipidemia on maximally tolerated **dose of** statin of at least moderate-intensity daily.

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

Co-secondary Endpoints:

For the mean of weeks 10 and 12 and for week 12:

- Tier 1
 - Change from baseline in LDL-C
 - Percent change from baseline in non-HDL-C
 - Percent change from baseline in ApoB
 - Percent change from baseline in TC
 - Achievement of target LDL-C < 70 mg/dL (1.8 mmol/L)
 - LDL-C response (50% reduction of LDL-C from baseline)
- Tier 2
 - Percent change from baseline in Lp(a)
 - Percent change from baseline in triglycerides

- Percent change from baseline in HDL-C
- Percent change from baseline in VLDL-C

Safety Endpoints:

- Subject incidence of treatment emergent adverse events
- Safety laboratory values and vital signs at each scheduled assessment

Study Design: This is a phase 3b, multicenter, double-blind, randomized, placebo-controlled study designed to assess the efficacy and safety of evolocumab in subjects with type 2 diabetes mellitus with hypercholesterolemia or mixed dyslipidemia.

Sample Size: Approximately 400 subjects **with type 2 diabetes mellitus with hypercholesterolemia or mixed dyslipidemia.**

Summary of Subject Eligibility Criteria: The study will enroll adult subjects (≥ 18 years of age) with type 2 diabetes mellitus **and elevated LDL-C or non-HDL-C levels** on a stable, maximally tolerated statin **dose** of at least moderate-intensity at **signing of the informed consent; statin therapy must remain unchanged during screening and the remainder of the study.**

Subjects must have hemoglobin A1c (HbA1c) $< 10\%$, **must have** been receiving pharmacologic treatment for diabetes mellitus for ≥ 6 months prior to screening, with stable diabetes therapy prior to randomization to investigational product (IP) and not expected to change throughout the duration of study participation. For a full list of eligibility criteria, please refer to [Section 4.1](#) through [Section 4.1.2](#).

Investigational Product: The Amgen investigational medicinal product (IMP) is evolocumab and placebo. The Amgen IP is the IMP plus the device (automated mini-doser [AMD] or prefilled autoinjector [AI]/Pen). In this document, IMP will be referred to as IP.

Amgen Investigational Product Dosage and Administration: Evolocumab 420 mg or matching placebo will be administered QM at day 1 and weeks 4 and 8 as an SC injection. The IP is expected to be delivered by AMD but may be achieved by 3 injections with AI/Pen if AMD is not available. Observed, in-clinic dosing should occur at day 1 and week 8 ± 3 days, and subjects will self-administer in an appropriate non-clinic setting (eg, at home) for week 4 ± 3 days.

Procedures: The study will consist of 2 periods: the screening/lipid stabilization period and the double-blind treatment period.

After signing the informed consent, subjects will enter a screening period up to 6 weeks including a 4-week lipid stabilization during which their appropriate-dose statin is continued. Subjects are required to be on a stable, maximally tolerated statin of at least moderate-intensity during screening. Screening laboratory tests, including lipid testing, will be conducted during week 2 of screening/lipid stabilization. Subjects must tolerate a SC injection of placebo **with device anticipated to be used during the study (either AI/Pen or AMD)** prior to randomization. Subjects who meet all eligibility criteria at the end of the screening/lipid stabilization period will be randomized and initiate their first dose of IP within 5 days of randomization.

During the double-blind treatment period, study visits will occur at day 1, week 8 (± 3 days), week 10 (± 3 days), and week 12 (± 3 days); with baseline evaluations performed on day 1 of treatment before subjects receive the first dose of IP. All subjects will complete a mixed meal tolerance test (MMTT) at the day 1 and week 12 study visits with a baseline and 2-hour (± 10 min) postprandial blood collection after the meal. Up to approximately 100 subjects not treated with prandial insulin or glucagon-like peptide-1 agonists will participate in MMTT Extended Timepoints assessments with 3 additional postprandial blood draws at 30 minutes (± 10 min), 1 hour (± 10 min), and 3 hours (± 10 min) after the meal. End of study for all subjects will be at the week 12 (± 3 days) visit.

The overall study design is described by a [study schema](#) at the end of this synopsis section. For a full list of study procedures, including the timing of each procedure, please refer to [Section 7](#) and the Schedule of Assessments ([Table 1](#)).

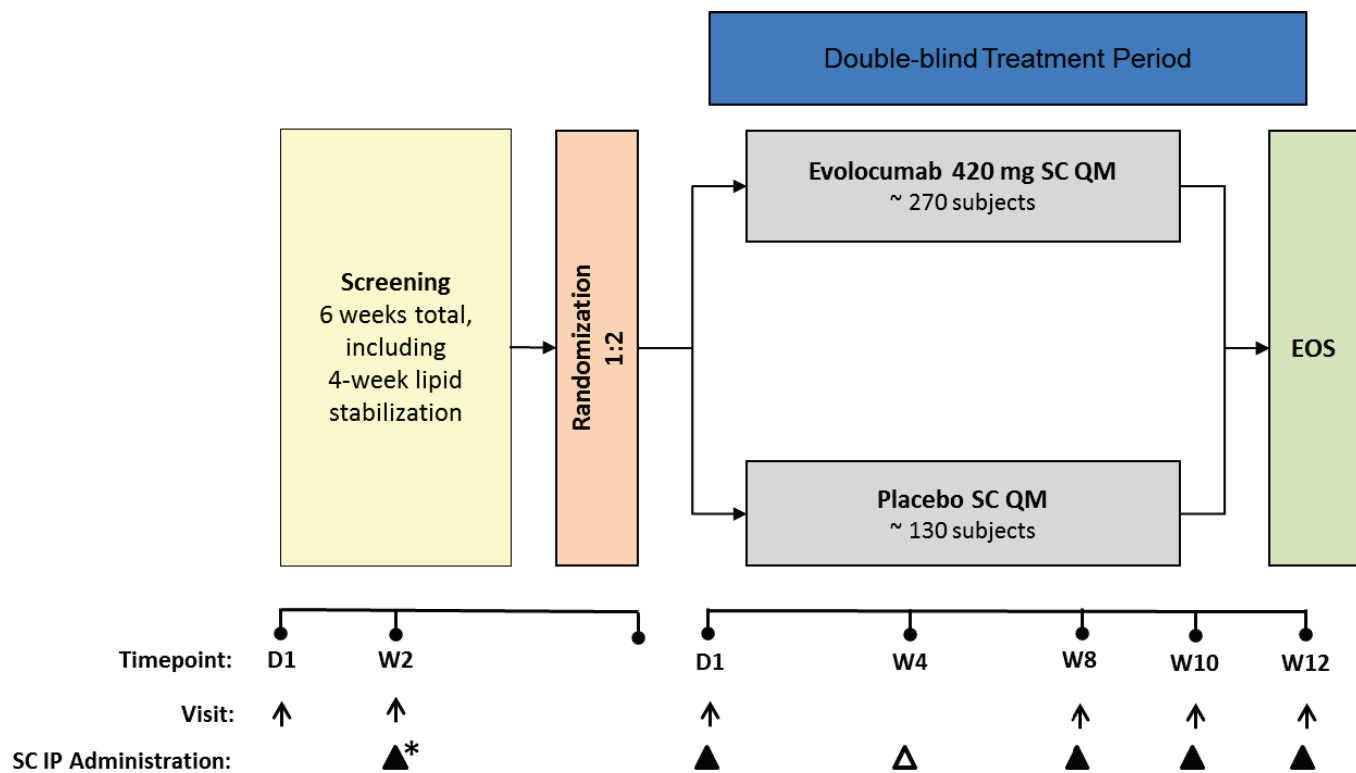
Statistical Considerations: The primary analysis will be performed when all randomized subjects in the double-blind treatment period have either completed all scheduled study visits in the double-blind treatment period or have terminated from the study. The superiority of evolocumab to placebo will be assessed for all efficacy endpoints on the full analysis set (FAS), which includes all randomized subjects who receive at least one dose of IP. Methods of adjusting for multiplicity due to multiple endpoints are provided in [Section 10.5.1](#). To assess the co-primary endpoints of the mean percent change from baseline (mean of **screening** week 2 and day 1) in LDL-C at weeks 10 and 12 and the percent change in LDL-C from baseline at week 12, a repeated measures linear effects model will be used on the FAS to compare the efficacy of evolocumab QM with placebo QM. The repeated measures model will include terms for treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit. Analysis of co-secondary endpoints will use the same analysis model as the co-primary endpoints. The co-secondary endpoints of LDL-C response (achievement of LDL-C < 70 mg/dL and achievement of > 50% LDL-C reduction from baseline) will be analyzed using the Cochran-Mantel Haenszel test adjusted by the stratification factor. Safety endpoints will be summarized descriptively by treatment group.

Sponsor: Amgen Inc.

Data Element Standards
Version(s)/Date(s):

Version 5/ 20 March 2015

Study Design and Treatment Schema



EOS=end of study; IP=investigational product; QM=once monthly; SC=subcutaneous

Study Glossary

Abbreviation or Term	Definition/Explanation
ADE	adverse device effect
AE	adverse event
AI	autoinjector
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMD	automated mini-doser
ApoA1	apolipoprotein A-I
ApoB	apolipoprotein B
ApoB48	apolipoprotein B48
AST	aspartate aminotransferase
BP	blood pressure
BUN	blood urea nitrogen
CAS	completer analysis set
CHD	coronary heart disease
CK	creatinine kinase
CPK	creatinine phosphokinase
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CVD	cardiovascular disease
CYP	cytochrome P450
DILI	drug-induced liver injury
DRE	device related event
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
End of Study (end of trial)	defined as the date when the last subject has completed all planned study procedures up to and including the visit as outlined in the Schedule of Assessments
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 the 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
EOS	end of study
FAS	full analysis set
FBG	fasting blood glucose

Abbreviation or Term	Definition/Explanation
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
ICF	informed consent form
ICH	International Conference on Harmonisation
IFU	Information for Use
IL-6	interleukin-6
IMP	investigational medicinal product
IP	investigational product
IPIM	Investigational Product Instruction Manual
IRB/IEC	institutional review board/independent ethics committee
IVRS	interactive voice response system, telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.
IWRS	interactive web response system
LDH	lactate dehydrogenase
LDL-C	low-density lipoprotein cholesterol
LDLR	low-density lipoprotein receptor
LH	luteinizing hormone
Lp(a)	lipoprotein(a)
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MMTT	mixed meal tolerance test
PCSK9	proprotein convertase subtilisin/kexin type 9
PO	orally
PT	prothrombin time
QD	once daily
QM	once monthly
RBC	red blood cells
RDW	red blood cell distribution width
SAE	serious adverse event
SD	standard deviation

Abbreviation or Term	Definition/Explanation
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline (E6)). Examples of source data include subject identification, randomization identification, and stratification value.
Study day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
TBL	total bilirubin
TC	total cholesterol
ULN	upper limit of normal
VLDL-C	very low-density lipoprotein cholesterol
WBC	white blood cells

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1. OBJECTIVES

1.1 Primary

- To evaluate the effect of 12 weeks of subcutaneous (SC) evolocumab monthly (QM) compared with placebo QM on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in subjects with type 2 diabetes mellitus and hypercholesterolemia or mixed dyslipidemia on maximally tolerated **dose of** statin of at least moderate-intensity oral daily.

1.2 Secondary

- To assess the effects of 12 weeks of SC evolocumab QM compared with placebo QM, in subjects with type 2 diabetes mellitus and hypercholesterolemia or mixed dyslipidemia in combination with maximally tolerated **dose of** statin of at least moderate-intensity oral daily on the following:
 - Change from baseline in LDL-C, and percent change from baseline in non-high-density lipoprotein cholesterol (HDL-C), apolipoprotein B (ApoB), total cholesterol (TC), lipoprotein(a) [Lp(a)], triglycerides, HDL-C, and very low-density lipoprotein cholesterol (VLDL-C)
 - Percent of subjects attaining LDL-C < 70 mg/dL (1.8 mmol/L)
 - Percent of subjects attaining a 50% reduction in LDL-C from baseline

1.3 Safety

- To evaluate the safety and tolerability of SC evolocumab QM compared with placebo QM in subjects with type 2 diabetes mellitus and hypercholesterolemia or mixed dyslipidemia in combination with maximally tolerated **dose of** statin of at least moderate-intensity oral daily.

1.4 Exploratory

To describe the effects over time of SC evolocumab QM compared with placebo QM, in subjects with type 2 diabetes mellitus and hypercholesterolemia or mixed dyslipidemia in combination with maximally tolerated statin of at least moderate-intensity oral daily on:

- change from baseline in proprotein convertase subtilisin/kexin type 9 (PCSK9) levels and on change from baseline and percent change from baseline of LDL-C, TC, non-HDL-C, ApoB, VLDL-C, HDL-C, apolipoprotein A-I (ApoA1), triglycerides, and Lp(a)
- change and percent change from baseline on fasting and postprandial plasma laboratory parameters of interest including glucose, insulin, pro-insulin, C-peptide, free fatty acids, glucagon, lipids, chylomicrons, apolipoprotein B48 (ApoB48), interleukin-6 (IL-6), adiponectin after a mixed meal tolerance test (MMTT)
- the relationship between novel and established biochemical cardiovascular and lipid biomarkers and effects of evolocumab
- potential correlations of study data including the subject response to evolocumab with genetic variation in markers of PCSK9 signaling, low-density lipoprotein receptor (LDLR) turnover, cholesterol metabolism, inflammation, and plaque stability in subjects consenting to the optional pharmacogenetic analysis

2. BACKGROUND AND RATIONALE

2.1 Disease

Cardiovascular diseases (CVD) accounted for over 17 million of these deaths, nearly 80% of which were due to heart attacks and strokes alone (responsible for 7.3 million and 6.2 million deaths, respectively). Type 2 diabetes mellitus is a major independent risk factor for CVD-coronary heart disease (CHD) and stroke, and conditions such as hypertension and dyslipidemia frequently coexist with diabetes ([American Diabetes Association, 2005](#)). Most diabetic patients have an approximately 2-fold increased level of cardiovascular risk compared to nondiabetics, even when established CHD is absent. Patients with type 2 diabetes also have an increased prevalence of lipid abnormalities contributing to the increased risk of cardiovascular disease ([Arca, 2007](#)). Therefore, treatment guidelines recommend aggressive lipid treatment goals for patients with diabetes (eg, [Brunzell et al, 2008](#); [Grundy et al, 2004](#); [Reiner et al, 2011](#); [Chinese Society of Cardiology of Chinese Medical Association, 2011](#)).

A direct correlation between dyslipidemia and cardiovascular-related deaths has been demonstrated across several global regions ([Menotti et al, 2008](#); [Imano et al, 2011](#); [Yang et al, 2012](#)). Because dyslipidemia is a major modifiable risk for the development of CVD, therapies for hyperlipidemia/dyslipidemia can translate into an opportunity for significantly reducing cardiovascular morbidity and mortality throughout different populations and world regions.

2.2 Amgen Investigational Product Background

Recycling of the hepatic cell surface LDLR plays a critical role in regulating serum LDL-C levels. Proprotein convertase subtilisin/kexin type 9 binds to the LDLR and down regulates hepatic cell surface LDLR, which, in turn, leads to increased levels of circulating LDL-C. Humans with PCSK9 loss-of-function mutations have cholesterol levels lower than normal and reduced incidence of CHD ([Abifadel et al, 2009](#)).

Evolocumab (formerly referred to as AMG 145) is a fully human monoclonal immunoglobulin G2, developed at Amgen Inc., that specifically binds to PCSK9 preventing its interaction with the LDLR. The inhibition of PCSK9 by evolocumab leads to increased LDLR expression and subsequent decreased circulating concentrations of LDL-C.

Refer to the [Evolocumab Investigator's Brochure](#) for more information on evolocumab.

2.3 Rationale

It is anticipated that evolocumab may be used in diabetic individuals who cannot achieve their LDL-C goals despite the use of maximally tolerated statin therapy (Bruckert et al, 2005; Franc et al, 2003). Therefore, it is important to understand the safety and efficacy of evolocumab on the background of statin therapy in diabetic patients.

2.4 Clinical Hypotheses

The primary hypothesis of this study is that SC evolocumab 420 mg QM in combination with statin once daily will be well tolerated and will result in greater reduction of LDL-C, defined as mean percent change from baseline at weeks 10 and 12 and percent change from baseline at week 12, compared with placebo QM in subjects with type 2 diabetes and hypercholesterolemia or mixed dyslipidemia on maximally tolerated **dose of** statin of at least moderate intensity daily.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 3b, multicenter, double-blind, randomized, placebo-controlled study designed to assess the efficacy and safety of evolocumab in subjects with type 2 diabetes mellitus with hypercholesterolemia or mixed dyslipidemia. All subjects will be treated with maximally tolerated statin of at least moderate-intensity (intensity as specified by the 2013 American College of Cardiology/American Heart Association guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults; see [Appendix D](#)). Baseline lipid-lowering therapy is expected to be continued unchanged throughout the study.

The study will consist of 2 periods:

- Screening up to 6 weeks including a 4-week lipid stabilization and placebo injection
- Double-blind treatment period (12 weeks)

After signing the informed consent, subjects will enter the screening/lipid stabilization period during which their appropriate-dose statin is continued. Screening laboratory tests including lipid testing will be conducted during week 2 of the screening/lipid stabilization period. Subjects must tolerate a SC injection of placebo **with device anticipated to be used during the study (either AI/Pen or AMD)** prior to randomization. Subjects who meet all eligibility criteria at the end of the screening/lipid stabilization period will be randomized in a 2:1 ratio into the following treatment arms:

- SC evolocumab 420 mg QM (~270 subjects)
- SC placebo QM (~130 subjects)

Randomization will be stratified by LDL-C (above or below 130 mg/dL).

Day 1 is defined as the calendar day when treatment with investigational product (IP) is initiated. Subjects should initiate their first dose of IP within 5 days of randomization. During the double-blind treatment period, study visits will occur at day 1, week 8 (± 3 days), week 10 (± 3 days), and week 12 (± 3 days); with baseline evaluations performed on day 1 of treatment before subjects receive the first dose of IP. All subjects will complete a MMTT at the day 1 and week 12 study visits with baseline (0 hours) and postprandial blood collection at 2 hours (± 10 min) after the meal. Up to approximately 100 subjects not treated with prandial insulin or glucagon-like peptide-1 (GLP-1) agonists will participate in MMTT Extended Timepoints assessments with 3 postprandial blood draws at 30 minutes (± 10 min), 1 hour (± 10 min), and 3 hours (± 10 min) after the meal in addition to the blood draws at 0 and 2 hours (± 10 min) after the meal for all subjects.

3.2 Number of Sites

Approximately 80 sites globally will participate in this study. Sites that do not enroll subjects within 3 months of site initiation may be closed.

3.3 Number of Subjects

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

Approximately 400 subjects **with type 2 diabetes mellitus with hypercholesterolemia or mixed dyslipidemia** will be enrolled.

3.4 Replacement of Subjects

Subjects who are withdrawn or removed from **investigational medicinal product (IMP)** treatment or the study will not be replaced.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

Including the screening/lipid stabilization period and study treatment period, the maximum total duration of study participation for a subject will be approximately 18 weeks, or approximately 4.5 months. After signing the informed consent, subjects should be randomized within 6 weeks.

3.5.2 End of Study

The primary completion is defined as the date when the last subject has completed the assessments for week 12 **or has terminated the study early, whichever is later.**

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). This log may be completed and updated via an interactive voice response system (IVRS)/interactive web response system (IWRS).

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

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria

- 101 Subject has provided written informed consent
- 102 Male or female ≥ 18 years of age at signing of informed consent
- 103 Type 2 diabetes mellitus:
 - with hemoglobin A1c (HbA1c) $< 10\%$
 - receiving pharmacologic treatment for diabetes mellitus for ≥ 6 months prior to screening
 - stable diabetes therapy prior to randomization to IP and not expected to change during the duration of study participation. Stable diabetes therapy is defined as no new agents added, and no dose change of any antihyperglycemic drug within 2 months prior to randomization and daily insulin dose not changed by $> 25\%$ and > 25 units within 1 month prior to randomization
- 104 Subject must be on maximally tolerated **dose** of statin of at least moderate intensity at **signing of the informed consent** (see [Appendix D](#)) and is expected to remain on stable statin intensity for the duration of study in the opinion of the investigator:
 - Subjects without known **clinical** CVD must be on at least moderate-intensity statin
 - Subjects with known **clinical** CVD must be on high intensity statin (or moderate intensity if certified by principal investigator to be highest tolerated dose). **Clinical CVD is defined as a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin**
- 105 Subjects without known **clinical** CVD must have a fasting LDL-C during lipid stabilization of ≥ 100 mg/dL (2.6 mmol/L) or non-HDL-C ≥ 130 mg/dL (3.4 mmol/L) as determined by the central laboratory

- 106 Subjects with known **clinical** CVD must have a fasting LDL-C during lipid stabilization of ≥ 70 mg/dL (1.8 mmol/L) or Non-HDL-C ≥ 100 mg/dL (2.6 mmol/L) as determined by the central laboratory
- 107 Fasting triglycerides ≤ 600 mg/dL (6.8 mmol/L) by central laboratory prior to randomization
- 108 Subject tolerates screening placebo injection

4.1.2 Exclusion Criteria

- 201 Myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft or stroke within 3 months prior to randomization
- 202 Uncontrolled hypertension defined as sitting systolic blood pressure (BP) > 180 mmHg or diastolic BP > 110 mmHg
- 203 Subject has taken a cholesterylester transfer protein inhibitor in the last 12 months prior to randomization, such as: anacetrapib, dalcetrapib, or evacetrapib
- 204 Moderate to severe renal dysfunction, defined as an estimated glomerular filtration rate < 20 mL/min/1.73 m² during screening
- 205 Persistent active liver disease or hepatic dysfunction, defined as Child-Pugh score of C (**see Appendix E**)
- 206 Female subject of childbearing potential not willing to use an acceptable method(s) of effective birth control during the screening/lipid stabilization period, during treatment with IP and for an additional 15 weeks after the end of treatment with IP.

Female subjects of non-childbearing potential are not required to use contraception during the study and include those who have had a hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or who are postmenopausal. Postmenopausal is defined as 12 months of spontaneous and continuous amenorrhea in a female ≥ 55 years old; or age < 55 years but no spontaneous menses for at least 2 years; or age < 55 years and spontaneous menses within the past 1 year, but currently amenorrheic (eg, spontaneous or secondary to hysterectomy), and with postmenopausal gonadotropin levels (luteinizing hormone and follicle stimulating hormone levels > 40 IU/L) or postmenopausal estradiol levels (< 5 ng/dL) or according to the definition of "postmenopausal range" for the laboratory involved.

Acceptable methods of effective birth control include:

- true sexual abstinence when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception),
- vasectomized partner (provided that partner is the sole sexual partner of the female participant who is of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success),
- bilateral tubal ligation/occlusion, use of hormonal birth control methods (**oral**, intravaginal [**eg, vaginal ring**], transdermal, injectable, or implantable),
- intrauterine devices,

- intrauterine hormonal releasing system, or
- 2 barrier methods (each partner must use one barrier method) and the female partner must use **if available** spermicide in addition to a barrier – males must use a condom; females must choose either a diaphragm, OR cervical cap, OR contraceptive sponge. **(Note: If spermicide is not commercially available in the country or region, the two barrier method without spermicide would then be considered acceptable).**

Note: Additional medications given during the study may alter the contraceptive requirements. These additional medications may require an increase in the number of contraceptive methods, the change in type of contraceptive methods and/or length of time that contraception is to be utilized **and/or** length of time breastfeeding is to be avoided. The investigator is to discuss these contraceptive changes with the study subject.

- 207 Female subject is pregnant or breast feeding, or planning to become pregnant or planning to breastfeed during the screening/lipid stabilization period, during treatment with IP and for an additional 15 weeks after the end of treatment **with IP**
- 208 Malignancy (except non-melanoma skin cancers, cervical in situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma) within the last 1 year prior to randomization
- 209 Subject has previously received evolocumab or any other therapy to inhibit PCSK9
- 210 Currently receiving treatment in another investigational device or IP, or < 30 days since ending treatment on another investigational device or drug study(s) or planning to receive other investigational procedures while participating in this study
- 211 Subject has known sensitivity to any of the active substances or their excipients to be administered during dosing, eg, carboxymethylcellulose
- 212 Subject likely to not be available to complete all protocol required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge
- 213 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

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 (ICF), and all other subject information and/or recruitment material, if applicable (see [Section 11.2](#)). All subjects must personally sign and date the ICF before commencement of study specific activities/procedures.

A subject is considered enrolled **upon randomization in IVRS/IWRS**, when the investigator decides that the subject has met all eligibility criteria, including 4 weeks of tolerating the appropriate dose of statin. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (defined as the point at which the subject signs the ICF) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by the 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 are unable to complete or meet eligibility on initial screening will be permitted to re-screen **once** except for subjects without known **clinical** CVD and fasting LDL-C < 100 mg/dL and non-HDL-C < 130 mg/dL **and subjects with known clinical CVD and LDL-C < 70 mg/dL and non-HDL-C < 100 mg/dL** by central lab result during screening (see [Section 7.2.2](#)) **who are considered screen failures and who 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.

5.1 Randomization/Treatment Assignment

Subjects who meet the eligibility requirements ([Section 4.1](#)) will be randomly assigned in a 2:1 allocation ratio to 2 treatment groups (evolocumab and placebo) in a double-blind manner. Randomization will be stratified by LDL-C (above or below 130 mg/dL).

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

Subjects can only be randomized 1 time for this study. **Once** subjects **are** randomized their first dose of IP **must be administered** within 5 days of randomization (**day 1 visit**).

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 Investigational Product Instruction Manual (IPIM) for a description regarding how responsible pharmacists and investigators will access treatment information via the IVR/IWR system, in the event that there is a need to break the blind.

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

6. TREATMENT PROCEDURES

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

The Amgen IP used in this study is evolocumab and matching placebo. In several countries, IP is referred to as IMP. In this document, IMP will be referred to as IP.

The investigational medical device is the automated mini-doser (AMD), or the spring based prefilled autoinjector (AI)/pen if AMD is not available. Note: Ancillary device(s) (ie, any medical device[s] not under study) are described in [Section 6.6](#).

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

6.2 Investigational Product

Evolocumab and matching placebo will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures.

Evolocumab 420 mg and placebo SC will be supplied as an AMD but may be supplied as a prefilled an AI/Pen if AMD not available:

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

Placebo will be presented in identical containers and stored/packaged the same as evolocumab.

6.2.1 Dosage, Administration, and Schedule

6.2.1.1 Screening/Lipid Stabilization

During screening/lipid stabilization, subjects will undergo SC placebo injection with the device to be used during the study (AMD or AI/Pen). Subjects must tolerate the placebo injection prior to randomization.

6.2.1.2 Double-blind Treatment Period

The IP (420 mg evolocumab or matching placebo via AMD, or AI/Pen if the AMD is not available) will be administered QM on day 1, week 4, and week 8. The IP is expected to be delivered by AMD but may be achieved by 3 injections with AI/Pen if AMD not available.

Subcutaneous evolocumab and placebo will be administered at the study site or in an appropriate non-clinic setting (eg, at home). Observed, in-clinic dosing should occur at day 1 and week 8 and at home by the subject at week 4. Subjects who do not wish to self-inject at home may return to the clinic for injection.

The IP will be administered in accordance with instructions in the IPIM and the Information for Use (IFU). The subject (or designee, if not a qualified healthcare professional) must have demonstrated competency, as per site judgment, at administration of SC injections before self-administration is permitted: the first self-administered dose by the subject (or designee, if not a healthcare professional) must be administered at the site under the supervision of a healthcare provider. If IP is to be administered during the study visit, administration must occur after all other procedures have been completed.

When IP is mandated to be administered at the study site, the date and completion time of administration, the body location of the injection, and whether the injection was administered fully, or partially, or not at all administered, in addition to the reason for a partial/lack of injection, are to be recorded on each subject's CRF provided. When IP can be administered at an appropriate non-clinic setting (eg, at home) a non-investigator site location, at a minimum, the dates the devices were dispensed and returned, the used devices returned, the number of devices dispensed and returned, and number of devices administered fully, partially, or not at all, in addition to the reason for a partial/lack of injection, must be provided whether each device was returned fully or partially used are to be recorded on each subject's CRF.

Overdose with this product has not been reported.

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

No dose adjustments are allowed 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 study (EOS).

If a dose of evolocumab is missed, administration should occur as soon as possible if there are more than 7 days until the next scheduled dose. If there are less than 7 days before the next scheduled dose, the missed dose should be omitted and the next dose should be administered according to the original schedule.

6.3 Other Protocol-required Therapies

All other protocol-required therapies including, at least moderate intensity statin and pharmacologic treatment for type 2 diabetes mellitus, that are commercially available are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-required therapies.

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

6.4 Hepatotoxicity Stopping and Rechallenge Rules

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

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

Amgen IP (evolocumab/placebo) 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 \geq 2x ULN
- AND increased AST or ALT \geq 3x ULN **if** baseline value were less than the ULN
- AND ALP $<$ 2x 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
 - Non-hepatic causes (eg, rhabdomyolysis, hemolysis)

6.4.2 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 IP (**evolocumab or placebo**) 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 IP 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	> 8 × ULN at any time
Any	> 5 × ULN but < 8 × ULN for ≥ 2 weeks
Any	> 5 × ULN but < 8 × ULN and unable to adhere to enhanced monitoring schedule
Any	> 3 × ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice).

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

Evolocumab/placebo and other protocol-required therapies should be withheld pending investigation into alternative causes of DILI. If IP 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 6.4.3](#)).

6.4.3 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/placebo should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in [Section 6.4.1](#)) should never be rechallenged.

6.5 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in [Section 6.8](#). Concomitant therapies are to be collected in the CRF from the signing of the ICF through the EOS.

Prior general and targeted therapies (**ie**, statins, other lipid-lowering **therapies**, and **pharmacologic treatment for type 2 diabetes mellitus**), taken 120 days prior to randomization should be collected with the following information: therapy name, indication, dose, unit, frequency, route, start date and stop date.

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

For all other concomitant therapies, collect therapy name, indication, unit, frequency, route, start date and stop date.

6.6 Medical Devices

The AMD and prefilled AI/Pen used in this study will be provided by Amgen. Additional details for the AMD and AI/Pen is to be provided in the IPIM and IFU.

Ancillary 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 that are commercially available are not usually provided or

reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

6.7 Product Complaints

A product complaint is defined by Amgen as any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug(s) or device(s) provisioned and/or repackaged/modified by Amgen. Drugs or devices include evolocumab/placebo and AMD or prefilled AI/Pen.

Concerns or irregularities about the packaging, appearance or usage of the IP or device are to be reported to Amgen within 24 hours of discovery or notification of the concern or irregularity. Should any such concerns or irregularities occur please do not use the IP 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 AMD or the prefilled AI/Pen);
- 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 study drug prefilled cartridge, or
- Evidence of tampering or stolen material.

If possible, please have the suspect product available for examination when making a product complaint and maintain the IP at appropriate storage conditions until further instructions are received from Amgen.

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

Additional details regarding the identification and reporting of any product **and/or device** complaint(s) associated with an investigational product(s) or non-investigational product(s) or device(s) supplied by Amgen are provided in the IPIM.

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

The following treatments are not permitted during the study:

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

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

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

- Medications or foods that are known potent inhibitors of CYP3A (eg, itraconazole, ketoconazole, and other antifungal azoles, macrolide antibiotics erythromycin, clarithromycin, and the ketolide antibiotic telithromycin, human immunodeficiency virus or hepatitis C virus (HCV) protease inhibitors, antidepressant nefazodone and grapefruit juice in large quantities (> 1 quart daily [approximately 1 L]) should not be used during the study.

7. STUDY PROCEDURES

Screening assessments and study procedures outlined in this section and in [Table 1](#) can only be performed after obtaining informed consent.

All on-study visits and dosing should be scheduled from day 1 (first IP administration). For example, the week 4 **dose** is 4 calendar weeks after the study day 1 visit, corresponding to study day 28. When it is not possible to perform the study visit at the specified time point, the visit should be performed within the visit window specified in [Table 1](#). If a study visit is missed or late, including visits outside the visit window, subsequent visits should resume on the original visit schedule. Missed assessments at prior visits should not be duplicated at subsequent visits. With the exception of screening, all study procedures for a visit should be completed on the same day if possible.

Refer to the applicable supplemental laboratory manuals for detailed collection and handling procedures.

7.1 Schedule of Assessments

Screening assessments and study procedures are outlined in this section and in [Table 1](#) (Schedule of Assessments).

Table 1. Schedule of Assessments

Study Day / Week / Timepoint	Screening/ Lipid Stabilization (up to 6 weeks including 4-week lipid stabilization)		Double-blind Treatment Period			
	Screening Day 1	Screening Week 2 ± 3 days	Week 4 ± 3 days	Week 8 ± 3 days	Week 10 ± 3 days	Week 12 EOS ± 3 days
General Procedures						
Informed consent	X					
Medical history	X					
Vital Signs (BP and heart rate)	X	X	X	X	X	X
Physical Exam	X	X	X	X	X	X
Safety Data	X	X	X	X	X	X
Collection/Reporting^a						
Concomitant therapy	X	X	X	X	X	X
Body weight, waist circumference			X			X
Body height			X			
Randomization			X			
Central Laboratory^p						
Fasting lipids ^c		X	X		X	X
ApoA1, ApoB, Lp(a)			X		X	X
PCSK9			X		X	X
Chemistry		X	X			X
eGFR		X				
Hematology			X			
Coagulation (Prothrombin time)		X				
HbA1c		X	X			X
MMTT ^d			X			X
MMTT Extended Timepoints ^d			X			X
Biomarkers (blood) ^e			X			X
HCV antibody testing		X				
HCV viral load ^f		X	X			X
Serum pregnancy ^g ; FSH/LH or estradiol ^h		X				X
Local urine pregnancy			X			

Table 1. Schedule of Assessments

Study Day / Week / Timepoint	Screening/ Lipid Stabilization (up to 6 weeks including 4-week lipid stabilization)		Double-blind Treatment Period			
	Screening Day 1	Screening Week 2 ± 3 days	Week 4 ± 3 days	Week 8 ± 3 days	Week 10 ± 3 days	Week 12 EOS ± 3 days
Urinalysis, Urine protein, Urine creatinine, urine microalbumin			X			X
<i>Investigational Product</i>						
Screening placebo injection		X				
In-clinic IP injection QM			X	X		
Non-clinic setting IP injection QM			X			
IP dispense			X	X		
IP reconciliation QM				X		

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ApoA1=apolipoprotein A-I; ApoB=apolipoprotein B; ApoB48=apolipoprotein B48; BP=blood pressure;
eGFR=estimated glomerular filtration rate; EOS=end of study; HbA1c=hemoglobin A1c; HCV=hepatitis
C virus; IL-6=interleukin-6; FSH/LH=follicle-stimulating hormone/luteinizing hormone; IP=investigational
product; Lp(a)=lipoprotein(a); MMTT=mixed meal tolerance test; PCSK9=proprotein convertase
subtilisin/kexin type 9; QM=once monthly

^a Review for adverse events/serious adverse events/disease-related events/adverse device effects. Only
adverse events possibly related to study procedures, adverse device effects and serious adverse events
are collected during screening from signing of the informed consent. **All serious adverse events must
be collected through 30 days after the last administration of IP or the EOS/ safety follow-up visit,
whichever is later, and submitted to Amgen.**

^b Blood samples must be taken prior to IP administration, if applicable.

^c If subject is not fasting on screening week 2 and day 1, reschedule; if subject is not fasting after day 1, do
all procedures except fasting labs and IP administration, if applicable; schedule another visit, if possible
within the visit window for fasting labs and IP administration.

^d Postprandial blood draw at 120 ± 10 mins after standardized mixed meal for all subjects; additional
postprandial blood draws at 30 ± 10 mins, 60 ± 10 mins, and 180 ± 10 mins for subjects participating in the
MMTT Extended Timepoints. Analytes collected include: plasma glucose, insulin, proinsulin, C-peptide,
free fatty acids, glucagon, lipids, chylomicrons, ApoB48, IL-6, adiponectin, measured after an overnight
fast just prior to a standardized meal (0 minutes), and then 120 minutes. Other markers for metabolic
status may be assessed as well.

^e **Anti-evolocumab antibodies may be tested, if needed.** If the subject consented to pharmacogenetic
portion of the study, DNA analysis may be performed. **One cell pellet is collected only at day 1
(residual cell pellet from the plasma biomarker sample).**

^f Viral load only in subjects positive for HCV.

^g **Serum** pregnancy testing in females of childbearing potential. Additional on-treatment **local** pregnancy
testing may be performed at the investigator's discretion or as required by local laws and regulations.

^h FSH/LH or estradiol only at screening, **and only if applicable per exclusion criteria.**

7.2 General Study Procedures

The procedures performed at each study visit are outlined [Table 1](#). Details regarding
each type of procedure are provided in subsequent sub-sections.

Before each study visit where fasting lipid samples are obtained, subjects must be fasting overnight. If the subject is not fasting for the screening or the day 1 visit, no visit procedures are performed and the visit should be rescheduled within the applicable protocol windows. If subject is not fasting after day 1, all procedures except fasting labs and IP administration, if applicable, will be performed and another visit should be scheduled, within the visit window if possible, for fasting labs and IP administration.

For each study visit when IP is administered at the site, administration must be after completion of blood draw procedures, if applicable.

Subjects will be encouraged to complete all planned visits regardless of their adherence to IP administration.

7.2.1 Screening Enrollment and Randomization

Informed consent must be obtained before completing any other screening procedure or discontinuation of standard therapy for any disallowed therapy. After signing the written ICF, site will register the subject in the IVRS/IWRS and screen the subject in order to assess eligibility for participation.

Subjects will undergo subcutaneous placebo injection with device anticipated to be used during study (either AI/Pen or AMD) prior to randomization. Subject must tolerate injection prior to randomization.

The screening window is 6 weeks. If a subject has not met all eligibility criteria at the end of the 6-week window, the subject will be registered as a screen fail. Screen fail subjects may be eligible for rescreening once as described in [Section 7.2.2](#).

Subjects on maximally tolerated statin (as determined by the PI) of at least moderate-intensity meeting study eligibility criteria will continue with screening/lipid stabilization. On week 2 of screening/lipid stabilization, study labs including lipid panel will be obtained. Subjects who continue to tolerate appropriate intensity statin therapy and meet laboratory eligibility criteria will be eligible for enrollment at the end of screening/ lipid stabilization.

7.2.2 Rescreening

Subjects who are unable to complete or meet eligibility on initial screening will be permitted to rescreen once. Rescreen subjects must first be registered as screen failed in IVRS/IWRS and subsequently registered as rescreened. Subjects will retain the same subject identification number assigned at the original screening. Subjects without known **clinical** CVD and fasting LDL-C < 100 mg/dL **and** non-HDL-C < 130 mg/dL during

screening are considered screen failures and cannot be rescreened for this study.

Subjects with known clinical CVD and LDL-C < 70 mg/dL and non-HDL-C < 100 mg/dL during screening are considered screen failures and cannot be rescreened for this study. Subjects who are to be rescreened must be re-consented and repeat all screening procedures other than the screening placebo injection.

7.2.3 Double-blind Treatment Period

Visits will occur per the Schedule of Assessments ([Table 1](#)) during the treatment period from day 1 through week 12. Visits during the treatment period must be completed within ± 3 days of the target visit date. For visits with IP administration at the study site, administration should be the last procedure to be performed during each visit.

Evolocumab/placebo is to be self-administered in an appropriate non-clinic setting (eg, at home) at week 4 ± 3 days. Subjects who do not wish to self-inject at home may return to clinic for injection. Observed, in-clinic dosing should occur at day 1 and at week 8 ± 3 days.

If a subject withdraws from the study early, all efforts should be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. The procedures for the EOS visit should be completed at the time of withdrawal ([Section 7.2.4](#)).

7.2.4 End of Study Visit

An EOS visit is scheduled to occur at week 12 ± 3 days.

Subjects who discontinue study participation before their week 12 ± 3 days visit per protocol are considered early termination.

7.2.5 Safety Follow-up

Sites are responsible for reporting safety information **through** 30 days after the last dose of IP or EOS, as applicable. For further details, see [Section 9.2](#).

7.3 Description of Study Procedures

The sections below provide a description of the individual study procedures.

7.3.1 Informed Consent

All subjects must sign and personally date the IRB/IEC approved informed consent before any study specific procedures are performed.

7.3.2 Demographic Data

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally demographic data will be used to study the impact on biomarkers variability of the protocol-required therapies.

7.3.3 Medical History

The investigator or designee will collect a complete medical covering the period within 120 days prior to randomization. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF.

In addition, a targeted cardiovascular history including, but not limited to, cardiovascular risk factors, history of cardiovascular disease, revascularization procedures, family history, and potential familial hypercholesterolemia diagnostic criteria will be collected. Targeted diabetes **mellitus** history including, but not limited to, duration, complications, and history of ketoacidosis from diagnosis will be collected.

7.3.4 Vital Signs

The following measurements must be performed: BP and heart rate will be determined after the subject has been seated for at least 5 minutes. The appropriate size cuff should be used.

During screening, blood pressure measurements can be repeated if the previous reading was outside of the eligibility range. The repeat blood pressure measurement should be taken at least 2 minutes after the previous one.

7.3.5 Physical Examination

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

7.3.6 Concomitant Therapy

Prior general and targeted therapies (eg, statins, other lipid-lowering **therapies**, **pharmacologic treatment for type 2 diabetes mellitus**) will be collected as specified in [Section 6.5](#).

Concomitant therapies are to be collected from the signing of the ICF through the EOS visit, and should include the therapy name, indication, dose, unit, frequency, route, start date, and stop date. Concomitant medications include over-the-counter products and vitamins administered while the subject is on study.

7.3.7 Height, Weight, and Waist Circumference

Body weight and height should be measured without shoes.

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

7.4 Laboratory Assessments

Central laboratory **assessments are to be used to assess subject eligibility (except for the urine pregnancy test, [Section 7.1](#))**. **All other screening or scheduled study laboratory assessments will also be by the central laboratory.** Concentration values are provided in mmol/L for investigator convenience. Conventional concentrations (mg/mL) will be used for the protocol, including for eligibility determination. The estimated glomerular filtration rate (eGFR) will be calculated by the central laboratory and provided to the site for eligibility determination.

The central laboratory will provide a study manual that outlines handling, labeling, and shipping procedures for all samples.

All blood samples will be obtained by venipuncture before IP administration. The date and time of sample collection will be recorded in the source documents at the site. Specific analytes for serum chemistry, coagulation, urinalysis, hematology, and other labs to be conducted on blood and urine samples are shown in [Table 2](#). Although not specifically listed, additional components, abnormal, and/or atypical cells will also be reported if present.

Table 2. Analyte Listing

Chemistry	Hematology	Coagulation	Urinalysis	Other Labs
Sodium	Hemoglobin	PT	Specific gravity	Fasting lipids
Potassium	Hematocrit		pH	• Total cholesterol
Chloride	RBC		Blood	• HDL-C
Bicarbonate	RDW		Protein	• LDL-C
Total protein	MCV		Glucose	• Triglycerides
Calcium	MCH		Bilirubin	• VLDL-C
Magnesium	MCHC		WBC	• non-HDL-C
Phosphorus	Platelets		RBC	ApoA1
Uric Acid	WBC		Epithelial cells	ApoB
CK	Morphology and differential:		Bacteria	ApoB48
Alkaline phosphatase	• Neutrophils		Casts	Lp(a)
LDH	• Eosinophils		Crystals	Insulin
Albumin	• Basophils		Microalbumin	Proinsulin
FBG	• Lymphocytes		Creatinine	C-peptide
BUN or Urea	• Monocytes			Free fatty acids
Creatinine				Glucagon
Total bilirubin				Chylomicrons
Direct bilirubin				IL-6
AST				Adiponectin
ALT				PCSK9
eGFR				HbA1c
				Urine and serum pregnancy test (females of childbearing potential)
				FSH/LH or Estradiol (if needed per exclusion 206)
				HCV antibody
				HCV viral load (if required)

7.4.1 Blinding of Laboratory Test Results

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

- Blinded to the Amgen study team and site staff: lipid panel, ApoA1, ApoB, lipoprotein(a), PCSK9
- Blinded to the site staff: insulin, proinsulin, C-peptide, free fatty acids, glucagon, chylomicrons, ApoB48, IL-6, and adiponectin. Analyses of proinsulin, C-peptide, free fatty acids, glucagon, chylomicrons, ApoB48, IL-6, and adiponectin may not be completed until end of study so results are not expected to be available during the trial.

In addition, investigators should not perform non-protocol testing of these analytes during a subject's study participation. **Investigators will be informed if triglycerides are > 1000 mg/dL (11.3 mmol/L) so that appropriate subject follow-up can be initiated.**

7.4.2 Mixed Meal Tolerance Test (All Subjects)

A liquid MMTT will be performed after an overnight fast at the day 1 and the week 12 study visits. Each MMTT should be done at approximately the same time of day throughout the study (± 2 hours) and must be completed prior to dosing with IP **at day 1**. The fasting venous blood samples at each of these 2 visits should be collected as close as possible before the subject consumes a standardized mixed meal (Table 3) and before the subject receives any food or drink (other than water).

Subjects are then fed a standardized mixed meal, as defined in Table 3, for example Boost®. The same standardized mixed meal should be used for day 1 and week 12. The subject should consume the standard meal in less than 20 minutes, and consumption should be observed by study staff.

The beginning of the consumption of the liquid mixed meal is considered time "0" of the MMTT. Postprandial blood samples are to be collected at 120 ± 10 minutes after consumption of the standardized mixed meal for assessment of plasma glucose, insulin, proinsulin, C-peptide, free fatty acids, glucagon, lipids, chylomicrons, ApoB48, IL-6, and adiponectin.

Table 3. Example Standardized Mixed Meal per 240 mL

Content	
Protein (grams)	10
Total Fat (grams)	4
Carbohydrate (grams)	41
Calories (kcal)	240

Note the component weight in the standardized mixed meal used should not differ by more than $\pm 15\%$. The same type standard mixed meal should be used for day 1 and week 12.

7.4.3 Mixed Meal Tolerance Test Extended Timepoints

Approximately the first 100 subjects not on prandial insulin or GLP-1 agonists will undergo the MMTT Extended Timepoints assessments. The assessments consist of 4 postprandial blood draws in the MMTT on day 1 and week 12. Postprandial blood draws for subjects participating in the assessments will be at the following timepoints after consumption of the standardized meal:

- 30 ± 10 min
- 60 ± 10 min
- 120 ± 10 min
- 180 ± 10 min

The same postprandial analytes will be measured at each of these timepoints.

7.4.4 Serum Pregnancy Test

All females, except those who are confirmed surgically sterile or at least 2 years postmenopausal or 1 year postmenopausal if ≥ 55 years old must have a negative serum pregnancy test at screening week 2, prior to administering the first dose of evolocumab/placebo. The central laboratory will provide the baseline pregnancy tests.

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

7.5 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Biomarker development can be useful in developing markers to identify disease subtypes, guide therapy, and/or predict disease severity. Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to evolocumab.

For all subjects in the study, blood will be collected at day 1 and week 12 so that biomarkers related to, but not limited to PCSK9 signaling, LDLR turnover, cholesterol metabolism, inflammation, and plaque stability such as certain glycosylated proteins, matrix metalloproteinases, additional markers of inflammation such as myeloperoxidase, bromo- and nitro-tyrosine, and tumor necrosis factor cellular adhesion molecules may be studied. The samples must be kept at -70°C at all times and shipped in 1 batch on dry ice at the end of the study.

7.6 Pharmacogenetic Studies

No additional blood will be collected for the pharmacogenetic analyses. If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations such as those of the *PCSK9* gene or the *LDLR* gene to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the

investigation of cardiovascular disease, hypercholesterolemia, and other metabolic disorders and/or to identify subjects who may have positive or negative response to evolocumab.

7.7 Sample Storage and Destruction

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

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

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

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

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

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

See [Section 11.3](#) for subject confidentiality.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

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

Subjects (or a legally acceptable representative) can decline to continue receiving IP 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 IP 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 IP 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 IP 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 IP or procedural assessments include any of the following, **but not limited to**:

- subject request
- safety concern (eg, due to an adverse event, pregnancy in a female subject)
- death
- lost to follow-up
- decision by **Sponsor** (other than subject request, safety concern or lost to follow-up)

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

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

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Disease-related Events

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

Disease-related events and/or disease-related outcomes that do not qualify as serious adverse events:

- An event which is part of the normal course of disease under study, **with no causal relationship with IP/protocol-required therapies** (eg, disease progression or

hospitalization due to disease progression) is to be reported as a disease-related event.

- Death **is** due to the disease under study; **the event** is to be recorded on the Event CRF **as a disease-related event**.

If the outcome of the underlying disease is worse than that which would normally be expected for the subject, or if the investigator believes there is a causal relationship between the IP/study treatment protocol-required therapies and disease worsening, the **event** must be reported as an adverse event or serious adverse event.

9.1.2 Adverse Events

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

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

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

9.1.3 Adverse Device Effects

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

9.1.4 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria (unless it meets the definition of a disease-related event as defined in [Section 9.1.1](#)):

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

A disease-related event as described above is to be reported as a serious adverse event if:

- the event meets at least 1 of the serious criteria above, **AND**
- the subject's pre-existing condition becomes worse than what the investigator would consider typical for a patient with the same underlying condition, OR
- the investigator believes a causal relationship exists between the IP/protocol-required therapies and the 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 DILI reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

If adverse events correspond to grade 4 "life threatening" Common Terminology Criteria for Adverse Events (CTCAE) grading scale criteria (eg, laboratory abnormality reported as Grade 4 without manifestation of life threatening status), it will be left to the investigator's judgment to also report these abnormalities as serious adverse events.

For any adverse event that applies to this situation, comprehensive documentation of the event's severity status must be recorded in the subject's medical record.

9.2 Safety Event Reporting Procedures

9.2.1 Disease-related Events

The investigator is responsible for ensuring that all disease-related events observed by the investigator or reported by the subject that occur from the time of randomization through the EOS/safety follow-up visit are reported using the Event CRF. Additionally, the investigator is required to report a fatal disease-related event on the Event CRF.

Events assessed by the investigator to be related to the IP/study treatment/protocol-required therapies, and determined to be serious, require reporting of the event on the Event CRF.

9.2.2 Adverse Events

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

Adverse events possibly related to study procedures, adverse device effects and serious adverse events are reported from signing of the ICF. All other adverse events are reported from the time of randomization. The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur **from signing of the ICF or from the time of** randomization through the EOS/safety follow-up visit are reported using the Event CRF.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Severity (and/or toxicity per protocol),
- Assessment of relatedness to IP (evolocumab/placebo and/or the medical devices: AMD or the AI/Pen), or any study-mandated activity or procedure or other protocol required therapies, and
- Action taken.

The adverse event grading scale used will be the 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 the IP (evolocumab or placebo). This relationship is indicated by a “yes” or “no” response to the question: “Is there a reasonable possibility that the event may have been caused by the IP?”

The investigator must assess whether the adverse event is possibly related to the AI/Pen or the AMD investigational device used to administer IP. The relationship is

indicated by a “yes” or “no” response to the question: “Is there a reasonable possibility that the event may have been caused by the investigational device?”

The investigator must assess whether the adverse event is possibly related to any other study-mandated activity or procedure (eg. administration of IP, 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/procedure” (eg. administration of IP, protocol-required therapies, device(s) and/or procedure?)

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

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

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

9.2.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the ICF through 30 days after the last administration of IP or the EOS/ safety follow-up visit, 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 Event CRF.

If the electronic data capture (EDC) system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen via an electronic serious adverse event Contingency Report Form within 24 hours of the investigator’s knowledge of the event. See [Appendix B](#) for a sample of the Serious Adverse Event Worksheet /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 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 Event CRF.

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

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities. 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 GCP.

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.

In addition to the attributes listed in [Section 9.2.2.1](#), the investigator must also complete the serious adverse event section of the Event CRF.

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

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after EOS. However, these serious adverse events can be reported to Amgen. In some countries (eg, European Union member states), investigators are required to report serious adverse events that they become aware of after EOS. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

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

9.2.2.4 Serious Adverse Events That are not to be Reported in an Expedited Manner

Hospitalizations due to chronic diabetic complications are anticipated to occur in the patient population **enrolled in this study and are therefore not planned to be reported individually in an expedited manner**. The Amgen safety and medical teams will review accumulating events on a regular basis.

9.3 Pregnancy and Lactation Reporting

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-required therapies 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 protocol-required therapies through 15 weeks after the end of treatment with evolocumab/placebo.

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

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

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through 15 weeks after the end of treatment with evolocumab/placebo.

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

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Co-primary Endpoints

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

10.1.1.2 Co-secondary Endpoints

For the mean of weeks 10 and 12 and for week 12:

- Tier 1
 - Change from baseline in LDL-C
 - Percent change from baseline in non-HDL-C
 - Percent change from baseline in ApoB
 - Percent change from baseline in TC
 - Achievement of target LDL-C <70 mg/dL (1.8 mmol/L)
 - LDL-C response (50% reduction of LDL-C from baseline)
- Tier 2
 - Percent change from baseline in Lp(a)
 - Percent change from baseline in triglycerides
 - Percent change from baseline in HDL-C
 - Percent change from baseline in VLDL-C

10.1.1.3 Exploratory Endpoints

- change and percent change from baseline at each scheduled assessment in each of the following parameters:
 - LDL-C
 - non-HDL-C
 - ApoB
 - TC
 - VLDL-C
 - HDL-C
 - ApoA1

- triglycerides
 - Lp(a)
- HbA1c at each scheduled assessment
- Fasting blood glucose (FBG) at each scheduled assessment
- PCSK9 change from baseline at each scheduled assessment
- fasting and post-prandial laboratory parameters of interest (including Mixed Meal Tolerance Test (MMTT) Extended Timepoints assessments) change and percent change from day 1 to week 12 in response to a MMTT in glucose, insulin, pro-insulin, C-peptide, free fatty acids, glucagon, lipids, chylomicrons, ApoB48, IL-6, adiponectin

10.1.1.4 Safety Endpoints

- subject incidence of treatment emergent adverse events
- safety laboratory values and vital signs at each scheduled assessment

10.1.2 Analysis Sets

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

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

10.1.3 Covariates and Subgroups

Baseline covariates include, but are not limited to:

- Stratification factor in the double-blind treatment period:
 - LDL-C < 130 mg/dL / ≥ 130 mg/dL
- Age: < 65 years / ≥ 65 years
- Sex
- Race
- Study baseline LDL-C: < median / ≥ median
- Family history of premature CHD: yes/no
- Baseline PCSK9

10.2 Sample Size Considerations

The planned sample size for the comparison between evolocumab 420 mg QM and placebo at a ratio of 2:1 in the double-blind treatment period is 400 total subjects.

The primary analysis will require the 2-sided tests of co-primary endpoints to be significant at a level of 0.05. The planned sample size should provide adequate power to determine the superiority of evolocumab 420 mg QM relative to placebo as measured by the co-primary endpoints. From the phase 3 studies integrated efficacy analysis, the treatment effect of evolocumab 420 mg QM compared to placebo and the corresponding 95% confidence interval at week 12 was -61.98% [-69.51%, -60.45%], with treatment effect ranges between -55.1% to -62.33% from Studies 20110114, 20110115, and 20110117. The assumed treatment effect between the primary endpoint in evolocumab 420 mg QM is 40%, with a common standard deviation (SD) of 20%. This SD assumption is based on evolocumab phase 3 results.

This sample size will provide approximately 99% power for the primary endpoint in testing the superiority of evolocumab dose regimen over placebo, assuming a dropout rate of 10%.

From the phase 3 studies the treatment effects measured as mean of week 10 and week 12 were as large or larger than week 12 and highly correlated (> 85%) with ones at week 12. Therefore the sample size as planned will provide at least 98% (99% × 99%) power in testing the superiority of evolocumab over placebo on the co-primary endpoints.

From the phase 3 evolocumab studies the treatment effect of evolocumab over placebo in the percentage reduction in triglycerides at week 12 was approximately 12% with a common SD of 35%. However, the SD for triglycerides in a diabetic population may be higher. [Table 4](#) displays the power associated with various SD assumptions.

Table 4. Power Associated With Standard Deviation Assumptions

Treatment effect = 12% reduction Sample size = 400 (5% dropout) Significance level = 5%	
Standard Deviation	Power
35	0.88
40	0.78
45	0.68
50	0.59

For HDL-C the treatment effect of evolocumab over placebo observed in the phase 3 studies at week 12 was a percentage increase of approximately 5% with a common SD of 15%. Assuming 400 subjects and a 5% drop out rate, this would provide approximately 86% power to test the superiority of evolocumab over placebo

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

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

10.4 Planned Analyses

To evaluate efficacy and safety of 12 weeks of evolocumab 420 mg QM compared with placebo, the primary analysis will be performed when all randomized subjects in the double-blind treatment period have either completed all the scheduled study visits in the double-blind treatment period 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.

10.5 Planned Methods of Analysis

10.5.1 General Considerations

Efficacy and safety analyses will be performed on FAS unless otherwise specified, and data will be summarized by randomized treatment group.

Subject disposition, demographics, baseline characteristics and exposure to IP will be summarized by treatment group. Summary statistics for continuous variables will include the number of subjects, mean, median, SD, or standard error, minimum, and maximum. For categorical variables, the frequency and percentage will be given.

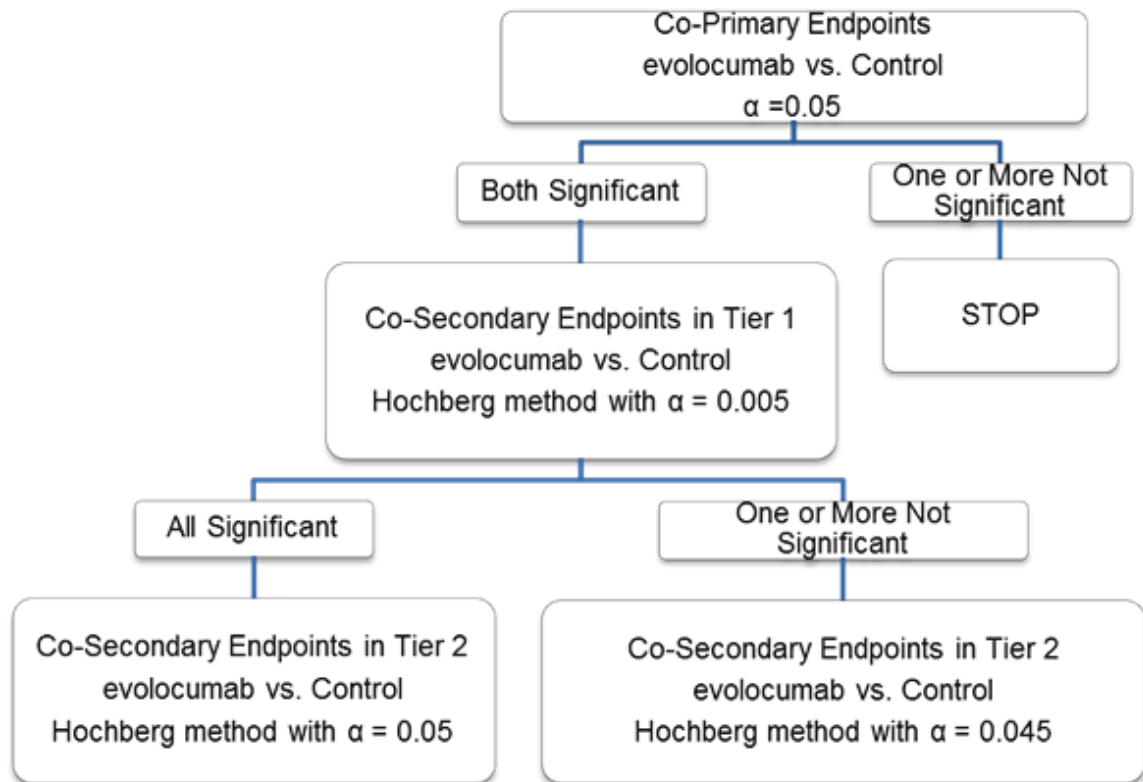
Methods of handling missing data for efficacy endpoints will be described below.

Missing data will not be imputed for safety endpoints.

10.5.1.1 Multiplicity Adjustment Method

Methods of adjusting for multiplicity due to multiple endpoints (primary and secondary efficacy endpoints) in order to preserve the familywise error rate at 0.05 are described in [Figure 1](#).

Figure 1. Multiplicity Adjustment Methods



Testing of each co-endpoint pair 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 method will be used to preserve the family wise 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 Co-primary Efficacy Endpoints

To assess the co-primary endpoints of the mean percent change from baseline (**mean of screening week 2 and day 1**) in LDL-C at weeks 10 and 12 and the percent change

in LDL-C from baseline at week 12, a repeated measures linear effects model will be used on the FAS to compare the efficacy of evolocumab QM with placebo QM. The repeated measures model will include terms for treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit. Missing values will not be imputed for primary analysis.

10.5.2.1 Sensitivity Analysis

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

- The primary analysis will be repeated using the CAS
- Non-parametric analyses will be performed

A sensitivity analysis under the assumption that subjects who discontinued IP with missing endpoint data have a mean zero percent change from baseline will be conducted.

10.5.2.2 Subgroup Analysis

If applicable, subgroup analyses on the primary endpoint will be conducted using the stratification factor or baseline covariates.

10.5.3 Co-secondary Efficacy Endpoints

Analysis of co-secondary endpoints will use the same analysis model as the co-primary endpoints. The co-secondary endpoints of LDL-C response (achievement of LDL-C < 70 mg/dL and achievement of > 50% LDL-C reduction from baseline) will be analyzed using the Cochran-Mantel Haenszel test adjusted by the stratification factor.

10.5.4 Safety Endpoints

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

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

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample ICF is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Clinical 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 IP is 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 ICF is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed ICF is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject.

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

11.2 Institutional Review Board/Independent Ethics Committee

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

copy of the written approval of the protocol and ICF must be received by Amgen before recruitment of subjects into the study and shipment of Amgen IP.

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 throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen.

11.3 Subject Confidentiality

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

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

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

11.4 Investigator Signatory Obligations

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

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

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

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

12.2 Study Documentation and Archive

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

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

In this study, the IVRS/IWRS system captures the following data points and these are considered source data:

- Case report form entries may be considered source data if the CRF is the site of the original recording (ie, there is no other written or electronic record of data).
- The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable

for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRFs, ICFs, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts, IP Accountability Record(s), Return of IP for Destruction Form(s), Final IP Reconciliation Statement, as applicable.

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

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

12.3 Study Monitoring and Data Collection

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

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

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

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global 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 CRFs must be maintained and readily available.
- Updates to CRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this EDC study or the investigator applies an electronic signature in the EDC system if the study is set up to accept an electronic signature. This signature indicates that investigator inspected or reviewed the data on the CRF, the data queries, and agrees with the content.

Amgen (or designee) will perform self-evident corrections 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 ([Table 1](#)), 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.

12.6 Publication Policy

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

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

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

12.7 Compensation

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

13. REFERENCES

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

Refer to the NCI Common Terminology Criteria for Adverse Events (CTCAE)
Version 4.0.

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 according to the criteria specified in [Section 6.4](#) require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate CRF (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to 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 9.2.2.2](#).

Additional Clinical Assessments and Observation

All subjects in whom IP or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in [Sections 6.4.1](#) and [6.4.2](#) or who experience AST or ALT elevations $> 3 \times \text{ULN}$ 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:

- AST, ALT, ALP, and bilirubin (total and direct) is to be repeated within 2 hours
- In cases of $\text{TBL} \geq 2 \times \text{ULN}$, retesting of liver tests, and bilirubin (total and direct) 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 IP 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 with differential to assess for eosinophilia
 - Obtain serum total immunoglobulin G, Anti-nuclear antibody, Anti-Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 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, and TBL) 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 IP 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 CRFs.

Appendix B. Sample Serious Adverse Event Report Form

AMGEN Study # 20130287 evolocumab (AMG 145)	Electronic Adverse Event Contingency Report Form For Restricted Use
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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																																																																																		
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2. SUBJECT INFORMATION																																																																																		
Subject ID Number		Age at event onset		Sex		Race		If applicable, provide End of Study date																																																																										
				<input type="checkbox"/> F <input type="checkbox"/> M																																																																														
If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____ and start date: Day ____ Month ____ Year ____																																																																																		
3. ADVERSE EVENT																																																																																		
Provide the date the Investigator became aware of this information: Day ____ Month ____ Year ____																																																																																		
<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th rowspan="3" style="width: 30%;">Adverse Event <u>diagnosis</u> or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report <small>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.</small></th> <th rowspan="3" style="width: 10%;">Date Started</th> <th rowspan="3" style="width: 10%;">Date Ended</th> <th rowspan="3" style="width: 10%;">Check only if event occurred before first dose of IPidrug under study</th> <th rowspan="3" style="width: 10%;">Is event serious?</th> <th rowspan="3" style="width: 10%;">Is event a potential endpoint?</th> <th rowspan="3" style="width: 10%;">If serious, enter Serious Criteria code (see codes below)</th> <th colspan="4" style="width: 20%;">Relationship</th> <th rowspan="3" style="width: 10%;">Outcome of Event</th> <th rowspan="3" style="width: 10%;">Check only if event is related to study procedure eg, biopsy</th> </tr> <tr> <th colspan="4">Is there a reasonable possibility that the Event may have been caused by IPidrug under study or an Amgen device used to administer the IPidrug under study?</th> </tr> <tr> <th>evolocumab (AMG 145)</th> <th>Profilin Autoneedle Pen (A/Pen)</th> <th>Automated Mini-Doser (AMD)</th> <th></th> </tr> <tr> <td></td> <td>Day Month Year</td> <td>Day Month Year</td> <td></td> <td> <input type="checkbox"/> Yes <input type="checkbox"/> No </td> <td> <input type="checkbox"/> Yes <input type="checkbox"/> No </td> <td></td> <td>No/ Yes/</td> <td>No/ Yes/</td> <td>No/ Yes/</td> <td></td> <td>Resolved Not resolved Fetal Unknown</td> <td></td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> <td> <input type="checkbox"/> Yes <input type="checkbox"/> No </td> <td> <input type="checkbox"/> Yes <input type="checkbox"/> No </td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> <td> <input type="checkbox"/> Yes <input type="checkbox"/> No </td> <td> <input type="checkbox"/> Yes <input type="checkbox"/> No </td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> <td> <input type="checkbox"/> Yes <input type="checkbox"/> No </td> <td> <input type="checkbox"/> Yes <input type="checkbox"/> No </td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </table>										Adverse Event <u>diagnosis</u> or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report <small>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.</small>	Date Started	Date Ended	Check only if event occurred before first dose of IPidrug under study	Is event serious?	Is event a potential endpoint?	If serious, enter Serious Criteria code (see codes below)	Relationship				Outcome of Event	Check only if event is related to study procedure eg, biopsy	Is there a reasonable possibility that the Event may have been caused by IPidrug under study or an Amgen device used to administer the IPidrug under study?				evolocumab (AMG 145)	Profilin Autoneedle Pen (A/Pen)	Automated Mini-Doser (AMD)			Day Month Year	Day Month Year		<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No		No/ Yes/	No/ Yes/	No/ Yes/		Resolved Not resolved Fetal Unknown						<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No												<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No												<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No							
Adverse Event <u>diagnosis</u> or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report <small>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.</small>	Date Started	Date Ended	Check only if event occurred before first dose of IPidrug under study	Is event serious?	Is event a potential endpoint?	If serious, enter Serious Criteria code (see codes below)	Relationship										Outcome of Event	Check only if event is related to study procedure eg, biopsy																																																																
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Serious Criteria: 01 Fatal 02 Immediately life-threatening 03 Required/prolonged hospitalization 04 Persistent or significant disability /incapacity 05 Congenital anomaly / birth defect 06 Other medically important serious event																																																																																		
4. Was subject hospitalized or was a hospitalization prolonged due this event? <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																																																																													

 Study # 20130287 evolocumab (AMG 145)	Electronic Adverse Event Contingency Report Form For Restricted Use
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	Site Number	Subject ID Number	

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

		Prior to, or at time of Event						Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #	
		Date of Initial Dose			Date of Dose					Dose
IP/Drug/Amgen Device:		Day	Month	Year	Day	Month	Year			
evolocumab (AMG 145)	<input checked="" type="checkbox"/> blinded									
Prefilled Autoinjector/Pen (AI/Pen) device	<input checked="" type="checkbox"/> open label									
Automated Mini-Doser (AMD) device	<input checked="" type="checkbox"/> open label									

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

	Test										
	Unit										
	Date										
Day	Month	Year									

FORM-056006

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Version 6.0 Effective Date 07 JUL 2014

[illegible]

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN[®] Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information				
Protocol/Study Number: 20130287				
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: _____		

Print Form

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: 20130287

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. High, Moderate, and Low-intensity Statin Therapy

Criteria modified from American College of Cardiology/American Heart Association (ACC/AHA) guidelines:

	High-intensity Statin Therapy	Moderate-intensity Statin Therapy	Low-intensity Statin Therapy	Notes (Modifications from ACC/AHA Guideline)
Atorvastatin	≥ 40 mg QD	10 mg to < 40 mg QD	<10 mg QD	Atorvastatin 30 mg QD is moderate intensity.
Rosuvastatin	≥ 20 mg QD	5 mg to < 20 mg QD	< 5 mg QD	Rosuvastatin < 5 mg QD is low intensity, Rosuvastatin 15 mg QD = moderate
Simvastatin	≥ 80 mg QD	20 mg to 80 mg QD	< 20 mg QD	Simvastatin > 40 and < 80 mg QD is moderate intensity Simvastatin 80 mg or greater QD is high intensity Simvastatin < 20 mg QD is low-intensity
Pravastatin	–	≥ 40 mg QD	< 40 mg QD	Pravastatin < 10 mg QD is low intensity
Lovastatin	–	≥ 40 mg QD	< 40 mg QD	Lovastatin 80 mg QD is moderate, Lovastatin 10 mg QD is low-intensity
Fluvastatin	–	80 mg QD	< 80 mg QD	Fluvastatin 10 mg QD is low-intensity
Pitavastatin	–	≥ 2 mg QD	< 2 mg QD	–

UNKNOWN-INTENSITY STATIN THERAPY if dose frequency is other or dose unit is other and therefore total daily dose in mg cannot be derived; **NO STATIN THERAPY** if subject does not use any statin at baseline.

Appendix E. Child-Pugh Score

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

^a Grade A = 5–6 points; grade B = 7–9 points; grade C = 10–15 points.

Schwartz M, Roayaie S, Konstadoulakis M: Nat Clin Pract Oncol 4:424-432, 2007.

Amendment 1

Protocol Title: A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability, and Efficacy of Evolocumab (AMG 145) on LDL-C in Subjects With Type 2 Diabetes Mellitus and Hypercholesterolemia/Mixed Dyslipidemia

Amgen Protocol Number (Evolocumab) 20130287

Date: 20 November 2015

Amendment 1 Date: 06 January 2016

Rationale:

- Updated schema to provide additional study design details.
- Reorganized inclusion criteria for better understanding.
- Provided additional details of contraceptive methods in the exclusion criteria.
- Clarified timing of randomization in relation to first dose.
- Added clinical research associate as an additional contact for the investigator prior to unblinding of subject's treatment assignment.
- Added non-clinic IP injection at Week 4 to the [Schedule of Assessments table](#) for clarity.
- Removed section for safety reporting as another section already details same information.
- Removed text kilograms and centimeters for body weight and height so sites can record in pounds and inches.
- Added that triglycerides > 1000 mg/dL would be reported to the investigators to allow appropriate follow-up to be initiated.
- Revised reasons for removal from treatment to be consistent with template text.
- Updated reporting requirements for adverse events for consistency throughout the protocol.
- Added appendix E of Child-Pugh Score to provide additional information.
- Made edits for grammatical and formatting errors.

Description of Changes:

Section: Global

Replace:

20 November 2015

With:

06 January 2016

Section: Title Page

Add:

Amendment 1 Date	06 January 2016
-------------------------	------------------------

Section: Investigator's Agreement

Paragraph 1

Replace:

I have read the attached protocol entitled "A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability, and Efficacy of Evolocumab on LDL-C in Subjects With Type 2 Diabetes Mellitus and Hypercholesterolemia/Mixed Dyslipidemia", dated 20 November 2015, and agree to abide by all provisions set forth therein.

With:

I have read the attached protocol entitled "A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability, and Efficacy of Evolocumab (**AMG 145**) on LDL-C in Subjects With Type 2 Diabetes Mellitus and Hypercholesterolemia/Mixed Dyslipidemia", dated **06 January 2016**, and agree to abide by all provisions set forth therein.

Section: Synopsis, Indication

Replace:

Hypercholesterolemia and/or Mixed Dyslipidemia

With:

Hypercholesterolemia/Mixed Dyslipidemia

Section: Synopsis, Primary Objective

Replace:

To evaluate the effect of 12 weeks of subcutaneous (SC) evolocumab monthly (QM) compared with placebo QM on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in subjects with type 2 diabetes mellitus and hypercholesterolemia or mixed dyslipidemia on maximally tolerated statin of at least moderate-intensity oral daily.

With:

To evaluate the effect of 12 weeks of subcutaneous (SC) evolocumab monthly (QM) compared with placebo QM on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in subjects with type 2 diabetes mellitus and hypercholesterolemia or mixed dyslipidemia on maximally tolerated **dose of** statin of at least moderate-intensity oral daily.

Section: Synopsis, Secondary Objective(s)

Sentence 1

Replace:

To assess the effects of 12 weeks of SC evolocumab QM compared with placebo QM, in subjects with type 2 diabetes mellitus and hypercholesterolemia or mixed dyslipidemia in combination with maximally tolerated statin of at least moderate-intensity oral daily on the following:

With:

To assess the effects of 12 weeks of SC evolocumab QM compared with placebo QM, in subjects with type 2 diabetes mellitus and hypercholesterolemia or mixed dyslipidemia in combination with maximally tolerated **dose of** statin of at least moderate-intensity oral daily on the following:

Section: Synopsis, Safety Objective

Replace:

To evaluate the safety and tolerability of SC evolocumab QM compared with placebo QM in subjects with type 2 diabetes mellitus and hypercholesterolemia or mixed dyslipidemia in combination with maximally tolerated statin of at least moderate-intensity oral daily.

With:

To evaluate the safety and tolerability of SC evolocumab QM compared with placebo QM in subjects with type 2 diabetes mellitus and hypercholesterolemia or mixed dyslipidemia in combination with maximally tolerated **dose of** statin of at least moderate-intensity oral daily.

Section: Synopsis, Hypotheses

Replace:

Subcutaneous evolocumab 420 mg QM in combination with statin once daily will be well tolerated and will result in greater reduction of LDL-C, defined as mean percent change from baseline at weeks 10 and 12 and percent change from baseline at week 12, compared with placebo QM in subjects with type 2 diabetes and hypercholesterolemia or mixed dyslipidemia on maximally tolerated statin of at least moderate-intensity daily.

With:

Subcutaneous evolocumab 420 mg QM in combination with statin once daily will be well tolerated and will result in greater reduction of LDL-C, defined as mean percent change from baseline at weeks 10 and 12 and percent change from baseline at week 12, compared with placebo QM in subjects with type 2 diabetes **mellitus** and hypercholesterolemia or mixed dyslipidemia on maximally tolerated **dose of** statin of at least moderate-intensity daily.

Section: Synopsis, Sample Size

Replace:

Approximately 400 subjects will be enrolled in the study, with approximately 270 subjects in the evolocumab group.

With:

Approximately 400 subjects **with type 2 diabetes mellitus with hypercholesterolemia or mixed dyslipidemia.**

Section: Synopsis, Summary of Subject Eligibility Criteria

Replace:

The study will enroll adult subjects (≥ 18 years of age) with type 2 diabetes mellitus with hemoglobin A1c (HbA1C) $< 10\%$ who must be on a stable, maximally tolerated statin of at least moderate-intensity at screening. Subjects must have been receiving pharmacologic treatment for diabetes mellitus for ≥ 6 months prior to screening, with stable diabetes therapy prior to randomization to investigational product (IP) and not expected to change during throughout the duration of study participation. For a full list of eligibility criteria, please refer to Section 4.1 through Section 4.1.2.

With:

The study will enroll adult subjects (≥ 18 years of age) with type 2 diabetes mellitus **and elevated LDL-C or non-HDL-C levels** on a stable, maximally tolerated statin **dose** of at least moderate-intensity at **signing of the informed consent; statin therapy must remain unchanged during screening and the remainder of the study**. Subjects must have hemoglobin A1c (HbA1c) $< 10\%$, **must have** been receiving pharmacologic treatment for diabetes mellitus for ≥ 6 months prior to screening, with stable diabetes therapy prior to randomization to investigational product (IP) and not expected to change throughout the duration of study participation. For a full list of eligibility criteria, please refer to Section 4.1 through Section 4.1.2.

Section: Synopsis, Amgen Investigational Product Dosage and Administration

Sentence 3

Replace:

Observed, in-clinic dosing should occur at day 1 and week 8, and subjects will self-administer in an appropriate non-clinic setting (eg, at home) for week 4.

With:

Observed, in-clinic dosing should occur at day 1 and week 8 **± 3 days**, and subjects will self-administer in an appropriate non-clinic setting (eg, at home) for week 4 **± 3 days**.

Section: Synopsis, Procedures

Paragraph 2, sentence 4

Replace:

Subjects must tolerate a SC injection of placebo prior to randomization.

With:

Subjects must tolerate a SC injection of placebo **with device anticipated to be used during the study (either AI/Pen or AMD)** prior to randomization.

Section: Synopsis, Procedures

Paragraph 3

Replace:

During the double-blind treatment period, study visits will occur at day 1, week 8, week 10, and week 12; with baseline evaluations performed on day 1 of treatment before subjects receive the first dose of IP. All subjects will complete a mixed meal tolerance test (MMTT) at the day 1 and week 12 study visits with a baseline and 2-hour postprandial blood collection after the meal. Up to approximately 100 subjects not treated with prandial insulin or glucagon-like peptide-1 agonists will participate in MMTT Extended Timepoints assessments with 3 additional postprandial blood draws at 30 minutes, 1 hour, and 3 hours after the meal. End of study for all subjects will be at the week 12 visit.

With:

During the double-blind treatment period, study visits will occur at day 1, week 8 (**± 3 days**), week 10 (**± 3 days**), and week 12 (**± 3 days**); with baseline evaluations performed on day 1 of treatment before subjects receive the first dose of IP. All subjects will complete a mixed meal tolerance test (MMTT) at the day 1 and week 12 study visits with a baseline and 2-hour (**± 10 min**) postprandial blood collection after the meal. Up to approximately 100 subjects not treated with prandial insulin or glucagon-like peptide-1 agonists will participate in MMTT Extended Timepoints assessments with 3 additional postprandial blood draws at 30 minutes (**± 10 min**), 1 hour (**± 10 min**), and 3 hours (**± 10 min**) after the meal. End of study for all subjects will be at the week 12 (**± 3 days**) visit.

Section: Synopsis, Statistical Considerations

Paragraph 1, sentence 4

Replace:

To assess the co-primary endpoints of the mean percent change from baseline (mean of week -2 and Day 1) in LDL-C at weeks 10 and 12 and the percent change in LDL-C from baseline at week 12, a repeated measures linear effects model will be used on the FAS to compare the efficacy of evolocumab QM with placebo QM.

With:

To assess the co-primary endpoints of the mean percent change from baseline (mean of **screening** week 2 and day 1) in LDL-C at weeks 10 and 12 and the percent change in LDL-C from baseline at week 12, a repeated measures linear effects model will be used on the FAS to compare the efficacy of evolocumab QM with placebo QM.

Section: Study Schema

Replaced old study schema with new updated schema and added abbreviations.

Section: Study Glossary

Add:

AE	adverse event
----	---------------

DRE	device related event
-----	----------------------

SAE	serious adverse event
-----	-----------------------

Section: Study Glossary

Delete:

DNA	deoxyribonucleic acid
-----	-----------------------

INR	international normalized ratio
-----	--------------------------------

Section: 1.1 Primary

Replace:

- To evaluate the effect of 12 weeks of subcutaneous (SC) evolocumab monthly (QM) compared with placebo QM on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in subjects with type 2 diabetes mellitus and hypercholesterolemia or mixed dyslipidemia on maximally tolerated statin of at least moderate-intensity oral daily.

With:

- To evaluate the effect of 12 weeks of subcutaneous (SC) evolocumab monthly (QM) compared with placebo QM on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in subjects with type 2 diabetes mellitus and hypercholesterolemia or mixed dyslipidemia on maximally tolerated **dose of** statin of at least moderate-intensity oral daily.

Section: 1.2 Secondary

Bullet 1

Replace:

- To assess the effects of 12 weeks of SC evolocumab QM compared with placebo QM, in subjects with type 2 diabetes mellitus and hypercholesterolemia or mixed dyslipidemia in combination with maximally tolerated statin of at least moderate-intensity oral daily on the following:

With:

- To assess the effects of 12 weeks of SC evolocumab QM compared with placebo QM, in subjects with type 2 diabetes mellitus and hypercholesterolemia or mixed dyslipidemia in combination with maximally tolerated **dose of** statin of at least moderate-intensity oral daily on the following:

Section: 1.3 Safety

Replace:

- To evaluate the safety and tolerability of SC evolocumab QM compared with placebo QM in subjects with type 2 diabetes mellitus and hypercholesterolemia or mixed dyslipidemia in combination with maximally tolerated statin of at least moderate-intensity oral daily.

With:

- To evaluate the safety and tolerability of SC evolocumab QM compared with placebo QM in subjects with type 2 diabetes mellitus and hypercholesterolemia or mixed dyslipidemia in combination with maximally tolerated **dose of** statin of at least moderate-intensity oral daily.

Section: 2.4 Clinical Hypotheses

Replace:

The primary hypothesis of this study is that SC evolocumab 420 mg QM in combination with statin once daily will be well tolerated and will result in greater reduction of LDL-C, defined as mean percent change from baseline at weeks 10 and 12 and percent change from baseline at week 12, compared with placebo QM in subjects with type 2 diabetes and hypercholesterolemia or mixed dyslipidemia on maximally tolerated statin of at least moderate intensity daily.

With:

The primary hypothesis of this study is that SC evolocumab 420 mg QM in combination with statin once daily will be well tolerated and will result in greater reduction of LDL-C, defined as mean percent change from baseline at weeks 10 and 12 and percent change from baseline at week 12, compared with placebo QM in subjects with type 2 diabetes and hypercholesterolemia or mixed dyslipidemia on maximally tolerated **dose of** statin of at least moderate intensity daily.

Section: 3.1 Study Design

Paragraph 3, sentence 3

Replace:

Subjects must tolerate a SC injection of placebo prior to randomization.

With:

Subjects must tolerate a SC injection of placebo **with device anticipated to be used during the study (either AI/Pen or AMD)** prior to randomization.

Section: 3.1 Study Design

Paragraph 4, sentence 1

Add:

Day 1 is defined as the calendar day when treatment with investigational product (IP) is initiated.

Section: 3.1 Study Design

Paragraph 4, sentence 2

Replace:

Subjects should initiate their first dose of investigational product (IP) within 5 days of randomization.

With:

Subjects should initiate their first dose of IP within 5 days of randomization.

Section: 3.1 Study Design

Paragraph 4, sentences 4 and 5

Replace:

All subjects will complete a MMTT at the day 1 and week 12 study visits with baseline (0 hours) and postprandial blood collection at 2 hours after the meal. Up to approximately 100 subjects not treated with prandial insulin or glucagon-like peptide-1 (GLP-1) agonists will participate in MMTT Extended Timepoints assessments with 3 postprandial blood draws at 30 minutes, 1 hour, and 3 hours after the meal in addition to the blood draws at 0 and 2 hours after the meal for all subjects.

With:

All subjects will complete a MMTT at the day 1 and week 12 study visits with baseline (0 hours) and postprandial blood collection at 2 hours (**± 10 min**) after the meal. Up to approximately 100 subjects not treated with prandial insulin or glucagon-like peptide-1 (GLP-1) agonists will participate in MMTT Extended Timepoints assessments with 3 postprandial blood draws at 30 minutes (**± 10 min**), 1 hour (**± 10 min**), and 3 hours (**± 10 min**) after the meal in addition to the blood draws at 0 and 2 hours (**± 10 min**) after the meal for all subjects.

Section: 3.3 Number of Subjects

Replace:

Approximately 400 subjects will be enrolled.

With:

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

Approximately 400 subjects **with type 2 diabetes mellitus with hypercholesterolemia or mixed dyslipidemia** will be enrolled.

Section: 3.4 Replacement of Subjects

Replace:

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

With:

Subjects who are withdrawn or removed from **investigational medicinal product (IMP)** treatment or the study will not be replaced.

Section: 3.5.2 End of Study

Replace:

The primary completion is defined as the date when the last subject has completed the assessments for week 12.

With:

The primary completion is defined as the date when the last subject has completed the assessments for week 12 **or has terminated the study early, whichever is later.**

Section: 4.1.1 Inclusion Criteria

Replace:

- 101 Subject has provided written informed consent
- 102 Male or female ≥ 18 years of age at signing of informed consent
- 103 Type 2 diabetes mellitus defined as:
 - with hemoglobin A1c (HbA1C) $< 10\%$
 - receiving pharmacologic treatment for diabetes mellitus for ≥ 6 months prior to screening
 - stable diabetes therapy prior to randomization to IP and not expected to change during the duration of study participation. Stable diabetes therapy is defined as no new agents added, and no dose change of any antihyperglycemic drug within 2 months prior to randomization and daily insulin dose not changed by $> 25\%$ and > 25 units within 1 month prior to randomization
- 104 Subjects without known CVD must be on at least moderate-intensity statin prior to randomization

- 105 Subjects with known CVD must be on high intensity statin (or moderate intensity if certified by principal investigator to be highest tolerated dose) prior to randomization
- 106 Fasting triglycerides \leq 600 mg/dL (6.8 mmol/L) by central laboratory prior to randomization
- 107 Subject tolerates screening placebo injection
- 108 Subjects without known CVD must have a fasting LDL-C during lipid stabilization of \geq 100 mg/dL (2.6 mmol/L) or non-HDL-C \geq 130 mg/dL (3.4 mmol/L) as determined by the central laboratory
- 109 Subjects with known CVD must have a fasting LDL-C during lipid stabilization of \geq 70 mg/dL (1.8 mmol/L) or Non-HDL-C \geq 100 mg/dL (2.6 mmol/L) as determined by the central laboratory
- 110 Subject must be on maximally tolerated of statin of at least moderate intensity at the end of screening/ lipid stabilization and is expected to remain on stable statin intensity for duration of study in the opinion of the investigator

With:

- 101 Subject has provided written informed consent
- 102 Male or female \geq 18 years of age at signing of informed consent
- 103 Type 2 diabetes mellitus:
 - with hemoglobin A1c (HbA1c) $<$ 10%
 - receiving pharmacologic treatment for diabetes mellitus for \geq 6 months prior to screening
 - stable diabetes therapy prior to randomization to IP and not expected to change during the duration of study participation. Stable diabetes therapy is defined as no new agents added, and no dose change of any antihyperglycemic drug within 2 months prior to randomization and daily insulin dose not changed by $>$ 25% and $>$ 25 units within 1 month prior to randomization
- 104 Subject must be on maximally tolerated **dose** of statin of at least moderate intensity at **signing of the informed consent (see Appendix D)** and is expected to remain on stable statin intensity for the duration of study in the opinion of the investigator
 - Subjects without known **clinical** CVD must be on at least moderate-intensity statin
 - Subjects with known **clinical** CVD must be on high intensity statin (or moderate intensity if certified by principal investigator to be highest tolerated dose). **Clinical CVD is defined as a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin**

- 105 Subjects without known **clinical** CVD must have a fasting LDL-C during lipid stabilization of ≥ 100 mg/dL (2.6 mmol/L) or non-HDL-C ≥ 130 mg/dL (3.4 mmol/L) as determined by the central laboratory
- 106 Subjects with known **clinical** CVD must have a fasting LDL-C during lipid stabilization of ≥ 70 mg/dL (1.8 mmol/L) or Non-HDL-C ≥ 100 mg/dL (2.6 mmol/L) as determined by the central laboratory
- 107 Fasting triglycerides ≤ 600 mg/dL (6.8 mmol/L) by central laboratory prior to randomization
- 108 Subject tolerates screening placebo injection

Section: 4.1.2 Exclusion Criteria

Criterion 205

Replace:

205. Persistent active liver disease or hepatic dysfunction, defined as Child-Pugh score of C

With:

205. Persistent active liver disease or hepatic dysfunction, defined as Child-Pugh score of C (**see Appendix E**)

Section: 4.1.2 Exclusion Criteria

Criterion 206, Paragraph 3, subbullet 3

Replace:

- bilateral tubal ligation/occlusion, use of hormonal birth control methods (PO, intravaginal, transdermal, injectable, or implantable),

With:

- bilateral tubal ligation/occlusion, use of hormonal birth control methods (**oral**, intravaginal [**eg, vaginal ring**], transdermal, injectable, or implantable),

Section: 4.1.2 Exclusion Criteria

Criterion 206, Paragraph 3, subbullet 6

Replace:

- 2 barrier methods (each partner must use one barrier method) and the female partner must use spermicide in addition to a barrier – males must use a condom; females must choose either a diaphragm, OR cervical cap, OR contraceptive sponge. If spermicide is not available in the country or region, the two barrier method without spermicide is acceptable.

With:

- 2 barrier methods (each partner must use one barrier method) and the female partner must use **if available** spermicide in addition to a barrier – males must use a condom; females must choose either a diaphragm, OR cervical cap, OR contraceptive sponge. *(Note: If spermicide is not **commercially** available in the country or region, the two barrier method without spermicide **would then be considered** acceptable).*

Section: 4.1.2 Exclusion Criteria

Criterion 206, Paragraph 4, sentence 2

Replace:

These additional medications may require an increase in the number of contraceptive methods, the change in type of contraceptive methods and/or length of time that contraception is to be utilized or length of time breastfeeding is to be avoided.

With:

These additional medications may require an increase in the number of contraceptive methods, the change in type of contraceptive methods and/or length of time that contraception is to be utilized **and/or** length of time breastfeeding is to be avoided.

Section: 4.1.2 Exclusion Criteria

Criterion 207

Replace:

207. Female subject is pregnant or breast feeding, or planning to become pregnant or planning to breastfeed during the screening/lipid stabilization period, during treatment with IP and for an additional 15 weeks after the end of treatment

With:

207. Female subject is pregnant or breast feeding, or planning to become pregnant or planning to breastfeed during the screening/lipid stabilization period, during treatment with IP and for an additional 15 weeks after the end of treatment **with IP**

Section: 5. SUBJECT ENROLLMENT

Paragraph 2, sentence 1

Replace:

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria, including 4 weeks of tolerating the appropriate dose of statin.

With:

A subject is considered enrolled **upon randomization in IVRS/IWRS**, when the investigator decides that the subject has met all eligibility criteria, including 4 weeks of tolerating the appropriate dose of statin.

Section: 5. SUBJECT ENROLLMENT

Paragraph 4

Replace:

Subjects who are unable to complete or meet eligibility on initial screening will be permitted to re-screen except for subjects without known CVD and fasting LDL-C < 100 mg/dL and non-HDL-C < 130 mg/dL by central lab result during screening (see Section 7.2.2).

With:

Subjects who are unable to complete or meet eligibility on initial screening will be permitted to re-screen **once** except for subjects without known **clinical** CVD and fasting LDL-C < 100 mg/dL and non-HDL-C < 130 mg/dL **and subjects with known clinical CVD and LDL-C < 70 mg/dL and non-HDL-C < 100 mg/dL** by central lab result during screening (see Section 7.2.2) **who are considered screen failures and who cannot be rescreened.**

Section: 5.1 Randomization/Treatment Assignment

Paragraph 3

Replace:

Subjects can only be randomized 1 time for this study. Subjects should be randomized before or on the date of the day 1 visit, and initiate their first dose of IP within 5 days of randomization.

With:

Subjects can only be randomized 1 time for this study. **Once** subjects **are** randomized their first dose of IP **must be administered** within 5 days of randomization (**day 1 visit**).

Section: 5.2 Site Personnel Access to Individual Treatment Assignments

Paragraph 3

Replace:

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.

With:

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

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

Paragraph 1

Replace:

The Amgen IP used in this study is evolocumab and matching placebo. In several countries, IP is referred to as investigational medicinal product (IMP). In this document, IMP will be referred to as IP.

With:

The Amgen IP used in this study is evolocumab and matching placebo. In several countries, IP is referred to as IMP. In this document, IMP will be referred to as IP.

Section: 6.4.1 Criteria for Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity

Paragraph 1, bullet 2

Replace:

- AND increased AST or ALT $\geq 3x$ ULN from a baseline value were less than the ULN

With:

- AND increased AST or ALT $\geq 3x$ ULN **if** baseline value were less than the ULN

Section: 6.4.2 Criteria for Conditional Withholding of Amgen Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity

Paragraph 1

Replace:

For subjects who do not meet the criteria for permanent discontinuation of Amgen IP 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 IP and other protocol-required therapies:

With:

For subjects who do not meet the criteria for permanent discontinuation of Amgen IP (**evolocumab or placebo**) 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 IP and other protocol-required therapies:

Section: 6.5 Concomitant Therapy

Paragraphs 2 and 3

Replace:

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

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

With:

Prior general and targeted therapies (**ie**, statins, other lipid-lowering **therapies**, and **pharmacologic treatment for type 2 diabetes mellitus**), taken 120 days prior to randomization should be collected with the following information: therapy name, indication, dose, unit, frequency, route, start date and stop date.

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

Section: 6.7 Product Complaints

Paragraph 5 and 6

Replace:

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

Additional details regarding the identification and reporting of any product complaint(s) associated with an investigational product(s) or non-investigational product(s) or device(s) supplied by Amgen are provided in the IPIM.

With:

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

Additional details regarding the identification and reporting of any product **and/or device** complaint(s) associated with an investigational product(s) or non-investigational product(s) or device(s) supplied by Amgen are provided in the IPIM.

Section: 7 STUDY PROCEDURES

Paragraph 2, sentence 2

Replace:

For example, the week 4 visit is 4 calendar weeks after the study day 1 visit, corresponding to study day 28.

With:

For example, the week 4 **dose** is 4 calendar weeks after the study day 1 visit, corresponding to study day 28.

Section: 7.1 Schedule of Assessments

Table 1

Replace:

Study Day / Week / Other Timepoint	Screening/ Lipid Stabilization (up to 6 weeks including 4-week lipid stabilization)		Double-blind Treatment Period			
	Screening		Week 8		Week 10	Week 12
	Screening Day 1	Week 2 ± 3 days	Day 1	± 3 days	± 3 days	EOS ± 3 days
<i>General Procedures</i>						
Informed consent	X					
Medical history	X					
Vital Signs (BP and heart rate)	X	X	X	X	X	X
Physical Exam	X	X	X	X	X	X
Safety Data Reporting ^a	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X
Body weight, waist circumference			X			X
Body height			X			
Randomization			X			
<i>Central Laboratory^b</i>						
Fasting lipids ^c		X	X		X	X
ApoA1, ApoB, Lp(a)			X		X	X
PCSK9			X		X	X
Chemistry		X	X			X
Hematology			X			
HbA1c		X	X			X
MMTT ^d			X			X
MMTT Extended Timepoints ^d			X			X
Biomarkers (blood) ^e			X			X
HCV antibody testing		X				
HCV viral load ^f		X	X			X
Serum pregnancy ^g ; FSH/LH/estradiol ^h		X				X
Urine pregnancy ^h			X			
Urinalysis, Urine protein, Urine creatinine, urine microalbumin			X			X
<i>Investigational Product</i>						
Screening placebo injection		X				
In-clinic IP injection QM ⁱ			X	X		
IP dispense			X			
IP reconciliation QM				X		

ApoA1=apolipoprotein A-I; ApoB=apolipoprotein B; ApoB48=apolipoprotein B48; BP=blood pressure; EOS=end of study; HbA1c=hemoglobin A1c; HCV=hepatitis C virus; IL-6=interleukin-6; FSH/LH=follicle-stimulating hormone/luteinizing hormone; IP=investigational product; Lp(a)=lipoprotein(a); MMTT=mixed meal tolerance test; PCSK9=proprotein convertase subtilisin/kexin type 9; QM=once monthly

With:

Study Day / Week / Timepoint	Screening/ Lipid Stabilization (up to 6 weeks including 4-week lipid stabilization)		Double-blind Treatment Period				
	Screening		Week 4				Week 12
	Screening Day 1	Week 2 ± 3 days	Day 1	± 3 days	Week 8 ± 3 days	Week 10 ± 3 days	EOS ± 3 days
General Procedures							
Informed consent	X						
Medical history	X						
Vital Signs (BP and heart rate)	X	X	X		X	X	X
Physical Exam	X	X	X		X	X	X
Safety Data Collection/Reporting ^a	X	X	X		X	X	X
Concomitant therapy	X	X	X		X	X	X
Body weight, waist circumference			X				X
Body height			X				
Randomization			X				
Central Laboratory ^b							
Fasting lipids ^c		X	X			X	X
ApoA1, ApoB, Lp(a)			X			X	X
PCSK9			X			X	X
Chemistry		X	X				X
eGFR		X					
Hematology			X				
Coagulation (Prothrombin time)		X					
HbA1c		X	X				X
MMTT ^d			X				X
MMTT Extended Timepoints ^d			X				X
Biomarkers (blood) ^e			X				X
HCV antibody testing		X					
HCV viral load ^f		X	X				X
Serum pregnancy ^g ; FSH/LH or estradiol ^h		X					X
Local urine pregnancy			X				
Urinalysis, Urine protein, Urine creatinine, urine microalbumin			X				X
Investigational Product							
Screening placebo injection		X					
In-clinic IP injection QM			X		X		
Non-clinic setting IP injection QM				X			
IP dispense			X		X		
IP reconciliation QM					X		

ApoA1=apolipoprotein A-I; ApoB=apolipoprotein B; ApoB48=apolipoprotein B48; BP=blood pressure;
eGFR=estimated glomerular filtration rate; EOS=end of study; HbA1c=hemoglobin A1c; HCV=hepatitis C virus; IL-6=interleukin-6; FSH/LH=follicle-stimulating hormone/luteinizing hormone; IP=investigational product; Lp(a)=lipoprotein(a); MMTT=mixed meal tolerance test; PCSK9=proprotein convertase subtilisin/kexin type 9; QM=once monthly

Section: 7.1 Schedule of Assessments

Table 1, footnote a

Replace:

a. Including review for adverse events/serious adverse events/disease related events/adverse device effects. Only adverse events/adverse device effects possibly related to study procedures and serious adverse events are collected during the screening from signing of the informed consent.

With:

a. Review for adverse events/serious adverse events/disease related events/adverse device effects. Only adverse events possibly related to study procedures, adverse device effects and serious adverse events are collected during screening from signing of the informed consent. **All serious adverse events must be collected through 30 days after the last administration of IP or the EOS/ safety follow-up visit, whichever is later, and submitted to Amgen.**

Section: 7.1 Schedule of Assessments

Table 1, footnote e

Replace:

e. If the subject consented to pharmacogenetic analyses, DNA will be extracted from some of the blood samples, eg, biomarker samples.

With:

e. **Anti-evolocumab antibodies may be tested, if needed.** If the subject consented to pharmacogenetic **portion of the study**, DNA analysis may be performed. **One cell pellet is collected only at day 1 (residual cell pellet from the plasma biomarker sample).**

Section: 7.1 Schedule of Assessments

Table 1, footnote g

Replace:

g. Pregnancy testing in females of childbearing potential. Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required by local laws and regulations.

With:

g. **Serum** pregnancy testing in females of childbearing potential. Additional on-treatment **local** pregnancy testing may be performed at the investigator's discretion or as required by local laws and regulations.

Section: 7.1 Schedule of Assessments

Table 1, footnote h

Replace:

h. FSH/LH/estradiol only at screening in females of childbearing potential if applicable.

With:

h. FSH/LH **or** estradiol only at screening, **and only if applicable per exclusion criteria.**

Section: 7.1 Schedule of Assessments

Table 1, footnote i

Delete:

~~i. In addition to the in-clinic QM-IP administration at day 1 and week 8, QM non-clinic IP administration is expected to occur once prior to the week 8 visit at week 4.~~

Section: 7.2.2 Rescreening

Sentence 4

Replace:

Subjects without known CVD and fasting LDL-C < 100 mg/dL or non-HDL-C < 130 mg/dL during screening are considered screen failures and cannot be rescreened for this study.

With:

Subjects without known **clinical** CVD and fasting LDL-C < 100 mg/dL **and** non-HDL-C < 130 mg/dL during screening are considered screen failures and cannot be rescreened for this study.

Section: 7.2.2 Rescreening

Sentence 5

Add:

Subjects with known clinical CVD and LDL-C < 70 mg/dL and non-HDL-C < 100 mg/dL during screening are considered screen failures and cannot be rescreened for this study.

Section: 7.2.3 Double-blind Treatment Period

Paragraph 2, sentence 1

Replace:

Evolocumab/placebo is to be self-administered in an appropriate non-clinic setting (eg, at home) at week 4.

With:

Evolocumab/placebo is to be self-administered in an appropriate non-clinic setting (eg, at home) at week 4 \pm 3 days.

Section: 7.2.3 Double-blind Treatment Period

Paragraph 2, sentence 3

Replace:

Observed, in-clinic dosing should occur at day 1 and at week 8.

With:

Observed, in-clinic dosing should occur at day 1 and at week 8 \pm 3 days.

Section: 7.2.4 End of Study Visit, 7.2.5 Safety Follow-up

Replace:

7.2.4 End of Study Visit

An EOS visit is scheduled to occur at week 12.

7.2.5 Safety Follow-up

Sites are responsible for reporting any safety information up to 30 days after the last dose of IP.

Subjects who do not complete their EOS visit and assessments are considered early termination.

With:

7.2.4 End of Study Visit

An EOS visit is scheduled to occur at week 12 \pm 3 days.

Subjects who discontinue study participation before their week 12 \pm 3 days visit per protocol are considered early termination.

7.2.5 Safety Follow-up

Sites are responsible for reporting safety information **through** 30 days after the last dose of IP or EOS, as applicable. For further details, see Section 9.2.

Section: 7.3.3 Medical History

Paragraph 2, sentence 2

Replace:

Targeted diabetes history including, but not limited to, duration, complications, and history of ketoacidosis from diagnosis will be collected.

With:

Targeted diabetes **mellitus** history including, but not limited to, duration, complications, and history of ketoacidosis from diagnosis will be collected.

Section: 7.3.6 Safety Data Reporting

Delete:

~~7.3.6 Safety Data Reporting~~

~~Adverse events, serious adverse events, adverse device effects (ADEs), and disease-related events observed by the investigator or reported by the subject will be collected at all study visits from the signing of the ICF through the EOS visit.~~

Section: 7.3.6 Concomitant Therapy

Paragraph 1

Replace:

Prior general and targeted therapies (eg, statins, other lipid-lowering, and diabetes therapy) will be collected as specified in Section 6.5.

With:

Prior general and targeted therapies (eg, statins, other lipid-lowering **therapies, pharmacologic treatment for type 2 diabetes mellitus**) will be collected as specified in Section 6.5.

Section: 7.3.7 Height, Weight, and Waist Circumference

Paragraph 1

Replace:

Body weight in kilograms and height in centimeters should be measured without shoes.

With:

Body weight and height should be measured without shoes.

Section: 7.4 Laboratory Assessments

Paragraph 1, sentences 1 and 2

Replace:

All laboratory samples will be sent to the central laboratory.

With:

Central laboratory **assessments are to be used to assess subject eligibility (except for the urine pregnancy test, Section 7.1). All other screening or scheduled study laboratory assessments will also be by the central laboratory.**

Section: 7.4 Laboratory Assessments

Table 2: Analyte Listing

Replace:

Chemistry	Hematology	Coagulation	Urinalysis	Other Labs
Sodium	Hemoglobin	PT/INR	Specific gravity	Fasting lipids
Potassium	Hematocrit		pH	• Total cholesterol
Chloride	RBC		Blood	• HDL-C
Bicarbonate	RDW		Protein	• LDL-C
Total protein	MCV		Glucose	• Triglycerides
Calcium	MCH		Bilirubin	• VLDL-C
Magnesium	MCHC		WBC	• non-HDL-C
Phosphorus	WBC		RBC	ApoA1
Uric Acid	Platelets		Epithelial cells	ApoB
CK			Bacteria	ApoB48
Alkaline phosphatase			Casts	Lp(a)
LDH			Crystals	Insulin
Albumin			Microalbumin	Proinsulin
FBG			Creatinine	C-peptide
BUN or Urea				Free fatty acids
Creatinine				Glucagon
Total bilirubin				Chylomicrons
Direct bilirubin				IL-6
AST				Adiponectin
ALT				PCSK9
eGFR				HbA1c
				Leutinizing Hormone (LH)
				Estradiol
				Urine and serum pregnancy test (females of childbearing potential)
				FSH (if needed per exclusion 206)
				HCV antibody
				HCV viral load (if required)

With:

Chemistry	Hematology	Coagulation	Urinalysis	Other Labs
Sodium	Hemoglobin	PT	Specific gravity	Fasting lipids
Potassium	Hematocrit		pH	Total cholesterol
Chloride	RBC		Blood	HDL-C
Bicarbonate	RDW		Protein	LDL-C
Total protein	MCV		Glucose	Triglycerides
Calcium	MCH		Bilirubin	VLDL-C
Magnesium	MCHC		WBC	non-HDL-C
Phosphorus	Platelets		RBC	ApoA1
Uric Acid	WBC		Epithelial cells	ApoB
CK	Morphology		Bacteria	ApoB48
Alkaline phosphatase	and differential:		Casts	Lp(a)
LDH	• Neutrophils		Crystals	Insulin
Albumin	• Eosinophils		Microalbumin	Proinsulin
FBG	• Basophils		Creatinine	C-peptide
BUN or Urea	• Lymphocytes			Free fatty acids
Creatinine	• Monocytes			Glucagon
Total bilirubin				Chylomicrons
Direct bilirubin				IL-6
AST				Adiponectin
ALT				PCSK9
eGFR				HbA1c
				Urine and serum pregnancy test (females of childbearing potential)
				FSH/LH or Estradiol (if needed per exclusion 206)
				HCV antibody
				HCV viral load (if required)

Section: 7.4.1 Blinding of Laboratory Test Results

Paragraph 2, sentence 2

Add:

Investigators will be informed if triglycerides are > 1000 mg/dL (11.3 mmol/L) so that appropriate subject follow-up can be initiated.

Section: 7.4.2 Mixed Meal Tolerance Test (All Subjects)

Paragraph 1, sentence 2

Replace:

Each MMTT should be done at approximately the same time of day throughout the study (± 2 hours) and must be completed prior to dosing with IP (if applicable).

With:

Each MMTT should be done at approximately the same time of day throughout the study (± 2 hours) and must be completed prior to dosing with IP **at day 1**.

Section: 7.4.4 Serum Pregnancy Test

Paragraph 2

Replace:

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

With:

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

Section: 7.6 Pharmacogenetic Studies

Sentence 2

Replace:

If the subject consents to the optional pharmacogenetic portion of this study, deoxyribonucleic acid (DNA) analyses may be performed.

With:

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

Section: 7.7 Sample Storage and Destruction

Paragraph 3, sentence 1

Replace:

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 hypercholesterolemia and/or mixed dyslipidemia, the dose response and/or prediction of response to evolocumab, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites).

With:

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 hypercholesterolemia/mixed dyslipidemia, the dose response and/or prediction of response to evolocumab, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites).

Section: 8.3.1 Reasons for Removal From Treatment

Sentence 1

Replace:

Reasons for removal from protocol-required IP or procedural assessments include any of the following:

With:

Reasons for removal from protocol-required IP or procedural assessments include any of the following, **but not limited to**:

Section: 8.3.1 Reasons for Removal From Treatment

Bullet 2

Delete:

- ~~subject request to end IP administration~~

Section: 8.3.1 Reasons for Removal From Treatment

Bullet 5

Replace:

- administrative decision by Amgen (other than subject request, safety concern or lost to follow-up)

With:

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

Section: 8.3.1 Reasons for Removal From Treatment

Bullet 6

Delete:

- ~~decision by the primary investigator/physician~~

Section: 8.3.2 Reasons for Removal From Study

Bullet 1

Replace:

- decision by Amgen

With:

- decision by **Sponsor**

Section: 9.1.1 Disease-related Events

Paragraph 2, Bullets 1 and 2

Replace:

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

With:

- An event which is part of the normal course of disease under study, **with no causal relationship with IP/protocol-required therapies** (eg, disease progression or hospitalization due to disease progression) is to be reported as a disease-related event.

- Death **is** due to the disease under study; **the event** is to be recorded on the Event CRF **as a disease-related event**.

Section: 9.1.1 Disease-related Events

Paragraph 3

Replace:

If the outcome of the underlying disease is worse than that which would normally be expected for the subject, or if the investigator believes there is a causal relationship between the IP/study treatment protocol-required therapies and disease worsening, this must be reported as an adverse event or serious adverse event.

With:

If the outcome of the underlying disease is worse than that which would normally be expected for the subject, or if the investigator believes there is a causal relationship between the IP/study treatment protocol-required therapies and disease worsening, **the event** must be reported as an adverse event or serious adverse event.

Section: 9.1.4 Serious Adverse Events

Bullets 7, 8 and 9

Replace:

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

With:

- the event meets at least 1 of the serious criteria above, **AND**
- the subject's pre-existing condition becomes worse than what the investigator would consider typical for a patient with the same underlying condition, OR
- the investigator believes a causal relationship exists between the IP/protocol-required therapies and the event

Section: 9.2.1 Disease-related Events

Paragraph 1, sentence 1

Replace:

The investigator is responsible for ensuring that all disease-related events observed by the investigator or reported by the subject that occur from the time of randomization through the EOS/safety follow-up visit, or 30 days after the last administration of IP, whichever is later, are reported using the Event CRF.

With:

The investigator is responsible for ensuring that all disease-related events observed by the investigator or reported by the subject that occur from the time of randomization through the EOS/safety follow-up visit are reported using the Event CRF.

Section: 9.2.2.1 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 randomization through the EOS/safety follow-up visit, or 30 days after the last administration of IP, whichever is later, are reported using the Event CRF. Only adverse events/ADEs possibly related to study procedures and serious adverse events are collected during screening after signing of the informed consent.

With:

Adverse events possibly related to study procedures, adverse device effects and serious adverse events are reported from signing of the ICF. All other adverse events are reported from the time of randomization. The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur **from signing of the ICF or from the time of** randomization through the EOS/safety follow-up visit are reported using the Event CRF.

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

Paragraph 6

Add:

The investigator must assess whether the adverse event is possibly related to any other study-mandated activity or procedure (eg. administration of IP, 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/procedure” (eg. administration of IP, protocol-required therapies, device(s) and/or procedure?)

Section: 9.2.2.4 Serious Adverse Events That are not to be Reported in an Expedited Manner

Replace:

Hospitalizations due to chronic diabetic complications are anticipated to occur in the enrolled patient population. The Amgen safety and medical teams will review accumulating events on a regular basis.

With:

Hospitalizations due to chronic diabetic complications are anticipated to occur in the patient population **enrolled in this study and are therefore not planned to be reported individually in an expedited manner.** The Amgen safety and medical teams will review accumulating events on a regular basis.

Section: Appendix C. Pregnancy and Lactation Notification Worksheets

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: 20130287

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

2. Contact Information

Investigator Name _____ Site # _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Gender: ☐ Female ☐ Male Subject DOB: mm ____ / dd ____ / yyyy ____

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

Pregnant female's LMP mm ____ / dd ____ / yyyy ____ ☐ Unknown

Estimated date of delivery mm ____ / dd ____ / yyyy ____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm ____ / dd ____ / yyyy ____

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

If yes, provide date of delivery: mm ____ / dd ____ / yyyy ____

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

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

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

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: <u>20130287</u>				
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: _____		

Print Form

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: 20130287

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: _____

Section: Appendix E. Child-Pugh Score

Add:

Appendix E. Child-Pugh Score

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

^a Grade A = 5–6 points; grade B = 7–9 points; grade C = 10–15 points.

Schwartz M, Roayaie S, Konstadoulakis M: Nat Clin Pract Oncol 4:424-432, 2007.