STATISTICAL ANALYSIS PLAN

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

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Table of Abbreviations

Abbreviation or Term	Definition/Explanation
ADE	Adverse device effect
AE	Adverse event
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)
BMI	Body mass index
BP	Blood pressure
CAS	Completer analysis set
CK	Creatine kinase
CHD	Coronary heart disease
CMH	Cochran-Mantel-Haenszel
CPMS	Clinial Pharmacology Modeling and Simulation
CRP	C-reactive protein
CSR	Clinical study report
CTCAE	NCI Common Terminology Criteria for AEs
DBP	Diastolic blood pressure
DQR	Data quality review
DMC	Data monitoring committee
EAS	European Atherosclerosis Society
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End-of-study
ESC	European Society of Cardiology
FAS	Full analysis set
GSO-DM	Global Study Operations – Data Management
HDL-C	High density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
hsCRP	High sensitivity CRP
IBG	Independent Biostatistical Group
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IRB	Institutional Review Board

Abbreviation or Term	Definition/Explanation
IP	Investigational product
IVRS/IWRS	Interactive Voice Response System / Interactive Web Response System
LDL-C	Low-density lipoprotein cholesterol
LDLR	LDL receptor
LFT	Liver function test
Lp(a)	Lipoprotein(a)
LSP	Lipid stabilization period
LSAS	Lipid stabilization analysis set
MedDRA	Medical dictionary for regulatory activities
MMTT	Mixed meal tolerance test
MOI	Medications of interest
NCEP	National Cholesterol Education Program
PCSK9	Proprotein convertase subtilisin/kexin type 9
PK	Pharmacokinetics
PKS	Pharsight knowledgebase server
PO	Oral administration
POSTD	Dose date of statin therapy
QM	Every 4 weeks
Q2W	Every 2 weeks
QD	Each day
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
SCIPD	Subcutaneous investigational product
SD	Standard deviation
SE	Standard error
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol
WHODRUG	World Health Organization Drug

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for evolocumab Study 20120119 amendment 3 dated 11 November 2015. The scope of this plan includes the final analyses that are planned and will be executed by the Biostatistics department unless otherwise specified.

2. Objectives

2.1 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.

2.2 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

2.3 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

2.4 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

3. Study Overview

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 C]) and by

the site's geographic region (China, Korea, other countries). Treatment and follow-up period will be 12 weeks with an additional phone call or other subject contact at week 14 for subjects receiving investigational product (IP) Q2W.

Evolocumab and placebo SC will be administered at the study site or appropriate non-investigator site settings, e.g., 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 a fasting blood collection (0 hours) and 1 postprandial blood collection 2 hours (± 10 min) 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 hour (± 10 min) and 3 hours (± 10 min) 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 (e.g., 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. Detailed study procedures are provided in Protocol Section 7.

The study endpoints are defined in Section 4.1

3.2 Sample Size

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 full analysis set (FAS). The primary analysis will require the tests of each co-primary endpoint to be significant at a level of 0.05 (Section 10.1). 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 II 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.

4. Study Endpoints and Covariates

4.1 Study Endpoints

4.1.1 Co-Primary Efficacy Endpoint

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

4.1.2 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

4.1.3 Co-Tertiary Efficacy Endpoints

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

4.1.4 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 postprandial laboratory parameters of interest (including MMTT Extended Timepoints Substudy assessments)

4.1.5 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

4.1.6 Pharmacokinetics Endpoints

- Serum concentration of evolocumab at selected time points

4.2 Planned Covariates

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 C]
- Site's geographic region (China, Korea, other countries)

Baseline characteristics

- Age
- Sex
- Race
- Baseline LDL-C
- Family history of premature coronary heart disease (yes, no)
- Baseline PCSK9

- Body Mass Index
- Hypertension (yes, no)
- Current smoker (yes, no)
- Baseline CHD risk factors ≥ 2 (yes, no)
- Triglycerides

5. Hypotheses and/or Estimations

Hypothesis testing between IP treatment groups will be conducted separately by SC IP dose frequency.

The primary statistical hypothesis of the co-primary endpoints is as follows:

Within each randomized SC IP dose frequency, the null hypothesis is that there is no mean difference in the mean percent change from baseline at weeks 10 and 12 or in the percent change from baseline at week 12 in LDL-C between evolocumab and placebo in combination with atorvastatin QD, and the alternative hypothesis is that a mean difference does exist.

6. Definitions

6.1 Study Time Points

Enrollment Date

Enrollment Date is the same as the start date of lipid stabilization as the date collected on the eCRF.

Randomization date

Randomization date is defined as the date subject was allocated to a treatment group in the interactive voice response system or interactive web response system (IVRS/IWRS) as recorded on the eCRF.

First Dose Date of SC Investigational Product (First SCIPD)

For each subject, the First Dose Date of SC Investigational Product is defined as the first administration date of the SC IP as recorded on the IP administration eCRF.

First Dose Date of Atorvastatin Therapy (First POSTD)

For each subject, the First Dose Date of Atorvastatin Therapy is defined as the first start date of the study-assigned atorvastatin therapy as recorded on the non-IP administration eCRF.

Study Day 1

For each subject, Study Day 1 is defined as the first day of investigational product (IP) administration.

Study Day

For each subject, and for a given date of interest, study day is defined as the number of days since Study Day 1:
Study day = (date of interest – Study Day 1 date) + 1.
If the date of interest is prior to the Study Day 1:
Study day = (date of interest – Study Day 1 date), so that the day prior to Study Day 1 is study day - 1.

Last Dose Date of SC Investigational Product (Last SCIPD)

For each subject, the Last Dose Date of SC Investigational Product is defined as the date of the last administration of the SC IP.

Last Dose Date of Atorvastatin Therapy (Last POSTD)

For each subject, the Last Dose Date of Atorvastatin Therapy is defined as the last stop date of the atorvastatin therapy.

End of IP Admin Date

End of IP Admin for each subject is defined as the date the decision was made to end IP as recorded on the End of IP eCRF page.

End of Study (EOS) Date

For each subject, the End of Study Date is the date recorded on the End of Study eCRF.

Study End Date

The Study End Date is the last EOS date of all randomized subjects.

6.2 Demographics and Baseline Related Definitions

Age

Subject age at enrollment will be collected in years on the eCRF.

Baseline Lipid and Lipid-related Parameters

Baseline values for fasting lipids (total cholesterol, HDL-C, LDL-C, VLDL-C, non-HDL-C and triglycerides), ApoA1, ApoB100, ApoB48, hsCRP, Lp(a) and their derived parameters (e.g., ratio between them) are defined as the fasting concentrations

measured through central lab on Study Day 1. If for any reason a concentration for a parameter is not observed on Study Day 1, the closest prior to Study Day 1 measurement for the parameter to Study Day 1 will be used.

Body mass index (BMI)

Subject's BMI will be derived in kg/m^2 in the clinical database.

Other Baseline Values

For ECG data, the baseline value is defined as the nonmissing triplicate average of 3 (or all available) readings taken on Study Day 1. If the Study Day 1 reading is missing, the closest nonmissing triplicate reading prior to Study Day 1 will be used as the baseline.

For PCSK9, the baseline value is defined as the last non-missing value collected prior to or on Study Day 1, but must be prior to first IP administration.

For all other variables, the baseline value is defined as the last non-missing value collected prior to or on Study Day 1.

Change (Absolute Change) from Baseline

The arithmetic difference between a post-baseline value and baseline for a given time point:

Change (absolute change) from baseline = (post-baseline value – baseline value)

Percent Change from Baseline

The percent change from baseline for a given variable at a given time point is defined as:

[(value at a given time point – baseline value) / baseline value] x 100%

Baseline CHD Risk Factors

A subject will be categorized as having 2 or more CHD Risk Factors (Y/N) from the list of the modified NCEP ATP III risk factors:

- current cigarette smoking,
- hypertension,
- type II diabetes mellitus,
- family history of premature CHD as recorded on the eCRF, and
- low HDL-C defined as baseline HDL-C < 40 mg/dL in males and < 50 mg/dL in females.

Systematic Coronary Risk Estimation (SCORE) Categories

The SCORE system estimates the 10 year risk of a first fatal atherosclerotic event, whether heart attack, stroke, or other occlusive arterial disease, including sudden cardiac death (ESC/EAS 2011). The SCORE risk estimates will be computed from the high and low risk region tables based on sex and baseline smoking status, systolic blood pressure, total cholesterol and age.

6.3 Other Study Related Definitions

Analytical Study Week/Timepoint Assignments

Analytical windows will be used to assign parameter measurements to study weeks and time points. The algorithm is provided in Appendix A.

Actual Treatment Group

A subject's actual treatment group is the randomized treatment group, unless the subject receives treatment throughout the study that is different than the randomized treatment group assignment, in which case the actual treatment group is the treatment received.

Investigational Product (IP)

SC IP includes evolocumab SC 140 mg Q2W, evolocumab SC 420 mg QM and their corresponding SC placebo.

Study Exposure Period in Months (Double Blind)

For each randomized subject, Study Exposure Period = (EOS date – Randomization date + 1) / 365.25 * 12

SC IP Exposure Period in Months

For each Q2W subject:

SC IP Exposure Period = [min (Last SCIPD + 14 days, EOS Date) - First SCIPD + 1]/ 365.25 * 12

For each QM subject:

SC IP Exposure Period = [min (Last SCIPD + 28 days, EOS Date) - First SCIPD +1] / 365.25 * 12

Atorvastatin Therapy Exposure Period in Months

For each subject:

Atorvastatin Therapy Exposure Period = [min (Last POSTD + 1 day, EOS Date) – First POSTD + 1] / 365.25 * 12

Treatment-emergent Adverse Event (TEAE)

Treatment-emergent adverse events are adverse events occurring between the first dose of IP and EOS. Treatment emergent adverse events can be identified if the values of the AE eCRF question “Did event start before first dose of investigational product?” is No or missing.

Serious Adverse Event (SAE)

Treatment-emergent adverse events (as defined above) that are indicated as serious on the Adverse Events eCRF.

Target IP TEAE (On-treatment IP TEAE)

Target IP TEAEs are adverse events occurring during IP exposure period.

Reflexive Approach for LDL-C and VLDL-C

For all analyses related to LDL-C and VLDL-C, unless specified otherwise, a reflexive approach will be used. When calculated LDL-C is less than 40 mg/dL or triglycerides are > 400 mg/dL, the UC LDL-C value and UC VLDL-C value from the same blood sample will be used instead, if available.

Achievement of LDL-C < 70 mg/dL

A subject has achievement of LDL-C < 70 mg/dL if the post-baseline LDL-C value at week 12 is less than 70 mg/dL. If the value is missing, the subject is considered without the achievement.

Mean achievement of LDL-C < 70 mg/dL at weeks 10 and 12 is defined using the mean of non-missing LDL-C values at those two timepoints (if one is missing, mean equals the available one).

7. Analysis Subsets

7.1 Full Analysis Set

The full analysis set (FAS) includes all randomized subjects who received at least one 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, regardless of the treatment received. For safety analyses, subjects will be grouped according to their actual treatment group (as defined in Section 6.3).

7.2 Lipid Stabilization Analysis Set

The lipid stabilization analysis set (LSAS) includes all subjects enrolled who receive at least one dose of assigned atorvastatin. The LSAS will be used in safety summaries during the lipid stabilization period.

7.3 Completer Analysis Set

The completer analysis set (CAS) includes subjects in the FAS who adhered to the scheduled IP regimen and atorvastatin therapy (i.e. the SC, and atorvastatin completion boxes are checked on the eCRF), and have observed values for the co-primary endpoints. The completer analysis set will be used in sensitivity analyses of the co-primary endpoints.

7.4 Subgroup Analyses

Subgroup by stratification factors

- Statin therapy at study entry (no statin use vs non-intensive statin use vs intensive statin use [see Appendix C])
- Site's geographic region (China, South Korea, other countries)

Subgroup by baseline characteristics

- Age (< 65 years, ≥ 65 years)
- Sex
- Race (black, white, and other)
- Baseline LDL-C (< median, ≥ median)
- Family history of premature coronary heart disease (yes, no)
- Baseline PCSK9 level (< median, ≥ median)
- Body Mass Index (BMI; < 25 kg/m^2, 25 - < 30 kg/m^2, ≥ 30 kg/m^2)
- Hypertension (yes, no)
- Current smoker (yes, no)
- Baseline CHD risk factors ≥ 2 (yes, no)
- Baseline triglycerides (< median, ≥ median; < 150 mg/dL, ≥ 150 mg/dL; < 200 mg/dL, ≥ 200 mg/dL)

8. Interim Analysis and Early Stopping Guidelines

No interim analysis is planned for this study.

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 of 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.

9. Data Screening and Acceptance

9.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

9.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations – Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database.

All data collected in the eCRF will be extracted from RAVE. Protocol deviations will be transferred from eClinical. Final PK data for all randomized subjects will be transferred from statistical programming to Amgen's CPMS group. Unblinded subject and box ID randomization lists will be provided by Amgen's randomization group and the IVRS/IWRS when the study stops. Details on data transfer will be provided in the Data Transfer Plan.

9.3 Handling of Missing and Incomplete Data

9.3.1 Patterns of Missing Data

Subjects may be missing specific data points for various reasons. In general, data may be missing due to a subject's early withdrawal from study, a missed visit, or non-evaluability of a data point or an endpoint at a particular point in time. In the Data Quality Review (DQR) process, queries will be made to the sites to distinguish true missing values from other unknown values (e.g. due to measurement or sample processing error). All attempts will be made to capture missing or partial data for this trial prior to the database lock.

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

9.3.2 Missing Lipid Measurements

For efficacy endpoints, where the analysis method is repeated measures linear effects model, missing lipid measurements will not be imputed. A sensitivity analysis will be performed based on multiple imputation method for the co-primary endpoint. The handling of missing LDL-C response (achievement of LDL-C < 70 mg/dL) is provided in Section 6.3.

9.3.3 Handling of Incomplete Dates

Adverse event and concomitant medication with completely or partially missing start dates will be queried. After the issue is queried, if the date is still incomplete with year only or year and month only, the start date will be imputed as described in Table below.

Table 1. Imputation Rules for Incomplete Dates

	Missing	Imputation	Exception
Start date (AE and concomitant medication)	Day	1	Default to Study Day 1 if an event starts the same year and month as Study Day 1
	Day / Month	1-Jan	Default to Study Day 1 if an event started the same year as Study Day 1

9.4 Detection of Bias

This study has been designed to minimize potential bias by the use of randomization of subjects into treatment groups and the use of blinding. Other factors that may bias the results of the study include:

- Major protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints
- Subject level unblinding before final database lock and formal unblinding
- DMC related analyses

Important protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints will be tabulated in the Clinical Study Report (CSR).

Any unblinding of individual subjects prior to formal unblinding of the study will be documented in the CSR. The impact of such unblinding on the results observed will be assessed.

For DMC related analyses, details of access to subject level treatment assignments are provided in the protocol, Section 10.3.

Additional sensitivity analyses may be included to assess the impact of potential biases on the primary endpoint. If any sensitivity analyses are required to evaluate potential biases in the study's conclusions, then the sources of the potential biases and results of the sensitivity analyses will be documented in the CSR.

9.5 Outliers

Various methods, including univariate summaries, histograms, scatter plots, box plots, and line graphs, may be used to identify outliers in key safety and efficacy variables. Extreme data points will be identified during the blinded review of the data prior to database lock. Such data points will be reviewed with clinical data management to ensure accuracy. The primary analyses will include outliers in the data. Sensitivity analyses may be undertaken if extreme outliers for a variable are observed.

9.6 Distributional Characteristics

Distributional assumptions for the primary and secondary endpoints will be assessed. If the assumptions are not met, then alternative methods will be utilized. The use of alternative methods will be fully justified in the CSR.

9.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.3 or later.

10. Statistical Methods of Analysis

10.1 General Principles

The final 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.

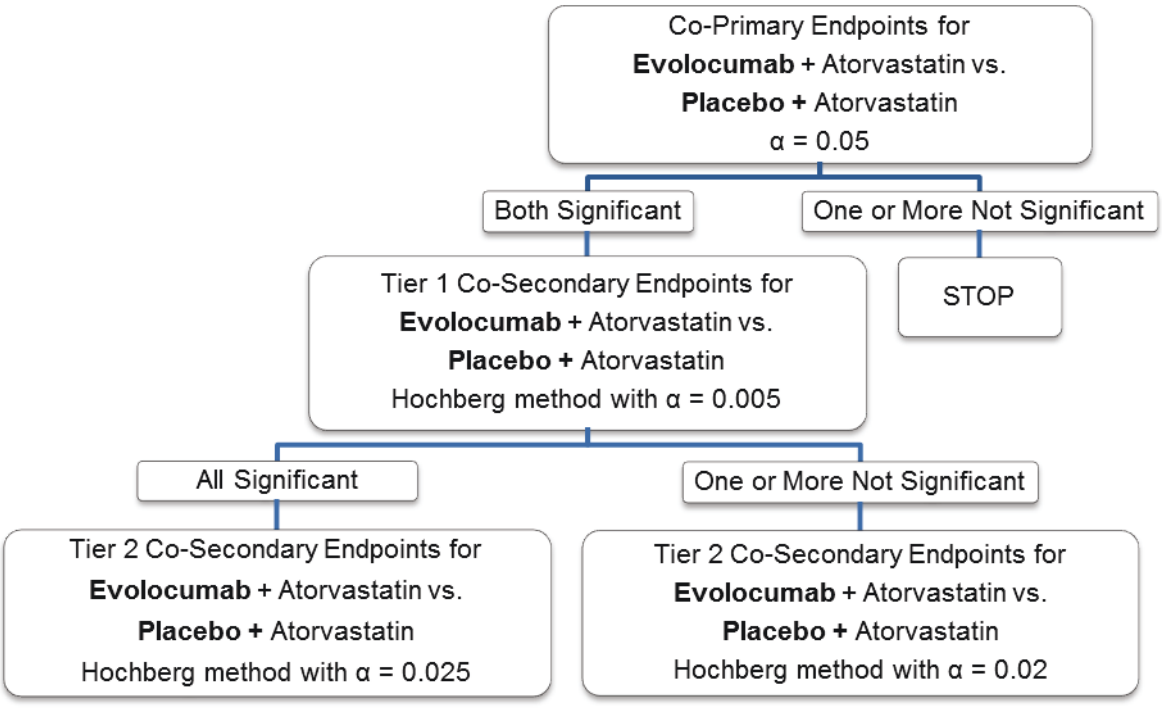
Analyses will be performed separately by each dose frequency (Q2W and QM) as two separate trials unless specified otherwise. Differences in model estimates between evolocumab QM and evolocumab Q2W and associated confidence intervals for the differences will be calculated for each lipid parameter. The superiority of evolocumab to placebo will be assessed for all efficacy endpoints. Unless specified otherwise, all other hypothesis testing will be 2-sided with a significance level of 0.05.

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 summarized.

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 the co-primary endpoints. 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 within each dose frequency are described in the diagram below.



The testing strategy outlined in the diagram will be executed two times: once for each IP dose frequency for testing versus placebo. Within each IP dose frequency, testing of each co-endpoint pair will result in a single p-value (see Table 2 for more details), and for co-secondary endpoints these p-values will then be used in the Hochberg procedure. The following method will be used to preserve the family wise error rate for co-primary and co-secondary efficacy endpoints for testing within each IP dose frequency:

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 4.1.2) 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).

10.2 Subject Accountability

The number of subjects screened, enrolled in lipid stabilization, randomized, received IP, and completed study will be summarized. Key study dates for the first subject enrolled, last subject enrolled and last subject's end of study will be presented.

Study discontinuation and IP discontinuation will be tabulated separately by reasons for discontinuation. This tabulation will include study discontinuations during the lipid stabilization period.

The number of subjects included in and excluded from each analysis set and reason for exclusion will also be summarized.

10.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, sub-category codes, and descriptions will be used during the course of the study.

Eligibility deviations are defined in the protocol.

10.4 Demographic and Baseline Characteristics

All baseline tables will be summarized by randomized treatment group and for all subjects in FAS. Baseline tables will summarize the following: baseline characteristics, demographics, cardiovascular medical history, laboratory parameters, and lipid-regulating concomitant medications.

Summary statistics for percent change from screening LDL-C to baseline LDL-C for subjects in the FAS will be provided.

10.5 Efficacy Analyses

The following table summarizes the key efficacy analyses that will be conducted:

Table 2. Key Efficacy Analyses Summary Table

Endpoint	Statistical Analysis Method	P-values from the Statistical Tests	Hierarchical Testing Procedure for testing of Treatment Effect vs. Placebo. As specified in the Multiplicity Adjustment Method Diagram
Co-primary Endpoints			
• Mean percent change from baseline at weeks 10 and 12 in LDL-C • Percent change from baseline at week 12 in LDL-C	Repeated measures model	P1 = Maximum of the two p-values for the co-primary endpoint pair from the primary analysis	P1 compare to α = 0.05
Co-secondary Endpoints (Tier 1)			
• Mean change from baseline at weeks 10 and 12 in LDL-C • Change from baseline at week 12 in LDL-C And • Mean percent change from baseline at weeks 10 and 12 and • Percent change from baseline at week 12 in each of the following lipid parameters: non-HDL-C, ApoB100, total cholesterol, total cholesterol/HDL-C ratio, and ApoB100/ApoA1 ratio And	Repeated measures model	For each lipid parameter, P2a = Maximum of the two p-values for each tier 1 co-secondary endpoint pair	If P1 < 0.05 ➔ All P2a's from each lipid parameter will be tested through Hochberg method with α = 0.005 Else (i.e. co-primary endpoint is not significant) ➔ No further testing

Table 2. Key Efficacy Analyses Summary Table

Endpoint	Statistical Analysis Method	P-values from the Statistical Tests	Hierarchical Testing Procedure for testing of Treatment Effect vs. Placebo. As specified in the Multiplicity Adjustment Method Diagram
• Mean achievement of LDL-C < 70 mg/dL at weeks 10 and 12 • Achievement of LDL-C < 70 mg/dL at week 12	Cochran Mantel-Haenszel (CMH) test		
Co-secondary Endpoints (Tier 2)			
• Mean percent change from baseline at weeks 10 and 12 • Percent change from baseline at week 12 in each of the following lipid parameters: Lp(a), triglycerides, HDL-C, and VLDL-C	Repeated measures model	For each lipid parameter, P2b = Union-intersection test p-value from the two contrasts of each tier 2 co-secondary endpoint pair	If all P2a's are significant through Hochberg method ➔ All P2b's from each lipid parameter will be tested through Hochberg method with $\alpha = 0.025$ Else (i.e. one or more co-secondary endpoints (tier 1) is not significant) ➔ All P2b's will be tested through Hochberg method with $\alpha = 0.02$

10.5.1 Analyses of Co-primary Endpoints

10.5.1.1 Primary Analysis of Co-primary Efficacy Endpoints

To assess the co-primary endpoints of the mean percent change from baseline in LDL-C at weeks 10 and 12 and the percent change from baseline in LDL-C at week 12, 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 (from IVRS/IWRS), scheduled visit and the interaction of treatment with scheduled visit. To account for the repeated LDL-C measurements within a subject across the visits, the repeated measures linear effects model will use an unstructured covariance (Littell, 2000). China and South Korea may be combined as one stratum if LS means estimates cannot be derived from the repeated measures model due to small sample size of South Korea. If there is still convergence issue due to sample size of China and South Korea, only the entry statin therapy stratification will be included in the model.

Multiplicity adjustment procedures are defined in Section 10.1.

10.5.1.2 Sensitivity Analyses of Co-primary Efficacy Endpoints

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 (Quade test) will be performed using the CAS.
- Multiple imputation for subjects who discontinue IP with missing endpoint data:
  - It will be assumed that the missing percent change values will be normally distributed with a mean 0 and a variance-covariance matrix the same as the observed variance-covariance matrix from subjects in the placebo group who did not discontinue IP with missing endpoint data.
  - If there is sufficient number of subjects in each treatment group who discontinue IP but have non-missing endpoint data, an additional multiple imputation will be carried out utilizing the information from these subjects to impute the missing data for subjects who discontinue IP and have missing endpoint data.

10.5.1.3 Subgroup Analyses of Co-primary Efficacy Endpoints

Subgroup analyses on the co-primary efficacy endpoints will be conducted using the subgroups specified in Section 7.4. Treatment effect differences among subgroups, which represent subgroup by treatment interactions, will be estimated based on statistics from the subgroup repeated measures models.

For subgroup analyses, the stratification factors and baseline covariates from the eCRF will be used. Differences in stratum assignment between data collection via IVRS/IWRS and eCRF will be tabulated.

10.5.2 Analyses of 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 as defined in Section 6.3 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. For each tier 2 endpoint, the alternative hypothesis of the union-intersection test is that at least 1 of the treatment effects from the co-endpoints is not equal to zero.

Multiplicity adjustment procedure of testing evolocumab in combination with atorvastatin vs. placebo in combination with atorvastatin for co-secondary endpoints is defined in Section 10.1.

10.5.3 Analyses of Tertiary Efficacy Endpoints

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

10.5.4 Analyses of Exploratory Endpoints

Exploratory endpoints related to lipid parameters and PCSK9 will be summarized by randomized treatment group and by scheduled visit using descriptive statistics.

Non-coronary revascularizations will be collected on the eCRF and will not be adjudicated. Subject incidence of non-coronary revascularizations will be summarized.

A shift table for hsCRP will be provided, for levels at baseline to maximum post-baseline value (<1, 1-3, >3 mg/L), by treatment group.

HbA1c will be summarized at each scheduled assessment by treatment group.

Fasting and postprandial laboratory parameters of interest (including MMTT Extended Timepoints Substudy assessments) will be summarized at each scheduled assessment by treatment group.

10.6 Safety Analyses

10.6.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 or later will be used to code all events categorized as adverse events (AEs) to a system organ class and a preferred term. Severity of AEs will be graded using the CTCAE (Appendix B) and recorded on the eCRF. All adverse event tables will be summarized by actual treatment group. Treatment-emergent adverse events are events with an onset after the administration of the first dose of IP.

Subject Incidence of AEs will be summarized for all treatment-emergent AEs, serious AEs, adverse device effects (ADEs; i.e. device-related adverse events), AEs leading to withdrawal of investigational product and fatal AEs. Subject incidence of all treatment-emergent AEs, serious AEs, AEs leading to withdrawal of investigational product, and fatal AEs will be tabulated by system organ class and preferred term.

Summaries of treatment-emergent AEs occurring in at least 1% of the subjects by preferred term in any treatment arm will be provided in descending order of frequency.

Subject incidence of adverse events related to a device will be tabulated by preferred term in descending order of frequency by treatment group.

A separate summary of any adverse events collected during the lipid stabilization period will be provided for all subjects in the LSAS.

Subject incidence of adverse events associated with lipid lowering therapies:

- Muscle-related
- Liver-related

associated with injectable protein therapies:

- Injection site reactions
- Hypersensitivity or allergic reactions

potential hepatitis C infections and potential neurocognitive events will be summarized by category and preferred term.

10.6.2 Laboratory Test Results

Descriptive statistics will be provided for actual values and changes from baseline in select laboratory parameters at each protocol-specified scheduled visit. Laboratory analytes are provided in the protocol Table 2. Lab shift tables using the CTCAE v4.03 or later grading will be used for select analytes of interest, when applicable. The results will

be based on the maximum (i.e., worst) shift from baseline to the EOS. In addition, CK and liver function test (LFT) abnormalities will be assessed by the incidence overall and by visits of the following categories:

- CK > 5 x ULN
- CK > 10 x ULN
- ALT or AST > 3 x ULN
- ALT or AST > 5 x ULN
- Total Bilirubin > 2 x ULN
- (ALT or AST > 3 x ULN) and Total Bilirubin > 2 x ULN and Alkaline Phosphatase < 2 x ULN

10.6.3 Vital Signs

Systolic and diastolic blood pressure and heart rate will be summarized for each treatment group using descriptive statistics at each scheduled visit.

10.6.4 Electrocardiogram (ECG)

For post-baseline assessments where ECG is performed in triplicate, the average of the 3 (or all available) readings will be used for analysis. Observations with the following diagnosis or findings will be excluded from analysis: artificial pacemaker, atrial fibrillation, atrial flutter, left bundle branch block, and right bundle branch block.

PR, QRS, QT, QTc (i.e., QTcB and QTcF) and RR intervals and their change from baseline will be summarized for each treatment group by scheduled visit. In each treatment group, subjects will be categorized and summarized per their maximum post-baseline absolute QTc interval using limits of 450 ms, 480 ms, and 500 ms. They will also be categorized per their maximum change from baseline QTc interval using limits of 30 ms and 60 ms.

10.6.5 Antibody Formation

The incidence and percentage of subjects who develop anti-evolocumab antibodies (binding and if positive, neutralizing) at anytime will be tabulated.

10.6.6 Exposure to Investigational Product

Descriptive statistics will be produced to describe the patient-month exposure to investigational product and the categorical representation of dose received.

Exposure definitions are provided in Section 6.3.

10.6.7 Exposure to Atorvastatin Therapy

Descriptive statistics will be produced to describe the patient-month exposure to atorvastatin background therapy and the total quantity of atorvastatin used by treatment group.

10.6.8 Exposure to Concomitant Medication

The number and proportion of subjects receiving the lipid regulating medications of interest (MOI) will be summarized by category and preferred term for each treatment group as coded by the World Health Organization Drug (WHO Drug) dictionary.

10.7 Pharmacokinetic Analysis

Individual and mean serum evolocumab and PCSK9 concentration graphs will be provided by nominal time. The data set will be analyzed and stored in the Pharsight Knowledgebase Server (PKS) data repository using the current version of Phoenix WinNonlin. Evolocumab or PCSK9 serum concentrations with values below the lower limit of quantification will be reported as less than their respective values but will be set to zero for analysis. PK parameters following the last dose will include but not limited to the maximum and minimum evolocumab serum concentrations observed at the collected time points. Individual and summary statistics for PK concentrations will be provided.

These analyses will be performed by the CPMS group.

Compartmental exposure-response analyses will not be specified in this analysis plan but may be included in a subsequent population PK analysis using a single study or as part of a metadata analysis.

11. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

12. Literature Citations / References

Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988;75:800-802.

Littell, R.M., Pendergast, J and Natarajan, R. Tutorial in Biostatistics. Modelling covariance structure in the analysis of repeated measures data. Stat Med. 2000;19: 1793-1819.

Wiens BL. A fixed sequence Bonferroni procedure for testing multiple endpoints. *Pharmaceut Statist*. 2003;2:211–215.

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). ESC/EAS Guidelines for the management of dyslipidaemias. *European Heart Journal.* 2011; 32:1769–1818.

13. Appendices

Appendix A. Analytical Study Week/Time Point Assignments

Selected endpoints will be summarized by scheduled study visits in descriptive analyses. Since the actual visits may not exactly coincide with their scheduled visit day, the actual visit day is mapped to the study visit generally by non-overlapping consecutive intervals covering the entire time continuum. The mapping intervals for all distinct schedules are summarized in the following table:

Analytical Study Week	Week 2	Week 8	Week 10	Week 12
Scheduled Visit Day	15	57	71	85
Lipids, PK, PCSK9	(1, 35]	(35, 63]	(63, 77]	(77, 91]
Vital Signs	(1, 42]		(42, 77]	(77, 91]
Lp(a), ApoA1, ApoB100			(1, 77]	(77, 91]
Chemistry, Hematology		(1, 70]		>70
12 lead ECG			(1, 77]	>77
Body Weight, Waist Circumference, hsCRP, HbA1c, MMTT , Anti-evolocumab Antibodies, Urinalysis				> 1

Handling multiple records assigned to an analytical study week:

If there is more than one record in a study week interval, the analytical record for that specific study week will be defined as the record closest to the scheduled visit day of that specific study week (7 x study week + 1). If two records are equidistant from the scheduled day, then the earlier record will be chosen. If there are multiple records on the same day, the last record will be used.

Appendix B. Common Terminology Criteria for AEs (CTCAE)

Refer to the NCI Common Terminology Criteria for Adverse Events (CTCAE) for adverse event grading and information. The CTCAE is available at the following link: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Appendix C. 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, e.g., 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:
[1] Statin includes atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.