STATISTICAL ANALYSIS PLAN

A Multicenter, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of Evolocumab

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Table of Abbreviations

Abbreviation or Term	Definition/Explanation
AE	Adverse event
AHA	American Heart Association
ALT (SGPT)	Alanine aminotransferase (serum glutamic-pyruvic transaminase)
AST (SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
BP	Blood pressure
CK	Creatine kinase
CHD	Coronary heart disease, includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia
CTCAE	NCI Common Terminology Criteria for AEs
CV	Cardiovascular
DBP	Diastolic blood pressure
eCRF	Electronic case report form
EOI	Event of Interest
EOIP	End of Investigational Product
EOS	End of Study (for individual subject)
FAS	Full analysis set
FRS	Framingham Risk Score
HDL-C	High density lipoprotein cholesterol
IAS	Interim analysis set
IP	Investigational product
IPD	Important protocol deviation
LDL-C	Low-density lipoprotein cholesterol
MedDRA	Medical dictionary for regulatory activities
NCEP ATP III TLC	National Cholesterol Education Program Adult Treatment Panel III Therapeutic Lifestyle Changes
NHLBI	National Heart, Lung, and Blood Institute
OLE	Open label extention
QM	Monthly (Every 4 weeks)
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure

Abbreviation or Term	Definition/Explanation
SC	Subcutaneous
Study day 1	defined as the first day that protocol-specified investigational product is administered to the subject
TEAE	Treatment emergent adverse event
TIA	Transient ischemic attack
ULN	Upper limit of normal
UC	Ultracentrifugation
VLDL-C	Very low-density lipoprotein cholesterol

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 20140128 dated 22 December 2014 (Amendment 1). The scope of this plan includes the interim analysis and the final analysis that are planned and will be executed by the Biostatistics department unless otherwise specified.

2. Objectives

2.1 Primary

To characterize the safety and tolerability of long-term administration of evolocumab in subjects with known coronary artery disease and hypercholesterolemia.

2.2 Secondary

To characterize the efficacy of long-term administration of evolocumab as assessed by LDL-C in subjects with known coronary artery disease and hypercholesterolemia.

2.3 Exploratory

To evaluate cardiovascular event rates in subjects treated with evolocumab.

3. Study Overview

3.1 Study Design

This is a multicenter, open-label extension study to assess the long-term safety and efficacy of evolocumab. The study endpoints are defined in Section 4.1. Approximately 230 sites in the US, Canada, Latin America, Asia, Australia, South Africa, and Europe will participate in the study. The number of sites may vary depending on the number of subjects from the parent study (20120153). Subjects that successfully complete Week 80 in the parent study (20120153) without discontinuing evolocumab will be eligible to enroll in this study. Subjects will visit the site on Day 1 and week 4. Thereafter, subjects will visit the site quarterly for the first year and two additional times during year 2. All subjects will receive open-label evolocumab for approximately 2 years (or until the investigator's recommendation of discontinuation, Amgen's recommendation of discontinuation, the subject's decision to discontinue for any reason or until an administrative decision is made to end the study).

3.2 Sample Size

The number of subjects entering this study will depend on the number of subjects completing the study 20120153 and their willingness to enroll. Past enrollment rates for other AMG 145 OLE studies were approximately 90%. Assuming 75% of

study 20110153 subjects are completers and eligible to enroll in this study, the sample size will be approximately 950 x 0.75 x 0.9 = 642 subjects.

4. Study Endpoints and Covariates

4.1 Study Endpoints

4.1.1 Primary Endpoint

Subject incidence of adverse events

4.1.2 Secondary Endpoint

LDL-C at Week 52

4.1.3 Safety Endpoints

Changes from baseline in safety laboratory values (including clinical chemistry) and vital signs at each scheduled visit

4.1.4 Exploratory Endpoints

- Subject incidence of adjudicated events
  - death by any cause
  - cardiovascular death
  - myocardial infarction
  - hospitalization for unstable angina
  - coronary revascularization
  - stroke
  - transient ischemic attack (TIA)
  - hospitalization for heart failure
- Subject incidence of non-coronary revascularization
- Change and percent change from baseline at each scheduled visit in each of the following parameters:
  - LDL-C
  - Total cholesterol
  - Non-HDL-C
  - Total cholesterol/HDL-C ratio
  - VLDL-C
  - HDL-C
  - Triglycerides

5. Hypothesis

The primary clinical hypothesis is that long-term exposure of evolocumab will be safe and well tolerated in subjects with known coronary artery disease and

hypercholesterolemia. There will be no formal statistical testing and all statistics will be descriptive in nature.

6. Definitions

6.1 Study Time Points

Enrollment Date

The enrollment date is the day a subject signed the informed consent form for this study.

Study Day 1 (First IP Dose Date)

Study Day 1 is defined as the first day of Investigational Product (IP) administration in this study.

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 IP Dose Date

For each subject, the Last IP Dose Date is defined as the last day of IP administration in this study:

- If the last dose was administered in-clinic, then Last IP Dose Date is the last start date captured on the IP Administration QM (In-Clinic) eCRF page.
- If the last dose was administered at home, then Last IP Dose Date is defined as the final dose date reported by the subject on the Non-Clinic Final Investigational Product Dose Date eCRF page.

End of Investigational Product (EOIP) Date

The End of Investigational Product Date is the date decision was made to end IP as recorded on the End of IP Administration 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 enrolled subjects.

6.2 Demographics and Baseline Related Definitions

Age

Age at baseline is the subject's age at the parent study baseline. Age at enrollment is the subject's age in years as recorded on the enrollment eCRF of this study.

Baseline Values

Baseline values for fasting lipids (total cholesterol, HDL-C, LDL-C, triglycerides, VLDL-C and non-HDL-C) and all other variables are defined as the parent study baseline values.

Change (nominal/absolute change) from Baseline

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

Change (nominal/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]

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

Investigational Product (IP)

IP is AMG 145 SC 420 mg QM

IP Exposure Period in Months

IP Exposure Period = [min (Last IP Dose Date + 28 days, EOS Date) - First IP Dose Date +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)

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

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 and VLDL-C value from the same blood sample will be used instead of calculated LDL-C and VLDL-C, if available.

7. Analysis Subsets

7.1 Full Analysis Set

The Full Analysis Set (FAS) includes all subjects enrolled in this study. This analysis set will be used for all final analyses.

7.2 Interim Analyses Set

The Interim Analysis Set (IAS) includes all subjects from the FAS that complete the Week 52 visit at the time of interim analysis, or discontinued study prior to Week 52.

7.3 Subgroup Analyses

Subgroup analysis of the primary endpoint will be conducted for the subgroup corresponding to each level of the following baseline variables:

- Age (< 65, ≥ 65)
- Sex
- Race (white, non-white)
- LDL-C (< median, ≥ median)
- ACC/AHA statin background therapy high intensity (yes, no)

8. Interim Analysis and Early Stopping Guidelines

There will be a 1-year interim analysis to summarize the data collected up to week 52 of all IAS subjects. There are no plans to modify or discontinue this study based on the results of the interim analysis. If required to satisfy evolocumab development program

needs, additional analyses may be performed periodically throughout the study after the parent study is closed and individual subjects are unblinded to their lipid values as required by overall evolocumab development program.

The 1-year interim analysis will summarize:

- Study and IP disposition up to week 52
- Demographics
- By-visit summary of LDL-C up to week 52
- Overall summary of treatment emergent AE/SAEs and summary by system organ class, high level term and preferred term in descending order of frequency up to week 52
- Summary of positively adjudicated clinical events up to week 52

Week 52 cutoff for disposition and adverse/clinical events is defined as the Week 52 LDL-C lab date. If Week 52 LDL-C value is missing, then use the Week 52 target day 365 as the cutoff.

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

9.3.2 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

A factor that may bias the results of the study is major protocol deviations likely to impact the analysis and interpretation of the endpoints. Important protocol deviations likely to impact the analysis and interpretation of the endpoints will be tabulated in the Clinical Study Report (CSR).

If any sensitivity analyses are required to evaluate potential biases in the study's conclusions, 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 review of the data prior to database snapshot. Such data points will be reviewed with clinical data management to ensure accuracy. Unless specified otherwise, all analyses will include outliers in the data. Sensitivity analyses may be undertaken if extreme outliers for a variable are observed.

9.6 Distributional Characteristics

There are no distributional requirements for the planned analyses.

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 9.4 or later.

10. Statistical Methods of Analysis

10.1 General Principles

Statistical analyses in this open-label extension study will be descriptive in nature. No statistical inference is planned. There will be no imputation for missing data.

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

Summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation or standard error, minimum, and maximum. For categorical variables, the frequency and percentage will be given.

One-year interim and final analyses will be based on data collected from this study. Descriptions of any integrated analyses with the parent study are out of scope for this SAP.

For all endpoints, results will be summarized by the treatment group to which subjects are randomized in Study 20120153, unless otherwise specified.

10.2 Subject Accountability

The number of subjects enrolled will be summarized by the randomized treatment groups in Study 20120153. Study, IP and background therapy discontinuation will be tabulated separately by reasons for discontinuation.

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 the randomized treatment groups in Study 20120153. Baseline tables will summarize the following: demographics, cardiovascular medical history, laboratory parameters and background therapy.

10.5 Efficacy Analyses

Lipid parameters and their change and percent change from baseline will be summarized by scheduled visits, including LDL-C at Week 52. Descriptive statistics will be provided.

10.6 Safety Analyses

10.6.1 Analyses of Primary Endpoints

Adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). 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 in Study 20120153.

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

Subject incidence of device-related TEAEs will be tabulated by high level group term (including “administrative site reactions” and “device issues”) and preferred term in descending order of frequency.

Summaries of all TEAEs and serious TEAEs occurring in at least 1% of the subjects by preferred term in any treatment group will be provided in descending order of frequency.

Subject incidence of treatment emergent events of interest (EOIs) will be summarized according to the EOI search strategy categories defined by the EOI steering committee. The definition of each EOI may be modified and new EOI may be added based on findings from ongoing pharmacovigilance. Updates of the search strategy due to MedDRA upgrades or other reasons may not trigger a SAP amendment. However, the most recent EOIs per Amgen EOI search strategy will be used at the time of the analysis and these search terms will be included in an appendix of the study report. As of the date of preparing this version, the current EOI are:

- potential hypersensitivity events (based on narrow and broad search strategies)
- potential injection site reaction events (based on narrow and broad search strategies)
- potential muscle events (based on narrow and broad search strategies)
- potential neurocognitive events (based on high level group terms)
- potential hepatitis C infection (based on narrow and broad search strategies)
- transaminase elevations and potential hepatic disorders (based on narrow and broad search strategies)

Overall AE summary will be also be provided in subgroups specified in Section 7.3.

10.6.2 Analyses of Exploratory Endpoints

Death, myocardial infarction, hospitalization for unstable angina, coronary revascularization, stroke, TIA, and hospitalization for heart failure will be adjudicated by an independent CEC. Non-coronary revascularizations will be collected on the eCRF and will not be adjudicated. Subject incidence of clinical events will be summarized by actual treatment group in Study 20120153.

10.6.3 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 1. Lab shift tables using the CTCAE v4.03 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

10.6.4 Vital Signs

Vital signs will be summarized using descriptive statistics at each scheduled visit.

10.6.5 Exposure to Investigational Product

Descriptive statistics will be produced to describe the patient-month exposure to investigational product, the categorical representation of dose received, and the total quantity of oral IP used by randomized treatment group in Study 153.

Exposure definitions are provided in section 6.3.

10.6.6 Exposure to Concomitant Medication

The number and proportion of subjects receiving the medications of interest (MOI) will be summarized by preferred term for each randomized treatment group in Study 20120153 as coded by the World Health Organization Drug (WHODRUG) dictionary.

11. 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, with scheduled visit time being the center of each interval. The mapping intervals for all distinct schedules are summarized in the following tables.

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 study day of that specific study week (7×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.

Scheduled Visit Week	Target Study Day	Vital Signs, Lipids, Chemistry	Physical Measurements
Week 0	1	≤ 1	≤ 1
Week 4	29	(1, 56]	NA
Week 12	85	(56, 126]	NA
Week 24	169	(126, 210]	NA
Week 36	253	(210, 294]	NA
Week 48	337	(294, 350]	NA
Week 52	365	(350, 448]	(1, 546]
Week 76	533	(448, 630]	NA
Week 104	729	> 630	> 546

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-functions/coronary-heart-disease/har-10-year-risk.php).

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	20.8111562
ln(age)*smoker[1]	-2.84367	1.2890301
ln(age)*ln(age)	-2.93323	15.2144965

[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 $L_{men} = \beta_{ln(age)}*ln(age) + \beta_{ln(t_chol)}*ln(t_chol) + \beta_{ln(hdl)}*ln(hdl) + \beta_{ln(sbp)}*ln(sbp) + \beta_{trt_htn}*(\text{if trt_htn}) + \beta_{smoker}*(\text{if smoker}) + \beta_{ln(age)*ln(t_chol)}*ln(age)*ln(t_chol) + \beta_{ln(age)*smoker}*ln(age)*(\text{if smoker}) + \beta_{ln(age)*ln(age)}*ln(age)*ln(age)$
2. Calculate $A_{men} = L_{men} - 172.300168$ (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 $P_{men} = 1 - 0.9402\text{^}B_{men}$
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 $P_{women} = 1 - 0.98767\text{^}B_{women}$
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

Appendix D. Lipid Modifying Background Therapy Intensity

Based on ACC/AHA guidelines:

	HIGH-INTENSITY STATIN THERAPY	MODERATE-INTENSITY STATIN THERAPY	LOW-INTENSITY STATIN THERAPY	Notes (classification of atypical doses)
Atorvastatin	40 mg or greater QD	10 mg QD up to less than 40 mg QD	Less than 10 mg QD	Atorvastatin 30 mg QD is Moderate intensity.
Rosuvastatin	20 mg or greater QD	5 – < 20 mg QD	less than 5 mg QD	Rosuvastatin < 5 mg QD is low intensity , Rosuvastatin 15 mg QD = moderate
Simvastatin	80 mg or greater QD	20-80 mg QD	< 20 mg QD	And Simvastatin > 40 and < 80 mg QD is moderate, Simvastatin 80 mg or greater QD = high, Simvastatin < 20 mg QD is low-intensity
Pravastatin		40 mg or greater QD	less than 40 mg QD	Pravastatin < 10 mg QD is low intensity
Lovastatin		40 mg or greater QD	less than 40 mg QD	Lovastatin 80 mg QD = moderate, Lovastatin 10 mg QD = Low-intensity
Fluvastatin		80 mg QD	less than 80 mg QD	Fluvastatin 10 mg QD = Low-intensity
Pitavastatin		≥ 2 mg QD	< 2 mg QD	

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