Supplementary Online Content 2


Statistical Analysis Plan
STATISTICAL ANALYSIS PLAN

A Double-Blind, Randomized, Multi-Center, Placebo-Controlled, Parallel-Group Study to Determine the Effects of Evolocumab (AMG 145) Treatment on Atherosclerotic Disease Burden As Measured By Intravascular Ultrasound in Subjects Undergoing Coronary Catheterization

Protocol Number: 20120153
Version: 2.0
Date: 21 July 2016
Authors: Jingyuan Yang
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<th>Definition/Explanation</th>
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</thead>
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<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
</tr>
<tr>
<td>ALT (SGPT)</td>
<td>Alanine aminotransferase (serum glutamic-pyruvic transaminase)</td>
</tr>
<tr>
<td>ApoA1</td>
<td>Apolipoprotein A-1</td>
</tr>
<tr>
<td>ApoB</td>
<td>Apolipoprotein B</td>
</tr>
<tr>
<td>AST (SGOT)</td>
<td>Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CAS</td>
<td>Complete analysis set</td>
</tr>
<tr>
<td>CK</td>
<td>Creatine kinase</td>
</tr>
<tr>
<td>CHD</td>
<td>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</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximal concentration</td>
</tr>
<tr>
<td>C&lt;sub&gt;min&lt;/sub&gt;</td>
<td>Minimum concentration</td>
</tr>
<tr>
<td>CMH</td>
<td>Cochran-Mantel Haenszel</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CTCAE</td>
<td>NCI Common Terminology Criteria for AEs</td>
</tr>
<tr>
<td>CV</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td>DMC</td>
<td>Data monitoring committee</td>
</tr>
<tr>
<td>DQR</td>
<td>Data Quality Review</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic case report form</td>
</tr>
<tr>
<td>EEM&lt;sub&gt;CSA&lt;/sub&gt;</td>
<td>External elastic membrane cross-sectional area</td>
</tr>
<tr>
<td>EOI</td>
<td>Event of Interest</td>
</tr>
<tr>
<td>EOIP</td>
<td>End of Investigational Product</td>
</tr>
<tr>
<td>EOS</td>
<td>End of Study (for individual subject)</td>
</tr>
<tr>
<td>FAS</td>
<td>Full analysis set</td>
</tr>
<tr>
<td>FRS</td>
<td>Framingham Risk Score</td>
</tr>
<tr>
<td>HDL-C</td>
<td>High density lipoprotein cholesterol</td>
</tr>
<tr>
<td>hsCRP</td>
<td>High sensitivity CRP</td>
</tr>
<tr>
<td>IAS</td>
<td>IVUS analysis set</td>
</tr>
<tr>
<td>Abbreviation or Term</td>
<td>Definition/Explanation</td>
</tr>
<tr>
<td>----------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>IBG</td>
<td>Independent Biostatistical Group</td>
</tr>
<tr>
<td>IEC/IRB</td>
<td>Independent Ethics Committee / Institutional Review Board</td>
</tr>
<tr>
<td>IP</td>
<td>Investigational product</td>
</tr>
<tr>
<td>IPD</td>
<td>Important protocol deviation</td>
</tr>
<tr>
<td>IVRS</td>
<td>Interactive Voice Response System</td>
</tr>
<tr>
<td>LDL-C</td>
<td>Low-density lipoprotein cholesterol</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>Lipoprotein(a)</td>
</tr>
<tr>
<td>LUMEN&lt;sub&gt;CSA&lt;/sub&gt;</td>
<td>Luminal cross-sectional area</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical dictionary for regulatory activities</td>
</tr>
<tr>
<td>NCEP ATP III TLC</td>
<td>National Cholesterol Education Program Adult Treatment Panel III Therapeutic Lifestyle Changes</td>
</tr>
<tr>
<td>NHLBI</td>
<td>National Heart, Lung, and Blood Institute</td>
</tr>
<tr>
<td>PAV</td>
<td>Percent atheroma volume</td>
</tr>
<tr>
<td>PCSK9</td>
<td>Proprotein convertase subtilisin/kexin type 9</td>
</tr>
<tr>
<td>PKDM</td>
<td>Pharmacokinetics and drug metabolism</td>
</tr>
<tr>
<td>PO</td>
<td>Oral administration</td>
</tr>
<tr>
<td>POSTD</td>
<td>Oral statin therapy administration date</td>
</tr>
<tr>
<td>QM</td>
<td>Monthly (Every 4 weeks)</td>
</tr>
<tr>
<td>QD</td>
<td>Each day</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical analysis plan</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>SC</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>SCIPD</td>
<td>Subcutaneous investigational product administration date</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>Study day 1</td>
<td>defined as the first day that protocol-specified investigational product is administered to the subject</td>
</tr>
<tr>
<td>TAV</td>
<td>Total atheroma volume</td>
</tr>
<tr>
<td>TEAE</td>
<td>Treatment emergent adverse event</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient ischemic attack</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper limit of normal</td>
</tr>
<tr>
<td>UC</td>
<td>Ultracentrifugation</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>Very low-density lipoprotein cholesterol</td>
</tr>
</tbody>
</table>
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 2 for AMG 145 Study 20120153 dated 20 December 2013. 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 AMG 145 on the change in burden of coronary atherosclerosis as measured by percent atheroma volume (PAV) in subjects with coronary artery disease requiring angiography for a clinical indication who are taking statins.

2.2 Secondary

To evaluate the effect of AMG 145 on the change in normalized total atheroma volume (TAV) and regression of coronary atherosclerosis either by PAV or TAV.

2.3 Exploratory

- To evaluate the effect of AMG 145 on plaque composition
- To assess the effects of AMG 145 on change and percent change from baseline in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, and ApoB/Apolipoprotein A-1 (ApoA1) ratio, Lipoprotein (a) [Lp(a)], triglycerides (TG), very low-density lipoprotein cholesterol (VLDL-C), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C)
- To evaluate cardiovascular event rates in subjects treated with AMG 145.

3. Study Overview

3.1 Study Design

This is a Phase III, multi-center, double blind, randomized, placebo-controlled study evaluating the effect of Evolocumab (AMG 145) upon coronary atherosclerotic disease burden as assessed by IVUS at baseline and following 78 weeks of treatment in subjects with coronary artery disease.

Subjects will be identified for eligibility on the basis of requiring coronary angiography for further clinical evaluation, LDL-C inclusion criteria, and completion of IVUS.

At randomization, subjects must be on stable, optimized background statin therapy (per protocol Appendix E) that is expected to be unchanged for the duration of study participation (up to 18 months). Optimal statin therapy is defined as an effective statin dose of at least atorvastatin 20 mg daily or equivalent titrated.
to achieve target LDL-C (change or goal) as defined by regional guidelines. Where locally approved, highly effective statin therapy, defined as at least atorvastatin 40 mg daily or equivalent, is recommended. For subjects with LDL-C > 100 mg/dL (2.6 mmol/L) who are not receiving highly effective statin therapy (atorvastatin ≥ 40 mg daily or equivalent), the investigator must attest that higher dose statin therapy is not appropriate for this subject (eg, dose not tolerated, dose not available in that country, other significant clinical concern). Subjects who, in the investigator’s opinion, are already at LDL-C goal at initial screening and are on stable (≥ 4 weeks), allowable lipid lowering therapy (per protocol Appendix E), with no changes planned or expected for the duration of the study, will be enrolled and proceed directly to randomization if all other eligibility criteria are met. These subjects may skip the lipid stabilization period. Subjects who have an acceptable IVUS and are currently on an appropriate statin dose with an LDL-C level that meets the inclusion criteria will be eligible for randomization. Subjects not on an optimal dose of a statin, in the opinion of the investigator, will enter a two to four week lipid stabilization period for initiation or titration of a statin with a maximum of one up titration step for optimization. No changes to lipid lowering therapies will be allowed (except for clinically compelling reasons) once subjects are randomized.

Subjects who fail to meet eligibility criteria will be considered screen failures, and cannot be rescreened. However, certain subjects may be eligible for retesting without rescreening: please refer to protocol section 7.1.1.2. The baseline IVUS examination may be performed only once for entry into the study. Repeating the baseline IVUS examination is prohibited.

Subjects will be randomized 1:1 into 2 treatment groups: AMG 145 420 mg QM SC or placebo QM SC. Randomization will be stratified for balance by region. Study visits will occur during screening, Day 1 (randomization) and week 4, 12, 24, 36, 52, 64, 76 (last dose of IP) and 78 (final IVUS procedure). During these visits, investigational product (IP) will be given via either self-administration or by a qualified staff member. Between study visits, IP can be administered at a location external to the study site, unless subjects choose to visit the site to have IP administered by site personnel. At applicable visits, vital signs, AEs, SAEs, and concomitant medications will be recorded and laboratory tests will be performed. Dietary instruction will be given at each visit. Central laboratory results of the lipid panel, ApoA1, ApoB, high sensitivity
C-reactive protein (hsCRP), and lipoprotein(a) (Lp(a)) will be blinded during the IP treatment period until unblinding of the clinical database and will not be reported to the investigator post-screening. Investigators should not perform non-protocol testing of these analytes during a subject’s study participation and until at least 12 weeks after the subject’s end-of-study visit. The primary efficacy measurement for this study is PAV and will be measured at baseline and week 78. The study includes collection of biomarker samples and, where approved by the independent ethics committee and/or institutional review board (IEC/IRB) and applicable regulatory and other authorities, all subjects will be invited to consent to pharmacogenetic analyses. Last IP will be administered at week 76. **The final visit will occur at week 80 for all subjects.** During this final visit, sites will contact (eg, phone call) subjects at week 80 to assess any potential AEs or SAEs. Subjects will be encouraged to complete all planned visits regardless of their adherence to IP administration. The study includes adjudication of deaths and specific cardiovascular events potential endpoints (PEPs) by an independent Clinical Events Committee (CEC) and formal review of the accumulating data by an independent Data Monitoring Committee (DMC). An Executive Committee (EC) has been formed to advise Amgen on trial design and for assistance in the communication of trial results. The EC will be blinded. Details for each committee will be provided in a committee charter.

### 3.2 Sample Size

The planned total sample size is 950 subjects (475 randomized to AMG 145 420 mg QM and 475 randomized to placebo QM). This sample size will provide sufficient power to determine whether there is a treatment effect of AMG 145 relative to placebo in the primary endpoint.

The assumptions in the sample size calculation are based on the study of coronary atheroma by intravascular ultrasound: effect of rosuvastatin versus atorvastatin (SATURN) (Nicholls, 2011). The SATURN study indicates that every 1 mg/dL reduction in LDL-C is estimated to be associated with reduction of 0.03026 in PAV at week 104. For this study, the assumed treatment effect is at least change of 0.706 in PAV at week 78, which is approximated from an expected treatment effect of > 31 mg/dL reduction in LDL-C from baseline to week 78. The assumed common standard deviation (SD) is 2.9.

Assuming 25% of randomized subjects will not be included in the primary analysis, the sample size of 950 subjects will provide approximately 712 subjects in the primary analysis to ensure 90% power to test the study hypothesis.
The sample size calculation was performed using a 2-sided t-test with a 0.05 significance level. The sample size calculation was derived using nQuery version 7.01.

4. Study Endpoints and Covariates

4.1 Study Endpoints

4.1.1 Primary Efficacy Endpoint
- Nominal change in percent atheroma volume (PAV) from baseline to week 78

4.1.2 Secondary Efficacy Endpoints
The secondary endpoints are listed in the following sequential order to reflect the multiplicity adjustment method stated in Section 10.
- Nominal change in total atheroma volume (TAV) from baseline to week 78
- Regression (any reduction from baseline) in PAV (yes, no)
- Regression (any reduction from baseline) in TAV (yes, no)

4.1.3 Exploratory Endpoints
- Plaque composition in a subset of subjects:
  - fibrous volume
  - fibrofatty volume
  - necrotic core
  - dense calcium
- 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
  - ApoB
- total cholesterol/HDL-C ratio
- ApoB/ApoA1 ratio
- Triglycerides
- VLDL-C
- HDL-C
- ApoA1
- Lp(a)

- hsCRP at each scheduled assessment
- HbA1c at each scheduled assessment
- PCSK9 change from baseline at each scheduled assessment

4.1.4 Safety Endpoints
- Subject incidence of treatment emergent adverse events
- Safety laboratory values and vital signs at each scheduled visit
- ECG parameters (such as RR, PR, QRS, QT and QTc intervals) at each scheduled visit
- Incidence of anti-AMG 145 antibody (binding and neutralizing) formation

4.1.5 Pharmacokinetics Endpoints
- Serum concentration of AMG 145 at selected time points

4.2 Planned Covariates
The following covariates will be used in their original format in covariate analyses of the primary endpoint.

Stratification factor
- Region (North America, Europe, Latin America, and Asia Pacific)

Baseline Covariates
- Age
- Sex
- Race (white, non-white)
- PAV
- TAV
- LDL-C
- Non-HDL-C
- PCSK9
- Family history of premature coronary heart disease (yes, no)
- Prior MI (yes, no)
5. Hypotheses

The primary statistical hypothesis is as follows:

The null hypothesis is that there is no difference in nominal change from baseline in PAV at week 78 due to LDL lowering between subjects receiving AMG 145 420 mg QM and placebo QM in combination with statin background therapy, and the alternative hypothesis is that the difference does exist.

6. Definitions

6.1 Endpoint Related Definitions

Total Atheroma Volume (TAV)

Total atheroma volume in a ≥40 mm segment of the targeted coronary artery is the average plaque area over the n images that were evaluated by IVUS multiplied by a constant factor:

$$TAV = \frac{\sum n (EEM_{CSA} - LUMEN_{CSA})}{n \times C},$$

where EEM_{CSA} is the external elastic membrane cross-sectional area; LUMEN_{CSA} is the luminal cross-sectional area; C is the median vessel length of subjects with evaluable IVUS data at both baseline and follow-up.

Percent Atheroma Volume (PAV)

Percent atheroma volume is the total atheroma volume out of the total vessel volume:

$$\frac{\sum n (EEM_{CSA} - LUMEN_{CSA})}{\sum n EEM_{CSA}} \times 100$$

6.2 Study Time Points

Enrollment Date

Enrollment date is the date a subject becomes eligible for the lipid stabilization period in the interactive voice response system (IVRS) as recorded on the eCRF.
Randomization Date

The date a subject is randomized to an IP treatment group in the interactive voice response system (IVRS) as recorded on the eCRF.

First Dose Date of SC Investigational Product (First SCIPD)

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

First Dose Date of Statin Therapy (First POSTD)

For each subject, the First Dose Date of Statin Therapy is defined as the first dispense date of the sponsor-provided statin therapy (atorvastatin 20 mg, 40 mg, or 80 mg QD), or the start date of the nonsponsor-provided statin therapy.

Study Day 1

For each subject, Study Day 1 is defined as the first day that protocol-specified investigational product is administered to the subject, which is the first SCIPD.

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:

\[
\text{Study day} = (\text{date of interest} - \text{Study Day 1 date}) + 1.
\]

If the date of interest is prior to the Study Day 1:

\[
\text{Study day} = (\text{date of interest} - \text{Study Day 1 date}), \text{ so that the day prior to Study Day 1 is study day } -1.
\]

Last Dose Date of SC Investigational Product (Last SCIPD)

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

Last Dose Date of Statin Therapy (Last POSTD)

For each subject, the Last Dose Date of Statin Therapy is defined as the later of the following two dates:

- the last return date of the sponsor-provided statin therapy, or the stop date of the nonsponsor-provided statin therapy
- the date decision was made to discontinue the statin therapy

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.

6.3 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, CRP, Lp(a) and their derived parameters (eg, ratio between them) are defined as the fasting concentrations measured through central lab on Study Day 1. If for any reason a concentration for a parameter is not observed on Study Day 1, the closest measurement prior to study Day 1 will be used.

Other Baseline Values
For ECG, the baseline value is defined as the mean over all non-missing triplicate averages of 3 (or all available) readings from each set of triplicate taken prior to or on Study Day 1.

For PCSK9, hbA1c, and all other variables, the baseline value is defined as the last non-missing value collected prior to or on Study Day 1.

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]

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

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated waist circumference:</td>
<td></td>
</tr>
<tr>
<td><strong>Non-Asian:</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>≥ 102 cm</td>
</tr>
<tr>
<td>Women</td>
<td>≥ 88 cm</td>
</tr>
<tr>
<td><strong>Asian:</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>≥ 90 cm</td>
</tr>
<tr>
<td>Women</td>
<td>≥ 80 cm</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥ 150 mg/dL</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt; 40 mg/dL</td>
</tr>
<tr>
<td>Women</td>
<td>&lt; 50 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
</tr>
<tr>
<td>SBP ≥ 130 mmHg or DBP ≥ 85 mmHg OR Hypertension checked ‘yes’ on CV Medical History eCRF</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥ 100 mg/dL</td>
</tr>
</tbody>
</table>

**Baseline CHD Risk Factors**

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

- current cigarette smoking
- hypertension
- type II diabetes mellitus
- family history of premature CHD as recorded on the eCRF
- 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**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Risk: CHD or CHD Risk Equivalent</strong></td>
<td></td>
</tr>
<tr>
<td>Coronary Artery Disease OR</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular or Peripheral Vascular Disease OR</td>
<td></td>
</tr>
<tr>
<td>Type 2 Diabetes Mellitus OR</td>
<td></td>
</tr>
<tr>
<td>2 or more Risk Factors (see below) AND FRS &gt; 20% (see Appendix C for FRS calculation)</td>
<td></td>
</tr>
<tr>
<td><strong>Moderately High Risk</strong></td>
<td></td>
</tr>
<tr>
<td>NOT High Risk AND</td>
<td></td>
</tr>
<tr>
<td>2 or more Risk Factors AND</td>
<td></td>
</tr>
<tr>
<td>FRS ≥ 10% AND ≤ 20%</td>
<td></td>
</tr>
<tr>
<td><strong>Moderate Risk</strong></td>
<td></td>
</tr>
<tr>
<td>NOT High Risk AND</td>
<td></td>
</tr>
<tr>
<td>2 or more Risk Factors AND</td>
<td></td>
</tr>
<tr>
<td>FRS &lt; 10%</td>
<td></td>
</tr>
<tr>
<td><strong>Lower Risk</strong></td>
<td></td>
</tr>
<tr>
<td>NOT High Risk AND</td>
<td></td>
</tr>
<tr>
<td>0 to 1 Risk Factor</td>
<td></td>
</tr>
</tbody>
</table>
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 eCRF form, low HDL-C cholesterol defined as baseline HDL-C < 40 mg/dL, age ≥ 45 years in men or ≥ 55 years in women.

Risk Classification According to ESC/EAS Guidelines

The Systematic Coronary Risk Estimation (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. Risk classification of very high, high, moderate and low risk will be according to the ESC/EAS guidelines.

6.4 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)

IP includes AMG 145 SC 420 mg QM and its SC placebo.

IP Exposure Period in Months

For each QM subject:

\[
\text{IP Exposure Period} = \frac{\min ( \text{Last SCIPD} + 28 \text{ days}, \ \text{EOS Date} ) - \text{First SCIPD} + 1}{365.25 \times 12}
\]

Study Exposure Period in Months

For each randomized subject, Study Exposure Period = ( EOS date – Randomization 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.**

**Target IP TEAE (On-treatment TEAE)**

TEAEs occurring from the first dose of IP date to 30 days after the last dose of IP date or EOS whichever occurs first.

**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 randomized subjects who received at least 1 dose of IP. It will be used for all analyses except for analyses of IVUS-related efficacy endpoints. In efficacy analyses, subjects will be grouped according to their randomized treatment group assignment, regardless of the treatment received. For safety analyses, subjects will be grouped according to their actual treatment group (as defined in Section 6.4).

7.2 IVUS Analysis Set

The IVUS analysis set (IAS) contains subjects in the FAS with a baseline IVUS and an IVUS measurement conducted after week 52 (IVUS data collected after week 52 is considered clinically meaningful to be used in the analysis). The IAS will be used for efficacy analysis of IVUS related endpoints.

7.3 Lipid Stabilization Analysis Set

The lipid stabilization analysis set (LSAS) includes all subjects who received at least one dose of statin during the lipid stabilization period. The LSAS will be used in safety summaries during the lipid stabilization period.
7.4 Completer Analysis Set
The Completer Analysis Set (CAS) includes subjects in the IAS who adhered to the scheduled IP (ie, the IP completion box is checked on the eCRF) and had an observed value for the primary endpoint.

7.5 Pharmacokinetic Analyses Set
The PK analysis set includes all subjects with serum AMG 145 or concentration PCSK9 results.

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

Subgroup by Stratification factor
- Region (North America, Europe, Latin America, and Asia Pacific)

Subgroup by Baseline Covariates
- Age (< median, ≥ median; < 65, ≥ 65)
- Sex
- Race (white, non-white)
- PAV (< median, ≥ median)
- TAV (< median, ≥ median)
- LDL-C (< median, ≥ median)
- Non-HDL-C (< median, ≥ median)
- PCSK9 (< median, ≥ median)
- Family history of premature coronary heart disease (yes, no)
- Prior MI (yes, no)
- Type 2 diabetes mellitus (yes, no)
- Prior statin use (yes, no)
- ACC/AHA statin background therapy high intensity at baseline (yes, no)
- SCORE risk classification (low, moderate, high, very high)
- Current cigarette use (yes, no)
8. **Interim Analysis and Early Stopping Guidelines**

No interim analysis is planned for this study.

An external independent DMC has been established to formally review the accumulating data from this and other completed and ongoing studies with AMG 145 to ensure there is no avoidable increased risk of harm to subjects. The independent DMC is chaired by an external academic cardiologist who is an expert in lipids and clinical trials. Analyses for the DMC are provided by the Independent Biostatistical Group (IBG), which is external to Amgen. Details are provided in the DMC charter.

9. **Data Screening and Acceptance**

9.1 **General Principles**

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

9.2 **Data Handling and Electronic Transfer of Data**

Amgen’s Clinical Data Management department will provide all data to be used in the planned analyses. This study will use the RAVE database.

All data collected in the eCRF will be extracted from RAVE. Protocol deviations will be transferred from eClinical. Final PK data for all randomized subjects will be transferred from statistical programming to Amgen’s PKDM group. 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. 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 IVUS Results**

The reason of missing final IVUS result will be tabulated. Missing primary endpoint will be imputed using multiple imputation (Section 10.5.1).
9.3.3 Handling of Incomplete Dates

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

<table>
<thead>
<tr>
<th>Start date (AE and concomitant medication)</th>
<th>Missing</th>
<th>Imputation</th>
<th>Exception</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>1</td>
<td>Default to Study Day 1 if an event starts the same year and month as Study Day 1</td>
<td></td>
</tr>
<tr>
<td>Day / Month</td>
<td>1-Jan</td>
<td>Default to Study Day 1 if an event started the same year as Study Day 1</td>
<td></td>
</tr>
</tbody>
</table>

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.

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

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

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

9.6 Distributional Characteristics
Distributional assumptions for the primary and secondary 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
The final analysis will be conducted when all subjects have either completed all the scheduled study visits or have early terminated from the study. At that time, the database will be cleaned, processed, locked and a snapshot will be taken; the study will also be unblinded. Based on the snapshot, efficacy and safety analyses will be performed. Unless specified otherwise, the FAS will be the default analysis set in this study and data will be summarized by randomized treatment group. IAS will be used for analyses of IVUS-related efficacy endpoints. The superiority of AMG 145 to placebo will be assessed for all efficacy endpoints. Unless specified otherwise, all hypothesis testing will be 2-sided with a significance level of 0.05.
Subject disposition, demographics, baseline characteristics, and exposure to IP will be summarized.

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

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

Multiplicity Adjustment Method

In order to preserve the family wise type I error rate at 0.05 for testing the primary and secondary endpoints, the primary analysis of primary endpoint will be tested first. If the treatment effect from the primary analysis of the primary endpoint is significant at a significance level of 0.05, the hierarchical statistical testing of the secondary endpoints will be tested at significance level of 0.05 in the sequential order as listed in Section 4.1.2.

10.2 Subject Accountability

The number of subjects screened, randomized to IP, receiving IP, and completing the study will be summarized.

Study discontinuation and IP discontinuation will be tabulated separately by reasons for discontinuation. This tabulation will also include discontinuation of the lipid stabilization period.

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

10.3 Important Protocol Deviations

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

Eligibility deviations are defined in the protocol.

10.4 Demographic and Baseline Characteristics

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

## 10.5 Efficacy Analyses

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

### Table 2. Summary of Key Efficacy Analyses

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Primary Analysis</th>
<th>Sensitivity Analysis</th>
<th>Multiplicity Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint</td>
<td></td>
<td></td>
<td>Sequential Testing in the following order:</td>
</tr>
<tr>
<td>• Nominal change in PAV from baseline to week 78</td>
<td>ANCOVA (IAS)</td>
<td>Multiple Imputation + ANCOVA (FAS) ANCOVA (CAS) Quade Test (IAS)</td>
<td></td>
</tr>
<tr>
<td>Secondary Endpoints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Nominal change in TAV from baseline to 78 week</td>
<td>ANCOVA (IAS)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>• Regression in PAV • Regression in TAV</td>
<td>Cochran Mantel-Haenszel (CMH) test (IAS)</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

### 10.5.1 Analyses of Primary Efficacy Endpoint

**Primary analysis**

To assess the primary endpoint of nominal change in PAV from baseline to week 78, an Analysis of Covariance (ANCOVA) model on the IAS will be used, including terms for treatment group, stratification factor (region) and baseline PAV as covariates. Least-square means and corresponding 95% confidence intervals will be provided for each treatment (AMG 154 and placebo) and for the difference between the treatment groups. The superiority of AMG 145 420 mg QM SC to placebo QM SC will be tested.

**Sensitivity Analysis**

A key sensitivity analysis will be conducted using a regression-based multiple imputation procedure to impute the missing primary endpoint in the FAS. The imputation model will include treatment group, **background therapy intensity** (Appendix D), stratification...
factor, baseline LDL, baseline PAV, age, and sex as covariates. Five imputations will be conducted, and each complete dataset after imputation will be analyzed using the same ANCOVA model as the primary analysis. SAS PROC MIANALYZE will be used to combine the results from individual ANCOVA models, estimate the treatment effect, and perform the test.

Another sensitivity analysis will repeat the ANCOVA model for the primary analysis on the CAS.

Quade test between the randomized treatment groups will also be conducted on the IAS, adjusting for the stratification factor and baseline PAV.

**Covariate and Subgroup Analysis**

In addition to the primary analysis, 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 ANCOVA model used in the primary analysis.

A linear regression analysis will also be performed for the primary efficacy endpoint within each treatment group and both treatment groups pooled together using percent change from baseline in LDL-C at week 78 as the covariate. Regression lines with 95% confidence limits will be plotted.

Subgroup analyses on the primary efficacy endpoint will be conducted using the subgroups specified in Section 7.4. Subgroup by treatment interactions will be tested and the p-value of the interaction term will be reported.

For covariate and subgroup analyses, the stratification factor from the eCRF will be used. Differences in stratum assignment between IVRS and eCRF will be tabulated, if any.

**10.5.2 Analyses of Secondary Efficacy Endpoints**

The secondary IVUS efficacy endpoint of change in TAV from baseline to week 78 will be analyzed using the similar method as for the primary endpoint but adjusting for baseline TAV. The secondary efficacy endpoint of regression in either PAV or TAV will be analyzed using the Cochran-Mantel Haenszel (CMH) test with the stratification factor being adjusted. Percentage of subjects demonstrating regression in PAV or TAV will be summarized by treatment group.
10.5.3 Analyses of Exploratory Endpoints

Exploratory endpoints related to plaque composition will be summarized based on IVUS data at baseline and follow-up when data are available. Absolute change from baseline will also be summarized by treatment group.

Lipid parameters and PCSK9 will be summarized by treatment group and by scheduled visit using descriptive statistics. Graphic descriptions may be provided for change from baseline and percent change from baseline.

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 exploratory endpoint events will be summarized for each treatment group.

A shift table for hsCRP will be provided, for levels at baseline to maximum post-baseline value (<0.1, 0.1-0.3, >0.3 mg/dL), by treatment group.

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

10.6 Safety Analyses

10.6.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 15.0 or later will be used to code all adverse events (AE) 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.

Subject incidence of all TEAEs, serious TEAEs, TEAEs leading to withdrawal of investigational product, target IP TEAEs and serious target IP TEAEs 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. A separate summary of adverse events during the lipid stabilization period will be provided for all subjects in the LSAS.
Subject incidence of **treatment emergent and target IP** 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 EOs 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*)

### 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 7. 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 × ULN
- CK > 10 × ULN
- ALT or AST > 3 × ULN
- ALT or AST > 5 × ULN
- Total bilirubin ≥ 2 × ULN
- (ALT or AST > 3 × ULN) and Total bilirubin ≥ 2 × ULN and ALP < 2 × ULN

### 10.6.3 Vital Signs

Systolic and diastolic blood pressure and heart rate will be summarized for each treatment group using descriptive statistics at each scheduled visit.
10.6.4 Electrocardiogram (ECG)
For post-baseline assessments where ECG is performed in triplicate, the average of the 3 (or all available) readings will be used for analysis. Observations with the following diagnosis or findings will be excluded from analysis: artificial pacemaker, atrial fibrillation, atrial flutter, left bundle branch block, and right bundle branch block.

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

10.6.5 Antibody Formation
The incidence and percentages of subjects who develop anti-AMG145 antibodies (binding and if positive, neutralizing) at anytime will be tabulated.

10.6.6 Exposure to Investigational Product
Descriptive statistics will be produced to describe the patient-month exposure to investigational product, the categorical representation of dose received, and the total quantity of oral IP used by treatment group.

Exposure definitions are provided in section 6.3.

10.6.7 Exposure to Concomitant Medication
The number and proportion of subjects receiving the medications of interest (MOI) will be summarized by preferred term for each treatment group as coded by the World Health Organization Drug (WHODRUG) dictionary.

10.7 Pharmacokinetic Analysis
Individual and mean serum AMG 145 and PCSK9 concentration graphs will be provided using nominal times. The data set will be analyzed and stored in the PKS data repository using the current version of Phoenix WinNonlin. AMG 145 or PCSK9 serum concentrations with values below the lower limit of quantification will be reported as less than their respective values but will be set to zero for analysis. PK parameters following the last dose will include but not limited to the maximum and minimum AMG 145 serum concentrations observed at the collected time points. Individual and summary statistics for PK concentrations will be provided.

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

11. Changes From Protocol-specified Analyses

Analyses of exploratory endpoints related to plaque composition will not be included in the CSR as the data will not be available at final database lock.

Subgroup analysis by NCEP risk category will not be performed due to small sample sizes of three out of four NCEP risk categories.
12. Literature Citations / References


13. **Data not Covered by This Plan**

Currently there are no pre-planned analyses for the biochemical cardiovascular biomarker objective.
14. 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:

<table>
<thead>
<tr>
<th>Analytical Study Week</th>
<th>Week 4</th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 36</th>
<th>Week 52</th>
<th>Week 64</th>
<th>Week 76</th>
<th>Week 78</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scheduled Visit Day</td>
<td>29</td>
<td>85</td>
<td>169</td>
<td>253</td>
<td>365</td>
<td>449</td>
<td>533</td>
<td>547</td>
</tr>
<tr>
<td>Vital Signs</td>
<td>(1, 56)</td>
<td>(56, 126)</td>
<td>(126, 210)</td>
<td>(210, 308)</td>
<td>(308, 406)</td>
<td>(406, 490)</td>
<td>(490, 539)</td>
<td>(539, 574)</td>
</tr>
<tr>
<td>IVUS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(364, 574)</td>
</tr>
<tr>
<td>Physical measurements, 12 Lead ECG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;1</td>
<td></td>
</tr>
<tr>
<td>Fasting lipids, ApoA1, ApoB, Lp(a)</td>
<td>(1, 126)</td>
<td>(126, 266)</td>
<td>(266, 406)</td>
<td>(406, 490)</td>
<td>(490, 539)</td>
<td>(539, 574)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK (AMG 145), PCSK9</td>
<td>(1, 266)</td>
<td>(266, 455)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(455, 574)</td>
<td></td>
</tr>
<tr>
<td>Chemistry, Hematology, HbA1c, Fasting Glucose</td>
<td>(1, 126)</td>
<td>(126, 210)</td>
<td>(210, 308)</td>
<td>(308, 406)</td>
<td>(406, 490)</td>
<td>(490, 539)</td>
<td>&gt;539</td>
<td></td>
</tr>
<tr>
<td>hsCRP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;455</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>(1, 168)</td>
<td>(168, 308)</td>
<td>(308, 455)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;455</td>
</tr>
</tbody>
</table>

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 βᵢ, 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

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Coefficient βᵢ</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>ln(age)</td>
<td>52.00961</td>
<td>3.8926095</td>
</tr>
<tr>
<td>ln(t_chol)</td>
<td>20.014077</td>
<td>5.3441475</td>
</tr>
<tr>
<td>ln(hdl)</td>
<td>-0.905964</td>
<td>3.7731132</td>
</tr>
<tr>
<td>ln(sbp)</td>
<td>1.305784</td>
<td>4.8618212</td>
</tr>
<tr>
<td>trt_htn (sbp&gt;120)</td>
<td>0.241549</td>
<td>0.1180474</td>
</tr>
<tr>
<td>smoker</td>
<td>12.096316</td>
<td>0.335602</td>
</tr>
<tr>
<td>ln(age)*ln(t_chol)</td>
<td>-4.605038</td>
<td>20.8111562</td>
</tr>
<tr>
<td>ln(age)*smoker</td>
<td>-2.84367</td>
<td>1.2890301</td>
</tr>
<tr>
<td>ln(age)*ln(age)</td>
<td>-2.93323</td>
<td>15.2144965</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Coefficient βᵢ</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>ln(age)</td>
<td>31.764001</td>
<td>3.9213204</td>
</tr>
<tr>
<td>ln(t_chol)</td>
<td>22.465206</td>
<td>5.3628984</td>
</tr>
<tr>
<td>ln(hdl)</td>
<td>-1.187731</td>
<td>4.0146369</td>
</tr>
<tr>
<td>ln(sbp)</td>
<td>2.552905</td>
<td>4.8376494</td>
</tr>
<tr>
<td>trt_htn (sbp&gt;120)</td>
<td>0.420251</td>
<td>0.142802</td>
</tr>
<tr>
<td>smoker</td>
<td>13.07543</td>
<td>0.3236202</td>
</tr>
<tr>
<td>ln(age)*ln(t_chol)</td>
<td>-5.060998</td>
<td>21.0557746</td>
</tr>
<tr>
<td>ln(age)*smoker</td>
<td>-2.996945</td>
<td>1.2519882</td>
</tr>
</tbody>
</table>

1 if age>70 then ln(70)*smoker
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 $L_{men} = \beta_{ln(age)}*ln(age) + \beta_{ln(t\_chol)}*ln(t\_chol) + \beta_{ln(hdl)}*ln(hdl) + \beta_{ln(sbp)}*ln(sbp) + \beta_{trt\_htn}(if\ trt\_htn) + \beta_{smoker}(if\ smoker) + \beta_{ln(age)*ln(t\_chol)*ln(age)*ln(t\_chol)} + \beta_{ln(age)*smoker*ln(age)*(if\ smoker) + \beta_{ln(age)*ln(age)*ln(age)*ln(age)}$

2. Calculate $A_{men} = L_{men} - 172.300168$ (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 $P_{men} = 1 - 0.9402^B_{men}$

5. $FRS_{men} = P_{men}*100$ (rounded to nearest integer)

**Women**

For each subject:

1. Calculate $L_{women} = \beta_{ln(age)}*ln(age) + \beta_{ln(t\_chol)}*ln(t\_chol) + \beta_{ln(hdl)}*ln(hdl) + \beta_{ln(sbp)}*ln(sbp) + \beta_{trt\_htn}(if\ trt\_htn) + \beta_{smoker}(if\ smoker) + \beta_{ln(age)*ln(t\_chol)*ln(age)*ln(t\_chol)} + \beta_{ln(age)*smoker*ln(age)*(if\ smoker) + \beta_{ln(age)*ln(age)*ln(age)*ln(age)}$

2. Calculate $A_{women} = L_{women} - 146.5933061$ (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 $\leq$ 120 mmHg, then trt_htn is no

Calculated scores should match the interactive calculator

Appendix D. Lipid Modifying Background Therapy Intensity

Based on ACC/AHA guidelines:

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

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.