STATISTICAL ANALYSIS PLAN

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

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Table of Abbreviations

Abbreviation or Term	Definition/explanation
ACC	American College of Cardiology
AE	Adverse event
AHA	American heart association
AI	Autoinjector
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMD	Automated mini-doser
ApoA1	Apolipoprotein A-I
ApoB	Apolipoprotein B
ApoB48	Apolipoprotein B-48
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
CAS	Completer analysis set
CHD	Coronary heart disease
CK	Creatine phosphokinase
CMH	Cochran mantel-haenszel
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DQR	Data quality review
DRE	Disease-related event
EAS	European Atherosclerosis Society
eCRF	Electronic case report form
EOIP	End of Investigational Product
End of Study (end of trial)	Defined as the date when the last subject has completed all planned study procedures up to and including the visit as outlined in the Schedule of Assessments
End of Study for Individual Subject	Defined as the last day that protocol-specified procedures are conducted for an individual subject
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
ESC	European Society of Cardiology
FAS	Full analysis set
FBG	Fasting blood glucose
GLP-1	Glucagon-like peptide-1

Abbreviation or Term	Definition/explanation
GSO-DM	Global study operations-data management
HbA1c	Hemoglobin a1c
HDL-C	High-density lipoprotein cholesterol
IL-6	Interleukin-6
IP	Investigational product
IPDs	Important protocol deviations
IVRS	Telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
LFT	Liver function test
Lp(a)	Lipoprotein(a)
MedDRA	Medical Dictionary for Regulatory Activities
MMTT	Mixed meal tolerance test
NCEP ATP III	National Cholesterol Education Panel Adult Treatment Panel III
PCSK9	Proprotein convertase subtilisin/kexin type 9
PO	Orally
QD	Once daily
QM	Once monthly
SAE	Serious Adverse Event
SC	Subcutaneous
SCORE	Systematic Coronary Risk Estimation
SD	Standard deviation
Study day 1	Defined as the first day that protocol-specified investigational product(s)/protocol required therapies is/are administered to the subject
TEAE	Treatment emergent adverse event
TEDRE	Treatment emergent disease-related event
UC	Ultracentrifugation
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 amendment 1 for Evolocumab Study 20130287 dated 6 January 2016. 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 monthly (QM) compared with placebo QM on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in subjects with type 2 diabetes mellitus and hypercholesterolemia or mixed dyslipidemia on maximally tolerated dose of statin of at least moderate-intensity oral (PO) daily (QD).

2.2 Secondary

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

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

2.3 Safety

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

2.4 Exploratory

To describe the effects over time of SC evolocumab QM compared with placebo QM, in subjects with type 2 diabetes mellitus and hypercholesterolemia or mixed dyslipidemia in combination with maximally tolerated dose of statin of at least moderate-intensity PO 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, ApoB, VLDL-C, HDL-C, apolipoprotein A-I (ApoA1), triglycerides, and Lp(a)

- Change and percent change from baseline on fasting and postprandial plasma laboratory parameters of interest including glucose, insulin, pro-insulin, C-peptide, fatty free acids, glucagon, lipids, chylomicrons, ApoB48, interleukin-6 (IL-6), adiponectin after a mixed meal tolerance test (MMTT).
- The relationship between novel and established biochemical cardiovascular and lipid biomarkers and effects of evolocumab
- Potential correlations of study data including the subject response to evolocumab with genetic variation in markers of PCSK9 signaling, low-density lipoprotein receptor (LDLR) turnover, cholesterol metabolism, inflammation, and plaque stability in subjects consenting to the optional pharmacogenetic analysis

3. Study Overview

3.1 Study Design

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

The study will consist of 2 periods:

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

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

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

Randomization will be stratified by LDL-C (< 130 mg/dL vs ≥ 130 mg/dL).

Day 1 is defined as the calendar day when treatment with investigational product (IP) is initiated. Subjects should initiate their first dose of IP within 5 days of randomization.

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

3.2 Sample Size

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

The primary analysis will require the 2-sided tests of co-primary endpoints to be significant at a level of 0.05. The planned sample size should provide adequate power to determine the superiority of evolocumab 420 mg QM relative to placebo as measured by the co-primary endpoints. From the phase 3 studies integrated efficacy analysis, the treatment effect of evolocumab 420 mg QM compared to placebo and the corresponding 95% confidence interval at week 12 was -60.39% [-64.57%, -56.21%], with treatment effect ranges between -55.1% to -62.33% from Studies 20110114, 20110115, and 20110117. The assumed treatment effect between evolocumab 420 mg QM and placebo for the co-primary endpoint at week 12 is 40%, with a common standard deviation (SD) of 20%. This SD assumption is based on evolocumab phase 3 results.

This sample size will provide approximately 99% power for the co-primary endpoint at week 12 in testing the superiority of evolocumab dose regimen over placebo, assuming a dropout rate of 10%.

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

From the phase 3 evolocumab studies the treatment effect of evolocumab over placebo in the percentage reduction in triglycerides at week 12 was approximately 12% with a

common SD of 35%. However, the SD for triglycerides in a diabetic population may be higher. Table 1 displays the power associated with various SD assumptions.

Table 1. Power Associated With Standard Deviation Assumptions

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

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

4. Study Endpoints and Covariates

4.1 Study Endpoints

4.1.1 Co-primary Endpoints

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

4.1.2 Co-secondary Endpoints

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

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

4.1.3 Safety Endpoints

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

4.1.4 Exploratory Endpoints

- change and percent change from baseline at each scheduled assessment in each of the following parameters:
  - LDL-C
  - non-HDL-C
  - ApoB
  - total cholesterol
  - VLDL-C
  - HDL-C
  - ApoA1
  - triglycerides
  - Lp(a)
- HbA1c at each scheduled assessment
- Fasting Blood Glucose (FBG) at each scheduled assessment
- PCSK9 change from baseline at each scheduled assessment
- fasting and post-prandial laboratory parameters of interest (including MMTT Extended Timepoints assessments) change and percent change from day 1 to week 12 in response to a mixed meal tolerance test in glucose, insulin, pro-insulin, C-peptide, free fatty acids, glucagon, lipids, chylomicrons, ApoB48, IL-6, adiponectin

4.2 Planned Covariates

Stratification factor in the double-blind treatment period:

- LDL-C < 130 mg/dL vs ≥ 130 mg/dL

Baseline Characteristics:

- Age
- Sex (male, female)
- Race (black, white, and other)
- LDL-C
- Family history of premature coronary heart disease (CHD) (yes,no)
- PCSK9
- Region (North America, Europe, other)
- Body Mass Index (BMI)
- Hypertension (yes, no)

- Current smoker (yes, no)
- Additional baseline CHD risk factor (yes, no)
- Triglycerides
- Insulin Use (yes, no)
- Statin intensity (High/Moderate/Low intensity as per ACC/AHA guidelines)
- Lipid entry target (above both non-HDL-C and LDL-C entry criteria thresholds, above non-HDL-C entry criteria threshold only, and above LDL-C criteria threshold only)
- Presence of diabetes complications (0 complications, presence of 1 or more complications)

5. Hypotheses and/or Estimations

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

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 420 mg QM and placebo, 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 randomization date (ie, the date a subject gets randomized in the interactive voice response system (IVRS) as recorded on the eCRF).

Study Day 1

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

End of Investigational Product (EOIP) Date

For each subject, the end of investigational product is defined as the date of the last administration of the investigational product.

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

Age will be calculated as the subject's age in years at enrollment as recorded on the eCRF.

Baseline Lipid and Lipid-related Parameters

Baseline values for fasting lipids (total cholesterol, HDL-C, LDL-C, VLDL-C and triglycerides), ApoA1, ApoB, Lp(a) and their derived parameters (eg, ratio between them) are defined as the mean of the two most recent non-missing fasting concentrations measured through central lab prior to or on Study Day 1. If for any reason only 1 value is available, then that value will be used as baseline.

Other Baseline Values

For PCSK9, the baseline value is defined as the average of the last two non-missing values collected prior to first IP administration. If for any reason only 1 value is available, then that value will be used as baseline.

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:

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

Baseline CHD Risk Factors

As all subjects in this study will have type II diabetes mellitus which is considered a CHD Risk Factor, a subject will be categorized as having an additional CHD Risk Factor (Y/N) if they have at least one from the list of the modified NCEP ATP III risk factors:

- current cigarette smoking
- hypertension
- family history of premature CHD as recorded on the eCRF
- low HDL-C defined as baseline HDL-C < 40 mg/dL in men and < 50 mg/dL in women.

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 Assignments

Analytical windows will be used to assign parameter measurements to study weeks. 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)

Evolocumab SC 420 mg QM and its corresponding SC placebo.

IP Exposure Period in Months

For each subject:

IP Exposure Period = [min (EOIP + 28 days, EOS Date) - Study day 1 + 1]/ 365.25 * 12

Study Exposure Period in Months

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

Treatment Emergent Adverse Event (TEAE)

Events categorized as Adverse Events (AEs) starting on or after first dose of investigational product as determined by the flag indicating if the adverse event started prior to the first dose on the Events eCRF and up to and including EOS.

Serious Adverse Event (SAE)

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

Treatment Emergent Disease-Related Event (TEDRE)

Events categorized as Disease-Related (DREs) starting on or after first dose of investigational product as determined by the flag indicating if the adverse event started prior to the first dose on the Events eCRF and up to and including EOS.

LDL-C Reflexive Approach

For all analyses related to LDL-C, unless specified otherwise, a LDL-C 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 from the same blood sample will be used instead, if available.

Achievement of target LDL-C < 70 mg/dL

A subject has achievement of LDL-C < 70 mg/dL if the post-baseline LDL-C value is less than 70 mg/dL. If the value is missing, the subject is considered without the achievement when statistical inference is performed.

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).

LDL-C reponse (50% reduction from baseline)

A subject has a response of 50% reduction from baseline in LDL-C if the LDL-C percent change from baseline value is less than or equal to -50%. If the value is missing, the subject is considered without the response when statistical inference is performed.

Mean response of LDL-C 50% reduction at weeks 10 and 12 is defined using the mean of non-missing LDL-C percent change from baseline 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 1 dose of IP. This analysis set will be used in both efficacy and safety analyses. In efficacy analysis, subjects will be analyzed according to their randomized treatment group assignment. For safety analyses, subjects will be grouped according to their actual treatment group (as defined in Section 6.3).

7.2 Completers Analysis Set

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

7.3 Subgroup Analyses

Subgroup by stratification factor

- LDL-C < 130 mg/dL vs ≥ 130 mg/dL

Subgroup by baseline characteristics

- Age < 65 years, ≥ 65 years
- Sex (female, male)
- Race (black, white, and other)
- LDL-C (< baseline median, ≥ baseline median)
- Family history of premature CHD (yes, no)
- PCSK9: (< baseline median, ≥ baseline median)
- Region (North America, Europe, other)
- BMI (<25, 25-30, ≥30)
- Hypertension (yes, no)
- Current smoker (yes, no)
- Additional baseline CHD risk factor (yes, no)
- Triglicerides (< baseline median, ≥ baseline median)
- Insulin Use (yes, no)
- Statin intensity (High/Moderate/Low intensity as per ACC/AHA guidelines)
- Lipid entry target (above both non-HDL-C and LDL-C entry criteria thresholds, above non-HDL-C entry criteria threshold only, and above LDL-C criteria threshold only)
- Presence of diabetes complications (0 complications, presence of 1 or more complications)

8. Interim Analysis and Early Stopping Guidelines

No interim analysis is planned for this study.

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. Unblinded subject and box ID randomization lists will be provided by Amgen's randomization group and the IVRS 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. The handling of missing LDL-C response (50% reduction of LDL-C from baseline) and achievement of target LDL-C < 70 mg/dL is provided in Section 6.3. Sensitivity analysis will be performed on the co-primary endpoints to evaluate the robustness of the missing at random assumption used in the repeated measures linear effects model, details are provided in section 10.5.1.2.

9.3.3 Handling of Incomplete Dates

Adverse events can be flagged as treatment emergent using valid answers to the question “Did event start before first dose of investigational product?” on the eCRF regardless of the AE onset date being complete or not. Adverse events that cannot be determined as prior to IP or not will be counted as treatment emergent adverse events.

Concomitant medication with completely or partially missing dates will be queried. If after the query is resolved, the date is still incomplete with year only or year and month only, the concomitant medication start date will be imputed as described below:

- If year is available but day and month are missing, the day and month for the start date will be set to the 1st of January of the onset year.
- If year and month are available but day is missing, the day will be set to the 1st of the month of the onset year.

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

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. Data from subjects whose treatment assignments are unblinded prior to formal unblinding will be listed. The timing and reason for unblinding will be included in these listings.

Additional sensitivity analyses may be included to assess the impact of potential biases on the co-primary endpoints. 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 co-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 9.2 or later.

10. Statistical Methods of Analysis

10.1 General Principles

To evaluate efficacy and safety of 12 weeks of evolocumab 420 mg QM compared with placebo, the primary analysis will be performed when all randomized subjects in the double-blind treatment period have either completed all the scheduled study visits in the double-blind treatment period or have early terminated from the study. At that time, the database of the study will be cleaned, processed and a snapshot will be taken; the study will also be unblinded.

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.

Subject disposition, demographics, baseline characteristics and exposure to IP will be summarized by treatment group. Summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation, or standard error,

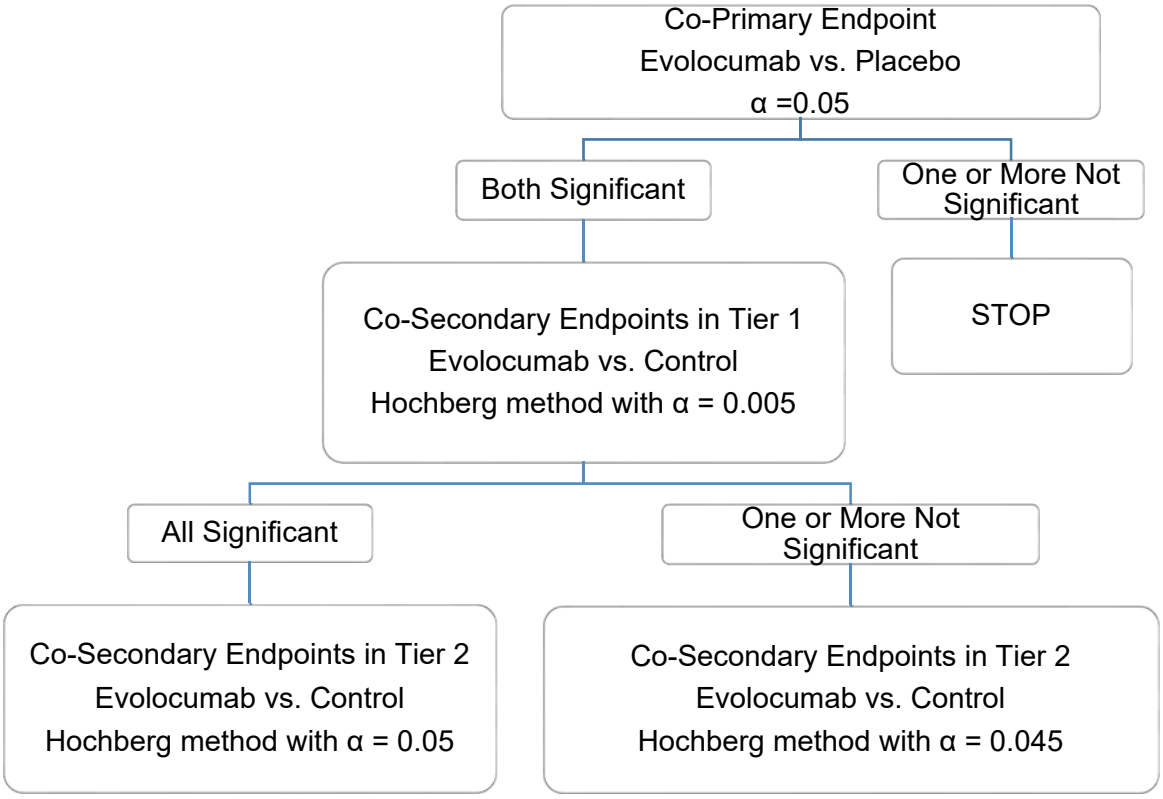
minimum, and maximum. For categorical variables, the frequency and percentage will be given.

Methods of handling missing data for efficacy endpoints will be described below. Missing data will not be imputed for safety endpoints.

Multiplicity Adjustment Method

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

Figure 1. Multiplicity Adjustment Methods



Testing of each co-endpoint pair will result in a single p-value, and for co-secondary endpoints these p-values will then be used in the Hochberg procedure. The following method will be used to preserve the family wise error rate for the co-primary and co-secondary endpoints:

- If the treatment effect from the primary analysis of the co-primary endpoints are both significant at a significance level of 0.05, statistical testing of the tier 1 co-secondary efficacy endpoints will follow the Hochberg procedure at a significance level of 0.005 (Hochberg, 1988)

- If all tier 1 co-secondary efficacy endpoints are significant, the tier 2 co-secondary efficacy endpoints will be tested using the Hochberg procedure at a significance level of 0.05.
- If not all tier 1 co-secondary efficacy endpoints are significant, the tier 2 co-secondary efficacy endpoints will be tested using the Hochberg procedure at a significance level of 0.045 (Wiens, 2003).

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

10.2 Subject Accountability

The number and percent of subjects who were screened, randomized, received IP, completed IP, discontinued IP and reasons for discontinuing, completed study, discontinued study and reasons for discontinuing will be summarized by treatment group.

Key study dates for the first subject enrolled, last subject enrolled, last subject's end of IP and last subject's end of study will be presented.

The number and percent of subjects randomized will be tabulated by the stratification factors.

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

Demographic (ie, age, geriatric age group [< 65, >= 65 and >= 75], sex, race, ethnicity) and baseline disease characteristics (cardiovascular medical history, diabetes disease history [eg, family history, complications], diabetes related medication and lipid-regulating medication) will be summarized by treatment group and overall using descriptive statistics. If multiple races have been reported for a subject, the subject will be categorized as multiple race.

10.5 Efficacy Analyses

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

Table 2. Key Efficacy Analyses Summary Table

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	P-values from the Statistical Tests	Hierarchical Testing Procedure for testing of Treatment Effect vs. Placebo. as specified in the Multiplicity Adjustment Method diagram	Sensitivity Analysis
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-endpoint pair from the primary analysis	P1 compare to α = 0.05	• The primary analysis will be repeated using the CAS • Non-parametric analyses will be performed • Multiple imputation for subjects with missing endpoint data who discontinue evolocumab
Co-Secondary Endpoints (Tier 1)				
• Mean LDL-C achievement of target LDL-C < 70 mg/dL and LDL-C response of ≥ 50% reduction from baseline at weeks 10 and 12 • LDL-C achievement and response at week 12	Cochran Mantel-Haenszel (CMH) test	For LDL-C achievement and LDL-C response, P2a=Maximum of the two p-values for the co-endpoint pair	If P1 < 0.05, ➔ Both P2a and all P2b'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	n/a

Table 2. Key Efficacy Analyses Summary Table

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	P-values from the Statistical Tests	Hierarchical Testing Procedure for testing of Treatment Effect vs. Placebo. as specified in the Multiplicity Adjustment Method diagram	Sensitivity Analysis
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 • Percent change from baseline at week 12 in each of the following lipid parameters: non-HDL-C,ApoB, total cholesterol	Repeated measures model	For each lipid parameter, P2b=Maximum of the two p values for each co-endpoint pair		n/a

Table 2. Key Efficacy Analyses Summary Table

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	P-values from the Statistical Tests	Hierarchical Testing Procedure for testing of Treatment Effect vs. Placebo. as specified in the Multiplicity Adjustment Method diagram	Sensitivity Analysis
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, P2c=Union-intersection test p-value from the two contrasts of each co-endpoint pair	If P2a and all P2b's are significant through Hochberg method, ➔ all P2c's from each lipid parameter will be tested through Hochberg method with α = 0.05 Else (i.e. not all tier 1 co-endpoints are significant), ➔ all P2c's from each lipid parameter will be tested through Hochberg method with α = 0.045	n/a

10.5.1 Analyses of Co-primary Efficacy Endpoints

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

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.

Multiplicity adjustment procedures are defined in Section 10.1.

10.5.1.2 Sensitivity Analyses of Co-primary 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 will be performed
- 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 are at least 25 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 Covariate and Subgroup Analyses of Co-Primary Endpoints

In addition to the primary analysis specified in Section 10.5.1.1, covariate-adjusted analyses of the co-primary efficacy endpoints will be performed as supportive analyses using the baseline covariates in Section 4.2 in their original format, one at a time, in the primary model used in the primary analyses as appropriate.

Subgroup analyses on the co-primary efficacy endpoints will be conducted using the subgroups specified in Section 7.3. Depending on the distribution of baseline LDL-C, analyses using different subgroups of baseline LDL-C will be performed if applicable. Treatment effect differences among subgroups, which represent subgroup by treatment

interactions, will be estimated and tested based on statistics from the subgroup repeated measures models.

For covariate and subgroup analyses, the stratification factor from the eCRF will be used. Differences in stratum assignment between data collection via IVRS 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 endpoints of achievement of target LDL-C < 70 mg/dL and LDL-C response of ≥ 50% reduction from baseline will be analyzed using the Cochran-Mantel Haenszel (CMH) test adjusted by the stratification factor.

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 procedures are defined in Section 10.1.

10.5.3 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.

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

Area under the curve (AUC) and incremental AUC will be calculated for laboratory parameters collected for the MMTT at day 1 and at week 12. Change and percent change from day 1 to week 12 in AUC and incremental AUC will be provided by actual treatment group. Analysis will be performed separately for those subjects who have the extended timepoint assessments.

10.6 Safety Analyses

10.6.1 Adverse Events and Disease-Related events

The Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 or later will be used to code all events categorized as adverse events (AEs) or disease-related events (DREs) 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 as defined in Section 6.3.

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 in descending order of frequency.

Summaries of treatment-emergent and serious 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 DREs will be summarized by system organ class and preferred term for all treatment-emergent DREs and fatal DREs.

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

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

and potential hepatitis C infections 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 the select analytes of interest, when applicable.

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 ALP < 2 x ULN)

10.6.3 Vital Signs

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

10.6.4 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.

10.6.5 Exposure to Other Protocol-specified Treatment

The number and proportion of subjects receiving selected lipid regulating medications captured on the Lipid Regulating Concomitant Medications eCRF will be summarized by treatment group. Summaries will be provided for baseline use and use after Study Day 1. The subject incidence of changes in lipid regulating medications during the treatment period will also be provided by treatment group.

10.6.6 Exposure to Concomitant Medication

The number and proportion of subjects receiving the diabetes related medications of interest will be summarized by category and preferred term for each treatment group as coded by the World Health Organization Drug (WHODRUG) dictionary. The subject incidence of changes in diabetes related medications, including the reason for change, during the treatment period will also be provided by treatment group.

11. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

12. Literature Citations / References

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.

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

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

Stone N, Robinson J, Lichtenstein A et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129(25 Suppl 2): S1-45.

13. Appendices

Appendix A. Analytical Study Week 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 8	Week 10	Week 12
Scheduled Visit Day	57	71	85
Chemistry, HbA1c, Urinalysis, Body Weight, Waist circumference, MMTT parameters,			>1
Vital Signs	(1, 63]	(63, 77]	(77, 91]
Fasting Lipids, ApoA1, ApoB, Lp(a), PCSK9,		(1, 77]	(77, 91]

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 latest version of the NCI Common Terminology Criteria for AEs (CTCAE) for AEs, DREs, and lab shift grading and information. The CTCAE is available at the following link:

http://evs.nci.nih.gov/ftp1/CTCAE/About.html