Supplemental Online Content 2


Statistical Analysis Plan

This supplemental material has been provided by the authors to give readers additional information about their work.
STATISTICAL ANALYSIS PLAN

A Double-blind, Randomized, Multicenter Study to Evaluate the Safety and Efficacy of AMG 145, Compared With Ezetimibe, in Hypercholesterolemic Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor Due to Muscle Related Side Effects

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<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>AHA</td>
<td>American Heart Association</td>
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<tr>
<td>AI</td>
<td>Autoinjector</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>ApoA1</td>
<td>Apolipoprotein A-1</td>
</tr>
<tr>
<td>ApoB</td>
<td>Apolipoprotein B</td>
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<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
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<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BPI-SF</td>
<td>Brief Pain Inventory – Short Form</td>
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<td>CAS</td>
<td>Completer analysis set</td>
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<td>CEC</td>
<td>Clinical Events Committee</td>
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<tr>
<td>CHD</td>
<td>Coronary Heart Disease</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CK</td>
<td>Creatine phosphokinase</td>
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<tr>
<td>CMH</td>
<td>Cochran Mantel-Haenszel</td>
</tr>
<tr>
<td>CV</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>CSR</td>
<td>Clinical study report</td>
</tr>
<tr>
<td>CTCAE</td>
<td>NCI Common Terminology Treatment Collaboration</td>
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<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
</tr>
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<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>EOI</td>
<td>Events of Interest</td>
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<tr>
<td>EOIIP</td>
<td>End of Investigational Product</td>
</tr>
<tr>
<td>EOS</td>
<td>End of study (for individual subject)</td>
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<td>EvoMab</td>
<td>Evolocumab (AMG 145)</td>
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<td>FAS</td>
<td>Full analysis set</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FRS</td>
<td>Framingham Risk Score</td>
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<td>HDL-C</td>
<td>High-density lipoprotein cholesterol</td>
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<tr>
<td>hsCRP</td>
<td>High sensitivity C-reactive protein</td>
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<tr>
<td>IBG</td>
<td>Independent biostatistical group</td>
</tr>
<tr>
<td>IEC/IRB</td>
<td>Independent Ethics Committee / Institutional Review Board</td>
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<td>Abbreviation or Term</td>
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<td>----------------------</td>
<td>------------------------</td>
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<tr>
<td>INR</td>
<td>International normalized ratio</td>
</tr>
<tr>
<td>IP</td>
<td>Investigational product</td>
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<tr>
<td>IPD</td>
<td>Important protocol deviation</td>
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<tr>
<td>IXRS</td>
<td>Interactive voice and web response system</td>
</tr>
<tr>
<td>LAS</td>
<td>Long-term analysis set</td>
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<tr>
<td>LDL-C</td>
<td>Low-density lipoprotein cholesterol</td>
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<tr>
<td>LDLR</td>
<td>LDL receptor</td>
</tr>
<tr>
<td>LFT</td>
<td>Liver function test</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>Lipoprotein(a)</td>
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<tr>
<td>MAS</td>
<td>Monotherapy Analysis Set</td>
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<tr>
<td>MedDRA</td>
<td>Medical dictionary for regulatory activities</td>
</tr>
<tr>
<td>Mol</td>
<td>Medications of interest</td>
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<tr>
<td>MRSE</td>
<td>Muscle-related side effects</td>
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<tr>
<td>NCEP</td>
<td>National Cholesterol Education Program</td>
</tr>
<tr>
<td>NCEP ATP III</td>
<td>National Cholesterol Education Panel Adult Treatment Panel III</td>
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<tr>
<td>NHLBI</td>
<td>National Heart, Lung, and Blood Institute</td>
</tr>
<tr>
<td>Part A</td>
<td>Rechallenge portion of study</td>
</tr>
<tr>
<td>Part B</td>
<td>Efficacy portion of study</td>
</tr>
<tr>
<td>Part C</td>
<td>Open Label Extension portion of study</td>
</tr>
<tr>
<td>PCSK9</td>
<td>Proprotein convertase subtilisin/kexin type 9</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetic</td>
</tr>
<tr>
<td>PKDM</td>
<td>Pharmacokinetics and drug metabolism</td>
</tr>
<tr>
<td>PO</td>
<td>Oral administration</td>
</tr>
<tr>
<td>POIPD</td>
<td>Dose date of oral investigational product</td>
</tr>
<tr>
<td>Q2W</td>
<td>Every 2 weeks</td>
</tr>
<tr>
<td>QM</td>
<td>Monthly (Every 4 weeks)</td>
</tr>
<tr>
<td>QD</td>
<td>Once a day</td>
</tr>
<tr>
<td>RAS</td>
<td>Rechallenge Analysis Set</td>
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<tr>
<td>SAE</td>
<td>Serious adverse event</td>
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<tr>
<td>SAP</td>
<td>Statistical analysis plan</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
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<tr>
<td>SC</td>
<td>Subcutaneous</td>
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<td>SCIPD</td>
<td>Dose date of SC investigational product</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>SF-36</td>
<td>Short Form (36) Health Survey</td>
</tr>
<tr>
<td>Abbreviation or Term</td>
<td>Definition/Explanation</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------------------------------------------------------</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>UC</td>
<td>Ultracentrifugation</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper limit of normal</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>Very low-density lipoprotein cholesterol</td>
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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 AMG 145 Study 20120332 Amendment 2 dated 15 January 2014. The scope of this plan includes the primary and 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 administered subcutaneously (SC) once every month (QM) compared with ezetimibe (Part B), on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in hypercholesterolemic subjects who are unable to tolerate an effective dose of a statin due to muscle related side effects (MRSE).

2.2 **Secondary**

- To evaluate the safety and tolerability of SC AMG 145 QM, compared with ezetimibe, in hypercholesterolemic subjects unable to tolerate an effective dose of a statin
- To assess the effect of 24 weeks of SC AMG 145 QM, compared with ezetimibe, on change from baseline in LDL-C, and percent change from baseline in total cholesterol, non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, ApoB/Apolipoprotein A1 (ApoA1) ratio, lipoprotein(a) [Lp(a)], triglycerides, HDL-C, and VLDL-C in hypercholesterolemic subjects unable to tolerate an effective dose of a statin
- To assess the effect of 24 weeks of SC AMG 145 QM, compared with ezetimibe, on percent of subjects attaining LDL-C < 70 mg/dL (1.81 mmol/L) in hypercholesterolemic subjects unable to tolerate an effective dose of a statin

2.3 **Tertiary**

Tertiary objectives are:

- To assess the effects of 24 weeks of SC AMG 145 QM, compared with ezetimibe, on percent change from baseline of ApoA1 in hypercholesterolemic subjects unable to tolerate an effective dose of a statin

2.4 **Exploratory**

Exploratory objectives are:

- To evaluate the incidence of MRSE elicited by a double-blind, cross-over atorvastatin rechallenge in Part A
- To describe the effects over time of SC AMG 145 QM, compared with ezetimibe, on change from baseline in proprotein convertase subtilisin/kexin type 9 (PCSK9) levels and on change from baseline and percent change from baseline of LDL-C, total cholesterol, non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio, triglycerides, VLDL-C, HDL-C, ApoA1, and Lp(a), and categorical change from
baseline in high sensitivity C-reactive protein (hsCRP) in hypercholesterolemic subjects unable to tolerate an effective dose of a statin

- To investigate the relationship between novel and established biochemical cardiovascular and lipid biomarkers and effects of AMG 145

- In subjects consenting to the optional pharmacogenetics analysis, to investigate potential correlations of study data including the subject response to AMG 145 with genetic variation in markers of PCSK9 signaling, low-density lipoprotein receptor (LDLR) turnover, cholesterol metabolism, inflammation, and plaque stability

- To estimate cardiovascular event rates in subjects treated with AMG 145, including aggregated exploratory analyses across the AMG 145 program

3. Study Overview

3.1 Study Design

This is a phase 3, multicenter, randomized, double-blind, ezetimibe-controlled, parallel group study of AMG 145 in hypercholesterolemic subjects unable to tolerate an effective dose of a statin. There are three parts to this study: Part A is a double-blind, placebo-controlled cross-over statin rechallenge to confirm presence of statin-related MRSE and is approximately 22 weeks in duration; Part B is a double-blind, active controlled comparing AMG 145 to ezetimibe and is 24 weeks in duration; Part C is a two-year open-label extension to evaluate the long-term safety and efficacy of AMG 145 in statin-intolerant subjects. Randomization will occur at two separate time points, prior to Part A and prior to Part B. Any subject with a documented history of CK elevation > 10 x ULN accompanied by muscle symptoms while on statin therapy levels and documented resolution of both CK elevation and muscle symptoms upon discontinuation of statin therapy, must bypass the statin rechallenge Part A and advance directly into Part B. During screening, potential subjects taking low dose statins or ezetimibe will discontinue these medications and allow for a minimum of 4-week washout period. Potential subjects will be given placebo subcutaneous injections administered via 3 prefilled autoinjector/pens (prefilled AI/pen). Randomization into Part A should occur within 5 – 10 days of the screening LDL-C evaluation used to determine eligibility. Eligible subjects who meet all inclusion/exclusion criteria will be randomized with an allocation ratio of 1:1 to atorvastatin or placebo. Part A consists of two 10-week periods (Period 1 and Period 2) for cross-over statin rechallenge of subjects. In Period 1, subjects will be assigned to 20 mg atorvastatin or matched placebo taken by mouth (PO) every day (QD). At the end of Period 1 and a 2-week washout, subjects will cross-over to the alternate therapy (either atorvastatin or placebo for Period 2), during which time subjects will be treated for an additional 10 weeks. During either treatment period the subject will complete the 10 week course or will discontinue oral IP due to
intolerable MRSE or MRSE that develop and persist for 2 weeks which in the opinion of the investigator will lead to discontinuation of IP. Upon completion of both Periods 1 and 2 in Part A of the study, subjects who report MRSE on atorvastatin and absence of MRSE on placebo will enter into a 2-week washout and advance to Part B. Subjects who do not develop MRSE on atorvastatin or develop MRSE on placebo will be removed from the study. During Part A, a CK elevation > 10 x ULN accompanied by muscle symptoms will be considered the equivalent of intolerable MRSE (ie, if occurring in Period 1 subject will cross-over to Period 2 and if occurring in Period 2 subject will complete Part A). Investigators, who are blinded to IP, will determine if subjects are experiencing MRSE and will report their findings using the IXRS system. To assist with determining that subjects are experiencing MRSE, sites will use questionnaires including the Brief Pain Inventory (BPI) and Short Form (36) Health Survey (SF-36) (Appendix E) to facilitate their discussion regarding MRSE.

In Part B, the subjects will be randomized with an allocation ratio 2:1 into one of 2 treatment groups:

1. 420 mg AMG 145 SC QM and placebo PO QD, or
2. Placebo SC QM and 10 mg ezetimibe PO QD

Randomization in Part B in will be stratified by screening LDL-C level (< 180 mg/dL [4.66 mmol/L] vs. ≥ 180 mg/dL) at study baseline. The following describes procedures and restrictions of Part B: 1) blinded Investigational Product (AMG 145 or placebo) will be administered at the study site using a prefilled autoinjector/pen (AI/Pen); 2) Central laboratory results of the lipid panel, ApoA1, ApoB, lipoprotein(a), and high sensitivity C-reactive protein (hsCRP) will be blinded for the duration of the study and will not be reported to the investigator (unless specified); 3) Investigators are not to perform non-protocol testing of these analytes until at least 12 weeks after last IP administration, or the subject’s end of study, whichever is later as drawing non-protocol labs could unblind treatment assignment. The last dose of blinded SC IP will be given at Week 20 of Part B for all subjects. Subjects will be encouraged to complete all planned visits regardless of their adherence to investigational product (IP) administration. Subjects in Part B will continue to be assessed for MRSE, sites will continue to use BPI and SF-36 to facilitate their discussion regarding MRSE.

Subjects who complete Part B and do not discontinue IP for any reason including an adverse event will be eligible to proceed to Part C, a two-year, open-label, safety extension phase during which all subjects will receive AMG 145. All subjects will be
invited to consent to pharmacogenetic analyses. The study includes collection of biomarker samples where approved by the independent ethics committee and/or institutional review board (IEC/IRB), applicable regulatory and other authorities. The study includes adjudication of deaths and major cardiovascular (CV) events by an independent Clinical Events Committee (CEC) and formal review of the accumulating data by an independent Data Monitoring Committee (DMC).

The study endpoints are defined in Section 4.1.

3.2 Sample Size
The planned total sample size for Part B of the study is 100 subjects at 2:1 ratio for AMG 145 arm and ezetimibe arm. The primary analysis will require the 2-sided tests of each co-primary endpoint to be significant at a level of 0.05. The planned sample size in Part B should provide adequate power to determine the superiority of AMG 145 (QM) relative to ezetimibe as measured by the co-primary endpoints. From the global phase 2 study 20090159, the treatment effect of AMG 145 QM 420 mg compared to ezetimibe in the % change from baseline in LDL-C at week 12 is -35.9% (-44.1%, -27.8%) and from other phase 2 studies in AMG 145 program, the treatment effect measured as mean of week 10 and 12 were as large or larger than week 12 and highly correlated (> 85%) with ones at week 12. The assumed smallest treatment effect between the co-primary endpoints in AMG 145 QM 420 mg is 25%, with a common standard deviation (SD) of 20%. This SD assumption is based on AMG 145 phase 2 results and is consistent with literature review (FDA statistical reviews of ezetimibe and pitavastatin).

It is anticipated that the treatment effect will be attenuated due to the following assumptions:

- Approximately 15% of randomized subjects will end IP early but will remain on study. There will be no treatment effect difference between the AMG 145 and ezetimibe subjects after they end IP early.
- Approximately 5% of randomized subjects will end the study early. The treatment effect of AMG 145 over ezetimibe is a LDL-C reduction of approximately 12%.

After accounting for treatment attenuation and assuming 2% of randomized subjects do not receive any IP, the sample size will provide approximately 98% power for each of the co-primary endpoints in testing the superiority of AMG 145 QM 420 mg over ezetimibe. The sample size calculation is performed using a two-sided t-test with a 0.05 significance level, an attenuated treatment effect of 21% reduction in LDL-C and an attenuated common SD of 24%.
As the co-primary endpoints are correlated, there is at least 96%(98% x 98%) power to simultaneously detect significant treatment effects of the co-primary endpoints. The power calculation is derived using nQuery version 7.01.

4. **Study Endpoints and Covariates**

4.1 **Study Endpoints**

4.1.1 **Co-Primary Endpoints**

- Mean percent change from baseline in LDL-C at Weeks 22 and 24 of Part B
- Percent change from baseline in LDL-C at Weeks 24 of Part B

4.1.2 **Co-Secondary Efficacy Endpoints**

Co-secondary endpoints of at week 24 and the means of weeks 22 and 24 of Part B for:

**Tier 1 endpoints**

- Change from baseline in LDL-C
- LDL-C response (LDL-C < 70 mg/dL [1.81 mmol/L])
- Percent change from baseline in total cholesterol
- Percent change from baseline in non-HDL-C
- Percent change from baseline in ApoB
- Percent change from baseline in the total cholesterol/HDL-C ratio
- Percent change from baseline in ApoB/ApoA1 ratio

**Tier 2 endpoints**

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

4.1.3 **Tertiary Efficacy Endpoints**

- Mean percent change from baseline in ApoA1 at Weeks 22 and 24 of Part B
- Percent change from baseline in ApoA1 at Week 24 of Part B

4.1.4 **Exploratory Endpoints**

- Incidence of MRSE following a lead-in statin rechallenge (Part A)
- Subject incidence of adjudicated events:
  - death by any cause
  - cardiovascular death
  - myocardial infarction
hospitalization for unstable angina
- coronary revascularization
- stroke
- hospitalization for heart failure
- transient ischemic attack (TIA)

- Subject incidence of non-coronary revascularization

For both Part B and Part C of the study,

- 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
  - VLDL-C
  - HDL-C
  - ApoA1
  - Triglycerides
  - Lp(a)

For Part B of the study,

- hsCRP at each scheduled assessment
- PCSK9 change from baseline at each scheduled assessment
- SF-36 domain score: change from baseline at each scheduled assessment
- BPI items: change from baseline at each scheduled assessment

4.1.5 Safety Endpoints

- Subject incidence of adverse events

For both Part B and Part C of the study,

- Safety laboratory values at each scheduled visit
- Incidence of anti-AMG 145 antibody (binding and neutralizing) formation

4.2 Planned Covariates

Stratification factor in Part B of the study

- Screening LDL-C: < 180 mg/dL [4.66 mmol/L] vs. ≥ 180 mg/dL
Baseline Covariates

- Age
- Sex
- Race (black, white, and other)
- Region (North America, Europe, other)
- Part A participation before entering Part B (take atorvastatin then placebo, take placebo then atorvastatin, bypass Part A)
- Take lipid lowering therapy in Part B (yes/no)
- LDL-C
- 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 $\geq 2$ (yes, no)
- Family history of premature coronary heart disease (yes, no)
- PCSK9
- Triglycerides
- NCEP (NCEP, 2002) high risk (yes, no)

5. Hypotheses and/or Estimations

The statistical hypothesis of the co-primary endpoints is:

The null hypothesis is that there is no mean difference in the percent change from baseline at week 24 of Part B or the mean percent change from baseline at weeks 22 and 24 of Part B in the in LDL-C between AMG 145 QM 420 mg and ezetimibe, and the alternative hypothesis is that a mean difference does exist.

6. Definitions

6.1 Study Time Points

Enrollment Date

For subjects who are randomized into Part A of the study, enrollment date is the same as Part A randomization date; for subjects who bypass Part A and are directly randomized into Part B of the study, enrollment date is the same as Part B randomization date.
Part A Randomization Date

The date a subject is randomized to Part A of the study in the interactive voice and web response system (IXRS) as recorded on the eCRF.

Part B Randomization Date

The date a subject is randomized to Part B of the study in the interactive voice and web response system (IXRS) as recorded on the eCRF.

First Dose Date of Oral Investigational Product of Part A (First POAIPD)

For each subject randomized into Part A of the study, the First Dose Date of Oral Investigational Product of Part A is defined as the first dispense date of the oral IP of Part A as recorded on the oral IP administration in Part A eCRF.

First Dose Date of Oral Investigational Product for Period 2 of Part A (First POAP2IPD)

For each subject randomized into Part A of the study, the First Dose Date of Oral Investigational Product for Period 2 of Part A is defined as the first dispense date of the oral IP for Period 2 of Part A as recorded on the oral IP administration in Part A eCRF.

First Dose Date of SC Investigational Product of Part B (First SCBIPD)

For each subject randomized into Part B of the study, the First Dose Date of SC Investigational Product of Part B is defined as the first administration date of the SC IP of Part B as recorded on the IP administration in Part B eCRF.

First Dose Date of Oral Investigational Product of Part B (First POBIPD)

For each subject randomized into Part B of the study, the First Dose Date of Oral Investigational Product of Part B is defined as the first dispense date of the oral IP of Part B as recorded on the oral IP administration in Part B eCRF.

First Dose Date of SC Investigational Product of Part C (First SCCIPD)

For each subject who participates Part C of the study, the First Dose Date of SC Investigational Product of Part C is defined as the first administration date of the SC IP of Part C as recorded on the IP administration in Part C eCRF.

Part A Day 1

For each subject randomized into Part A of the study, Part A Day 1 is defined as the first POAIPD.
Part B Day 1

For each subject randomized into Part B of the study, Part B Day 1 is defined as the first day that protocol-specified investigational product of Part B is administered, which is the earlier of the first SCBIPD and the first POBIPD.

Part C Day 1

For each subject who participates Part C of the study, Part C Day 1 is defined as the first SCCIPD.

Study Day 1

- For each subject who is randomized into Part A of the study, Study Day 1 is defined as the Part A Day 1;
- For each subject who bypasses Part A and is directly randomized into Part B of the study, Study Day 1 is defined as Part B Day 1.

Part A Day

For each subject randomized into Part A of the study, and for a given date of interest, Part A Day is defined as the number of days since Part A Day 1:

Part A Day = (date of interest – Part A Day 1 date) + 1.

If the date of interest is prior to the Part A Day 1:

Part A Day = (date of interest – Part A Day 1 date), so that the day prior to Part A Day 1 is Part A Day -1.

Part B Day

For each subject randomized into Part B of the study, and for a given date of interest, Part B Day is defined as the number of days since Part B Day 1:

Part B Day = (date of interest – Part B Day 1 date) + 1.

If the date of interest is prior to the Part B Day 1:

Part B Day = (date of interest – Part B Day 1 date), so that the day prior to Part B Day 1 is Part B Day -1.

Part C Day

For each subject who participates Part C of the study, and for a given date of interest, Part C Day is defined as the number of days since Part C Day 1:

Part C Day = (date of interest – Part C Day 1 date) + 1.

If the date of interest is prior to the Part C Day 1:

Part C Day = (date of interest – Part C Day 1 date), so that the day prior to Part C Day 1 is Part C Day -1.
Study Day

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

Last Dose Date of SC Investigational Product of Part B (Last SCBIPD)
For each subject randomized into Part B of the study, the Last Dose Date of SC Investigational Product of Part B is defined as the date of the last administration of the SC IP of Part B as recorded on the IP administration in Part B eCRF.

Last Dose Date of Oral Investigational Product of Part B (Last POBIPD)
For each subject randomized into Part B of the study, the Last Dose Date of Oral Investigational Product of Part B is defined as the earliest of the following three dates:
- EOS date
- The day before Part C Day 1
- The later of the last return date of the oral IP (recorded on the oral IP administration in Part B eCRF) and the date decision was made to discontinue oral investigational product (recorded on the end of the oral IP in Part B eCRF)

Last Dose Date of SC Investigational Product of Part C (Last SCCIPD)
For each subject who participates Part C of the study, the Last Dose Date of SC Investigational Product of Part C is defined as the date of the last administration of the SC IP of Part C as recorded on the IP administration in Part C eCRF.

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

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

6.2 Demographics and Baseline Related Definitions

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

Other Baseline Values
For 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, the baseline value is defined as the average of the last two non-missing values collected prior to or on Study Day 1. If for any reason only 1 value is available, then that value will be used as baseline.

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

Change (absolute change) from Baseline
The arithmetic difference between a post-baseline value and baseline for a given time point:

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

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

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

Baseline 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:
<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>Non-Asian:</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>≥ 102 cm</td>
</tr>
<tr>
<td>Women</td>
<td>≥ 88 cm</td>
</tr>
<tr>
<td>Asian:</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>SBP ≥ 130 mmHg or DBP ≥ 85 mmHg</td>
</tr>
<tr>
<td></td>
<td>OR Hypertension checked ‘yes’ on CV Medical History eCRF</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>High Risk: CHD or CHD Risk Equivalent</td>
<td>Coronary Artery Disease OR</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular or Peripheral Vascular Disease OR</td>
</tr>
<tr>
<td></td>
<td>Type 2 Diabetes Mellitus OR</td>
</tr>
<tr>
<td></td>
<td>2 or more Risk Factors (see below) AND FRS &gt; 20%</td>
</tr>
<tr>
<td></td>
<td>(see Appendix D for FRS calculation)</td>
</tr>
<tr>
<td>Moderately High Risk</td>
<td>NOT High Risk AND</td>
</tr>
<tr>
<td></td>
<td>2 or more Risk Factors AND</td>
</tr>
<tr>
<td></td>
<td>FRS ≥ 10% AND ≤ 20%</td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>NOT High Risk AND</td>
</tr>
<tr>
<td></td>
<td>2 or more Risk Factors AND</td>
</tr>
<tr>
<td></td>
<td>FRS &lt; 10%</td>
</tr>
<tr>
<td>Lower Risk</td>
<td>NOT High Risk AND</td>
</tr>
<tr>
<td></td>
<td>0 to 1 Risk Factor</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.

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 B.
Randomized Treatment Sequence Group in Part A

Based on the crossover design of Part A, each subject in Part A is in fact assigned into one of these two randomized treatment sequence groups:

| Atorvastatin in Period 1, then Placebo PO in Period 2 |
| Placebo PO in Period 1, then Atorvastatin in Period 2 |

Actual Treatment Sequence Group in Part A

A subject’s actual treatment received in Period 1 (or 2) of Part A is the randomized treatment assignment, unless the subject receives treatment throughout Period 1 (or 2) that is different than the randomized treatment assignment, in which case the actual treatment received is the treatment received. Therefore, there are 4 possible actual treatment sequence group in Part A:

| Atorvastatin 20 mg QD in Period 1, then Placebo PO QD in Period 2 |
| Placebo PO QD in Period 1, then Atorvastatin 20 mg QD in Period 2 |
| Placebo PO QD in Period 1, then Placebo PO QD in Period 2 |
| Atorvastatin 20 mg QD in Period 1, then Atorvastatin 20 mg QD in Period 2 |

Actual Treatment Group in Part B

A subject’s actual treatment group in Part B is the randomized treatment group of Part B, unless the subject receives treatment throughout Part B that is different than the randomized treatment group assignment, in which case the actual treatment group is the treatment received.

Investigational Product (IP)

Part A: Oral IP includes Atorvastatin 20 mg and its corresponding placebo PO QD;

Part B:

- SC IP includes AMG 145 SC 420 mg QM and its corresponding SC placebo;
- Oral IP includes ezetimibe PO 10 mg QD and its corresponding placebo PO QD;

Part C: SC IP includes AMG 145 SC 420 mg QM and AMG 145 SC 140 mg Q2W.
SC IP Exposure Period (Months) in Part B

SC IP Exposure Period in Part B = \([ \text{min} (\text{EOS date, the day before Part C Day 1, last SCBIPD + 28 days}) - \text{First SCBIPD} + 1] / 365.25 * 12\)

Oral IP Exposure Period (Months) in Part B

Oral IP Exposure Period in Part B = \([ \text{min} (\text{EOS date, the day before Part C Day 1, last POBIPD + 1 day}) - \text{First POBIPD} + 1] / 365.25 * 12\)

SC IP Exposure Period (Months) in Part C

SC IP Exposure Period in Part C = \([ \text{min} (\text{EOS date, last SCCIPD + 28 days}) - \text{First SCCIPD} + 1] / 365.25 * 12\)

Target Investigational Product in Part B

Target Investigational Product in Part B is defined as the investigational product of more scientific interest in each arm of Part B (ie, not the IP administered to maintain blinding).

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Target IP</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMG 145 SC 420 mg QM and placebo PO QD</td>
<td>AMG 145 SC 420 mg QM</td>
</tr>
<tr>
<td>Placebo SC QM and ezetimibe PO 10 mg QD</td>
<td>Ezetimibe PO 10 mg QD</td>
</tr>
</tbody>
</table>

Target IP Exposure Period (Months) in Part B

- For each subject randomized into arm of AMG 145 SC 420 mg QM and placebo PO QD in Part B, the Target IP Exposure Period is the SC IP Exposure Period in Part B;
- For each subject randomized into arm of Placebo SC QM and ezetimibe PO 10 mg QD in Part B, the Target IP Exposure Period is the Oral IP Exposure Period in Part B.

Treatment Emergent Adverse Events (TEAE)

The definitions are listed in Table 1.
## Table 1. Adverse Event

<table>
<thead>
<tr>
<th>Treatment-emergent AE (TEAE)</th>
<th>Summary Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAE in Part A</td>
<td>Part A Day 1 through min(EOS date, the day before Part B Day 1)</td>
</tr>
<tr>
<td>TEAE in Period 1 of Part A</td>
<td>Part A Day 1 through min(EOS date, the day before the first oral IP dispense date in Period 2 of Part A)</td>
</tr>
<tr>
<td>TEAE in Period 2 of Part A</td>
<td>The first oral IP dispense date in Period 2 of Part A through min(EOS date, the day before Part B Day 1)</td>
</tr>
<tr>
<td>TEAE in Part B</td>
<td>Part B Day 1 through min(EOS date, the day before Part C Day 1)</td>
</tr>
<tr>
<td>Target IP TEAE in Part B</td>
<td>The first dose date of target IP in Part B through the min(EOS date, the day before Part C Day 1, last dose date of target IP + X day) [X = 1 for oral IP; X = 28 for SC IP]</td>
</tr>
<tr>
<td>TEAE in Part C</td>
<td>Part C Day 1 through EOS date</td>
</tr>
<tr>
<td>Target IP TEAE in Part C</td>
<td>Part C Day 1 through min(EOS date, last dose date of AMG 145 + 28)</td>
</tr>
</tbody>
</table>

*same summary period for serious TEAEs

### SC IP Exposure Period (Months) in Part C

For each subject who participates Part C:

\[
\text{SC IP Exposure Period in Part C} = \left[ \min ( \text{Last SCCIPD + 28 days, EOS Date} ) - \text{First SCCIPD +1} \right] / 365.25 \times 12
\]

### Study Exposure Period in Months

For each randomized subject:

\[
\text{Study Exposure Period} = ( \text{EOS date – Enrollment Date + 1} ) / 365.25 \times 12
\]

### 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 greater than 400 mg/dL, the UC LDL-C value from the same blood sample will be used instead, if available.

### Achievement of LDL-C < 70 mg/dL

A subject has achievement of LDL-C < 70 mg/dL if the post-baseline LDL-C value is less than 70 mg/dL. If the value is missing, the subject is considered without the achievement.
Mean achievement of LDL-C < 70 mg/dL at weeks 22 and 24 of Part B is defined using the mean of non-missing LDL-C values at those two timepoints (if one is missing, mean equals the available one).

**Short Form-36 Health Survey (SF-36)**

The SF-36 Health Survey (version 2) contains 36 items and is an improved version of the SF-36 Health Survey. It measures the same 8 domains of health-related quality of life measured by the SF-36 Health Survey. They are: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. The information obtained on these 8 domains of health can be further aggregated into 2 summary component measures of physical and mental health. The domain scores and component summary scores will both be evaluated.

**Brief Pain Inventory - Short Form (BPI-SF)**

The BPI-SF is a pain assessment tool, which measures both the intensity of pain (sensory dimension) and interference of pain in the patient's life (reactive dimension). It also queries the patient about pain relief, pain quality, and patient perception of the cause of pain.

7. **Analysis Subsets**

7.1 **Full Analysis Set**

The full analysis set (FAS) will include all randomized subjects in Part B of the study who received at least 1 dose of Part B IP. This analysis set will be used in both efficacy and safety analyses for Part B of the study. In efficacy and PRO (BPI/SF-36) analyses for Part B of the study, subjects will be grouped according to their randomized treatment group assignment. In safety analyses for Part B of the study, subjects will be grouped according to their actual treatment group (as defined in Section 6.3).

7.2 **Completer Analysis Set**

The completer analysis set (CAS) will include subjects in the FAS who adhered to the scheduled IP regimen in Part B and have observed values for the co-primary endpoints.

7.3 **Rechallenge Analysis Set**

The rechallenge analysis set (RAS) will include all randomized subjects in Part A of the study who received at least 1 dose of oral IP of Part A. The safety analysis for Part A will be conducted based on RAS by actual treatment sequence group (as defined in
Section 6.3). Other analyses, if not specified, will be conducted by randomized
treatment sequence group assignment (as defined in Section 6.3).

7.4 Long-term Analysis Set
The long-term analysis set (LAS) will include all subjects enrolled in Part C of the study
who received at least 1 dose of open label IP. This analysis set will be used in all
analyses for Part C of the study.

7.5 Subgroup Analyses
Subgroup by stratification factor

- Screening LDL-C: < 180 mg/dL [4.66 mmol/L] vs. ≥ 180 mg/dL

Subgroup by baseline characteristics

- Age (< 65, ≥ 65)
- Sex
- Race (black, white, and other)
- Region (North America, Europe, other)
- Part A participation before entering Part B (take atorvastatin then placebo, take
  placebo then atorvastatin, bypass Part A)
- Take lipid lowering therapy in Part B (yes/no)
- LDL-C (< baseline median, ≥ baseline median)
- Body Mass Index (BMI) (< 25, 25 - < 30, ≥ 30)
- 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)
- Family history of premature coronary heart disease (yes, no)
- PCSK9 (< baseline median, ≥ baseline median)
- Triglycerides (< baseline median, ≥ baseline median; <150 mg/dL, ≥ 150 mg/dL;
  < 200 mg/dL, ≥ 200 mg/dL)
- NCEP high risk (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 for 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 IXRS when the study stops. Details on data transfer will be provided in the Data Transfer Plan.

9.3 Handling of Missing and Incomplete Data

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

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

9.3.2 Missing Lipid Measurements
For efficacy endpoints, where the analysis method is repeated measures linear effects model then missing lipid measurements will not be imputed. The handling of missing LDL-C response (achievement of LDL-C < 70 mg/dL) is provided in Section 6.3.

9.3.3 Handling of Incomplete Dates
Adverse events can be flagged as treatment emergent in Part A (B or C) using valid answers to the questions “Did event start before first dose of investigational product of
Part A?”, “Did event start before first dose of oral investigational product of Part B?”, “Did event start before first dose of subcutaneous investigational product of Part B?”, and “Did event start before first dose of investigational product of Part C?” on the eCRF regardless of the AE onset date being complete or not.

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

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

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

9.4 Detection of Bias

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

- major protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints
- subject level unblinding before primary 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 SAS System version 9.2 or later.

10. Statistical Methods of Analysis
10.1 General Principles
The primary analysis will be conducted when all randomized subjects in Part B of the study have either completed all the scheduled study visits in Part B or have early terminated from the study. At that time, the database of the study will be cleaned, processed and a snapshot will be taken. The study will also be unblinded. Based on the snapshot for the primary analysis, efficacy and safety analyses will be performed on FAS. Unless otherwise specified, the FAS will be the default analysis set in analyses for Part B of the study and data will be summarized by randomized treatment group. The superiority of AMG 145 to ezetimibe will be assessed for all efficacy endpoints. Based on the snapshot for primary analysis, the safety analysis in Part A will be conducted based on RAS.

The final analysis will be conducted when all enrolled subjects in Part C of the study have either completed all the scheduled study visits in Part C or have early terminated from the study. At that time, the database of the study will be cleaned, processed and a
snapshot will be taken. Based on the snapshot for the final analysis, long-term efficacy and safety analyses will be performed on LAS and the analyses will be descriptive.

Subject disposition, demographics, baseline characteristics, and exposure to IP will be summarized. Unless otherwise specified, the baseline is as defined in Section 6.2).

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.

A summary of the analyses for each part of the study can be found in Table 2.

### Table 2. Analyses Summary

<table>
<thead>
<tr>
<th>Analyses</th>
<th>Part A</th>
<th>Part B</th>
<th>Part C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>• Summary on lipid parameters assessments by randomized treatment sequence assigned in Part A</td>
<td>• Summary by randomized treatment group in Part B For co-primary and co-secondary endpoints:</td>
<td>• Summary by randomized treatment group in Part B/AMG 145 in Part C</td>
</tr>
<tr>
<td></td>
<td>• No statistical inference</td>
<td>• Repeated measures model</td>
<td>• No statistical inference</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cochran Mantel-Haenszel test for LDL-C achievement</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Multiplicity adjustment</td>
<td></td>
</tr>
<tr>
<td><strong>AE, Safety lab</strong></td>
<td>• Summary by actual treatment sequence assigned in Part A</td>
<td>• Summary by actual treatment group in Part B</td>
<td>• Summary by actual treatment group in Part B/AMG 145 in Part C</td>
</tr>
<tr>
<td></td>
<td>• No statistical inference</td>
<td>• No statistical inference</td>
<td>• No statistical inference</td>
</tr>
<tr>
<td><strong>PRO (BPI, SF-36)</strong></td>
<td>• Summary by randomized treatment sequence assigned in Part A</td>
<td>• Summary by randomized treatment group in Part B</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>• No statistical inference</td>
<td>• No statistical inference</td>
<td></td>
</tr>
</tbody>
</table>

**Multiplicity Adjustment Method**

Methods of adjusting for multiplicity due to multiple endpoints (co-primary and co-secondary efficacy endpoints) are described in the diagram below.
Testing of each co-endpoint pair will result in a single p-value, and for co-secondary endpoints these p-values will then be used in the Hochberg procedure. The following method will be used to preserve the familywise error rate at 0.05 for testing the co-primary and co-secondary efficacy endpoints:

1. If the treatment effect from the primary analysis of the co-primary endpoints are significant at a significance level of 0.05, statistical testing of the tier 1 co-secondary efficacy endpoints (as defined in Section 4.1.2) will follow the Hochberg procedure at a significance level of 0.005 (Hochberg, 1988).

2. If all tier 1 co-secondary efficacy endpoints are significant, the tier 2 co-secondary efficacy endpoints will be tested using the Hochberg procedure at a significance level of 0.05.

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

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

The number of subjects screened, randomized (Part A and B), receiving IP (in Part A, B and C), completing Part A, B and C, and completing the study will be summarized. The number and percent of subjects randomized will be tabulated by the stratification factor and study site.

Part A, B and C discontinuation, the study discontinuation, and IP (in Part A, B and C) discontinuation will be tabulated separately by reasons for discontinuation.

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

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

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

Demographics (ie, age, sex, race, cardiovascular medical history, laboratory parameters) and baseline disease characteristics will be summarized by randomized treatment group and overall using descriptive statistics. If multiple races have been reported for a subject, the subject will be categorized as multiple races.

10.5 Efficacy Analyses

The following table summarizes the key efficacy analyses that will be conducted.
## Table 3. Key Efficacy Analyses Summary

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Statistical Analysis Method</th>
<th>P-values from the Statistical Tests</th>
<th>Testing of Treatment Effect vs. Ezetimibe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Co-Primary Endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mean percent change from baseline at weeks 22 and 24 of Part B in LDL-C</td>
<td>Repeated measures model</td>
<td>P1 = Maximum of the two p-values for the co-endpoint pair from the primary analysis in FAS</td>
<td>P1 compare to $\alpha = 0.05$</td>
</tr>
<tr>
<td>• Percent change from baseline at week 24 of Part B in LDL-C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Co-Secondary Endpoints</strong> (Tier 1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mean LDL response (achievement of LDL-C &lt; 70 mg/dL) at weeks 22 and 24 of Part B</td>
<td>Cochran Mantel-Haenszel (CMH) test</td>
<td>P2a = Maximum of the two p-values for the co-endpoint pair in FAS</td>
<td>If $P1 &lt; 0.05$, $\Rightarrow$ P2a and all P2b’s will be tested through Hochberg method with $\alpha = 0.005$</td>
</tr>
<tr>
<td>• LDL response at week 24 of Part B</td>
<td></td>
<td></td>
<td>Else (ie, co-primary endpoint in FAS is not significant) $\Rightarrow$ No further testing.</td>
</tr>
<tr>
<td>• Mean change from baseline at weeks 22 and 24 of Part B in LDL-C</td>
<td>Repeated measures model</td>
<td>For each lipid parameter,</td>
<td></td>
</tr>
<tr>
<td>• Change from baseline at week 24 of Part B in LDL-C and</td>
<td></td>
<td>P2b = Maximum of the two p-values for each co-endpoint pair in FAS</td>
<td></td>
</tr>
<tr>
<td>• Mean percent change from baseline at weeks 22 and 24 of Part B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Percent change from baseline at week 24 of Part B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in each of the following lipid parameter:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total cholesterol, non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Co-Secondary Endpoints</strong> (Tier 2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mean percent change from baseline at weeks 22 and 24 of Part B</td>
<td>Repeated measures model</td>
<td>For each lipid parameter,</td>
<td>If P2a and all P2b’s are significant through Hochberg method, $\Rightarrow$ P2c will be tested through Hochberg method with $\alpha = 0.05$.</td>
</tr>
<tr>
<td>• Percent change from baseline at week 24 of Part B</td>
<td></td>
<td>P2c = Union-intersection test p-value from the two contrasts of each co-endpoint pair in FAS</td>
<td>Else (ie, not all tier 1 co-endpoints in FAS are significant), $\Rightarrow$ P2c will be tested through Hochberg method with $\alpha = 0.045$.</td>
</tr>
<tr>
<td>in each of the following lipid parameters:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lp(a), triglycerides, HDL-C, and VLDL-C</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
10.5.1 Analysis of Co-Primary Efficacy Endpoints

10.5.1.1 Primary Analysis of Co-Primary Endpoints

To assess the co-primary endpoints of the percent change in LDL-C from baseline at week 24 of Part B and the mean percent change from baseline in LDL-C at weeks 22 and 24 of Part B, a repeated measures linear effects model will be used to compare the efficacy of AMG 145 with ezetimibe. The repeated measures model will include terms for treatment group, stratification factor (Part B), scheduled visit and the interaction of treatment with scheduled visit. Missing values will not be imputed when the repeated measures linear effects model is used.

10.5.1.2 Sensitivity Analyses of Co-Primary Endpoints

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

- The primary analysis will be repeated on the CAS.
- Non-parametric analyses (Quade test) will be performed on the FAS and CAS.

10.5.1.3 Covariate and Subgroup Analyses of Co-Primary Endpoints

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

Subgroup analyses on the co-primary efficacy endpoints will be conducted using the subgroups specified in Section 7.5. 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 data-derived stratification factor (ie, baseline LDL-C level) will be used. Difference in stratum assignment between IXRS stratum and data-derived stratum will be tabulated.

10.5.2 Analysis of Co-Secondary Efficacy Endpoints

The statistical model and testing of the tier 1 co-secondary efficacy endpoints will be similar to the primary analysis of the co-primary endpoints. The co-secondary efficacy endpoints of LDL-C response will be analyzed using the Cochran-Mantel Haenszel (CMH) test adjusted by the stratification factor.
Analyses of the tier 2 co-secondary efficacy endpoints will use the same analysis model as the tier 1 endpoints, and the testing will use a union-intersection test. For each tier 2 endpoint, the alternative hypothesis of the union-intersection test is that at least 1 of the treatment effects from the co-endpoints is not equal to zero.

Multiplicity adjustment procedures are defined in Section 10.1.

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

10.5.4 Analyses of Exploratory Endpoints
Incidence of MRSE following a lead-in statin rechallenge (Part A) will be summarized in each period of Part A by actual treatment sequence group (as defined in Section 6.3) in Part A.

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 safety related exploratory endpoint events will be summarized for actual treatment received (as defined in Section 6.3).

Other exploratory endpoints, including BPI and SF-36, will be summarized using descriptive statistics.

10.5.5 Additional Analyses
The cross-over between atorvastatin and placebo during Part A will introduce the variability in lipid lab of Part B Day 1. Additional analyses will be performed to evaluate the impact of Part A participation (the covariate defined in Section 7.5) on efficacy endpoints. The fasting lipid measurement at Part B Day 1 will be used as the baseline. A repeated measures model that includes terms for treatment group (Part B), stratification factor (Part B), Part A participation, scheduled visit and the interaction of treatment with scheduled visit, will be used.

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 C. Common Terminology Criteria for AEs) and recorded on the eCRF. All adverse event tables will be summarized by actual treatment received (as defined in Section 6.3). Treatment-emergent adverse events (TEAE) are defined in Table 1.

Subject incidence of AEs will be summarized for all TEAEs, serious TEAEs, TEAEs leading to withdrawal of investigational product, target IP TEAEs (as defined in Section 6.3), fatal AEs and TEAEs of interest (EOI). Subject incidence of all TEAEs, serious TEAEs, TEAEs leading to withdrawal of investigational product, target IP TEAEs and fatal AEs will be tabulated by system organ class and preferred term in descending order of frequency.

Summaries of TEAEs, 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 TEAEs related to a device (for Part B and C) will be tabulated by preferred term in descending order of frequency.

Subject incidence of adverse events associated with lipid lowering therapies:
- Diabetes-related
- Muscle-related
- Liver-related

associated with injectable protein therapies:
- Injection site reactions
- Hypersensitivity or allergic reactions

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

10.6.2 Laboratory Test Results
Descriptive statistics will be provided for actual values and changes from baseline in select laboratory parameters at each protocol-specified scheduled visit. Laboratory analytes are provided in the protocol section 7. 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 baseline and any post-baseline for 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)
- (ALT or AST > 3 x ULN) and (Total bilirubin > 2 x ULN or INR > 1.5)

10.6.3 Vital Signs
Vital signs 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-AMG145 antibodies (binding and if positive, neutralizing) at any time will be tabulated.

10.6.5 Exposure to Investigational Product
For Part B and Part C of the study, descriptive statistics will be produced to describe the patient-month exposure to SC IP, the categorical representation of dose received, and the total quantity of oral IP used (for Part B only) by randomized treatment group. Exposure definitions are provided in Section 6.3.

10.6.6 Exposure to Other Protocol-specified Treatment
For each part of the study, the number and proportion of subjects receiving selected lipid regulating medications captured on the Concomitant Medications 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 part of the study. The subject incidence of changes in lipid regulating medications during Part B and Part C will also be provided.

11. Changes From Protocol-specified Analyses
There are no changes to the protocol-specified analyses.
12. Literature Citations / References


13. Appendices
Appendix A. Study Design and Treatment Schema

GAUSS-3 Schema – High Level

Part A  Part B  Part C
Up to 6-Months  6-Months  2-Year OLE

Subjects with documented history of CK elevation > 10 x ULN and muscle symptoms
Subjects screened per iE criteria
Double-blind cross-over rechallenge
Pass

Safety & Efficacy vs. Ezetimibe
Long-term Safety, Tolerability & Efficacy

Fail
(Do not advance to Part B)

GAUSS-3 Schema - Detail

Part A  Part B  Part C
Period 1  Period 2

N ≥ 500
Atorvastatin
20mg
Randomization 1:1
Go Directly to Part B

N ≈ 100
Atorvastatin
20mg

AMG 145 SC + Placebo PO
Placebo SC + Ezetimibe PO

AMG 145

4-8 weeks

- Part A: All subjects in Period 1 will cross-over to alternate therapy in Period 2
- Subjects must have presence of MRSE on atorvastatin and absence of MRSE on PBO to advance to Part B
- Part B cross-over occurs 2 weeks after onset of MRSE or immediately if MRSE is deemed intolerable (i.e., subjects are not obligated to take Part A IP for 20 weeks)
- Subjects who complete Part B are eligible to enroll in a 2-year open-label extension of AMG 145
Appendix B. 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 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 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.

For Part A of the study, the analytical windows can have many different versions given that subjects will cross-over to period 2 after 2 weeks washout if developed MRSE at any time during period 1. The table at below just show one of the scenario where subject complete all the scheduled visits in Part A. For other scenarios, the analytical windows will change according the MRSE registration and the crossover from Period 1 to Period 2 of Part A.

**Part A:**

<table>
<thead>
<tr>
<th>Scheduled Visit Week in Part A</th>
<th>Scheduled Visit Day in Part A</th>
<th>Vital Signs, Fasting plasma Lipids, BPI-SF and SF-36 Questionnaire</th>
<th>Lp(a), ApoA1, ApoB Chemistry, Urinalysis</th>
<th>Hematology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>29</td>
<td>(1, 42)</td>
<td>(1, 42)</td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>57</td>
<td>(42, 63)</td>
<td>(42, 63)</td>
<td></td>
</tr>
<tr>
<td>Week 10</td>
<td>71</td>
<td>(63, 77)</td>
<td>(63, 77)</td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>85</td>
<td>(77, 91)</td>
<td>(77, 91)</td>
<td></td>
</tr>
<tr>
<td>Week 16</td>
<td>113</td>
<td>(91, 126)</td>
<td>(91, 126)</td>
<td></td>
</tr>
<tr>
<td>Week 20</td>
<td>141</td>
<td>(126, 147)</td>
<td>(126, 147)</td>
<td></td>
</tr>
<tr>
<td>Week 22</td>
<td>155</td>
<td>(147, 161)</td>
<td>(1, 161)</td>
<td>(147, 161)</td>
</tr>
</tbody>
</table>
For Part B of the study, when subjects complete the Part B at week 24, they will start Part C dosing if eligible. Therefore, the upper bound of the analytical windows for week 24 is depending on the first dose of SC IP in Part C, which can be defined as

\[ \text{min} \{ \text{Part B day 175, Part B Day of (first dose date of Part C – 1)} \} \]

**Part B:**

<table>
<thead>
<tr>
<th>Scheduled Visit Week in Part B</th>
<th>Scheduled Visit Day in Part B</th>
<th>Vital Signs, Fasting plasma Lipids, Lp(a), ApoA1, ApoB, PCSK9, BPI-SF and SF-36 Questionnaire</th>
<th>Chemistry, Hematology, Urinalysis</th>
<th>Body weight, hsCRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>29</td>
<td>(1, 42)</td>
<td>(1, 42)</td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>57</td>
<td>(42, 70)</td>
<td>(42, 70)</td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>85</td>
<td>(70, 98)</td>
<td>(70, 98)</td>
<td></td>
</tr>
<tr>
<td>Week 16</td>
<td>113</td>
<td>(98, 126)</td>
<td>(98, 126)</td>
<td></td>
</tr>
<tr>
<td>Week 20</td>
<td>141</td>
<td>(126, 147)</td>
<td>(126, 154)</td>
<td></td>
</tr>
<tr>
<td>Week 22</td>
<td>155</td>
<td>(147, 161)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>169</td>
<td>(161, 175)</td>
<td>(154, 175)</td>
<td>(1, 175)</td>
</tr>
</tbody>
</table>

**Part C:**

<table>
<thead>
<tr>
<th>Scheduled Visit Week in Part C</th>
<th>Vital Signs, Fasting Plasma Lipids, ApoA1, ApoB, Lp(a), Vitamin E, Chemistry, CK, Hematology, Urinalysis</th>
<th>HbA1c, hsCRP, Anti-AMG 145 antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 12</td>
<td>(1, 126)</td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>(126, 252)</td>
<td></td>
</tr>
<tr>
<td>Week 48</td>
<td>(252, 420)</td>
<td>(1, 532)</td>
</tr>
<tr>
<td>Week 72</td>
<td>(420, 588)</td>
<td></td>
</tr>
<tr>
<td>Week 96</td>
<td>(588, 700)</td>
<td></td>
</tr>
<tr>
<td>Week 104</td>
<td>(700, 742)</td>
<td>&gt; 532</td>
</tr>
</tbody>
</table>
Appendix C. 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 D. Framingham Risk Score (FRS)

Method to calculate the Framingham Risk Score (FRS):

The $\beta$ 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, 1998).

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

$t_{\text{chol}} = \text{total cholesterol, hdl = HDL-C, sbp = systolic blood pressure, trt\_htn = treatment}$

for hypertension (if sbp $>$ 120), smoker = current smoker

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Coefficient $\beta_i$</th>
<th>mean</th>
<th>Independent variable</th>
<th>Coefficient $\beta_i$</th>
<th>mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>ln(age)</td>
<td>52.00961</td>
<td>3.8926095</td>
<td>ln(age)</td>
<td>31.764001</td>
<td>3.9213204</td>
</tr>
<tr>
<td>ln(t_chol)</td>
<td>20.014077</td>
<td>5.3441475</td>
<td>ln(t_chol)</td>
<td>22.465206</td>
<td>5.3628984</td>
</tr>
<tr>
<td>ln(hdl)</td>
<td>-0.905964</td>
<td>3.7731132</td>
<td>ln(hdl)</td>
<td>-1.187731</td>
<td>4.0146369</td>
</tr>
<tr>
<td>ln(sbp)</td>
<td>1.305784</td>
<td>4.8618212</td>
<td>ln(sbp)</td>
<td>2.552905</td>
<td>4.8376494</td>
</tr>
<tr>
<td>trt_htn (spb&gt;120)</td>
<td>0.241549</td>
<td>0.1180474</td>
<td>trt_htn (spb&gt;120)</td>
<td>0.420251</td>
<td>0.142802</td>
</tr>
<tr>
<td>smoker</td>
<td>12.096316</td>
<td>0.335602</td>
<td>smoker</td>
<td>13.07543</td>
<td>0.3236202</td>
</tr>
<tr>
<td>ln(age)$^*$ln(t_chol)</td>
<td>-4.605038</td>
<td>20.8111562</td>
<td>ln(age)$^*$ln(t_chol)</td>
<td>-5.060998</td>
<td>21.0557746</td>
</tr>
<tr>
<td>ln(age)$^*$smoker$^1$</td>
<td>-2.84367</td>
<td>1.2890301</td>
<td>ln(age)$^*$smoker$^2$</td>
<td>-2.996945</td>
<td>1.2519882</td>
</tr>
<tr>
<td>ln(age)$^*$ln(age)</td>
<td>-2.93323</td>
<td>15.2144965</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


\[1 \text{ if age} > 70 \text{ then ln(70)$^*$smoker} \]

\[2 \text{ if age} > 78 \text{ then ln(78)$^*$smoker} \]

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

**Men**

For each subject:

1. Calculate $L_{\text{men}} = \beta_{\ln(age)^*\ln(age)} + \beta_{\ln(t_{\text{chol})^*\ln(t_{\text{chol})}} + \beta_{\ln(hdl)^*\ln(hdl)} + \beta_{\ln(sbp)^*\ln(sbp)} + \beta_{\text{trt\_htn}^*(\text{if trt\_htn})} + \beta_{\text{smoker}^*(\text{if smoker})} + \beta_{\ln(age)^*\ln(t_{\text{chol})} + \beta_{\ln(age)^*\text{smoker}^*(\text{if smoker})} + \beta_{\ln(age)^*\ln(age)}$
2. Calculate $A_{\text{men}} = L_{\text{men}} - 172.300168$ (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$_{men} = P_{men} \times 100$ (rounded to nearest integer)

**Women**

For each subject:

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

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$_{women} = P_{women} \times 100$ (rounded to nearest integer)

**Notes**

- For men, if subject is > age 70, then use $\ln(70) \times \text{smoker}$
- For women, if subject is > age 78, then use $\ln(78) \times \text{smoker}$
- For dichotomous variables $\text{trt\_htn}$ and $\text{smoker}$ use 1/0 to represent yes/no respectively
  - If a subject has $\text{sbp} \leq 120$ mmHg, then $\text{trt\_htn}$ is no

Calculated scores should match the interactive calculator

Appendix E. Patient-reported Outcome Forms/Instruments

D1. The Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?
   1. Yes
   2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.

3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

   0 1 2 3 4 5 6 7 8 9 10
   No Pain Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

   0 1 2 3 4 5 6 7 8 9 10
   No Pain Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

   0 1 2 3 4 5 6 7 8 9 10
   No Pain Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

   0 1 2 3 4 5 6 7 8 9 10
   No Pain Pain as bad as you can imagine
The BPI-SF captures information on the intensity of pain (pain severity) as well as the degree to which pain interferes with function (pain interference). Raw scores (0-10) for single item question will be used for each item. The scoring for composite pain severity and pain interference base on the developer approved algorithm. No imputation on the missing PRO data.
**Brief Pain Inventory Scoring Instructions:**

1. **Pain Severity Score**

This is calculated by adding the scores for questions 3, 4, 5 and 6 and then dividing by 4. This gives a severity score out of 10.

2. **Pain Interference Score**

This is calculated by adding the scores for questions 9a, b, c, d, e, f and g and then dividing by 7. This gives an interference score out of 10.
D2. Short Form (36) Health Survey

SF-36 items will be scored according to the SF-36 version 2.0 QualityMetric Scoring Software.

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

For each of the following questions, please mark an ☐ in the one box that best describes your answer.

1. In general, would you say your health is:

   - Excellent  ▼
   - Very good  ▼
   - Good  ▼
   - Fair  ▼
   - Poor  ▼

   ☐ 1  ☐ 2  ☐ 3  ☐ 4  ☐ 5

2. Compared to one year ago, how would you rate your health in general now?

   - Much better now than one year ago  ▼
   - Somewhat better now than one year ago  ▼
   - About the same as one year ago  ▼
   - Somewhat worse now than one year ago  ▼
   - Much worse now than one year ago  ▼

   ☐ 1  ☐ 2  ☐ 3  ☐ 4  ☐ 5
3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

<table>
<thead>
<tr>
<th></th>
<th>Yes, limited a lot</th>
<th>Yes, limited a little</th>
<th>No, not limited at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>b</td>
<td>Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>c</td>
<td>Lifting or carrying groceries</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>d</td>
<td>Limming several flights of stairs</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>e</td>
<td>Climbing one flight of stairs</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>f</td>
<td>Bending, kneeling, or stooping</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>g</td>
<td>Walking more than a mile</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>h</td>
<td>Walking several hundred yards</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>i</td>
<td>Walking one hundred yards</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>j</td>
<td>Bathing or dressing yourself</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
</tbody>
</table>
4. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

- a. Cut down on the amount of time you spent on work or other activities
  - □ 1 □ 2 □ 3 □ 4 □ 5

- b. Accomplished less than you would like
  - □ 1 □ 2 □ 3 □ 4 □ 5

- c. Were limited in the kind of work or other activities
  - □ 1 □ 2 □ 3 □ 4 □ 5

- d. Had difficulty performing the work or other activities (for example, it took extra effort)
  - □ 1 □ 2 □ 3 □ 4 □ 5

5. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?**

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

- a. Cut down on the amount of time you spent on work or other activities
  - □ 1 □ 2 □ 3 □ 4 □ 5

- b. Accomplished less than you would like
  - □ 1 □ 2 □ 3 □ 4 □ 5

- c. Did work or other activities less carefully than usual
  - □ 1 □ 2 □ 3 □ 4 □ 5
6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7. How much bodily pain have you had during the past 4 weeks?

<table>
<thead>
<tr>
<th>None</th>
<th>Very mild</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very severe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little bit</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
</tbody>
</table>

a. Did you feel full of life?

b. Have you been very nervous?

c. Have you felt so down in the dumps that nothing could cheer you up?

d. Have you felt calm and peaceful?

e. Did you have a lot of energy?

f. Have you felt downhearted and depressed?

g. Did you feel worn out?

h. Have you been happy?

i. Did you feel tired?

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
</tbody>
</table>
11. How TRUE or FALSE is each of the following statements for you?

<table>
<thead>
<tr>
<th>Definitely true</th>
<th>Mostly true</th>
<th>Don’t know</th>
<th>Mostly false</th>
<th>Definitely false</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="square" alt="Definitely true" /></td>
<td><img src="square" alt="Mostly true" /></td>
<td><img src="square" alt="Don’t know" /></td>
<td><img src="square" alt="Mostly false" /></td>
<td><img src="square" alt="Definitely false" /></td>
</tr>
</tbody>
</table>

a. I seem to get sick a little easier than other people
   - [ ] 1
   - [ ] 2
   - [ ] 3
   - [ ] 4
   - [ ] 5

b. I am as healthy as anybody I know
   - [ ] 1
   - [ ] 2
   - [ ] 3
   - [ ] 4
   - [ ] 5

c. I expect my health to get worse
   - [ ] 1
   - [ ] 2
   - [ ] 3
   - [ ] 4
   - [ ] 5

d. My health is excellent
   - [ ] 1
   - [ ] 2
   - [ ] 3
   - [ ] 4
   - [ ] 5