Title: A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Safety and Efficacy of Evolocumab (AMG 145) in Combination With Statin Therapy in Diabetic Subjects With Hyperlipidemia or Mixed Dyslipidemia

Evolocumab (AMG 145)

Amgen Protocol Number Evolocumab 20120119
EudraCT number 2013-000723-14

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Investigator's Agreement

I have read the attached protocol entitled "A Double-blind, Randomized, Placebo-Controlled, Multicenter Study to Evaluate Safety and Efficacy of Evolocumab (AMG 145) in Combination With Statin Therapy in Diabetic Subjects With Hyperlipidemia or Mixed Dyslipidemia", dated **11 November 2015**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

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

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

_____

Signature

_____   _____

Name of Investigator   Date (DD Month YYYY)

Protocol Synopsis

Title: A Double-blind, Randomized, Placebo-Controlled, Multicenter Study to Evaluate Safety and Efficacy of Evolocumab (AMG 145) in Combination With Statin Therapy in Diabetic Subjects With Hyperlipidemia or Mixed Dyslipidemia

Study Phase: 3

Indication: Hyperlipidemia or mixed dyslipidemia

Primary Objective: To evaluate the effect of 12 weeks of subcutaneous (SC) evolocumab every 2 weeks (Q2W) and monthly (QM), in combination with oral (PO) atorvastatin daily (QD), compared with placebo Q2W and QM, in combination with PO atorvastatin QD, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in diabetic subjects with hyperlipidemia or mixed dyslipidemia.

Secondary Objective(s):

- to evaluate the safety and tolerability of SC evolocumab Q2W and QM in combination with atorvastatin QD, compared with placebo Q2W and QM, in combination with atorvastatin QD, in diabetic subjects with hyperlipidemia or mixed dyslipidemia

- to assess the effects of 12 weeks of SC evolocumab Q2W and QM in combination with atorvastatin QD, compared with placebo Q2W and QM, in combination with atorvastatin QD, on change from baseline in LDL-C, and percent change from baseline in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B100 (ApoB100), total cholesterol, total cholesterol/HDL-C ratio, ApoB100/Apolipoprotein A-1 (ApoA1) ratio, lipoprotein(a) [Lp(a)], triglycerides, very low-density lipoprotein cholesterol (VLDL-C), and HDL-C in diabetic subjects with hyperlipidemia or mixed dyslipidemia

- to assess the effects of 12 weeks of SC evolocumab Q2W and QM in combination with atorvastatin QD, compared with placebo Q2W and QM, in combination with atorvastatin QD, on percent of subjects attaining LDL-C < 70 mg/dL (1.8 mmol/L) in diabetic subjects with hyperlipidemia or mixed dyslipidemia

Hypotheses: The primary hypothesis is that both dosing regimens of SC evolocumab (140 mg Q2W and 420 mg QM) in combination with atorvastatin QD 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 (Q2W and QM), in combination with atorvastatin QD in diabetic subjects with hyperlipidemia or mixed dyslipidemia.

Co-primary Efficacy 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 Efficacy Endpoints:

Co-secondary efficacy endpoints are (1) the mean of weeks 10 and 12 and (2) week 12 for:

Tier 1

- change from baseline in LDL-C

- percent change from baseline in non-HDL-C

- percent change from baseline in ApoB100

- percent change from baseline in the total cholesterol

- percent change from baseline in the total cholesterol/HDL-C ratio

- percent change from baseline in ApoB100/ApoA1 ratio

- achievement of target LDL-C < 70 mg/dL (1.8 mmol/L)

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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

- Electrocardiogram (ECG) parameters (such as RR, PR, QRS, QT and QTc intervals) at each scheduled assessment

- incidence of anti-evolocumab antibody (binding and neutralizing) formation

Study Design: This is a phase 3, multicenter, double-blind, randomized, stratified, placebo-controlled study of evolocumab for diabetic subjects with hyperlipidemia or mixed dyslipidemia. Subjects will undergo screening procedures, including laboratory assessments and a screening placebo injection, and will enter a lipid stabilization period where they will receive 20 mg atorvastatin daily (QD). Upon ≥ 4 weeks lipid stabilization, subjects will be randomized 2:2:1:1 into the following treatment arms:

- Evolocumab SC 140 mg Q2W and atorvastatin PO 20 mg QD,

- Evolocumab SC 420 mg QM and atorvastatin PO 20 mg QD,

- placebo SC Q2W and atorvastatin PO 20 mg QD, or

- placebo SC QM and atorvastatin PO 20 mg QD.

The sample size for each of the evolocumab dosing regimens, in combination with atorvastatin, will be approximately 300 subjects. The sample size for each of the placebo dosing regimens, in combination with atorvastatin, will be approximately 150 subjects. Randomization will be stratified by entry statin therapy (no statin use vs non-intensive statin use vs intensive statin use [see Appendix D of the protocol]) and by the site's geographic region. Treatment and follow-up period will be 12 weeks with an additional phone call or other subject contact at week 14 for subjects receiving IP Q2W.

Evolocumab and placebo SC will be administered at the study site or appropriate non-investigator site settings, eg, at the subject's home, per protocol Section 6 and Section 7 by spring-based prefilled autoinjector/pen (prefilled AI/Pen) for subjects receiving IP Q2W and by 3.5 mL Personal Injector for subjects receiving IP QM. The dose frequencies of Q2W and QM will not be blinded but the identity of IP (evolocumab and matching SC placebo) will be blinded. Post-IP treatment central laboratory results of the lipid panel, ApoA1, ApoB100, ApoB48, free fatty acids, chylomicrons, lipoprotein(a), PCSK9, insulin, proinsulin, C-peptide, glucagon, IL-6, adiponectin, vitamin E, PK, and high sensitivity C-reactive protein (hsCRP) will be blinded until unblinding of the clinical database and will not be reported to the investigator post-screening. Investigators should not perform non-protocol testing of these analytes during a subject's study participation and until at least 12 weeks after last IP administration, or the subject's end of study, whichever is later.

The study includes collection of biomarker samples and, where approved by the institutional review board and/or independent ethics committee (IRB/IEC) and applicable regulatory and other authorities, subjects will be invited to consent to pharmacogenetics analyses. All subjects will complete a mixed meal tolerance test (MMTT) at the day 1 and week 12 study visits with 1 postprandial blood collection 2 hours after the meal and up to approximately 240 subjects will participate in a MMTT Extended Timepoints Substudy with 2 additional postprandial blood draws at 1 and 3 hours after the meal. End of study (EOS) for subjects on QM IP is at the week 12

visit. EOS for subjects on Q2W IP is by contact (eg, phone call) from the site at week 14 for any potential adverse events (AEs), **adverse device effects (ADEs), and** serious AEs (SAEs). Subjects will be encouraged to complete all planned visits regardless of their adherence to IP administration. Accumulating safety and other data will be reviewed by an independent external Data Monitoring Committee (DMC). Concentration values are provided in mmol/L for investigator convenience. Conventional concentrations (mg/mL) will be used for the protocol, including for eligibility determination.

Sample Size: Approximately 900 subjects will be randomized.

Summary of Subject Eligibility Criteria: Males and females age ≥ 18 to ≤ 80 years with type 2 diabetes (≥ 6 months) and with hyperlipidemia or mixed dyslipidemia are eligible for this study. For enrollment, LDL-C in subjects receiving statin therapy (any statin) at the time of entering screening must be ≥ 100 mg/dL (2.6 mmol/L), and in subjects not receiving statin therapy ≥ 130 mg/dL (3.4 mmol/L) by central laboratory at screening. Fasting triglycerides must be ≤ 400 mg/dL (4.5 mmol/L) by central laboratory at screening.

Major exclusion criteria include, but are not limited to: receiving lipid-lowering therapy by 20 mg atorvastatin QD alone for 16 weeks is medically contraindicated or inappropriate based on opinion of investigator; heart failure of New York Heart Association (NYHA) class III or IV or last known left ventricular ejection fraction < 30%; type 1 diabetes or poorly controlled type 2 diabetes; systolic blood pressure (SBP) > 160 mmHg or diastolic BP (DBP) > 100 mmHg; previously received evolocumab or any other investigational therapy to inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9); unwillingness or inability to discontinue until end of study the following: red yeast rice, niacin (> 200 mg/day), > 1000 mg/day omega-3 fatty acids, and all prescription lipid-regulating drugs except study-provided atorvastatin; any of the following drugs in the last 2 months: systemic cyclosporine, systemic steroids, vitamin A derivatives and retinol derivatives for the treatment of dermatologic conditions (eg, Accutane), or a cholesterylester transfer protein (CETP) inhibitor in the last 12 months. Female subjects cannot be pregnant, breast feeding, planning to become pregnant, or planning to breastfeed and premenopausal females must have to be willing to use (an) acceptable method(s) of **effective** birth control during treatment with investigational product (evolocumab or placebo) and for an additional 15 weeks after the end of treatment with investigational product (evolocumab or placebo).

For a full list of eligibility criteria, please refer to Section 4.1.1 and Section 4.1.2.

Investigational Product

Amgen Investigational Product Dosage and Administration: Evolocumab and placebo SC will be administered using a spring-based prefilled AI/Pen or by 3.5 mL Personal Injector. Each prefilled AI/Pen will contain 1.0 mL deliverable volume; each Personal Injector will contain 3.5 mL deliverable volume.

Evolocumab will be administered at 1 of 2 regimens:

Evolocumab 140 mg SC Q2W by prefilled AI/Pen or

Evolocumab 420 mg SC QM by 3.5 mL Personal Injector

Placebo will be administered at 1 of 2 regimens:

Placebo SC Q2W by prefilled AI/Pen or

Placebo SC QM by 3.5 mL Personal Injector.

Non-Amgen Non-investigational Product Dosage and Administration: Atorvastatin 20 mg will be provided by Amgen.

Procedures: Subjects who have signed informed consent will undergo screening procedures including laboratory assessments and a 1-time administration of placebo by AI/Pen and will enter a lipid stabilization period where they will receive 20 mg atorvastatin daily (QD). Subjects should maintain their diet, any allowed therapy, and exercise regimen throughout screening and study participation. Eligible subjects will be scheduled to return to the study site after ≥ 4 weeks of lipid stabilization to initiate IP administration and other day 1 procedures. For randomization, the site

will contact the interactive voice response system or interactive web response system (IVRS/IWRS). Day 1 is defined as the day of first administration of IP and should occur as close as possible or on the day of randomization but not later than 5 days after randomization. Subsequent mandatory study visits are at weeks 2, 8, 10, and 12 (EOS for QM subjects). In addition, subjects receiving IP Q2W will be contacted (eg, by phone call) by the study site at week 14 (EOS for Q2W subjects) to obtain AE, **ADE,** and SAE information, if applicable. For subjects randomized to receive IP Q2W, IP will be administered by AI/Pen at the study site on day 1, and weeks 2, 8, and 10. For subjects randomized to receive IP QM, IP will be administered by 3.5 mL Personal Injector at the study site on day 1, and week 8. For other administrations of IP by AI/Pen or 3.5 mL Personal Injector, respectively, subjects will have the option of self-administration, defined as SC administration of IP by the subject, designee or a qualified health care professional in a non-investigator site setting (eg, at home). The subject (or designee, if not a qualified healthcare professional) must have demonstrated competency 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. Final administration of IP (evolocumab or placebo) is at week 8 for QM treatment and week 10 for Q2W treatment. Subjects who discontinue IP for any reason will be asked to continue to return for all other study procedures and measurements until the end of the study.

Vital signs, AEs/**ADEs**/SAEs, concomitant therapy, evaluation of fasting lipids, dietary instruction, physical exam, measuring waist circumference, body height and weight, 12-lead ECGs, other laboratory assessments, including assessment for anti-evolocumab antibodies, biomarker sample collection, serum pregnancy testing (females of childbearing potential), MMTT, urinalysis, and steroid analyte testing will be carried out per the Schedule of Assessment (Table 1) of the protocol. If the subject consented to pharmacogenetics analyses, deoxyribonucleic acid (DNA) will be extracted from some of the blood samples. IP administration by SC injection, if applicable, will be done after other procedures have been completed.

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:

General Considerations

Efficacy and safety analyses will be performed on the full analysis set (FAS), which includes all randomized subjects who have received at least 1 dose of IP. Analyses will be performed separately by dose frequency (Q2W and QM) unless specified otherwise. Methods of adjusting for multiplicity due to testing the superiority of evolocumab in combination with atorvastatin to placebo in combination with atorvastatin for both the co-primary and co-secondary efficacy endpoints within each dose frequency are provided in Section 10.5. Subject incidence of exploratory endpoint events will be summarized for each treatment group.

Analyses of Co-Primary Efficacy Endpoints

To assess the co-primary efficacy endpoints of the mean percent change from baseline at weeks 10 and 12 and percent change from baseline at week 12 in LDL-C, a repeated measures linear effects model will be used in each dose frequency to compare the efficacy of evolocumab in combination with atorvastatin and placebo in combination with atorvastatin. The repeated measures model will include terms for treatment group, stratification factors, scheduled visit and the interaction of treatment with scheduled visit. Missing values will not be imputed when the repeated measures linear effects model is used.

Analyses of Co-Secondary Efficacy Endpoints

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

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Safety Analyses

AEs will be coded using the current version of MedDRA. Subject incidence of treatment-emergent adverse events, serious adverse events, and adverse events leading to discontinuation of IP will be tabulated by system organ class and preferred term by randomized treatment group.

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

Safety Monitoring

An independent DMC will formally review the accumulating data from this and other completed and ongoing studies with evolocumab to ensure there is no avoidable increased risk for harm to subjects. Analyses for the DMC will be provided by a group which is external to Amgen*.*
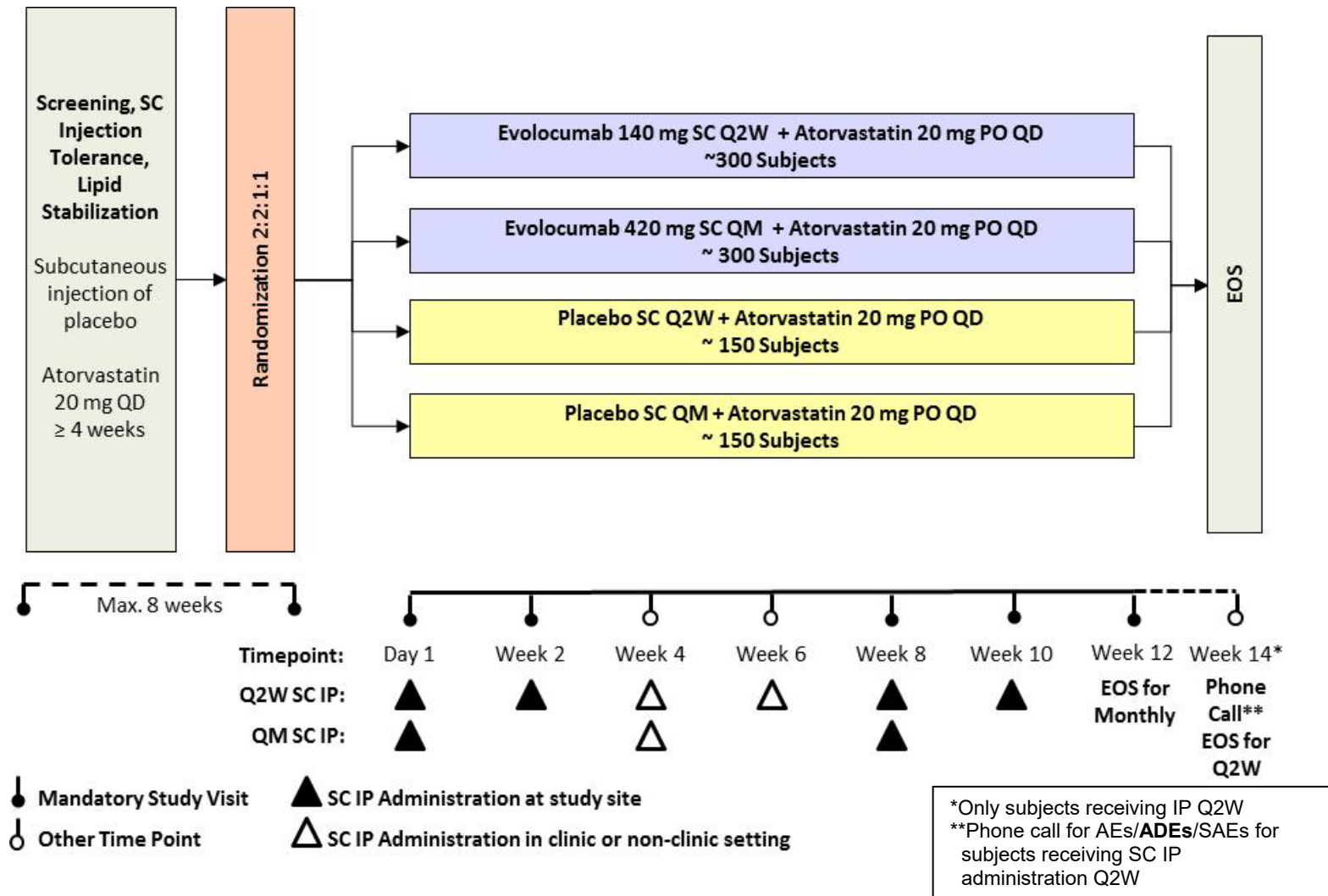
For a full description of statistical analysis methods, please refer to Section 10.

Sponsor: Amgen

Data Element Standards Version / Date:	Version 2.0 / 12 October 2012

Study Design and Treatment Schema

Screening, SC Injection Tolerance, Lipid Stabilization

Subcutaneous injection of placebo

Atorvastatin 20 mg QD ≥ 4 weeks

Randomization 2:2:1:1

Evolocumab 140 mg SC Q2W + Atorvastatin 20 mg PO QD
~300 Subjects

Evolocumab 420 mg SC QM + Atorvastatin 20 mg PO QD
~ 300 Subjects

Placebo SC Q2W + Atorvastatin 20 mg PO QD
~ 150 Subjects

Placebo SC QM + Atorvastatin 20 mg PO QD
~ 150 Subjects

EOS

Max. 8 weeks

Timepoint:	Day 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14*
Q2W SC IP:	▲	▲	△	△	▲	▲	EOS for Monthly	Phone Call** EOS for Q2W
QM SC IP:	▲		△		▲			

- 🔹 Mandatory Study Visit
- 🔾 Other Time Point
- ▲ SC IP Administration at study site
- △ SC IP Administration in clinic or non-clinic setting

*Only subjects receiving IP Q2W
Phone call for AEs/ADEs**/SAEs for subjects receiving SC IP administration Q2W

Study Glossary

Abbreviation or Term	Definition/Explanation
ADE	**Adverse device effect**
AE	Adverse event
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase (serum glutamic-pyruvic transaminase)
ApoA1	Apolipoprotein A-1
ApoB48	Apolipoprotein B48
ApoB100	Apolipoprotein B100
AST (SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
BAS	Bile acid sequestrants
BP	Blood pressure
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CAS	Completer analysis set
CBC	Complete blood count
CK	Creatine kinase
CHD	Coronary heart disease
CRP	C-reactive protein
CTCAE	NCI Common Terminology Criteria for AEs
CTT	Cholesterol Treatment Trialists
CV	Cardiovascular
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DHA	Docosahexaenoic acid
DILI	Drug-induced liver injury
DMC	Data monitoring committee (Efficacy and Safety Evaluation Committee)
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate; eGFR will be calculated by the central laboratory and provided to the investigator.
EDC	Electronic data capture
End of study / Primary completion date	The end of the study / primary completion date is defined as the last day on which a randomized subject completes the end-of-study visit or phone follow-up (week 12 for subjects on QM IP administration; week 14 for subjects on Q2W IP administration) or terminates the study early, whichever is later

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Abbreviation or Term	Definition/Explanation
End of study for individual subject	Defined as the last day that protocol-specified procedures are conducted for an individual subject or day the subject ends study early. Subjects will complete the study at week 12 (subjects on QM IP administration) or week 14 (subjects on Q2W IP administration).
End of treatment	Defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
EOS	End-of-study (for the individual subject)
EPA	Eicosapentaenoic acid
FAS	Full analysis set
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HDL-C	High density lipoprotein cholesterol
HepG2 cells	Human hepatocellular carcinoma cell line
HR	Heart Rate
hsCRP	High sensitivity CRP
IBG	Independent Biostatistical Group
ICF	Informed consent form
ICH	International Conference on Harmonization
IFU	Instructions for Use
IM	Intramuscular
INR	International normalized ratio
IRB	Institutional Review Board
IP	Investigational product
IPIM	Investigational Product Instruction Manual
IVRS/IWRS	Interactive Voice Response System / Interactive Web Response System
IV	Intravenous
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LDLR	LDL receptor
LH	luteinizing hormone
LLN	Lower limit of normal
LOF	Loss of function
Lp(a)	Lipoprotein(a)
MedDRA	Medical dictionary for regulatory activities
Monthly	Defined as every 4 weeks with a window of ± 3 days. For practical considerations, study visits are scheduled based on a weekly calendar with a window of +/- 3 days for each visit, thus dosing intervals are allowed to be up to 31 days for the QM regimen.

Abbreviation or Term	Definition/Explanation
MMTT	Mixed meal tolerance test
NASH	Nonalcoholic steatohepatitis
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
PO	Oral administration
QM	QM is defined as every 4 weeks with a window of ± 3 days for each visit, thus dosing intervals are allowed to be up to 31 days for the QM regimen.
Q2W	Q2W is defined as every 2 weeks with a window of ± 3 days for each visit, thus dosing intervals are allowed to be up to 17 days for the Q2W regimen.
QD	Each day
RBC	Red blood cells
SAE	Serious adverse event
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
Source Data	Information from an original record or certified a copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline (E6)). Examples of source data include Subject ID, Randomization ID, and Stratification Value.
Study day 1	Defined as the first day that protocol-specified subcutaneous (SC) investigational product is administered to the subject
TBL	Total bilirubin
TIA	Transient ischemic attack
TNF	Tumor necrosis factor
TSH	Thyroid Stimulating Hormone
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol
w/v	Weight/volume (grams per 100 milliliter)
WBC	White blood cell

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1.   OBJECTIVES

1.1   Primary

To evaluate the effect of 12 weeks of subcutaneous (SC) evolocumab every 2 weeks (Q2W) and monthly (QM), in combination with oral (PO) atorvastatin daily (QD), compared with placebo Q2W and QM, in combination with PO atorvastatin QD, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in diabetic subjects with hyperlipidemia or mixed dyslipidemia.

1.2   Secondary

- to evaluate the safety and tolerability of SC evolocumab Q2W and QM in combination with atorvastatin QD, compared with placebo Q2W and QM, in combination with atorvastatin QD, in diabetic subjects with hyperlipidemia or mixed dyslipidemia

- to assess the effects of 12 weeks of SC evolocumab Q2W and QM in combination with atorvastatin QD, compared with placebo Q2W and QM, in combination with atorvastatin QD, on change from baseline in LDL-C, and percent change from baseline in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B100 (ApoB100), total cholesterol, total cholesterol/HDL-C ratio, ApoB100/Apolipoprotein A-1 (ApoA1) ratio, lipoprotein(a) [Lp(a)], triglycerides, very low-density lipoprotein cholesterol (VLDL-C), and HDL-C in diabetic subjects with hyperlipidemia or mixed dyslipidemia

- to assess the effects of 12 weeks of SC evolocumab Q2W and QM in combination with atorvastatin QD, compared with placebo Q2W and QM, in combination with atorvastatin QD, on percent of subjects attaining LDL-C < 70 mg/dL (1.8 mmol/L) in diabetic subjects with hyperlipidemia or mixed dyslipidemia

1.3   Tertiary

- to assess the treatment effects of 12 weeks SC evolocumab Q2W and QM in combination with atorvastatin QD, compared with placebo Q2W and QM, in combination with atorvastatin QD, on percent change from baseline of ApoA1 in diabetic subjects with hyperlipidemia or mixed dyslipidemia

- to characterize evolocumab PK exposure

1.4   Exploratory

- to describe the effects over time of SC evolocumab Q2W and QM in combination with atorvastatin QD, compared with placebo Q2W and QM, in combination with atorvastatin QD, on change from baseline in proprotein convertase subtilisin/kexin type 9 (PCSK9) levels and on change from baseline and percent change from baseline of LDL-C, total cholesterol, non-HDL-C, ApoB100, total cholesterol/HDL-C ratio, ApoB100/ApoA1 ratio, triglycerides, VLDL-C, HDL-C, ApoA1, and Lp(a), and categorical change from baseline in high sensitivity C-reactive protein (hsCRP) in diabetic subjects with hyperlipidemia or mixed dyslipidemia

- to explore the effect of SC evolocumab Q2W and QM in combination with atorvastatin QD, compared with placebo Q2W and QM, in combination with atorvastatin QD, on fasting and postprandial plasma laboratory parameters of interest

- to investigate the relationship between novel and established biochemical cardiovascular and lipid biomarkers and effects of evolocumab

- to investigate 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 pharmacogenetics analysis

- to explore evolocumab population pharmacokinetics in diabetic subjects

- to explore evolocumab exposure/response relationships in diabetic subjects

2.   BACKGROUND AND RATIONALE

2.1   Cardiovascular Disease and Diabetes

Collectively, cardiovascular diseases (CVD) are regarded as a world-wide epidemic; and although CVD mortality has declined (primarily in developed countries) over the last two decades, it still represents the leading cause of death and disability in the world, as well as over 10% of the global total disease burden. In 2008, the WHO estimated 57 million deaths world-wide, of which 36 million were due to non-communicable causes. 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).

The facts below illustrate the magnitude of the problem in the US (Roger et al, 2011):

(i) In excess of one in three individuals in the US has some form of CVD. Coronary heart disease (CHD) affects almost 17 million Americans. Of those almost 8 million suffer from myocardial infarction; nearly 10 million from angina pectoris; nearly 6 million from heart failure; and 6 to 7 million from stroke. The aging of the population and the explosive increase in the prevalence of obesity and type 2 diabetes and their related complications (hypertension, hyperlipidemia, and atherosclerotic vascular disease) will only serve to increase the prevalence of CVD.

(ii) CVD claims more lives each year than cancer, chronic lower respiratory disease, and accidents combined. Over 2200 Americans die of CVD each day. Mortality data show that CVD accounted for more than one in three deaths (over 800,000) in the United States. Since 1900, CVD has been the number 1 killer in the United States every year, with the exception of 1 year only (1918).

(iii) CHD caused approximately 1 of every 6 deaths in the United States. CHD mortality was slightly more than 400,000. It is estimated that each year 785,000 and 470,000 Americans will have a new and recurrent acute coronary syndrome,

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respectively. An additional 195,000 silent first myocardial infarctions are estimated to occur each year.

(iv) Approximately 795,000 people experience a new or recurrent stroke each year. About 610,000 of these are first attacks, and 185,000 are recurrent attacks. Preliminary data from 2006 indicate that stroke accounted for about 1 of every 18 deaths in the United States.

The situation in the European Union (EU) is similar. CHD by itself remains the single most common cause of deaths in the EU (Allender et al, 2008). Each year CVD causes over 4.3 million deaths in Europe and over 2.0 million deaths in the EU. CVD causes nearly half of all deaths in Europe (48%) and in the EU (42%).

CVD remains a significant cause of morbidity in non-Western regions as well. For example, in China, heart attacks and strokes account for the number 1 and 3 causes of death among men and women combined, respectively (He et al, 2005). China now ranks among the top 10 countries in the world for total incidence of CVD, thus representing a significant and growing public health problem (Liu et al, 2007). Similar trends have been noted in other Asian countries, India, and Brazil (Iso, 2011; Celermajer et al, 2012; Mansur et al, 2010). These trends are thought to result from growing urbanization and industrialization which has resulted in a rise in cardiovascular risk factors such as glucose intolerance, dyslipidemia, and hypertension (Ueshima et al, 2008; Khoo, 2003). Importantly, elevated blood glucose has been estimated to contribute to 22% of coronary heart disease deaths and 16% of stroke deaths (World Health Organization, 2009).

Type 2 diabetes mellitus is a major independent risk factor for cardiovascular disease-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, 2011).

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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 Current Therapies for Reducing the Risk of Cardiovascular Disease Events

Extensive clinical trial data in both primary and secondary prevention demonstrate that the reduction in total cholesterol, non-high-density lipoprotein cholesterol (HDL-C), and most importantly, LDL-C, through pharmacological therapies, lowers the risk of CVD events (Kannel et al, 1974; Kannel, 1995; Kannel et al, 1979). To decrease the burden of CVD, over 50 million patients in the United States, Europe, and Asia are currently treated with dyslipidemia therapies (World Health Organization, 2011).

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are currently the treatment of choice for hypercholesterolemia (Chinese Society of Cardiology, 2011; Teramoto et al, 2007; Grundy et al, 2004; Reiner et al, 2011). As in other regions of the world, in Asian countries higher potency statin use has been associated with lower LDL-C levels and higher proportions of patients achieving their LDL-C goals (Kim et al, 2008).

Emerging data indicate that more aggressive treatment of hypercholesterolemia is associated with even lower risk for CVD events (Baigent et al, 2010; LaRosa et al, 2005; Cannon et al, 2004); data derived from primary and secondary prevention studies in Asian populations for example are consistent with these findings (Teramoto, 2011; Hiro et al, 2009; Sato et al, 2008; Nakamura et al, 2006; Koizumi et al, 2002). A recent Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis (CTT Collaboration, 2010), which included 21 randomized controlled trials of statin versus control involving nearly 170,000 patients, showed that for every ~ 1 mmol/L reduction in LDL-C, there was an approximately 20% reduction in the risk of major vascular events (coronary death, non-fatal myocardial infarction, coronary revascularization, or stroke). Importantly, this meta-analysis, which evaluated 5 trials that compared more versus less intensive statin therapy, did not find a LDL-C threshold; additional vascular risk reduction is possible in patients with low LDL-C.

Despite achieving their LDL-C goals, approximately two-thirds of patients on lipid reduction therapy still have cardiovascular events (Libby, 2005). While it is unlikely that this residual risk is entirely due to LDL-C concentrations above the goal articulated in recent treatment guidelines (NCEP, 2002; Grundy et al, 2004), CTT Collaboration data suggest that novel agents that are capable of providing additional reductions in LDL-C above what is possible with statins may further reduce cardiovascular morbidity and mortality (CTT Collaboration, 2010). Furthermore, novel therapies are needed for individuals who are intolerant to statin therapy and cannot achieve their respective LDL-C goals (Bruckert et al, 2005; Franc et al, 2003).

Non-statin treatment options are currently available to lower LDL-C but their potency is limited, such that LDL-C reductions occur on the order of 15% to 20%. Considering the remaining cardiovascular risk despite the availability of statin therapy, and given that non-statin treatment options have modest efficacy (ezetimibe, bile acid sequestrants [BAS], plant stanols) and/or are poorly tolerated (niacin and BAS), there is an unmet medical need for a potent, effective non-statin agent that will get a significant proportion of patients to LDL-C goal and further reduce cardiovascular risk. This need is especially evident among individuals at high risk for future cardiovascular events, for example those who have already suffered from a myocardial infarction or stroke or individuals with diabetes. Based on the current data, evolocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9), may fulfill this need and may provide an important addition to the treatment of hyperlipidemia/dyslipidemia for individuals with hyperlipidemia, including individuals with concomitant diabetes.

2.3 Evolocumab Background

2.3.1 Mechanism of Action and Therapeutic Potential

Recycling of the hepatic cell surface LDLR plays a critical role in the maintenance of cellular and whole body cholesterol balance by regulating plasma LDL-C levels. Recently it has been shown that PCSK9 plays an important role in the recycling and regulation of LDLR (Horton et al, 2007; Brown and Goldstein, 2006). PCSK9 is a member of the subtilisin family of serine proteases and is expressed predominantly in the liver, kidney, and intestine (Zaid et al, 2008). Following secretion, it causes post-translational downregulation of hepatic cell surface LDLR by a mechanism that involves direct binding to the LDLR. Downregulation of hepatic LDLR in turn leads to increased levels of circulating LDL-C. Thus PCSK9 may represent a target for inhibition by novel therapeutics in the setting of dyslipidemia. The rationale for such an approach

is available from studies in preclinical models, and from human genetic data that provide strong validation for the role of PCSK9 in modulating LDL-C levels and the incidence of CHD in man. These human studies have identified gain-of-function mutations in the PCSK9 gene that are associated with elevated serum LDL-C levels (> 300 mg/dL [approximately 7.8 mmol/L]) and premature CHD (Abifadel et al, 2003); and loss-of-function (LOF) mutations that are associated with low serum LDL-C levels (≤ 100 mg/dL [approximately 2.6 mmol/L]) (Cohen et al, 2005). Strikingly, subjects with heterozygous LOF mutations exhibit lower serum PCSK9 levels and as much as 88% reduction in the incidence of CHD over a 15-year period compared with noncarriers of the mutations (Cohen et al, 2006). Moreover, despite complete loss of PCSK9 and associated very low serum LDL-C levels (< 20 mg/dL [approximately 0.5 mmol/L]), the 2 subjects who have been identified with compound heterozygote LOF mutations appear healthy (Hooper et al, 2007; Zhao et al, 2006).

Evolocumab is a fully human monoclonal immunoglobulin (Ig) G2 that binds specifically to human PCSK9 and prevents the interaction of PCSK9 with LDLR. Details of the biochemistry, nonclinical pharmacology, nonclinical pharmacokinetics (PK), and nonclinical toxicology with evolocumab are contained in the AMG 145 Investigator's Brochure. Evolocumab binds to human, monkey, and hamster PCSK9 with high affinity (K_d < 100 pM). Evolocumab caused a dose-dependent inhibition of PCSK9 binding to the LDLR and of PCSK9-mediated reduction in low-density lipoprotein (LDL) uptake in human hepatocellular carcinoma cell line (HepG2) cells in culture. In cynomolgus monkeys and in hamsters, in vivo administration of evolocumab resulted in reduced serum lipoprotein cholesterol levels in a dose-dependent manner. Based on a comprehensive package of PK, pharmacodynamics (PD), and toxicology studies (AMG 145 Investigator's Brochure), a program to develop evolocumab as a treatment for dyslipidemia was initiated.

2.3.2 Clinical Experience: Efficacy

In a single-dose, phase 1a study (20080397), complete suppression of circulating PCSK9 was observed at doses ≥ 70 mg SC, which correlated well with the effects seen on circulating LDL-C). Following a SC dose, PCSK9 suppression was rapid and was observed at the first measured time point after administration (4 hours).

In the ascending, multiple-dose, phase 1b study (20080398), regimens of 140 mg Q2W, 280 mg Q2W, and 420 mg Q4W were associated with near complete suppression of PCSK9, and the degree of PCSK9 suppression correlated well with the effects seen on

circulating LDL-C (see AMG 145 Investigator's Brochure). Following a SC dose, PCSK9 suppression was rapid and the time course of suppression was consistent with that observed following a single dose (Study 20080397). Subjects receiving evolocumab with high-dose statins had a similar degree of PCSK9 suppression as subjects receiving evolocumab with lower doses of statins. Subjects with heterozygous familial hypercholesterolemia who received evolocumab exhibited a similar degree of PCSK9 suppression as subjects without heterozygous familial hypercholesterolemia who received evolocumab (Dias et al, 2012).

Findings from 4 completed phase 2 studies (20101154, 20101155, 20090158, and 20090158) and ongoing results from phase 2 open-label extension Study 20110110 demonstrated that evolocumab is effective in various patient populations (Giugliano et al, 2012; Koren et al, 2012; Sullivan et al, 2012; Raal et al, 2012). Treatment with evolocumab as monotherapy or in combination with statins (or other lipid lowering therapies) was effective in lowering serum concentrations of LDL-C, total cholesterol, ApoB100, VLDL-C, triglycerides, Lp(a), non-HDL-C, total cholesterol/HDL-C ratio, ApoB100/ApoA1 ratio, and PCSK9, and in increasing serum concentrations of HDL-C and ApoA1, in subjects with hyperlipidemia or mixed dyslipidemia (including heterozygous familial hypercholesterolemia and statin-intolerant subjects). Of the 6 evolocumab doses tested in phase 2, SC doses of 140 mg Q2W and 420 mg Q4W resulted in the greatest effects on lipid parameters and produced comparable results over the dosing interval.

Sensitivity analyses and non-parametric analyses confirmed that the primary endpoint analysis of efficacy was robust. Subgroup analyses of the primary efficacy endpoint of percent change in LDL-C from baseline to week 12 demonstrated consistent treatment effects across all subgroups including sex, presence or absence of diabetes, presence or absence of metabolic syndrome, screening LDL-C < or ≥ 130 mg/dL, baseline triglyceride level, age (< 65 or ≥ 65 years), intensive statin use at baseline (yes/no), and race.

For further details on evolocumab efficacy results refer to the AMG 145 Investigator's Brochure.

2.3.3   Clinical Experience: Safety

Adverse events reported in completed phase 2 clinical studies (20101154, 20101155, 20090158, and 20090159) or in the open-label phase 2 study (20110110) demonstrate

that evolocumab has an acceptable benefit:risk profile up to the highest dose tested (420 mg). Specifically:

- In completed phase 2 studies, subjects treated with evolocumab had a higher overall incidence of treatment emergent adverse events compared with placebo (57% and 48%, respectively); however, there was no relationship between the dose or dosing frequency of evolocumab and the incidence of treatment emergent adverse events.

- In completed phase 2 studies, adverse events with a subject incidence of ≥ 2% in the evolocumab group and exceeding the placebo incidence by ≥ 1% were as follows (evolocumab, placebo): nasopharyngitis (8.2%, 6.6%), myalgia (2.7%, 1.0%), and nausea (2.7%, 1.7%).

- In completed phase 2 studies, the overall incidence of serious adverse events was similar between the evolocumab and placebo groups (2.1% and 1.3%, respectively). No individual serious adverse event was reported for > 2 (0.2%) subjects treated with evolocumab in these studies.

- There was a higher incidence of creatine kinase elevations in the evolocumab group compared with placebo. These elevations were generally associated with obvious precipitating events in the form of strenuous physical activity. All of these events were transient (1 laboratory abnormality followed by normal laboratory values), resolved spontaneously (by next laboratory assessment), and did not lead to discontinuation of investigational product (IP).

For further details on evolocumab safety results refer to the

AMG 145 Investigator's Brochure.

Refer to the specific section of the AMG 145 Investigator's Brochure for additional information related to the physical, chemical, and pharmaceutical properties and formulation(s).

2.4　　　　Statin Background

In this study, evolocumab in combination with 20 mg QD atorvastatin will be compared with placebo in combination with 20 mg QD atorvastatin. The clinical benefits of statin treatment in primary prevention as well as secondary prevention have been documented in multiple trials (Weart and Hogan, 2011). A recent meta-analysis confirmed a beneficial effect on all-cause mortality as well as combined fatal and non-fatal cardiovascular endpoints in primary prevention (Taylor et al, 2011).

Several large-scale clinical trials have assessed the efficacy of atorvastatin in the primary and secondary prevention of cardiovascular events in patients with diabetes mellitus and/or metabolic syndrome (Arca, 2007).

A study conducted specifically in patients with type 2 diabetes found atorvastatin to be safe and efficacious in reducing the risk of first cardiovascular disease events, including stroke (Colhoun et al, 2004). The study was terminated 2 years earlier than expected

because the prespecified early stopping rule for efficacy had been met. Median duration of follow-up was 3.9 years. Risk rate reduction for having at least one major cardiovascular event was 37% [95% CI -52 to -17], p=0.001). Assessed separately, acute coronary heart disease events were reduced by 36% (-55 to -9), coronary revascularizations by 31% (-59 to 16), and rate of stroke by 48% (-69 to -11). Atorvastatin reduced the death rate by 27% (-48 to 1, p=0.059). No excess of adverse events was noted in the atorvastatin group. These results are similar to the results of the ASCOT-LLA trial (Sever et al, 2005) which included 2532 hypertensive diabetic patients, where atorvastatin (vs placebo) reduced the relative risk of all cardiovascular events and procedures by 23% (p = 0.036) and the Heart Protection Study (HPS) where simvastatin reduced the relative risk (vs placebo) of major cardiovascular events by 33% (p = 0.0003) over 5 years (Collins et al, 2003).

In secondary prevention, substudies of the GREACE (GREek Atorvastatin and Coronary-heart-disease Evaluation), TNT (Treating to New Targets) and PROVE-IT (PRavastatin Or atorVastatin Evaluation and Infection Therapy) trials reported results for the approximately 15-25% of study participants who had diabetes (Athyros et al, 2003; Shepherd et al, 2006; Ahmed et al, 2006). In the GREACE substudy, atorvastatin (vs physicians' standard care) significantly reduced the relative risk of total mortality by 52% (p = 0.049), coronary mortality by 62% (p = 0.042), coronary morbidity by 59% (p < 0.002) and stroke by 68% (p = 0.046). In the TNT substudy, incidence of the primary endpoint was significantly lower in diabetic patients treated with atorvastatin 80 mg/day rather than 10 mg/day (13.8% vs 17.9%; relative risk 0.75; p = 0.026). In the PROVE-IT substudy, a significantly lower incidence of acute cardiac events was reported for atorvastatin versus pravastatin recipients (21.1% vs 26.6%; p = 0.03) and, therefore, an absolute risk reduction of 5.5% was associated with atorvastatin therapy.

Reported adverse events arising from statin therapy are infrequent and rarely severe (Weart and Hogan, 2011). Though some studies have suggested an association between lower LDL cholesterol levels and hemorrhagic stroke or intracranial hemorrhage (Iso et al, 1989; Collins et al, 2004; Amarenco et al, 2006), several contemporary studies utilizing high doses of potent statins as well as two large meta-analyses have not observed this association (Waters et al, 2006; CTT Collaboration, 2010; Hackam et al, 2011). Regarding other safety profile data available for statins, a pooled analysis of 49 atorvastatin trials demonstrated that the overall safety profiles for the 10- and 80-mg/day doses are comparable, with the

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exception of a slightly increased rate of elevations in levels of the hepatic enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) for the higher dose (Newman et al, 2006). The most common adverse effects experienced by patients taking statins are those associated with the musculoskeletal system, and these effects occur with all statins. Symptoms are usually restricted to muscle pain, weakness and/or cramps. Myalgia, which according to various definitions may include some or all of these relatively minor symptoms, typically affects 5% to 10% of patients receiving statins (Weart and Hogan, 2011).

Refer to the regional manufacturer package insert for additional information.

2.5   Rationale

It is anticipated that evolocumab may be used in diabetic individuals who cannot achieve their LDL-C goals despite the use of statin therapy or are intolerant to 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.

Because lipid levels may vary with diet and body weight it is not possible to assess the true effect of evolocumab on lipid parameters as well as its safety and tolerability without a double-blind, randomized placebo-controlled comparator arm.

The statin background therapy chosen for this study is atorvastatin which is also used in other evolocumab phase 3 trials including FOURIER, a large cardiovascular (CV) outcomes study. Atorvastatin has been selected because of the robust clinical outcomes data that supports its use as well as the fact that it has been studied in a dedicated Diabetes cardiovascular outcomes trial (Colhoun et al, 2004). Atorvastatin also has a favorable safety and tolerability profile in comparison to other statins (SEARCH Study Collaborative Group 2007; Olyaei et al, 2011, Cannon et al, 2004) Based on regional medical practices, the 20 mg dose of atorvastatin was included in this study. It is a frequently used dose and renders a significant proportion of the maximal LDL-C reduction available with higher doses (LIPITOR® [atorvastatin calcium] package insert).

The percent change from baseline in LDL-C has been chosen as the primary assessment for this study because current guidelines focus on LDL-C as a target for therapy. There is an extensive body of data from interventional studies and epidemiological evidence demonstrating a strong causal relationship between serum

LDL-C and the risk of CHD. These data also support the relationship with other clinical manifestations of atherosclerosis such as cerebrovascular disease (stroke) or peripheral vascular disease. These relationships are present over a broad range of LDL-C levels.

Non-HDL cholesterol (non-HDL-C), ApoB100, total cholesterol, the ratio of total cholesterol/HDL-C, and the ratio of ApoB100/ApoA1 have been included as secondary efficacy endpoints because these markers are known and/or useful markers of cardiovascular risk under certain circumstances and have been identified in prior studies to be affected by treatment with evolocumab. Some of these measures may be employed as future targets for lipid lowering therapy.

Triglycerides and HDL-C were included because subjects with diabetes frequently have low HDL and/or high triglycerides and because data from Amgen's phase 1 and phase 2 studies (Dias et al, 2012; Giugliano et al, 2012; Koren et al, 2012; Sullivan et al, 2012; Raal et al, 2012) suggest lowering of triglycerides and raising of HDL-C may be effects of treatment with evolocumab. In addition, triglycerides and HDL-C are independent risk factors for cardiovascular disease (Austin et al, 1998; Sarwar et al, 2007).

2.6 Clinical Hypotheses

The primary hypothesis is that both dosing regimens of SC evolocumab (140 mg Q2W and 420 mg QM) in combination with atorvastatin QD 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 (Q2W and QM) in combination with atorvastatin QD in diabetic subjects with hyperlipidemia or mixed dyslipidemia.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 3, multicenter, double-blind, randomized, stratified, placebo-controlled study of evolocumab for diabetic subjects with hyperlipidemia or mixed dyslipidemia. After undergoing screening procedures, including laboratory assessments and a screening placebo injection, approximately 900 subjects meeting eligibility criteria and completing at least 4 weeks of lipid stabilization on atorvastatin 20 mg QD will be randomized 2:2:1:1 into the following treatment arms:

- evolocumab SC 140 mg Q2W and atorvastatin PO 20 mg QD
- evolocumab SC 420 mg QM and atorvastatin PO 20 mg QD
- placebo SC Q2W and atorvastatin PO 20 mg QD, or
- placebo SC QM and atorvastatin PO 20 mg QD.

The sample size for each of the evolocumab plus atorvastatin dosing regimens will be approximately 300 subjects. The sample size for each of the placebo plus atorvastatin dosing regimens will be approximately 150 subjects.

Randomization into the 4 treatment groups will be stratified by entry statin therapy (no statin use vs non-intensive statin use vs intensive statin use [see Appendix D]) and by the site's geographic region. Treatment and follow-up period will be 12 weeks with an additional phone call or other subject contact at week 14 for subjects receiving IP Q2W.

Evolocumab and placebo SC will be administered at the study site or appropriate non-investigator site settings, eg, at the subject's home, per protocol Section 6 and Section 7 by spring-based prefilled autoinjector/pen (prefilled AI/Pen) for subjects receiving IP Q2W and by 3.5 mL Personal Injector for subjects receiving IP QM. The dose frequencies of Q2W and QM will not be blinded but the identity of IP (evolocumab or matching SC placebo) will be blinded. Post-IP treatment central laboratory results of the lipid panel, ApoA1, ApoB100, ApoB48, free fatty acids, chylomicrons, lipoprotein(a), PCSK9, insulin, proinsulin, C-peptide, glucagon, IL-6, adiponectin, vitamin E, PK, and high sensitivity C-reactive protein (hsCRP) will be blinded until unblinding of the clinical database and will not be reported to the investigator post-screening. Investigators should not perform non-protocol testing of these analytes during a subject's study participation and until at least 12 weeks after last IP administration, or the subject's end of study, whichever is later.

The study includes collection of biomarker samples and, where approved by the institutional review board and/or independent ethics committee (IRB/IEC) and applicable regulatory and other authorities, subjects will be invited to consent to pharmacogenetics analyses. All subjects will complete a mixed meal tolerance test (MMTT) at the day 1 and week 12 study visits with 1 postprandial blood collection 2 hours after the meal and up to approximately 240 subjects will participate in a MMTT Extended Timepoints Substudy with 2 additional postprandial blood draws at 1 and 3 hours after the meal. End of study (EOS) for subjects on QM IP is at the week 12 visit. EOS for subjects on Q2W IP is by contact (eg, phone call) from the site at week 14 for any potential adverse events (AEs), **adverse device effects (ADEs), and** serious AEs (SAEs). Subjects will be encouraged to complete all planned visits regardless of their adherence to IP administration. Accumulating safety and other data will be reviewed by an independent external Data Monitoring Committee (DMC). Where analyte concentrations are provided

in mmol/L, it is for investigator convenience. Conventional concentrations (mg/mL) will be used for the protocol, including for eligibility determination.

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

The study endpoints are defined in Section 10.1.1.

3.2   Number of Sites

This study will include approximately 100 sites in North America, Europe, Asia, and may include sites in Australia, Latin America, Middle East, and/or in Africa. Additional sites may be added if necessary to achieve the enrollment goal within the planned time.

Sites that do not randomize subjects within 3 months of being open for enrollment may be closed.

3.3   Number of Subjects

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

There will be approximately 900 subjects randomized in this study. Justification for the sample size can be found in Section 10.2 Sample Size Considerations.

3.4   Replacement of Subjects

There will be no replacement for randomized subjects. Enrollment will continue until the target number of subjects (Section 3.3) have been randomized to IP, regardless of the number of subjects starting lipid stabilization on atorvastatin.

3.5   Estimated Study Duration

3.5.1   Study Duration for Subjects

After signing the informed consent, subjects should be randomized within 8 weeks. Including the screening, study treatment, and follow-up, the maximal total duration of study participation for a subject on QM IP schedule will be 20 weeks or approximately 5 months. For a subject on Q2W IP schedule, maximal study duration will be 22 weeks or approximately 5 ½ months, including the contact by the site at week 14 to obtain potential AE, **ADE,** and SAE information.

3.5.2   End of Study

The end of the study (primary completion) is defined as the last day on which a randomized subject completes the end-of-study visit or phone follow-up (week 12 for subjects on QM IP administration; week 14 for subjects on Q2W IP administration) or terminates 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).

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 to ≤ 80 years of age at signing of informed consent.

103   Type 2 diabetes, defined as receiving pharmacologic treatment for type 2 diabetes for ≥ 6 months prior to screening, with 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, no dose change of any oral antihyperglycemic drug within 2 months, and daily insulin dose not changed by > 25% and > 25 units within 1 month prior to randomization

104   Lipid-lowering therapy status (eg, not receiving any therapy or receiving any statin, ezetimibe, bile-acid sequestering resin, stanols, probucol, omega 3 fatty acids or niacin) must be unchanged for ≥ 4 weeks prior to LDL-C screening.

105   Subjects receiving statin therapy at screening must have a fasting LDL-C at screening of ≥ 100 mg/dL (2.6 mmol/L) as determined by central laboratory.

106   Subjects not receiving statin therapy at screening must have a fasting LDL-C at screening of ≥ 130 mg/dL (3.4 mmol/L) as determined by central laboratory.

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

4.1.2   Exclusion Criteria

201   Receiving 20 mg atorvastatin QD monotherapy for approximately 16 weeks is medically contraindicated or inappropriate based on opinion of investigator.

202   NYHA III or IV heart failure, or last known left ventricular ejection fraction < 30%.

203   Uncontrolled cardiac arrhythmia defined as recurrent and highly symptomatic ventricular tachycardia, atrial fibrillation with rapid ventricular response, or supraventricular tachycardia that is not controlled by medications, in the past 6 months prior to randomization.

204   Myocardial infarction, unstable angina, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) or stroke within 6 months prior to randomization.

205   Planned cardiac surgery or revascularization within 6 months after randomization.

206   Type 1 diabetes or poorly controlled type 2 diabetes (HbA1c > 10.0 % at screening and at lipid stabilization or not on stable pharmacologic therapy for

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type 2 diabetes. Stable therapy is defined as no new agents added, no dose change of any oral antihyperglycemic drug within 2 months, and daily insulin dose not changed by > 25% and > 25 units within 1 month prior to randomization.

207   Uncontrolled hypertension defined as sitting systolic blood pressure (SBP) > 160 mmHg or diastolic BP (DBP) > 100 mmHg (see Section 7.7.1 regarding repeat measurement).

208   Subject is unwilling or unable to discontinue between start of lipid stabilization with 20 mg/day atorvastatin and end of study (week 12 for QM and week 14 for Q2W subjects) the following drugs or supplements: red yeast rice, niacin (> 200 mg/day), > 1000 mg/day omega-3 fatty acids (eg, Docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA], prescription and non-prescription combined), and all other prescription lipid-regulating drugs (eg, fibrates and derivatives, ezetimibe, bile-acid sequestering resin, stanols, or probucol) except study-provided atorvastatin.

209   Subject has taken a cholesterylester transfer protein (CETP) inhibitor in the last 12 months prior to randomization, such as: anacetrapib, dalcetrapib or evacetrapib.

210   Treatment in the last 2 months prior to screening and lipid stabilization assessments with any of the following drugs: systemic cyclosporine, systemic steroids (eg, intravenous [IV], intramuscular [IM], or oral [PO] administration), vitamin A derivatives and retinol derivatives for the treatment of dermatologic conditions (eg, Accutane); (Note: vitamin A in a multivitamin preparation is permitted).

211   Hyperthyroidism or hypothyroidism as defined by thyroid stimulating hormone (TSH) below the lower limit of normal (LLN) or > 1.5 times the upper limit of normal (ULN), respectively, at screening.

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

213   Persistent active liver disease or hepatic dysfunction, defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 times the ULN as determined by central laboratory analysis at screening or lipid stabilization assessments.

214   Creatine kinase (CK) > 3 times the ULN at screening or lipid stabilization assessments.

215   Known active infection or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction (except diabetes).

216   Deep vein thrombosis or pulmonary embolism within 3 months prior to randomization.

217   Female subject who has either (1) not used (an) acceptable method(s) of **effective** birth control (see below) for at least 1 month prior to screening **and** (2) is not willing to inform her partner of her participation in this clinical study and to use such (an) acceptable method(s) **of effective birth control** during treatment with IP (evolocumab or placebo) and for an additional 15 weeks after the end of treatment with IP (evolocumab or placebo), unless the female subject is **permanently** sterilized or postmenopausal (see below);

- A female is considered of childbearing potential unless **permanently** sterilized or postmenopausal with menopause defined as:

  − 12 months of spontaneous and continuous amenorrhea in a female ≥ 55 years old, or

  − 12 months of spontaneous and continuous amenorrhea with a follicle-stimulating hormone (FSH) level > 40 IU/L (or according to the definition of "postmenopausal range" for the laboratory involved) in a female < 55 years old

  − unless the subject has undergone bilateral oophorectomy

- acceptable methods of preventing pregnancy include not having intercourse, (**true** sexual abstinence), surgical contraceptive methods - (vasectomy of the male partner or bilateral tubal ligation/occlusion), use of hormonal birth control methods (pills, shots/injections, implants, or patches), intrauterine devices (IUDs), or <u>two</u> (2) barrier methods (each partner must use one barrier method) **and at least one of the barrier methods must include** spermicide - males must use a condom with spermicide; females must choose either a diaphragm with spermicide, OR cervical cap with spermicide, OR contraceptive sponge with spermicide. **Note: a male and female condom cannot be used together due to the risk of tearing.**

  o *Note: If additional medications are given during treatment which may alter the contraceptive requirements (these additional medications may require an increase in the number of contraceptive methods and/or length of time that contraception is to be utilized after the last dose of protocol-required therapies) the investigator is to discuss these changes with the study subject.*

218   Subject is pregnant or breast feeding, or planning to become pregnant or planning to breastfeed during treatment with IP (evolocumab or placebo) and/ or within 15 weeks after the end of treatment with IP (evolocumab or placebo).

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

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

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

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

223   Subject likely to not be available to complete all protocol-required study visits or procedures, or unreliability as a study participant (eg, alcohol or other drug abuse in the past year or psychosis), to the best of the subject's and Investigator's knowledge.

224   History or evidence of any other clinically significant disorder, condition or disease that, in the opinion of the Investigator or Amgen physician, if consulted,

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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 (IRB) 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 consent form before commencement of study-specific procedures. SAEs, **ADEs,** and study-related AEs will be collected upon signing the informed consent form.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria assessed at screening. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment eCRF.

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

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.

5.1   Randomization/Treatment Assignment

Assignment to the 4 treatment arms (Section 3.1) will be based on a computer-generated randomization schedule prepared by Amgen before the start of the study.

Each subject will receive a unique randomization number. Randomization will be stratified by entry statin therapy (no statin use vs non-intensive statin use vs intensive statin use [see Appendix D] and by the site's geographic region.

Once a subject has completed the end of lipid stabilization assessments and continues to meet all eligibility criteria, a site representative will make the randomization call to the IVRS/IWRS to assign a randomization number to the subject. The randomization call to the IVRS/IWRS is accomplished by entering the pertinent information detailed in the IVRS/IWRS user manual. A confirmation fax or email will be sent to the site to verify that

the correct information has been entered and to confirm the assignment of a randomization number. A subject will be considered randomized into the study when a randomization number is assigned.

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

5.2   Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject on this study. Unblinding at the study site for any other reason will be considered a protocol deviation. The investigator is strongly encouraged to contact the Clinical Study Manager 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 Products and/or Medical Devices

The Amgen investigational products used in this study include: evolocumab and matching placebo.

The non-Amgen non-investigational products used in this study include: atorvastatin 20 mg.

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

The medical devices used in this study include: prefilled autoinjector/pen and 3.5 mL Personal Injector.

6.2   Investigational Product

6.2.1   Evolocumab (Amgen Investigational Product)

Evolocumab and placebo will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical IP distribution procedures. Evolocumab and placebo SC will be provided in 2 different injection devices:

- A single use, disposable, handheld mechanical (spring-based) prefilled autoinjector/pen (AI/Pen) for fixed dose, subcutaneous injection of 140 mg evolocumab in 1.0 mL deliverable volume or an identical volume of placebo. The AI/Pen is intended for Q2W administration.
- A single-use, disposable, on-body electro-mechanical 3.5 mL Personal Injector that is co-packaged with a prefilled Crystal Zenith® (CZ) cartridge assembly for

fixed dose, subcutaneous injection of 420 mg evolocumab in 3.5 mL deliverable volume or an identical volume of placebo. The 3.5 mL Personal Injector is intended for QM administration. If the 3.5 mL Personal Injector is unavailable, QM dosing may be provided by 3 injections by AI/Pen.

The prefilled AI/Pen contains a 1.0 mL deliverable volume of 140 mg/mL evolocumab in CCI mM proline, CC mM acetate, CCI % (weight/volume [w/v]) polysorbate 80, pH CCI or, for placebo, a 1.0 mL deliverable volume of CC % (w/v) sodium carboxymethylcellulose, CCI mM proline, CCI mM acetate, and CCI % (w/v) polysorbate 80, pH CC.

The prefilled Crystal Zenith® (CZ) cartridge assembly of the Personal Injector contains a 3.5 mL deliverable volume of 120 mg/mL evolocumab in CCI mM proline, CCI mM acetate, CCI % (w/v) polysorbate 80, pH CC or, for placebo, a 3.5 mL deliverable volume of CC % (w/v) sodium carboxymethylcellulose, CCI mM proline, CC mM acetate, and CCI % (w/v) polysorbate 80, pH CC.

Evolocumab and placebo should be stored refrigerated and protected from light according to the storage and expiration information provided on the label (where required).

AI/Pen and 3.5 mL Personal Injector should be inspected for IP quality, expiry, and damage before using per the instructions provided in the IPIM. Damaged, expired, or degraded product should not be used and any issues with the prefilled AI/Pen or 3.5 mL Personal Injector should be reported to Amgen.

Further details are provided in Section 6.7, in the IPIM and the respective Instructions for Use (IFU) for the devices.

6.2.1.1   Dosage, Administration, and Schedule

Subcutaneous IP (evolocumab or matching placebo) will be administered SC in accordance with instructions in the IPIM. IP administration by SC injection if performed during a study visit must occur after vital signs, electrocardiogram (ECG), and blood draw procedures, if applicable. After IP administration at the first dosing visit, subjects will be held for observation for at least 30 minutes before being discharged.

IP will be administered at either 140 mg evolocumab or placebo in 1.0 mL (administration by prefilled AI/Pen) Q2W or 420 mg evolocumab or placebo in 3.5 mL (administration by 3.5 mL Personal Injector) QM.

In this study, subjects have the option of self-administration, defined as SC administration of IP by the subject, designee or a qualified health care professional in a

non-investigator site setting (eg, at home). The subject (or designee, if not a qualified healthcare professional) must have demonstrated competency 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.

Details of preparing IP and the injection procedures are included in the IPIM provided by Amgen prior to the start of the study. The dosing schedule is described by a schema in the protocol synopsis.

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 fully or partially administered are to be recorded on each subject's CRF.

When IP can be administered at a non-investigator site location, at a minimum, the dates the devices were dispensed and the used devices returned, and for each device whether it was returned fully or partially used are to be recorded on each subject's CRF.

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

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

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

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

6.2.2 Atorvastatin (Non-Amgen Non-investigational Product)

Atorvastatin (non-Amgen non-investigational product) will be used in this study as background therapy. Atorvastatin will be provided by Amgen. Additional details regarding this product are provided in the Investigational Product Instruction Manual (IPIM).

6.2.2.1 Dosage, Administration, and Schedule

Atorvastatin 20 mg will be taken orally once daily and should be taken every day at about the same time in accordance with instructions in the IPIM. If taken during a study visit, it must be taken after vital signs, ECG, and blood draw procedures have been completed, if applicable.

The start date of atorvastatin administration, the dates atorvastatin is dispensed and the used containers returned, and the quantity returned are to be recorded on each subject's CRF.

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

There will be no dose adjustments for atorvastatin in this study. If, in the opinion of the investigator, a subject is unable to tolerate a specific dose of atorvastatin after having been randomized to IP, the Amgen medical monitor should be contacted. If atorvastatin is discontinued, IP (evolocumab or matching placebo) should be continued unless there is a reason to discontinue IP as well. In either case, the subject should return for all other study procedures and measurements until the end of the study.

Subjects who miss a dose of atorvastatin will be advised to take the missed dose as soon as they can; subsequent doses will be taken at the usual time. However, if the next scheduled dose would be due in less than 6 hours, the subject will be advised to omit the missed dose entirely and to take the next dose at the normal time.

6.3 Non-investigational Products

All other lipid-lowering drugs that are allowed per protocol and that the subject may be taking, must be commercially available and are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these drugs. All such therapy needs to be stable and unchanged during the entire time of screening and study participation.

6.4 Withholding of Investigational Product or Atorvastatin due to Elevation of Creatine Kinase (CK)

If CK is > 5x ULN, CK must be retested before atorvastatin and IP is administered. In addition, investigators will ask study subjects to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever. If such symptoms occur, the subject's CK levels should be measured and if CK is > 5x ULN, the subject should be instructed to discontinue atorvastatin and IP. CK must be retested before any atorvastatin or IP is administered.

The following rules apply:

CK at prior visit	CK on retest	Investigational Product Administration
> 5x ULN	> 10x ULN	Discontinue atorvastatin and IP[a]. Contact Amgen Medical Monitor
	> 5x to ≤ 10x ULN	Discontinue atorvastatin and retest CK before atorvastatin administration. Consider continuing IP if alternative explanation
	≤ 5x ULN	Consider continuing IP and atorvastatin

[a] CK elevations >10x ULN that have been confirmed to be secondary to myocardial infarction do not require discontinuation of IP or atorvastatin

If muscular symptoms are severe and cause daily discomfort, even if the CK levels are elevated to ≤ 5x ULN, in consultation with the Amgen medical monitor, discontinuation of atorvastatin, or introduction of an alternative statin may be considered at the lowest dose and with close monitoring. Please note that Amgen will not be providing the alternative statin.

6.5 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 international normalized ratio [INR] and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other protocol-required therapies as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009).

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

Atorvastatin and investigational product should be discontinued permanently and the subject should be followed according to the recommendations in Appendix A (Additional

Safety Assessment Information) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:

- TBL > 2x ULN or INR > 1.5 (testing determined per Appendix A)

AND

- AST or ALT > 3x ULN

AND

- no other cause for the combination of the above laboratory abnormalities is immediately apparent; important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:
  - hepatobiliary tract disease
  - viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
  - right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia.
  - exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
  - heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
  - alpha-one antitrypsin deficiency
  - alcoholic hepatitis
  - autoimmune hepatitis
  - Wilson's disease and hemochromatosis
  - nonalcoholic fatty liver disease including steatohepatitis (NASH)
  - Non-hepatic causes (eg, rhabdomyolysis, hemolysis)

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

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

- AST or ALT > 8x ULN at any time
- AST or ALT > 5x ULN but < 8x ULN for ≥ 2 weeks (or subject unable to adhere to enhanced monitoring schedule)

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- ALT or AST > 3x ULN with clinical signs or symptoms that are, in the opinion of the investigator, consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice, rash or eosinophilia > 5%)

- TBL > 3x ULN at any time

- ALP > 8x ULN at any time

Both atorvastatin and investigational product should be withheld pending investigation into alternative causes of DILI. If atorvastatin or investigational product 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 6.5.3).

6.5.3 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 investigational product should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.5.1) should never be rechallenged.

6.6 Concomitant Therapy, Physical Exercise, and Diet

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.9.

Concomitant therapies are to be collected from screening (informed consent date) through the end of study. Therapy name, indication, dose, unit, frequency, route, start date and stop date will be collected.

6.7 Medical Devices

IP will be provided by prefilled AI/pen for Q2W administration and by 3.5 mL Personal Injector for QM administration (Section 6.2.1). The prefilled AI/pen is a modified version of the SureClick™ autoinjector, a device that is commercially available for the administration of Aranesp® or Enbrel® drug product by patients or caregivers in a non-healthcare environment, or by healthcare professionals in the clinic environment in the United States (Enbrel® only) and in Europe. The 3.5 mL Personal Injector is a novel single-use, disposable injector with prefilled cartridge assembly that delivers 3.5 mL of

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evolocumab to subcutaneous tissue over a period of several minutes (less than 10 minutes).

Medical devices (eg, syringes, sterile needles, alcohol prep pads), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

6.8   Product Complaints

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

Any product complaints associated with the prefilled AI/Pen, the 3.5 mL Personal Injector, or other Amgen provided, protocol-required product (ie, atorvastatin) in this study must be reported to Amgen. Please do not use the device or product that is subject of a complaint until Amgen confirms that it is permissible to do so.

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

- broken or cracked containers
- subject or healthcare provider cannot appropriately use the product despite training (eg, due to malfunction of the AI/Pen or 3.5 mL Personal Injector)
- missing labels, illegible labels, incorrect labels, and/or suspect labels
- change in IP appearance, for example color change or visible presence of foreign material
- unexpected quantity or volume, for example number of tablets or amount of fluid in the prefilled AI/Pen or 3.5 mL Personal Injector
- evidence of tampering or stolen material

If possible, please have the device or product associated with the complaint available for examination when making a product complaint. Maintain device or other Amgen provided protocol-required suspect product at appropriate storage conditions until further instructions are received from Amgen.

The investigator is responsible for ensuring that all product complaints observed by the investigator or reported by the subject that occur after signing of the informed consent 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.

For more details regarding the identification and reporting of product and device complaints, refer to the IPIM and the IFU.

6.9 Excluded Treatments and/or Procedures During Study Period

The following treatments are not permitted during the study:

- prescription lipid regulating medications other than fish oil (omega-3 fatty acids) and study-provided atorvastatin, eg, fibrates and derivatives, ezetimibe, bile-acid sequestering resin, stanols, or probucol

- red yeast rice

- niacin > 200 mg/day

- omega-3 fatty acids (eg, DHA and EPA combined) > 1000 mg/day

- other drugs (besides those mentioned above) that significantly affect lipid metabolism (eg, systemic cyclosporine, systemic steroids [IV, IM, or PO; *Note: hormone replacement therapy is permitted*], vitamin A derivatives and retinol derivatives for the treatment of dermatologic conditions [eg, Accutane; *Note: Vitamin A as part of a multivitamin preparation is permitted*]).

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

- Other investigational therapies than evolocumab

The following treatments are not recommended 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, HIV or HCV protease inhibitors, antidepressant nefazodone and grapefruit juice in large quantities (> 1 quart daily [approximately 1 Liter]) should not be used during the study.

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

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Table 1. Schedule of Assessments

Study Day / Week / Other Timepoint[a]	Screen & Lipid Stabilization			Treatment Period							Phone
	Screen	Enroll Start Atorva	End of Lipid Stabil	D1 Visit Rand.	W2 Visit	W4	W6	W8 Visit	W10 Visit	W12 Visit (QM EOS)	W14[b] Q2W EOS
General Procedures											
Informed consent	X										
Medical history	X										
Vital Signs (sitting BP, HR)	X			X	X				X	X	
Review for AEs/**ADEs**/SAEs	X[c]		X[c]	X	X	(X)[d]	(X)[d]	X	X	X	X
Concomitant therapy	X		X	X	X			X	X	X	
Dietary instruction	X			X	X			X	X		
Physical exam	X										
Body weight, waist circumference				X						X	
Body height	X										
12 lead ECG	X			X					X	X	
Randomization				X[e]							
Central Laboratory[f]											
Fasting lipids[g]	X		X	X	X			X	X	X	
ApoA1, ApoB100, Lp(a)				X					X	X	
PK (evolocumab), PCSK9				X	X			X	X	X	
Chemistry, including fasting glucose[g]	X		X	X				X		X	
Hematology	X			X				X		X	
hsCRP				X						X	
HbA1c	X									X	
TSH	X										
MMTT: Plasma glucose, insulin, proinsulin, C-peptide, free fatty acids, glucagon, lipids, chylomicrons, ApoB48, IL-6, adiponectin, vitamin E, measured after a ≥ 9 hour fast just prior to a standardized meal (0 minutes), and then 120 minutes after [h]				X						X	
MMTT Extended Timepoints Substudy: Same analytes as for MMTT, measured at additional timepoints (60, 180 minutes) in subjects participating in the substudy) [h]				X						X	
Biomarkers (blood)[ji]				X						X	
Anti-evolocumab antibodies				X						X	
HCV testing[j]	X										
HCV viral load[j]				X	X			X		X	
Serum pregnancy; FSH[k]	X		X							X	
Urine pregnancy				X	X				X		
Urinalysis, urine microalbumin				X						X	

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Footnotes defined on last page of this table.

Table 1. Schedule of Assessments

| Study Day / Week / Other Timepoint[a] | Screen & Lipid Stabilization | | | Treatment Period | | | | | | | Phone |
	Screen	Enrol Start Atorva	End of Lipid Stabil	D1 Visit Rand.	W2 Visit	W4	W6	W8 Visit	W10 Visit	W12 Visit (QM EOS)	W14[b] Q2W EOS
Steroid analytes[l]				X						X	
Investigational Product											
Screening placebo injection	X										
Atorvastatin dispensation[m]	X	x	X	x	X			x			
Atorvastatin tablet count[m]	X		x	x	X			x		X	
AI/Pen / 3.5 mL Personal Injector Instruction	X			X	X			X			
AI/Pen / 3.5 mL Personal Injector dispensation					X			X			
AI/Pen / 3.5 mL Personal Injector reconciliation								X			
Q2W IP on-site				X	X			X	X		
QM IP on-site				X				X			
Q2W IP on-site or in non-investigator site setting						X	X				
QM IP on-site or in non-investigator site setting						X					

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[a] D1 = day of first administration of IP; a visit window of ± 3 days applies to all other visits; atorvastatin will be taken orally every day for ≥ 4 weeks of lipid stabilization before randomization and then continuously until the week 12 visit; atorvastatin should be taken every day at about the same time

[b] subjects on Q2W IP schedule; subject is being contacted by the site at week 14, eg, by phone call

[c] only AEs possibly related to study procedures and **ADEs**/SAEs are collected during the screening and lipid stabilization period

[d] only if a visit to the study site is performed instead of IP administration at a non-investigator site location

[e] randomization should be on day 1 or as close as possible and must not be earlier than 5 days prior to day 1

[f] blood samples must be taken prior to IP administration, if applicable

[g] if subject is not fasting on 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

[h] postprandial blood draw at 120 ± 10 mins after standardized mixed meal (see Section 7.7.6) for all subjects; additional postprandial blood draws at 60 ± 10 mins and 180 ± 10 mins for subjects participating in the MMTT Extended Timepoints Substudy (see Section 7.7.7). Other markers for metabolic status may be assessed as well.

[i] if the subject consented to pharmacogenetics analyses, deoxyribonucleic acid (DNA) will be extracted from some of the blood samples, eg, biomarker samples

[j] HCV antibodies only in subjects at high risk for, or with history of, HCV infection, or born between 1945 and 1965 (see Section 7.2.1.1) or if ALT or AST > 2x ULN at any time during screening; viral load only in subjects positive for HCV

[k] pregnancy testing in females of childbearing potential, FSH only if applicable per Section 4.1.2, exclusion 217

[l] Applies to subjects in China only: steroid analytes include cortisol, adrenocorticotropic hormone, estradiol, testosterone, luteinizing hormone (LH), and FSH

[m] timepoints of atorvastatin dispensation and tablet count may vary regionally and differ from the timepoints shown here

Refer to Sections 7.2 through 7.7 and the applicable supplemental laboratory manual, ECG manual, and IPIM for detailed study procedures.

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

7.2   General Study Procedures

This is a multi-center, randomized, double-blind, placebo-controlled trial. The study consists of 2 periods:

- screening period
- double-blind treatment period

For the purpose of this study, a week is defined as 7 calendar days.

Written informed consent must be obtained and will be implemented before protocol specific procedures are carried out. The risks and benefits of participating in the study will be verbally explained to each potential subject prior to entering into the study. The procedures to be performed at each study site visit are described below and the timing of the procedures is provided in Table 1. If IP is administered during a study visit, administration must be after completion of vital signs, ECG, and blood draw procedures, as applicable.

Subjects must be fasting for ≥ 9 hours before each study visit. For procedures if the subject is not fasting when presenting at the study site for a visit, please see Section 7.2.1.1 and Section 7.2.2 below.

All screening and on-study laboratory samples will be processed and sent to the central laboratory. Amgen or designee will be responsible for the evaluation of PK (evolocumab) and PCSK9 serum levels, anti-evolocumab antibody, and biomarker development assessments and the central laboratory will ship the samples to Amgen or a specialty laboratory for assay (depending on the assessment).

The central laboratory will provide a study manual that outlines handling, labeling, and shipping procedures for all blood samples. The date and time of sample collection will be recorded in the source documents at the site.

Table 2 below outlines the specific analytes for serum chemistry, hematology, urinalysis, and other testing to be conducted.

Table 2. Analyte Listing

Chemistry	Coagulation	Urinalysis	Hematology	Other Labs
Sodium	PT/INR (per Appendix A)	Specific gravity	Hemoglobin	Fasting lipids
Potassium		pH	Hematocrit	• Total cholesterol
Chloride		Blood	RBC	• HDL-C
Bicarbonate		Protein	RDW	• LDL-C
Total protein		Glucose	MCV	• Triglycerides
Albumin		Bilirubin	MCH	• VLDL-C
Calcium		WBC	MCHC	• non-HDL-C
Magnesium		RBC	WBC	ApoA1
Phosphorus		Epithelial cells	Platelets	ApoB100
Fasting glucose		Bacteria	Differential	ApoB48
BUN or Urea		Casts	• Neutrophils	hsCRP
Creatinine		Crystals	• Bands	Lp(a)
Uric acid			• Eosinophils	Insulin
Total bilirubin			• Basophils	Proinsulin
Direct bilirubin			• Lymphocytes	C-peptide
CK			• Monocytes	Free fatty acids
ALP				Glucagon
LDH				Chylomicrons
AST (SGOT)				Vitamin E
ALT (SGPT)				IL-6
				Adiponectin
				Anti-evolocumab antibodies
				PCSK9
				evolocumab (PK)
				HbA1c
				Pregnancy test (females of childbearing potential)
				FSH (if needed per exclusion 217)
				TSH
				HCV antibody*
				HCV viral load**
				Steroid analytes:***
				• Cortisol
				• Adrenocorticotropic hormone
				• Estradiol
				• Testosterone
				• Luteinizing hormone (LH)
				• FSH

*HCV antibodies are measured before initiating treatment with IP in subjects at high risk for (see Section 7.2.1.1), or with history of, HCV infection, or born between 1945 and 1965, and in subjects with ALT or AST > 2x ULN at any time during screening. Please note that subjects with ALT or AST > 2x ULN must be screen failed unless the elevation is transient as confirmed by retesting per Section 7.2.1.3.
** Viral load will be tested at the time points indicated in Table 1 in subjects who are positive for HCV.
***Applies to subjects in China only.

Some laboratory results may inadvertently unblind investigators to treatment assignment to evolocumab. Central laboratory results of the lipid panel, ApoA1, ApoB, Lp(a), and hsCRP will not be reported to the investigator (or study personnel) post-screening. Investigators should not perform non-protocol testing of these analytes during a subject's study participation from first administration of IP until at least 12 weeks after last IP administration, or the subject's end of study, whichever is later.

7.2.1 Screening, Lipid Stabilization, and Randomization

Subjects who are considered for entry into the study and have the risk and benefits of participating in the study explained will enter screening by signing and dating the informed consent form for this study. Screening should be completed and the subject randomized or screen failed within 8 weeks of signing the informed consent.

7.2.1.1 Screening Placebo Injection

In order to reduce the burden of unnecessary procedures on subjects who subsequently elect not to participate in the study or continue with study procedures, all subjects will undergo a placebo administration to confirm tolerance of SC administration by SC injection prior to enrollment. This placebo administration can be done before or after screening venipuncture procedures but must be done before enrollment. The administration corresponds to the IP dose volume for Q2W administration and consists of 1 injection of 1.0 mL placebo, using 1 AI/Pen. This administration is following the same procedures as injections of IP during the treatment period. Further details are provided in the IPIM.

7.2.1.2 Screening and Lipid Stabilization

The following procedures are to be completed during the screening period:

- confirmation that the Informed Consent Form has been signed
- demographic data including sex, date of birth, age, race, and ethnicity will be collected in order to study their possible association with treatment effectiveness, subject safety, or, for example, to further study biomarker variability
- medical history
- vital signs (sitting BP, heart rate [HR]; see Section 7.7.1)
- review for AEs/**ADEs**/SAEs (AEs possibly related to study procedures, **ADEs and SAEs** are collected during screening)
- concomitant therapy
- physical examination
- body height
- 12-lead ECG in triplicate using centralized ECG services equipment

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- blood draw for fasting lipids (≥ 9 hour fasting sample), chemistry (including fasting glucose), hematology, HbA1c, TSH, serum pregnancy (females of childbearing potential only), and FSH (only if required to ensure menopause in a female subject [see exclusion criterion 217]) by central laboratory *(Note: eGFR will be calculated by the central laboratory and will be provided to the site for eligibility determination)*

- blood draws for hepatitis C virus (HCV) antibodies in subjects at high risk for, or with history of, HCV infection, or born between 1945 and 1965, or with AST or ALT > 2x ULN at any time during screening*

  - High risk subjects for this protocol are those who meet any of the following conditions:

    - ever injected illegal drugs
    - received clotting factors made before 1987
    - received blood or organ donation before July 1992 or were exposed to blood known to be infected with HCV
    - were ever on chronic hemodialysis
    - are known to be infected with HIV
    - have a known HCV-infected sexual partner

- the subject will be instructed to maintain his/her current diet throughout the course of the study and avoid going on any strict diet or aiming to lose weight during the study

- screening placebo injection as per Section 7.2.1.1; includes instruction/training on AI/Pen use

- randomization, if eligible

* Please note that subjects with ALT or AST > 2x ULN must be screen failed unless the elevation is transient as confirmed by retesting per Section 7.2.1.4.

If a fasting sample could not be obtained at the initial screening visit and the other screening laboratory assessments confirm eligibility for the study, fasting lipid and glucose samples to determine eligibility must be obtained before changing or discontinuing the current lipid lowering treatment.

Eligible subjects will be enrolled (Section 5) and will start their lipid stabilization on 20 mg QD atorvastatin background therapy. If during lipid stabilization a subject is found not to tolerate the assigned atorvastatin background therapy, the subject should not continue but should early terminate the study. In contrast, if intolerance is discovered after randomization to IP, the subject should continue the study until completion. Before reducing or discontinuing treatment with atorvastatin, please contact the Amgen medical monitor. All prohibited lipid lowering therapy (see exclusion 208 and Section 6.9) must be discontinued at the start of lipid stabilization.

After ≥ 4 weeks of lipid stabilization, subjects will return to the study site for the end of lipid stabilization assessments.

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7.2.1.3   Randomization

Subjects who continue to meet all eligibility criteria at the end of lipid stabilization will be randomized and will return to the study site again for day 1 procedures while continuing their atorvastatin background treatment. Randomization should be on day 1 or as close as possible and not earlier than maximally 5 days prior. Subjects can only be randomized 1 time for this study.

7.2.1.4   Retesting

If, in the investigator's judgment, lab abnormalities are likely to be transient, (ie, subject participated in vigorous exercise and CK is elevated immediately afterwards), laboratory tests can be repeated. Triglycerides, CK, and liver function and other laboratory values, except LDL-C, can be retested at any time during screening as long as the subject can be evaluated for eligibility and randomized within the allowed screening period. LDL-C should not be retested due to out-of-range LDL-C concentration during screening.

7.2.1.5   Rescreening

Subjects receiving statin therapy (any statin) when entering screening and with LDL-C < 100 mg/dL (2.6 mmol/L) at screening and subjects not receiving any statin therapy when entering screening and with LDL-C < 130 mg/dL (3.4 mmol/L) at screening are considered screen failures and cannot be rescreened for this study. Suitable subjects who are ineligible at the initial screening for other reasons and have not been randomized can be re-consented and rescreened at a later time unless they withdraw from screening. For subjects who are rescreened, data from the first screening period will not be used for the analysis.

With the exception of the screening placebo injection, rescreened subjects who are re-consented will repeat all screening procedures. Rescreened subjects will maintain the originally assigned subject identification number.

7.2.1.6   Screen Fail

Subjects who fail any of the eligibility criteria during screening or rescreening and have not been randomized need to be screen failed in IVRS/IWRS before they can be re-consented and re-registered in IVRS/IWRS for rescreening.

7.2.2   Treatment

Subjects who are randomized will visit the study site for treatment start. The first administration of IP should be on the day, or as close as possible to the day, of randomization but not later than 5 calendar days after randomization. Day 1 is defined

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as the day of first administration of IP. The date of first administration of IP will be recorded in IVRS/IWRS and will determine the schedule of subsequent study visits.

Subjects must be fasting for ≥ 9 hours before each study visit where fasting lipid samples are obtained. If the subject is not fasting for the scheduled study day 1 visit, no visit procedures are performed. The subject must return as soon as possible in a fasting state for study day 1 visit procedures. If the subject is not fasting as required for a visit after study day 1, visit procedures should be completed except for fasting laboratory sample collection and IP administration, if applicable. An extra visit must be completed for the omitted procedures as soon as possible and, if possible, within the window for the respective visit.

The following procedures will be completed during the 12 week treatment period at the times designated in the Schedule of Assessments (Table 1):

- vital signs (sitting BP, HR; see Section 7.7.1)
- review for AEs/**ADEs**/SAEs
- review of concomitant therapy
- encourage subject to maintain a stable diet
- body weight and waist circumference (see Section 7.7.2)
- 12-lead ECG in triplicate using centralized ECG services equipment
- blood draw for fasting lipids (≥ 9 hour fasting sample), ApoA1, ApoB, chemistry, hematology, PK, PCSK9, hsCRP, Lp(a), biomarkers, anti-evolocumab antibodies, and viral load in subjects positive for HCV
- subjects in China only: blood draw for steroid analytes including cortisol, adrenocorticotropic hormone, estradiol, testosterone, luteinizing hormone (LH), and FSH
- mixed meal tolerance test
- urine sample for urinalysis
- urine pregnancy testing for females of childbearing potential
- dispense and reconcile atorvastatin and instruct subject in administration
- IP administration at the study site (must be after completion of vital signs, ECG, and blood draw procedures, if applicable)
- dispense AI/Pen or 3.5 mL Personal Injector, respectively, with instructions for use at week 4 (all subjects) and week 6 (Q2W subjects only)

No additional blood will be collected for the pharmacogenetics analyses. For subjects who have consented to the pharmacogenetic portion of this study, DNA will be extracted from blood samples already collected on day 1 or another visit (see Section 7.5 "Pharmacogenetic Studies" and Section 7.6 "Sample Storage and Destruction").

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. If possible, the procedures of week 12 should be completed at the time of withdrawal.

7.2.3 Safety Follow-up Visit(s)/End of Study Visit

Subjects receiving IP QM will end the study with the week 12 visit. Subjects on Q2W IP schedule will end the study by being contacted by the site, eg, by phone call, at week 14 to collect any AEs, **ADEs, or** SAEs.

7.3 Antibody Testing Procedures

Blood samples for antibody testing are to be collected per Table 1 for the measurement of anti-evolocumab binding antibodies. All subjects who have received at least 1 administration of evolocumab will have samples assayed for binding and, if positive, neutralizing antibodies. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity and presence of immune complexes. Sites will be notified of any positive neutralizing antibody results to evolocumab. If results are not provided, no neutralizing antibodies to evolocumab have been detected. Additional blood samples may be obtained to rule out anti-evolocumab antibodies during the study. Subjects who test positive for neutralizing antibodies to evolocumab at the final scheduled study visit will be asked to return for additional follow-up testing. This testing should occur approximately every 3 months starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable or (2) the subject has been followed for a period of at least 1 year (± 4 weeks). More frequent testing (eg, every month) or testing for a longer period of time may be requested in the event of safety-related concerns. Follow-up testing will not be required where it is established that the subject did not receive evolocumab. All follow-up results, both positive and negative will be communicated to the sites. Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-evolocumab antibody response may also be asked to return for additional follow-up testing.

7.4 Biomarker Development

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

It is expected that further advances will occur in the future in investigational techniques that look at markers of PCSK9 signaling, LDLR turnover, cholesterol metabolism, inflammation, and plaque stability. It is not possible at this stage to anticipate what these advances will be; however, considerable benefit could accrue to future sufferers of coronary artery disease if these markers can be correlated with the data from the study. It is also important to clarify any potential drug interactions in this population of subjects who will be on a number of other drugs. For biomarker analysis 14.5 mL of blood will be collected at each of the time points indicated in Table 1 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 (TNF) cellular adhesion molecules may be studied.

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

7.5 Pharmacogenetic Studies

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetics 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, hyperlipidemia and other metabolic disorders and/or to identify subjects who may have positive or negative response to evolocumab. No additional blood will be collected for this analysis. For subjects who have consented to the pharmacogenetic portion of this study, DNA will be extracted from blood samples already collected. Subjects can participate in the main trial irrespective of whether they do or do not consent to the pharmacogenetic portion of the study.

7.6 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.

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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 processes related 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 (TNF) cellular adhesion molecules, the dose response and/or prediction of response to PCSK9 inhibition, eg, by evolocumab*,* characterize antibody response, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic, biomarker development, or other exploratory studies are not placed in the subject's medical record and are not 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 samples can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

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

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discoveries, or derivative materials gained or produced from the sample.

See Section 11.3 for subject confidentiality.

7.7　　　　Standardization of Study Procedures

7.7.1　　　　Measurement of Vital Signs

Blood pressure (BP) and heart rate (HR) will be measured at each visit. Use of an automated oscillometric device for BP measurement is preferred and recommended. BP will initially be recorded in both of the subject's arms unless a concomitant condition favors the use of a particular arm. The arm with the higher systolic reading at screening will then be used for BP determinations throughout the study. The appropriate size cuff should be used. BP and HR measurements will be determined after the subject has been seated for at least 5 minutes. The subject's pulse should be measured for 30 seconds and the number multiplied by 2 to obtain heart rate. Before randomization, BP measurement can be repeated if the previous reading is outside of the eligibility range. The repeat BP measure should be taken at least 2 minutes following the previous measure.

7.7.2　　　　Waist Circumference

Subjects should wear minimal clothing to ensure that the measuring tape is correctly positioned. Subjects should stand erect with the abdomen relaxed, arms at the sides, feet together and with their weight equally divided over both legs. To perform the waist measurement, the lowest rib margin is first located and marked with a pen. The iliac crest is then palpated in the midaxillary line, and also marked. It is recommended to apply an elastic tape horizontally midway between the lowest rib margin and the iliac crest, and tie firmly so that it stays in position around the abdomen about the level of the umbilicus. The elastic tape thus defines the level of the waist circumference, which can then be measured by positioning the measuring tape over the elastic tape. Subjects are asked to breathe normally, and to breathe out gently at the time of the measurement to prevent them from contracting their muscles or from holding their breath. Measurements should be performed using the same procedure throughout the study. The reading is taken to the nearest centimeter or ½ inch and entered in the source document.

7.7.3　　　　Subject Compliance With Atorvastatin Dosing

Once the subject has been enrolled, if compliance with atorvastatin falls below 80% or goes above 120% (as determined by evaluation of the number of tablets prescribed), the investigator (or designee) must re-instruct the subject on proper dosing of the study medication as well as determine the factors that resulted in poor compliance with study

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medication. Subject compliance will be determined by counting the number of tablets returned against the number of days the subject should have taken the drug. Compliance should be assessed at the timepoints indicated in Table 1 or as instructed by Amgen.

7.7.4 Electrocardiograms

At each scheduled visit where ECGs are being obtained ECGs will be collected in triplicate approximately 1 minute apart. Using equipment supplied to each site, all protocol-specified ECGs will be acquired and transmitted to the centralized ECG services provider. The PI or designated physician will review acquired ECGs. One (1) signed, original ECG tracing should be retained with the subject's source documents. At the request of the sponsor, the original ECG should be made available to Amgen to be manually read by a central reader.

The centralized ECG services cardiologists will perform standard interpretations of all tracings. A cardiologist reviewed ECG report will be provided to the study site. Investigators must initial and date the ECG reports upon receipt. If the investigator's interpretation of any protocol-specified or unscheduled ECG differs from that supplied by centralized ECG services provider, it is the responsibility of the investigator to make the final clinical decisions. The investigator's interpretation does not need to be reconciled with that supplied by centralized ECG services cardiologists. Any clinical interventions based on these results need to be documented in the appropriate source documents and eCRF as applicable. It is the responsibility of the investigator to obtain additional ECGs required for the clinical management of the subject, using centralized ECG services equipment or equipment on-site.

Further detail about the equipment provided and its use for this study will be provided in an Investigator ECG Manual distributed to the sites before start of enrollment.

7.7.5 Lipid Measurements

Only the screening LDL-C concentration will be reported to the site for the eligibility decision. Central laboratory results of the lipid panel, as well as ApoA1, ApoB, and lipoprotein(a) (and PCSK9 and hsCRP) will be blinded post-treatment until unblinding of the clinical database. and will not be reported to the investigator post-screening. In addition, investigators and staff involved with this trial and all medical staff involved in the subject's medical care should refrain from obtaining lipid panels from randomization until at least 12 weeks after the subject's last administration of IP or until the subject ends the study, whichever is later (to avoid potential unblinding). If a lipid panel is

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drawn, all reasonable steps must be undertaken to avoid informing the subject and study personnel of the results.

7.7.6 Mixed Meal Tolerance Test (All Subjects)

A liquid mixed meal tolerance test (MMTT) will be performed after an overnight fast (no food or drinks other than water for ≥ 9 hours) at the day 1 and the week 12 study visit. Each MMTT should be done at approximately the same time of day throughout the study (± 2 hours). The fasting venous blood samples at each of these 2 visits should be collected as close as possible before consuming a standardized mixed meal (see below) and before the subject receives any food or drink (other than water) or investigational product. Subjects are then fed a standardized mixed meal, as defined in Table 3 below, for example Boost®. The same type standardized mixed meal should be used for day 1 and for week 12.

The beginning of the consumption of the liquid mixed meal is considered time "0" of the MMTT. Postprandial blood samples are collected at 120 ± 10 min after consumption of the standardized mixed meal for assessment of the following analytes:

- plasma glucose, insulin, proinsulin, C-peptide, free fatty acids, glucagon, lipids, chylomicrons, ApoB48, IL-6, adiponectin, vitamin E.

Table 3. Standardized Mixed Meal

Content component	Grams	Grams %	Calories (kcal)	Calories %
Protein	15	28	60	25
Total Fat	6	11	48	20
Carbohydrate	33	61	132	55
Totals	54	100	240	100

[a]Component weight in standardized mixed meal used can differ but total calories should not differ by more than ± 10% of 240 kcal. The same type standard mixed meal should be used for day 1 and week 12.

7.7.7 Mixed Meal Tolerance Test Extended Timepoints Substudy

Where offered and locally approved for the study center, subjects can be invited to participate in a MMTT Extended Timepoints Substudy. Enrollment into the substudy will be capped at approximately 240 subjects. The substudy consists of 2 additional postprandial blood draws in the MMTT on day 1 and week 12 as per Section 7.7.6. Postprandial blood draws for subjects participating in the substudy will be at the following timepoints after consumption of the standardized meal:

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

The same postprandial analytes as per Section 7.7.6 will be measured at each of these timepoints.

8.   WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1   Subject's 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. The investigator should ask the subject's consent to perform the procedures listed under the final study visit.

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

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

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

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8.3 **Reasons for Removal From Screening, Lipid Stabilization, Treatment, or Study**

8.3.1 **Reasons for Removal From Screening or Lipid Stabilization**

Reasons for removal from screening or lipid stabilization include any of the following:

- subject request
- safety concern (eg, due to an adverse event, failure to follow contraception, pregnancy, breast feeding, and/or atorvastatin withholding requirements)
- decision by sponsor (other than subject request or safety concern)
- death
- lost to follow-up

8.3.2 **Reasons for Removal From Treatment**

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

- subject request
- safety concern (eg, due to an adverse event, failure to follow contraception, pregnancy, breast feeding, and/or protocol requirements)
- death
- lost to follow-up
- decision by Sponsor (other than subject request, safety concern, lost to follow-up)

8.3.3 **Reasons for Removal From Study**

Reasons for removal of a subject from the study are:

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

9. **SAFETY DATA COLLECTION, RECORDING, AND REPORTING**

9.1 **Adverse Events**

9.1.1 **Definition of Adverse Events**

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

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition **or underlying disease** (eg,

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

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

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

9.1.2 Definition of Serious Adverse Events

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

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

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

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

9.2 Reporting of Adverse Events

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

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after randomization and all adverse events possibly related to study procedures from signing the informed consent through the end of study are reported using the applicable eCRF (eg, Adverse Event Summary).

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
- assessment of relatedness to investigational products **(evolocumab or placebo and/or the medical device(s)** AI/Pen or 3.5 mL Personal Injector**)**, **or any study-mandated activity or procedure,** respectively, and
- action taken.

The adverse event grading scale used will be the most current version of the NCI Common Terminology Criteria for AEs (CTCAE) grading scale. The grading scale used in this study is referenced in Appendix A.

The investigator must assess whether the adverse event is possibly related to 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 IP?

The investigator must assess whether the adverse event is possibly related to the prefilled AI/Pen or 3.5 mL Personal Injector **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 device?

The investigator must assess whether the adverse event is possibly related to any other study-mandated activity (eg, screening / lipid stabilization procedure or background therapy). 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 another study activity (eg, screening / lipid stabilization procedure or background therapy)?"

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. 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 Adverse Event eCRF.

9.2.2   Reporting Procedures for Serious Adverse Events

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

After the protocol-required reporting period defined above, the investigator does not need to actively monitor subjects for serious adverse events. However, if the investigator becomes aware of a serious adverse event after this protocol-required reporting period, the investigator will report the event to Amgen within 24 hours following the investigator's knowledge of the event. Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

If the electronic data capture (EDC) system is unavailable to the site staff to report the Serious Adverse Event, the information is to be reported to Amgen via an electronic Serious Adverse Event (eSAE) Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix B for a sample of the Serious Adverse Event Worksheet/electronic Serious Adverse Event Contingency Report Form. If the first notification of a Serious Adverse Event is reported to Amgen via the eSerious Adverse Event (eSAE) 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 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 IP?

The investigator must assess whether the serious adverse event is possibly related to the prefilled AI/Pen or 3.5 mL Personal Injector **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 device?

The investigator must assess whether the serious adverse event is possibly related to any other study-mandated activity (eg, screening / lipid stabilization procedure or background therapy). 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 another study activity (eg, screening / lipid stabilization procedure or background therapy)?"

The investigator is expected to follow reported serious adverse events until stabilization or reversibility. If the severity of a serious 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 Adverse Event eCRF.

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

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

9.3 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 IP.

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).

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 IP.

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).

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Co-primary Efficacy 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 Efficacy Endpoints

Co-secondary efficacy endpoints are (1) the mean of weeks 10 and 12 and (2) week 12 for:

Tier 1 endpoints

- change from baseline in LDL-C
- percent change from baseline in non-HDL-C
- percent change from baseline in ApoB100
- percent change from baseline in the total cholesterol
- percent change from baseline in the total cholesterol/HDL-C ratio
- percent change from baseline in ApoB100/ApoA1 ratio
- achievement of target LDL-C < 70 mg/dL (1.8 mmol/L)

Tier 2 endpoints

- 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   Co-tertiary Efficacy Endpoints

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

10.1.1.4   Exploratory Endpoints

- subject incidence of non-coronary revascularization
- change and percent change from baseline at each scheduled assessment in each of the following parameters:
    - LDL-C
    - total cholesterol
    - non-HDL-C
    - ApoB100
    - total cholesterol/HDL-C ratio
    - ApoB100/ApoA1 ratio
    - VLDL-C
    - HDL-C
    - ApoA1

- triglycerides

- Lp(a)

• hsCRP at each scheduled assessment

• HbA1c at each scheduled assessment

• PCSK9 change from baseline at each scheduled assessment

• fasting and post-prandial laboratory parameters of interest (including MMTT Extended Timepoints Substudy assessments)

10.1.1.5   Safety Endpoints

• subject incidence of treatment emergent adverse events

• safety laboratory values and vital signs at each scheduled assessment

• ECG parameters (such as RR, PR, QRS, QT and QTc intervals) at each scheduled assessment

• incidence of anti-evolocumab antibody (binding and neutralizing) formation

10.1.1.6   Pharmacokinetics Endpoints

• serum concentration of evolocumab at selected time points

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 analyses, subjects will be grouped according to their randomized treatment group assignment. For safety analyses, subjects will be grouped according to their randomized treatment group assignment with the following exception: if a subject receives treatment throughout the study that is different than the randomized treatment group assignment, then the subject will be grouped by the actual treatment group.

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

10.1.3   Covariates and Subgroups

Baseline covariates include, but are not limited to:

• stratification factors:

- statin therapy at study entry (no statin use vs non-intensive statin use vs intensive statin use [see Appendix D]

- site's geographic region

• age: < 65 years, ≥ 65 years

• sex

• race

- baseline LDL-C: < median, ≥ median
- family history of premature coronary heart disease: yes, no
- baseline PCSK9 level: < median, ≥ median

10.2   Sample Size Considerations

The sample size is 300 subjects for each of the evolocumab SC in combination with atorvastatin arms, and 150 subjects for each of the placebo in combination with atorvastatin arms. The sample size should provide adequate power to determine the superiority of evolocumab in combination with atorvastatin to placebo in combination with atorvastatin as measured by the co-primary endpoints in both dose frequencies using the FAS. The primary analysis will require the tests of each co-primary endpoint to be significant at a level of 0.05 (Section 10.5). From the global phase 2 studies in the evolocumab program, the treatment effect measured as the mean of week 10 and week 12 were as large or larger than week 12 and highly correlated (> 85%) with ones at week 12. From the global phase 2 study 20110155, the treatment effects (on top of stable background statin therapy) of evolocumab compared to placebo for 140 mg Q2W and 420 mg QM in the mean percent change from baseline in LDL-C are -66.10 (95% CI [-71.48,-60.72]) and -50.33 (95% CI [-56.04,-44.62]) at week 12, respectively and the observed evolocumab dose group means in the type 2 diabetes mellitus cohort were comparable to the overall population. The power calculation is derived assuming a treatment effect in the percent reduction of LDL-C of at least 35% at week 12 in each dose frequency, with a common standard deviation (SD) of 20%. It is assumed that approximately 15% of subjects randomized into IP will end IP early, thus attenuating the treatment effects. It is assumed there will be no treatment effect differences among treatment groups after these subjects end IP early. After accounting for treatment attenuation due to early IP termination, the assumed treatment effect is a 30% reduction in LDL-C with a common SD of 30%. Assuming 2% of randomized subjects do not receive any IP, the planned sample size will provide at least 99% power in testing the superiority of evolocumab in combination with atorvastatin to placebo in combination with atorvastatin at week 12 in each dose frequency. Therefore, the sample size as planned will provide at least 98% (99% x 99%) power for the co-primary endpoints in each of the dose frequencies.

Since the testing statistics from the Q2W and QM groups are independent, there is approximately a 96% (98% x 98%) chance to show the superiority of both dose frequencies for the co-primary endpoints.

Sample size assumptions, such as the missing value rate, will be monitored by the study team while maintaining study blind.

The power calculation is derived using nQuery version 7.01.

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Unblinding and potentially unblinding information should not be distributed to the study team, investigators or subjects prior to the study being formally unblinded (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).

Individual subject treatment assignments will be maintained by the IVRS/IWRS. Any unplanned unblinding occurring during the study period will be documented and reported in the final clinical study report.

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

10.4 Planned Analyses

10.4.1 Data Monitoring Committee (DMC)

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

10.4.2 Primary Analysis

The primary analysis will be conducted when all subjects have either completed all the scheduled study visits or have early terminated from the study. At that time, the database will be cleaned, processed and a snapshot will be taken; the study will also be unblinded. Based on the snapshot, efficacy and safety analyses will be performed on

the FAS. Unless specified otherwise, the FAS will be the default analysis set in this study and data will be summarized by randomized treatment group.

Analyses will be performed separately by each dose frequency (Q2W and QM) unless specified otherwise.

10.5   Planned Methods of Analysis

General Considerations

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

Summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation 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 throughout this section. Missing data will not be imputed for safety endpoints.

Multiplicity Adjustment Method

In order to preserve the familywise error rate at 0.05, each independent dose frequency (Q2W and QM) will be allocated a significance level of 0.05. For FAS, methods of adjusting for multiplicity due to testing the superiority of evolocumab in combination with atorvastatin to placebo in combination with atorvastatin for both the co-primary and co-secondary efficacy endpoints for the co-primary endpoints within each dose frequency are described in the diagram below.
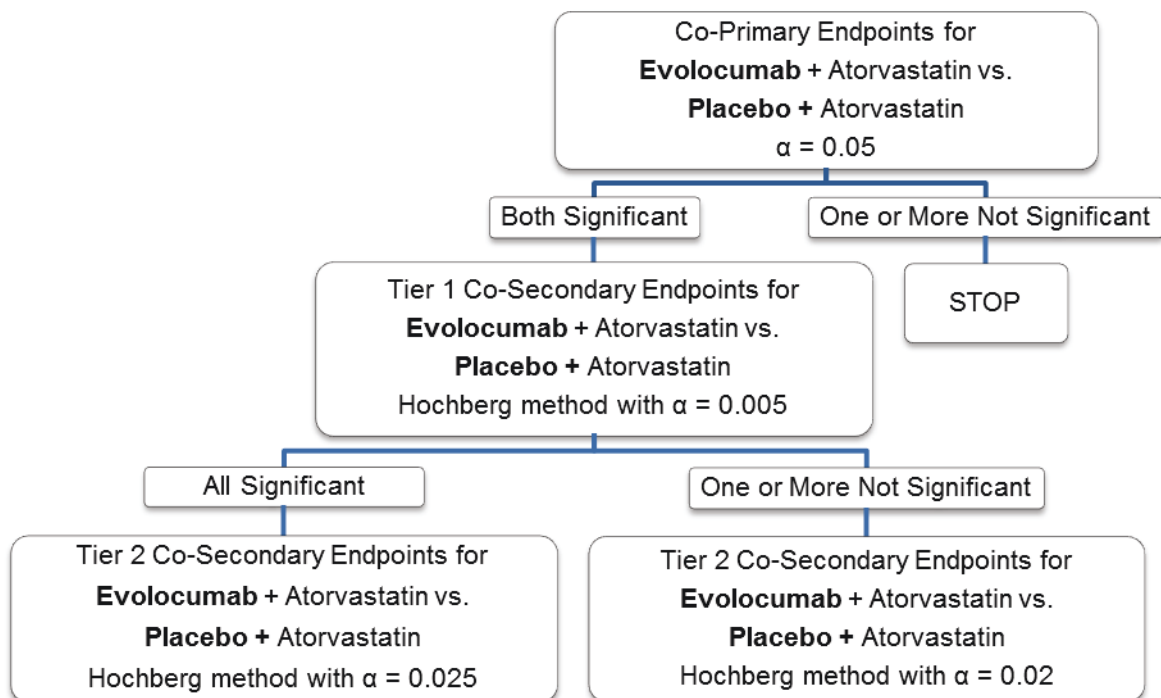
The multiplicity adjustment method for testing the co-primary and co-secondary efficacy endpoints within each dose frequency using the FAS is described below:

1. If the treatment effect differences between evolocumab in combination with atorvastatin and placebo in combination with atorvastatin 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 (as defined in Section 10.1.1.2) 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 for evolocumab in combination with atorvastatin vs. placebo in combination with atorvastatin will be tested using the Hochberg procedure at a significance level of 0.025.

3. If not all tier 1 co-secondary efficacy endpoints are significant, the tier 2 co-secondary efficacy endpoints for evolocumab in combination with atorvastatin vs. placebo in combination with atorvastatin will be tested using the Hochberg procedure at a significance level of 0.02 (Wiens, 2003).

10.5.1   Co-primary Efficacy Endpoints

<u>Primary analyses</u>

To assess the co-primary endpoints, a repeated measures linear effects model will be used in each dose frequency to compare the efficacy of evolocumab in combination with atorvastatin and placebo in combination with atorvastatin in the FAS. The repeated

measures model will include terms for treatment group, stratification factors, scheduled visit and the interaction of treatment with scheduled assessment. Missing values will not be imputed when the repeated measures linear effects model is used.

The statistical significance of the treatment effect difference between evolocumab in combination with atorvastatin and placebo in combination with atorvastatin will be tested.

Multiplicity adjustment procedures are defined in Section 10.5.

<u>Sensitivity Analysis</u>

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.

<u>Subgroup Analysis</u>

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

10.5.2   Co-secondary Efficacy Endpoints

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

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

Multiplicity adjustment procedure of testing evolocumab in combination with atorvastatin vs. placebo in combination with atorvastatin for co-secondary endpoints is defined in Section 10.5.

10.5.3   Safety Endpoints

<u>Adverse Events</u>

Adverse events will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Subject incidences of treatment-emergent adverse events, serious adverse events and adverse events leading to discontinuation of IP will be tabulated by system organ class and preferred term for each treatment group.

Safety Laboratory Parameters

Laboratory parameters will be summarized for each treatment group using descriptive statistics at each scheduled assessment. Laboratory shift tables for certain analytes will be provided using the CTCAE v.4 toxicity criteria. The results will be based on the maximum (ie, worst) shift from baseline to the EOS.

Vital Signs

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

Electrocardiogram

RR, PR, QRS, QT, and QTc intervals will be summarized by treatment group at each scheduled assessment. Frequency tables for maximal QTc and maximal change in QTc at post-dose period using the categories suggested in the ICH E14 guidelines will be provided by treatment group.

Concomitant Medications

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

Anti-evolocumab antibodies

The incidence and percentages of subjects who develop anti-AMG145 antibodies (binding and neutralizing) at anytime will be tabulated.

11.   REGULATORY OBLIGATIONS

11.1   Informed Consent

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

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

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The acquisition of informed consent is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject.

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

11.2   Institutional Review Board/Independent Ethics Committee

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

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

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

11.3   Subject Confidentiality

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

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

- For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).

- Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

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

11.4   Investigator Signatory Obligations

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

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

- a recognized expert in the therapeutic area

- an Investigator who provided significant contributions to either the design or interpretation of the study

- an Investigator contributing a high number of eligible subjects

12.   ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1   Protocol Amendments and Study Termination

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

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

Subjects may be eligible for continued treatment with Amgen investigational product(s) by an extension protocol or as provided for by the local country's regulatory mechanism.

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However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

12.2　　　Study Documentation and Archive

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

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

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

eCRF 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 should include:

- Subject files containing completed CRF, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, AMG 145 Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB and Amgen
- If kept, proof of receipt, Investigational Product Accountability Record, Return of Investigational Product for Destruction, Final Investigational Product Reconciliation Statement (if applicable), and all drug-related correspondence
- Non-investigational product(s) and or medical device documentation, as applicable.

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

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

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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 and/or site notifications are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that investigator inspected or reviewed the data on the CRF, the data queries, and the site notifications, and agrees with the content.

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

12.4   Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (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

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

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), which states (August 2013 revision):

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

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

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

- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.

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

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

12.7 Compensation

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

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14.   APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

Refer to the NCI Common Terminology Criteria for AEs (CTCAE) Version 4.0 for AE grading and information. The CTCAE is available at the following link: http://ctep.cancer.gov/protocolDevelopment/electronic_applications\ctc.htm.

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation according to the criteria specified in Section 6.4 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, Adverse 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.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Sections 6.5.1 and 6.5.2 or who experience AST or ALT elevations >3 x ULN are to undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels. Assessments that are to be performed during this period include:

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

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

- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL:

  – Obtain complete blood count (CBC) with differential to assess for eosinophilia

  – Obtain serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis

  – Obtain serum acetaminophen (paracetamol) levels

  – Obtain a more detailed history of:

  – Prior and/or concurrent diseases or illness

  – Exposure to environmental and/or industrial chemical agents

  – Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever

  – Prior and/or concurrent use of alcohol, recreational drugs and special diets

  – Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms

  – Obtain viral serologies

  – Obtain CPK, haptoglobin, Lactate dehydrogenase (LDH), and peripheral blood smear

  – Perform appropriate liver imaging if clinically indicated

- Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected

- Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist)

- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

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

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Appendix B. Sample eSerious Adverse Event Contingency Reporting Form

AMGEN Study # 20120119 AMG 145	Electronic Serious Adverse Event (eSAE) Contingency Reporting Form **For Restricted Use**

Complete either Section A *or* Section B and follow the instructions provided:

Section A

EDC system (eg, Rave) is active for this study but is not accessible to allow reporting within 24 hours of the Investigator's knowledge of the event. I am submitting (check/complete all that apply):

An event that applies to a specialty CRF page titled _____ (eg, clinical fracture)

Screening event (as defined by the protocol)　　**OR**　　On-study event (as defined by the protocol)

- Complete ONLY Sections 1, 2 and 3 (page 1)
- Sign and date the signature section following Section 3
- Fax completed page of the form to the number noted in the header above Section 1

Section B

Access to the EDC system (eg, Rave) has either not begun or has ended for this study. I am submitting (check all that apply):

Screening event (as defined by the protocol)

This is a new event report

This is follow-up information for a previously reported event

OR

Event after access to the EDC system (eg, Rave) has ended (*provide subject's End of Study date in Section 2*)

This is a new event report

This is follow-up information for a previously reported event

- Complete ALL sections of the form (all 3 pages)
- Sign and date the signature section at the end of the form
- Fax completed form (all 3 pages) to the number noted in the header above Section 1

SELECT OR TYPE IN A FAX#

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number (　　)	Fax Number (　　)

2. SUBJECT INFORMATION

Subject ID Number	Date of Birth Day　Month　Year	Sex ☐F ☐M	Race	If applicable, provide End of Study date

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

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this Serious Adverse Event Information: Day____ Month____ Year____

Serious Adverse Event Diagnosis or Syndrome. If diagnosis is unknown, enter Signs / Symptoms. When Final Diagnosis is known, enter as Adverse Event List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.	Date Started Day　Month　Year	Date Ended Day　Month　Year	Check only if event occurred before first dose of IP	Enter Serious Criteria code *(see codes below)*	Relationship Is there a reasonable possibility that the event may have been caused by IP? No　Yes		Relationship Is there a reasonable possibility that the event may have been caused by an Amgen device? No　Yes　If yes, what device?		Outcome of Event Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy

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

If you temporarily cannot access the EDC system (eg, Rave), sign below and submit ONLY this page to the number noted in the header above Section 1.

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

FORM-056006　　　　　　　　　　　　　　　　Version 3.0 Effective Date 04-FEB-2013

Page 1 of 3

AMGEN Study # 20120119 AMG 145	Electronic Serious Adverse Event (eSAE) Contingency Reporting Form **For Restricted Use**

If access to the EDC system (eg, Rave) has either not begun or has ended for this study, *complete the remainder of this form.*

Site Number	Subject ID Number

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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

IMP: _____ ☐ (✓) Blinded ☐ (✓) Open Label	Initial Start Date Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld

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

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

Date Day Month Year	Test Unit				

AMGEN Study # 20120119 AMG 145	Electronic Serious Adverse Event (eSAE) Contingency Reporting Form **For Restricted Use**

	Site Number	Subject ID Number	

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

Date Day Month Year	Additional Tests	Results	Units

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

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

FORM-056006   Version 3.0 Effective Date 04-FEB-2013
Page 3 of 3

Appendix C. Pregnancy and Lactation Notification Worksheets

Print Form

AMGEN® Lactation Notification Worksheet

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

1. Case Administrative Information

Protocol/Study Number: 20120119

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

2. Contact Information

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

3. Subject Information

Subject ID # _____   Subject Date of Birth: mm_____ / dd_____ / yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes   ☐ No
If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____
Did the subject withdraw from the study? ☐ Yes   ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes   ☐ No
If No, provide stop date: mm_____/dd_____/yyyy_____
Infant date of birth: mm_____/dd_____/yyyy_____
Infant gender: ☐ Female   ☐ Male
Is the infant healthy? ☐ Yes   ☐ No   ☐ Unknown   ☐ N/A

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

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

Effective Date: 03 April 2012, version 2.

Page 1 of 1

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: 20120119

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: _____

Appendix D. Lipid Modifying Background Therapy Intensity

(Group A) Intensive statin usage	Subject has at least one of the following recorded for the last 4 weeks prior to screening: • atorvastatin ≥ 40 mg QD • rosuvastatin ≥ 20 mg QD • simvastatin ≥ 80 mg QD (note that simvastatin 80 mg QD is not approved in some countries, eg, the United States) • any statin[1] QD plus ezetimibe
(Group B) Non-intensive statin usage	Subject has been taking any dose of a statin at least weekly for the last 4 weeks prior to screening and is not included in Group A
(Group C) No statin	Subject is not included in Group A or Group B

Note: Statin includes atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.

Amendment 3

Protocol Title: A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Safety and Efficacy of Evolocumab (AMG 145) in Combination With Statin Therapy in Diabetic Subjects With Hyperlipidemia or Mixed Dyslipidemia

Amgen Protocol Number Evolocumab 20120119

EudraCT number 2013-000723-14

Original Protocol Date:	22 February 2013
Amendment 1 Date:	10 December 2013
Superseding Amendment 1 Date:	07 February 2014
Amendment 2 Date: (applies to subjects in China only)	29 July 2015
Amendment 3 Date:	11 November 2015

Rationale:

This protocol is being amended to remove potential endpoint (PEP) adjudication by the clinical events committee (CEC) and add/update safety language and adverse device effect reporting.

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Description of Changes:

Section: Global

Change: Version dates updated throughout document from 29 July 2015 to **11 November 2015**.

Section: Global

Change: Typographic, grammatical, and formatting errors were corrected throughout the protocol.

Section: Title Page, Key Sponsor Contact(s)

Replace:

PPD , MD

One Amgen Center Drive

Thousand Oaks, CA 91320, USA

Phone: PPD

Fax: PPD

Email: PPD

With:

PPD

One Amgen Center Drive **MS 27-2-C**

Thousand Oaks, CA 91320, USA

Phone: PPD

Fax: PPD

Email: PPD

Section: Title Page

Add:

 Amendment 3 Date: **11 November 2015**

Section: Synopsis, Study Design, 4th paragraph

Replace:

EOS for subjects on Q2W IP is by contact (eg, phone call) from the site at week 14 for any potential adverse events (AEs) or serious AEs (SAEs). Subjects will be encouraged to complete all planned visits regardless of their adherence to IP administration. Deaths

and specific cardiovascular (CV) events will be adjudicated by an independent external Clinical Events Committee (CEC) and accumulating safety and other data will be reviewed by an independent external Data Monitoring Committee (DMC).

With:

EOS for subjects on Q2W IP is by contact (eg, phone call) from the site at week 14 for any potential adverse events (AEs), **adverse device effects (ADEs), and** serious AEs (SAEs). Subjects will be encouraged to complete all planned visits regardless of their adherence to IP administration. Accumulating safety and other data will be reviewed by an independent external Data Monitoring Committee (DMC).

Section: Synopsis, Study Design, Summary of Subject Eligibility Criteria, 2nd paragraph

Add:

Female subjects cannot be pregnant, breast feeding, planning to become pregnant, or planning to breastfeed and premenopausal females must have to be willing to use (an) acceptable method(s) of **effective** birth control during treatment with investigational product (evolocumab or placebo) and for an additional 15 weeks after the end of treatment with investigational product (evolocumab or placebo).

Section: Synopsis, Study Design, Procedures, 1st paragraph

Add:

In addition, subjects receiving IP Q2W will be contacted (eg, by phone call) by the study site at week 14 (EOS for Q2W subjects) to obtain AE, **ADE** and SAE information, if applicable.

Section: Synopsis, Study Design, Procedures, 2nd paragraph

Add:

Vital signs, AEs/**ADEs**/SAEs, concomitant therapy, evaluation of fasting lipids, dietary instruction, physical exam, measuring waist circumference, body height and weight, 12-lead ECGs, other laboratory assessments, including assessment for anti evolocumab antibodies, biomarker sample collection, serum pregnancy testing (females of childbearing potential), MMTT, urinalysis, and steroid analyte testing will be carried out per the Schedule of Assessment (Table 1) of the protocol.

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Section: Synopsis, Study Design, Statistical Considerations, General Considerations

Delete:

Methods of adjusting for multiplicity due to testing the superiority of evolocumab in combination with atorvastatin to placebo in combination with atorvastatin for both the co-primary and co-secondary efficacy endpoints within each dose frequency are provided in Section 10.5. ~~Events of death, myocardial infarction (MI), hospitalization for unstable angina, coronary revascularization, stroke, transient ischemic attack (TIA), and hospitalization for heart failure will be adjudicated by an independent CEC.~~

Section: Study Design, Study Design and Treatment Schema

Add:

> *Only subjects receiving IP Q2W
> **Phone call for AEs/**ADEs**/SAEs for
>   subjects receiving SC IP
>   administration Q2W

Section: Study Glossary

Add:

ADE	**Adverse device effect**

Section: Study Glossary

Delete:

~~CEC~~	~~Clinical events committee~~

Section: 1.4, Exploratory

Delete:

- ~~to estimate cardiovascular event rates in subjects treated with evolocumab, including aggregated exploratory analyses across the evolocumab program~~

Section: 3.1, Study Design, 5th paragraph

Replace:

EOS for subjects on Q2W IP is by contact (eg, phone call) from the site at week 14 for any potential adverse events (AEs) or serious AEs (SAEs). Subjects will be encouraged to complete all planned visits regardless of their adherence to IP administration. Deaths and specific cardiovascular (CV) events will be adjudicated by an independent external

Clinical Events Committee (CEC) and accumulating safety and other data will be reviewed by an independent external Data Monitoring Committee (DMC).

With:

EOS for subjects on Q2W IP is by contact (eg, phone call) from the site at week 14 for any potential adverse events (AEs), **adverse device effects (ADEs), and** serious AEs (SAEs). Subjects will be encouraged to complete all planned visits regardless of their adherence to IP administration. Accumulating safety and other data will be reviewed by an independent external Data Monitoring Committee (DMC).

Section: 3.5.1, Study Duration for Subjects

Add:

For a subject on Q2W IP schedule, maximal study duration will be 22 weeks or approximately 5 ½ months, including the contact by the site at week 14 to obtain potential AE, **ADE,** and SAE information.

Section: 4.1.2, Exclusion Criteria

Replace:

217   Female subject who has either (1) not used (an) acceptable method(s) of birth control (see below) for at least 1 month prior to screening or (2) is not willing to inform her partner of her participation in this clinical study and to use such (an) acceptable method(s) during treatment with IP (evolocumab or placebo) and for an additional 15 weeks after the end of treatment with IP (evolocumab or placebo), unless the female subject is sterilized or postmenopausal (see below);

- A female is considered of childbearing potential unless sterilized or postmenopausal with menopause is defined as:
    - 12 months of spontaneous and continuous amenorrhea in a female ≥ 55 years old, or
    - 12 months of spontaneous and continuous amenorrhea with a follicle-stimulating hormone (FSH) level > 40 IU/L (or according to the definition of "postmenopausal range" for the laboratory involved) in a female < 55 years old
    - unless the subject has undergone bilateral oophorectomy

With:

217   Female subject who has either (1) not used (an) acceptable method(s) of **effective** birth control (see below) for at least 1 month prior to screening **and** (2) is not willing to inform her partner of her participation in this clinical study and to use such (an) acceptable method(s) **of effective birth control** during treatment with IP (evolocumab or placebo) and for an additional 15 weeks after the end of

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treatment with IP (evolocumab or placebo), unless the female subject is **permanently** sterilized or postmenopausal (see below);

- A female is considered of childbearing potential unless **permanently** sterilized or postmenopausal with menopause defined as:

  − 12 months of spontaneous and continuous amenorrhea in a female ≥ 55 years old, or

  − 12 months of spontaneous and continuous amenorrhea with a follicle-stimulating hormone (FSH) level > 40 IU/L (or according to the definition of "postmenopausal range" for the laboratory involved) in a female < 55 years old

  − unless the subject has undergone bilateral oophorectomy

Section: 4.1.2, Exclusion Criteria, 217

Replace:

- acceptable methods of preventing pregnancy include not having intercourse, (sexual abstinence), surgical contraceptive methods - (vasectomy of the male partner or bilateral tubal ligation/occlusion), use of hormonal birth control methods (pills, shots/injections, implants, or patches), intrauterine devices (IUDs), or <u>two</u> (2) barrier methods (each partner must use one barrier method) with spermicide - males must use a condom with spermicide; females must choose either a diaphragm with spermicide, OR cervical cap with spermicide, OR contraceptive sponge with spermicide.

With:

- acceptable methods of preventing pregnancy include not having intercourse, (**true** sexual abstinence), surgical contraceptive methods - (vasectomy of the male partner or bilateral tubal ligation/occlusion), use of hormonal birth control methods (pills, shots/injections, implants, or patches), intrauterine devices (IUDs), or <u>two</u> (2) barrier methods (each partner must use one barrier method) **and at least one of the barrier methods must include** spermicide - males must use a condom with spermicide; females must choose either a diaphragm with spermicide, OR cervical cap with spermicide, OR contraceptive sponge with spermicide. **Note: a male and female condom cannot be used together due to the risk of tearing.**

Section: 5, Subject Enrollment

Add:

SAEs**, ADEs**, and study-related AEs will be collected upon signing the informed consent form.

Section: 6.1, Classification of Products and/or Medical Devices, 3rd paragraph

Add:

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

Section: 6.8, Product Complaints, 1st paragraph

Replace:

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of any investigational or non-investigational product or device.

With:

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

Section: Table 1. Schedule of Assessments

Replace:

Review for AEs/SAEs/CV events	X^c		X^c	X	X	(X)^d	(X)^d	X	X	X	X

With:

Review for AEs/**ADEs**/SAEs	X^c		X^c	X	X	(X)^d	(X)^d	X	X	X	X

Section: Table 1. Schedule of Assessments, footnotes

Add:

[c] only AEs possibly related to study procedures and **ADEs**/SAEs are collected during the screening and lipid stabilization period

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Section: 7.2.1.2, Screening and Lipid Stabilization, bullet point

Replace:

- review for AEs/SAEs (AEs possibly related to study procedures and SAEs are collected during screening)

With:

- review for AEs/**ADEs**/SAEs (AEs possibly related to study procedures and **ADEs and** SAEs are collected during screening)

Section: 7.2.2, Treatment, 3rd paragraph, bullet point

Replace:

- review for AEs/SAEs/CV events

With:

- review for AEs/**ADEs/**SAEs

Section: 7.2.3, Safety Follow-up Visit(s)/End of Study Visit

Replace:

Subjects receiving IP QM will end the study with the week 12 visit. Subjects on Q2W IP schedule will end the study by being contacted by the site, eg, by phone call, at week 14 to collect any AEs, SAEs, or CV events.

With:

Subjects receiving IP QM will end the study with the week 12 visit. Subjects on Q2W IP schedule will end the study by being contacted by the site, eg, by phone call, at week 14 to collect any AEs, **ADEs, or** SAEs.

Section: 9.1.1, Definition of Adverse Events, 2nd paragraph

Add:

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.

Section: 9.2.1, Reporting Procedures for Adverse Events That do not Meet Serious Criteria, 2nd paragraph, bullet point

Replace:

- assessment of relatedness to investigational products or the AI/Pen or 3.5 mL Personal Injector), respectively, and

With

- assessment of relatedness to investigational products **(evolocumab or placebo and/or the medical device(s)** AI/Pen or 3.5 mL Personal Injector), **or any study-mandated activity or procedure,** respectively, and

Section: 9.2.1, Reporting Procedures for Adverse Events That do not Meet Serious Criteria, 5th paragraph

Add:

The investigator must assess whether the adverse event is possibly related to the prefilled AI/Pen or 3.5 mL Personal Injector **device** used to administer IP.

Section: 9.2.2, Reporting Procedures for Serious Adverse Events, 5th paragraph

Add:

The investigator must assess whether the serious adverse event is possibly related to the prefilled AI/Pen or 3.5 mL Personal Injector **device** used to administer IP.

Section: 9.3, Pregnancy and Lactation Reporting, 3rd paragraph

Replace:

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

With:

The pregnancy should be reported to Amgen **Global Patient Safety** within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C).

Section: 9.3, Pregnancy and Lactation Reporting, 6th paragraph

Replace:

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

With:

Any lactation case should be reported to Amgen **Global Patient Safety** within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C).

Section: 10.1.1.4, Exploratory Endpoints

Delete:

~~subject incidence of adjudicated events:~~

- ~~death by any cause~~
- ~~cardiovascular death~~
- ~~myocardial infarction~~
- ~~hospitalization for unstable angina~~
- ~~coronary revascularization~~
- ~~stroke~~
- ~~hospitalization for heart failure~~
- ~~transient ischemic attack (TIA)~~

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Section: Appendix C: Pregnancy and Lactation Notification.Worksheets

Replace:

Print Form

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: 20120119

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: _____

∗∗

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

Effective Date: 03 April 2012, version 2.

Page **1** of **1**

With:

Print Form

AMGEN® Lactation Notification Worksheet

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

1. Case Administrative Information

Protocol/Study Number: 20120119

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

2. Contact Information

Investigator Name _____   **Site #** _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____   **Subject Date of Birth:** mm_____ / dd_____ / yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

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

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

Form Completed by:

Print Name: _____   **Title:** _____

Signature: _____   **Date:** _____

Effective Date: 03 April 2012, version 2.

Page 1 of 1

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: 20120119

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: _____

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

Effective Date: March 27, 2011

Page **1** of **1**

With:

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX# ▼

1. Case Administrative Information

Protocol/Study Number: 20120119

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:** _____

Superseding Amendment 1

A Double-blind, Randomized, Placebo-Controlled, Multicenter Study to Evaluate Safety and Efficacy of Evolocumab (AMG 145) in Combination With Statin Therapy in Diabetic Subjects With Hyperlipidemia or Mixed Dyslipidemia

Evolocumab (AMG 145)

Amgen Protocol Number Evolocumab 20120119

 Superseding Amendment 1 Date: 07 February 2014

Rationale:

This document provides the rationale and detailed list of changes for Superseding

Amendment 1, dated 07 February 2014, from the original protocol, dated

22 February 2013.

The purpose of the amendment is to:

Add mixed meal tolerance testing (MMTT) with 1 timepoint for all subjects, and optional MMTT substudy with 2 additional timepoints for approximately 240 subjects

Replace the Amgen product number "AMG 145" with the generic name "evolocumab"

Update the contraception language

Minor updates and clarifications, including clarification that atorvastatin in this study is background therapy

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Amendment 1

A Double-blind, Randomized, Placebo-Controlled, Multicenter Study to Evaluate Safety and Efficacy of Evolocumab (AMG 145) in Combination With Statin Therapy in Diabetic Subjects With Hyperlipidemia or Mixed Dyslipidemia

Evolocumab (AMG 145)

Amgen Protocol Number Evolocumab 20120119

  Amendment 1 Date: 10 December 2013

Rationale:

This document provides the rationale and detailed list of changes for Amendment 1, dated 10 December 2013, from the original protocol, dated 22 February 2013.

The purpose of the amendment is to:

- Add mixed meal tolerance testing (MMTT) with 1 timepoint for all subjects
- Replace the Amgen product number "AMG 145" with the generic name "evolocumab"
- Update the contraception language
- Minor updates and clarifications

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