Statistical Analysis Plan

A Double Blind, Randomized, Placebo Controlled, Multicenter Study to Evaluate Safety, Tolerability, and Efficacy on LDL-C of Evolocumab (AMG 145) in Subjects with HIV and with Hyperlipidemia and/or Mixed Dyslipidemia

BEIJERINCK: evolocumaB Effect on LDL-C lowerIng in subJECts with human immunodeficiency viRus and INcreased Cardiovascular risK

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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
AST	Aspartate aminotransferase
BP	Blood pressure
CAS	Completer analysis set
CD4	Cluster of differentiation 4
[redacted]	
CHD	Coronary heart disease
CK	Creatine kinase
CMH	Cochran Mantel-Haenszel
CRF	Case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	
DMC	Data Monitoring Committee
DQR	Data Quality Review
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 (Primary completion)	The date when the last subject has completed the assessments for week 24
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

Abbreviation or Term	Definition/Explanation
EOS	End of study
FAS	Full analysis set
FRS	Framingham Risk Score
GSO-DM	Global Study Operations-Data Management
[redacted]	
HbA1c	Hemoglobin A1c
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonisation
[redacted]	
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.
LAS	Long-term analysis set
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
LFT	Liver function test
LH	Luteinizing hormone
Lp(a)	Lipoprotein(a)
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
[redacted]	
PI	Protease inhibitor
QM	Once monthly
SC	Subcutaneous
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
TBL	Total bilirubin
TC	Total Cholesterol
TEAE	Treatment Emergent Adverse Event
ULN	Upper limit of normal

Abbreviation or Term	Definition/Explanation
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 20130286 dated 30 January 2017. The scope of this plan includes the primary analysis and final analysis that are planned and will be executed by the Biostatistics department unless otherwise specified.

2. Objectives

2.1 Primary

To evaluate the effect of 24 weeks of subcutaneous (SC) evolocumab administered every month (QM) compared with placebo QM on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in human immunodeficiency virus (HIV)-positive subjects with hyperlipidemia or mixed dyslipidemia

2.2 Secondary

- To assess the effects of 24 weeks of SC evolocumab QM compared with placebo QM on change from baseline in LDL-C, and percent change from baseline in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol (TC), lipoprotein(a) [Lp(a)], triglycerides, HDL-C, and very low-density lipoprotein cholesterol (VLDL-C), in HIV-positive subjects with hyperlipidemia or mixed dyslipidemia
- To assess the effects of 24 weeks of SC evolocumab QM compared with placebo QM on percent of subjects attaining LDL-C < 70 mg/dL (1.8 mmol/L) in HIV-positive subjects with hyperlipidemia or mixed dyslipidemia
- To assess the effects of 24 weeks of SC evolocumab QM compared with placebo QM on percent of subjects attaining a 50% reduction in LDL-C from baseline in HIV-positive subjects with hyperlipidemia or mixed dyslipidemia

2.3 Safety

To evaluate the safety and tolerability of SC evolocumab QM compared with placebo QM in HIV-positive subjects with hyperlipidemia or mixed dyslipidemia

2.4 Exploratory

[redacted]

3. Study Overview

3.1 Study Design

This is a phase 3b, multicenter, double-blind, randomized, placebo-controlled study with an open-label extension period designed to assess the efficacy and safety of evolocumab in HIV-positive subjects with hyperlipidemia and/or mixed dyslipidemia. Treatment with baseline HIV and lipid-lowering (if applicable) medications being taken at randomization will continue throughout the clinical study. The study consists of 3 periods:

- Screening (to ensure tolerance of SC injections, includes a placebo injection)
- Double-blind treatment period
- Open-label extension period

Subjects will undergo screening procedures, including laboratory assessments and a screening placebo injection, before being randomized 2:1 into the following treatment groups for the double-blind treatment period:

- SC evolocumab 420 mg QM
- SC placebo QM

The overall sample size will be approximately 450 subjects, with approximately 300 subjects in the evolocumab group. Randomization will be stratified by entry statin treatment (yes/no) and hepatitis C status (yes/no). The size of the subgroup not on statin therapy is expected to be approximately 10% and no more than 20% of the subjects. This enrollment projection is expected to be reflective of clinical practice.

The double-blind treatment period will be 24 weeks, after which subjects who received a dose of investigational product (IP) at week 20 will continue in an open-label period during which all subjects will be treated with QM evolocumab. The open-label period will continue up through the end of study (EOS) visit at week 52.

SC evolocumab and placebo will be administered QM at the study site or appropriate non-investigator site settings (eg, at the subject's home) by automated mini-doser (AMD) or by spring-based prefilled autoinjector/pen (AI/Pen).

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 450 total subjects.

The primary analysis will require the 2-sided tests of the primary endpoint 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 primary endpoint. From the integrated efficacy analysis of completed phase 3 studies, the treatment effect of evolocumab 420 mg QM compared to placebo and the corresponding 95% confidence interval at the mean of weeks 10 and 12 was -64.98% [-69.51%, -60.45%], with treatment effect ranges between -55.1% and -62.33% from Studies 20110114, 20110115, and 20110117. The assumed treatment effect between the primary endpoint in evolocumab 420 mg QM is 40%, with a common standard deviation (SD) of 20%. This SD assumption is based on evolocumab phase 3 results.

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

In addition, 300 subjects in the evolocumab 420 mg QM group will provide approximately 95% probability of detecting adverse events that occur at a rate of 1%.

It is expected that the proportion of subjects assigned to the no statin use at baseline stratum will be approximately 10%. In this stratum, 30 subjects in the evolocumab 420 mg QM group will provide approximately 79% probability of detecting adverse events that occur at a rate of 5%.

4. Study Endpoints and Covariates

4.1 Study Endpoints

4.1.1 Primary efficacy endpoint

Percent change from baseline in LDL-C at week 24

4.1.2 Secondary efficacy endpoints

For week 24 the following secondary endpoints will be characterized:

- Tier 1
    - Change from baseline in LDL-C
    - Percent change from baseline in non-HDL-C
    - Percent change from baseline in ApoB
    - Percent change from baseline in TC

- Achievement of target LDL-C <70 mg/dL (1.8 mmol/L)
- LDL-C response (50% reduction of LDL-C from baseline)

- Tier 2
  - Percent change from baseline in Lp(a)
  - Percent change from baseline in triglycerides
  - Percent change from baseline in HDL-C
  - Percent change from baseline in VLDL-C

4.1.3 Safety endpoints

- Subject incidence of treatment emergent adverse events
- Safety laboratory values and vital signs at each scheduled assessment
- Incidence of anti-evolocumab antibody (binding and neutralizing) formation

4.1.4 Exploratory endpoints

4.2 Planned Covariates

Baseline covariates include:

- Stratification factors in Double-blind Treatment Period:
  - Statin use at baseline (yes/no)
  - Hepatitis C status (yes/no)
- Age
- Sex
- Race (black, white, and other)
- LDL-C
- Family history of premature coronary heart disease (yes/no)
- [redacted]
- Region (North America, Europe, other)
- Body Mass Index (BMI)
- Glucose tolerance status (type 2 diabetes mellitus, metabolic syndrome, neither type 2 diabetes mellitus nor metabolic syndrome)
- Hypertension (yes, no)
- Current smoker (yes, no)
- Baseline CHD risk factors ≥ 2 (yes, no)
- Triglycerides
- NCEP high risk (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)
- Protease inhibitor use

5. Hypotheses and/or Estimations

The null hypothesis is that there is no mean difference in the mean percent change from baseline at week 24 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 is 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 (SC evolocumab 420 mg QM or SC placebo QM). If a subject enrolled but never received IP, Study Day 1 is defined as the enrollment day.

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.

First Dose Date of SC IP (TR01SDTM)

For each subject, the first dose date of SC IP is defined as the first date of investigational product administration, equivalent to study day 1.

First Dose Date of SC IP in the Open-label period (TR02SDTM)

For each subject, the first dose date of SC IP in the open-label period is defined as the first date of open-label investigational product administration.

Last dose date of Double-blind Investigational Product

For each subject, the last dose date of double-blind investigational product is defined as the date of the last administration of double-blind investigational product.

End of Investigational Product (EOIP) Date

For each subject, the end of investigational product date is defined as the date of decision to end 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.

6.2 Demographics and Baseline Related Definitions

Age

Subject age at enrollment will be collected in years in the clinical database.

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

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 Metabolic Syndrome

For each subject without type 2 diabetes mellitus, metabolic syndrome is identified by the presence of 3 or more of the components listed below (modified AHA/NHLBI criteria). Subjects with type 2 diabetes cannot be categorized as having metabolic syndrome.

Risk Factor	Defining Level

Elevated waist circumference:
Non-Asian:
  Men
  Women
Asian:
  Men
  Women
	
	≥ 102 cm
	≥ 88 cm
	
	≥ 90 cm
	≥ 80 cm

Triglycerides	≥ 150 mg/dL

HDL cholesterol
  Men
  Women
	
	< 40 mg/dL
	< 50 mg/dL

Blood Pressure	SBP ≥ 130 mmHg or DBP ≥ 85 mmHg OR Hypertension checked ‘yes’ on Cardiovascular Medical History eCRF
Fasting glucose	≥ 100 mg/dL

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 Cardiac Risk Factors eCRF
- low HDL-C defined as baseline HDL-C < 40 mg/dL in men and < 50 mg/dL in women.

Baseline National Cholesterol Education Program (NCEP) Risk Categories

Risk Factor	Defining Level
High Risk: CHD or CHD Risk Equivalent	Coronary Artery Disease OR Cerebrovascular or Peripheral Vascular Disease OR Type 2 Diabetes Mellitus OR 2 or more Risk Factors (see below) AND FRS > 20% (see Appendix C for FRS calculation)
Moderately High Risk	NOT High Risk AND 2 or more Risk Factors AND FRS ≥ 10% AND ≤ 20%
Moderate Risk	NOT High Risk AND 2 or more Risk Factors AND FRS < 10%
Lower Risk	NOT High Risk AND 0 to 1 Risk Factor

Risk Factors for NCEP Risk Categories:

Risk factors are: current cigarette smoking, hypertension or (baseline SBP ≥ 140 or DBP ≥ 90 mmHg), family history of premature CHD as recorded in the Cardiac Risk Factors eCRF form, low HDL-C cholesterol defined as baseline HDL-C < 40 mg/dL, age ≥ 45 years in men or ≥ 55 years 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 double-blind period that is different from the randomized treatment group assignment, in which case the actual treatment group is the treatment received.

Investigational Product (IP)

Double-blind period IP: evolocumab SC 420 mg QM and corresponding SC placebo.
Open-label period IP: evolocumab SC 420 mg QM

Double-blind IP Exposure Period in Months

For each subject:

Double-blind IP Exposure Period = [min (TR01EDT

-1, EOIP + 28 days, EOS Date) - Study day 1 + 1]/ 365.25 * 12

Open-label IP Exposure Period in Months

For each subject receiving at least one dose of open-label IP:

Open-label IP Exposure Period = [min (EOIP + 28 days, EOS Date) - TR02SDT + 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 before the first dose on the Events eCRF and up to and including EOS. Double-blind TEAEs are those that start before the earlier of last dose date of double blind

IP + 28 days and first dose date of open-label IP. Open-label TEAEs are those that start on or after the date of first dose of open-label IP and start before the earlier of last dose date of open-label IP + 28 days and EOS.

Serious Adverse Event (SAE)

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

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 week 24 LDL-C value is less than 70 mg/dL. If the value is missing, the subject is considered without the achievement.

LDL-C response (50% reduction from baseline)

A subject has a response of 50% reduction from baseline in LDL-C if the week 24 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.

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 an observed value for the primary endpoint. Subjects who did not adhere are identified as those who have an EOIP reason other than completed and EOIP date not after first dose of open-label IP.

7.3 Long-term Analysis Set

The long-term analysis set (LAS) will include all subjects who received at least 1 dose of open-label IP in the open-label period. This analysis set will be used in all analyses for the open-label period.

7.4 Subgroup Analyses

Subgroup by stratification factor

- Statin use at baseline (yes/no)
- Hepatitis C Status (yes/no)

Subgroup by baseline characteristics

- Age: < 65 years, ≥ 65 years
- Sex
- Race (black, white, and other)
- LDL-C: (< baseline median, ≥ baseline median)
- Family history of premature CHD (yes, no)
- [redacted]
- Region (North America, Europe, other)
- BMI (<25, 25-30, ≥30)
- Hypertension (yes, no)
- Current smoker (yes, no)
- Baseline CHD risk factors ≥ 2 (yes, no)
- Triglicerides (< baseline median, ≥ baseline median)
- NCEP high risk (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)
- Glucose tolerance status (type 2 diabetes mellitus, metabolic syndrome, neither type 2 diabetes mellitus nor metabolic syndrome)
- Protease inhibitor use

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 issue identification and resolution (DIIR) process, queries will be made to the sites to distinguish true missing values from other unknown values (eg, 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 uses a repeated measures linear effects model, missing lipid measurements will not be imputed. The handling of missing LDL-C response (50% reduction of week 24 LDL-C from baseline) and achievement of target week 24 LDL-C < 70 mg/dL is provided in Section 6.3. Sensitivity analysis will be performed on the primary endpoint 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 and concomitant medication ([eg, lipid regulatory medication] collected start date data) 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 1 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. 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 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 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 24 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. Data will be locked at each clean snapshot (the primary analysis and final analysis).

Based on the locked snapshot for the primary analysis, efficacy and safety analyses will be performed on FAS unless otherwise specified, and data will be summarized by randomized treatment group. Data occuring after the first dose of open-label evolocumab will be excluded from the primary analysis dataset.

The final analysis will be performed when all subjects have completed all scheduled study visits in the open-label period or have early terminated from the study. Based on the final locked snapshot for the final analysis, long-term efficacy and safety analyses will be performed on LAS and the analyses will be descriptive. Safety endpoints and exploratory endpoints will be evaluated for the open-label period and summarized overall and by treatment in the double-blind period.

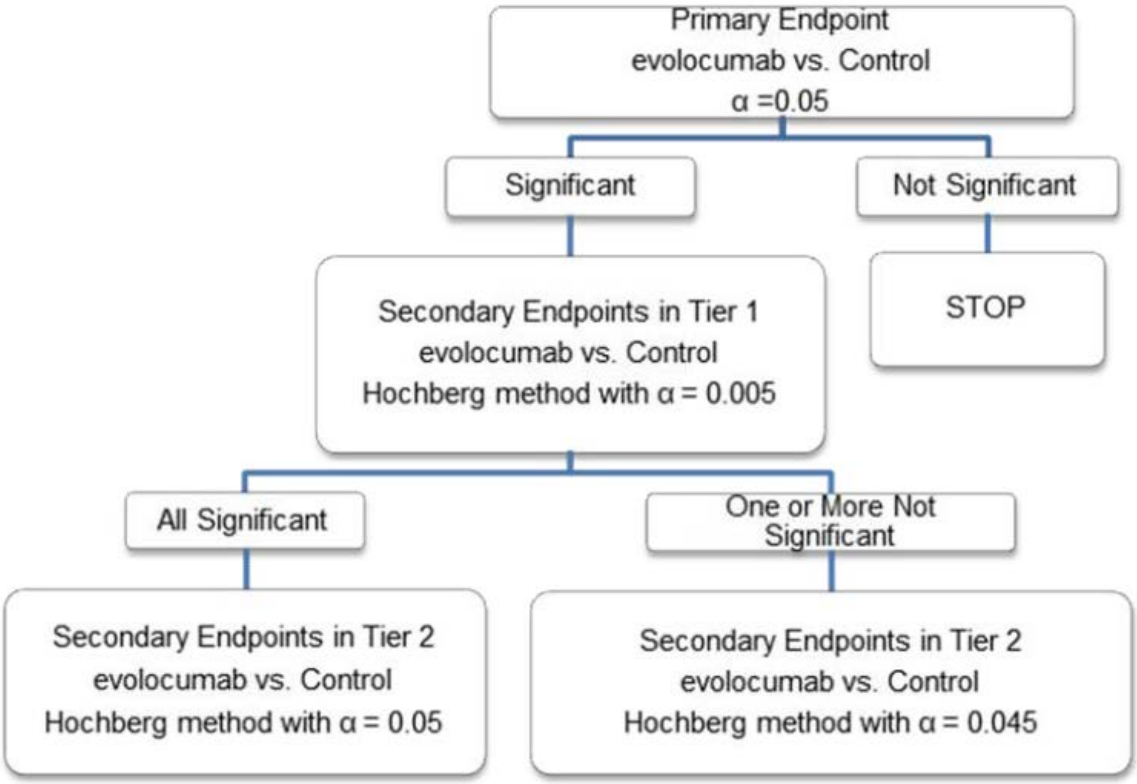
Subject disposition, demographics, baseline characteristics, and exposure to IP will be summarized by treatment group. Summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation or standard error, minimum, and maximum. For categorical variables,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

Methods of handling missing data for efficacy endpoints are 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



The following method will be used to preserve the family-wise error rate for the primary and secondary endpoints:

1. If the treatment effect from the primary analysis of the primary endpoint is significant at a significance level of 0.05, statistical testing of the tier 1 secondary efficacy endpoints will follow the Hochberg procedure at a significance level of 0.005 (Hochberg, 1988)
2. If all tier 1 secondary efficacy endpoints are significant, the tier 2 secondary efficacy endpoints will be tested using the Hochberg procedure at a significance level of 0.05.
3. If not all tier 1 secondary efficacy endpoints are significant, the tier 2 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 treatment period, discontinued study and reasons for discontinuing will be summarized by treatment group.

Key study dates for the first subject enrolled, last subject enrolled and last subject's end of double-blind IP, last subject's end of open-label 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, age group [< 65, >= 65], sex, race, ethnicity) and baseline disease characteristics (cardiovascular medical history, HIV medical history, laboratory parameters, antiretroviral therapy 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 for the primary analysis

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
Primary Endpoint				
• Percent change from baseline at week 24 in LDL-C	Repeated measures model	P1	P1 compare to α = 0.05	• Non-parametric analyses will be performed • Multiple imputation for subjects who discontinue evolocumab and are missing primary endpoint data.
Secondary Endpoints (Tier 1)				
• LDL-C achievement at week 24 • LDL-C response at week 24	Cochran Mantel-Haenszel (CMH) test	P2a	If P1 < 0.05, ➔ P2a for each tier 1 endpoint will be tested through Hochberg method with α = 0.005	

• Change from baseline at week 24 in LDL-C
• Percent change from baseline at week 24 in:
  • non-HDL-C
  • ApoB
  • total cholesterol
	Repeated measures model	P2a	Else (ie, primary endpoint is not significant)
			➔ No further testing	

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Footnotes are defined on next page of the table

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
Secondary Endpoints (Tier 2)				

• Percent change from baseline at week 24 in:
  • Lp(a)
  • Triglycerides
  • HDL-C
  • VLDL-C
	Repeated measures model	P2b	If all P2a values are significant through Hochberg method,
			➔ all P2b values will be tested through Hochberg method with α = 0.05
			
			Else (ie, not all tier 1 endpoints are significant),
			➔ all P2b values will be tested through Hochberg method with α = 0.045	

Supportive analysis: the primary analysis will be repeated using the CAS.

10.5.1 Analyses of Primary Efficacy Endpoint

10.5.1.1 Primary Analysis of Primary Endpoint

To assess the primary endpoint of the percent change from baseline in LDL-C at week 24, a repeated measures linear effects model will be used on the FAS to compare the efficacy of evolocumab with placebo. The repeated measures model will include terms for treatment group, stratification factors, scheduled visit and the interaction of treatment with scheduled visit. All LDL-C values observed will be used irrespective of whether a subject remained on IP, and missing values will not be imputed for primary analysis. If there are fewer than 5 subjects in one stratum, then the Hepatitis C status stratification factor will not be included in the repeated measures model. 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 Primary Endpoint

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

- 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.
  - If there are at least 25 subjects who discontinue evolocumab but have non-missing week 24 endpoint data, an additional multiple imputation will be carried out utilizing the information from these subjects (mean and variance) to impute the missing data for subjects who discontinue evolocumab and have missing endpoint data

10.5.1.3 Covariate and Subgroup Analyses of Primary Endpoints

As a supportive analysis, the primary analysis will be repeated using the CAS to estimate the on-treatment treatment effect.

In addition to the primary analysis specified in Section 10.5.1.1, covariate-adjusted analyses of the primary efficacy endpoint 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 primary efficacy endpoint 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 factors 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 Secondary Efficacy Endpoints

The statistical model and testing of the secondary efficacy endpoints (change from baseline and percent change from baseline) will be similar to the primary analysis of the primary endpoint. The secondary endpoints of achievement of target LDL-C < 70 mg/dL at week 24 and LDL-C response of 50% reduction of week 24 LDL-C from baseline will be analyzed using the Cochran-Mantel Haenszel test adjusted by the stratification factors.

Multiplicity adjustment procedures are defined in Section 10.1.

10.5.3 Analyses of Exploratory Endpoints

[redacted]

10.6 Safety Analyses

10.6.1 Adverse 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) to a system organ class and a preferred term. Severity of TEAEs will be graded using the CTCAE (Appendix B) and recorded on the Events eCRF. All adverse event tables will be summarized by actual treatment group. Double-blind period TEAEs will be summarized in the primary analysis; open-label period TEAEs will be summarized in the final analysis.

Subject incidence of all TEAEs, serious TEAEs, TEAEs leading to withdrawal of investigational product, and fatal TEAEs will be tabulated by system organ class, high level group term and preferred term in descending order of frequency. Additionally, the

subject incidence of all treatment-emergent adverse events will be tabulated by system organ class, high level group term and preferred term in descending order of frequency for each baseline statin use stratum.

Summaries of treatment-emergent, serious TEAEs and target IP TEAEs 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 treatment-emergent adverse events related to a device will be tabulated by preferred term in descending order of frequency by treatment group.

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

10.6.4 Antibody Formation

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

10.6.5 Exposure to Investigational Product

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

Exposure definitions are provided in Section 6.3.

10.6.6 Exposure to Other Protocol-specified Treatment

The number and proportion of subjects receiving selected lipid-lowering medications captured on Other Protocol Required Therapy (Lipid Lowering Therapy) eCRF will be summarized by category and preferred term for each treatment group as coded by the World Health Organization Drug (WHODRUG) dictionary. Summaries will be provided for baseline use and use during each study period. The use of antiretroviral therapies captured on the Other Protocol Required Therapy (Antiretroviral Therapy) eCRF will be summarized similarly. In addition, the reasons for a change in Antiretroviral Therapy will be summarized.

11. Changes From Protocol-specified Analyses

[redacted]

12. Literature Citations / References

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.

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.

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:

	Double-Blind Period			Open-Label Period	
Analytical Study Week	Week 12	Week 20	Week 24	Week 36	Week 52
Scheduled Visit Day	85	141	169	253	365
Vital Signs	(1, 112]	(112, 154]	(154, 210]	(210, 308]	(308, 378]
Body Weight, Waist circumference			(1, 210]		(210, 378]
Fasting Lipids, ApoA1, ApoB, Lp(a), [redacted] HIV viral load, CD4, Hepatitis C viral load, chemistry, [redacted], urinalysis, hematology, HbA1c	(1, 126]		(126, 210]	(210, 308]	(308, 371]

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 AEs (CTCAE) for AEs and lab shift grading and information. The CTCAE is available at the following link:

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

Appendix C. Framingham Risk Score (FRS)

Method to calculate the Framingham Risk Score (FRS):

The β coefficients given in the two tables below are used to compute a linear function. The latter is corrected for the averages of the participants' risk factors (mean) from the Framingham study, and the subsequent result is exponentiated and used to calculate a 10-year probability of HCHD after insertion into a survival function (Wilson et al).

The calculation is different for men and women and use the following coefficients β_i, where *i* represents each of the independent variables. The values below are from the Framingham heart study (http://www.framinghamheartstudy.org/risk/hrdcoronary.html).

t_chol = total cholesterol, hdl = HDL-C, sbp = systolic blood pressure, trt_htn = treatment for hypertension (if sbp > 120), smoker = current smoker

Men		
Independent variable	Coefficient βi	mean
ln(age)	52.00961	3.8926095
ln(t_chol)	20.014077	5.3441475
ln(hdl)	-0.905964	3.7731132
ln(sbp)	1.305784	4.8618212
trt_htn (spb>120)	0.241549	0.1180474
smoker	12.096316	0.335602
ln(age)* ln(t_chol)	-4.605038	20.811156 2
ln(age)*smoker[1]	-2.84367	1.2890301
ln(age)*ln(age)	-2.93323	15.214496 5
[1] if age>70 then ln(70)*smoker		

Women		
Independent variable	Coefficient βi	mean
ln(age)	31.764001	3.9213204
ln(t_chol)	22.465206	5.3628984
ln(hdl)	-1.187731	4.0146369
ln(sbp)	2.552905	4.8376494
trt_htn (spb>120)	0.420251	0.142802
smoker	13.07543	0.3236202
ln(age)* ln(t_chol)	-5.060998	21.0557746
ln(age)*smoker[2]	-2.996945	1.2519882
[2] if age>78 then ln(78)*smoker		

The steps to determine the FRS is the same for men and women.

Men

For each subject:

1. Calculate $L_{men} = \beta_{ln(age)}$*ln(age) + $\beta_{ln(t\_chol)}$*ln(t_chol) + $\beta_{ln(hdl)}$ *ln(hdl) + $\beta_{ln(sbp)}$*ln(sbp) + β_{trt_htn}*(if trt_htn) + β_{smoker}*(if smoker) + $\beta_{ln(age)*ln(t\_chol)}$*ln(age)*ln(t_chol) + $\beta_{ln(age)*smoker}$*ln(age)*(if smoker) + $\beta_{ln(age)*ln(age)}$*ln(age)*ln(age)
2. Calculate Amen = Lmen - 172.300168 (note: the value of 172.300168 was derived based on the mean columns in above table)
3. Calculate $B_{men} = \exp(A_{men})$

4. Calculate $P_{men} = 1 - 0.9402^{B_{men}}$
5. $FRS_{men} = P_{men}*100$ (rounded to nearest integer)

Women

For each subject:

1. Calculate $L_{women} = \beta_{ln(age)}*ln(age) + \beta_{ln(t\_chol)}*ln(t\_chol) + \beta_{ln(hdl)}*ln(hdl) + \beta_{ln(sbp)}*ln(sbp) + \beta_{trt\_htn}*(\text{if trt\_htn}) + \beta_{smoker}*(\text{if smoker}) + \beta_{ln(age)*ln(t\_chol)}*ln(age)*ln(t\_chol) + \beta_{ln(age)*smoker}*ln(age)*(\text{if smoker})$
2. Calculate $A_{women} = L_{women} - 146.5933061$ (note: the value of 146.5933061 was derived based on the mean columns in above table)
3. Calculate $B_{women} = \exp(A_{women})$
4. Calculate $P_{women} = 1 - 0.98767^{B_{women}}$
5. $FRS_{women} = P_{women}*100$ (rounded to nearest integer)

Notes

- For men, if subject is > age 70, then use ln(70)*smoker
- For women, if subject is > age 78, then use ln(78)*smoker
- For dichotomous variables trt_htn and smoker use 1/0 to represent yes/no respectively
    - If a subject has sbp ≤ 120 mmHg, then trt_htn is no

Calculated scores should match the interactive calculator

http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof