Statistical Analysis Plan

Protocol Title:	A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Safety and Efficacy of Evolocumab (AMG 145) in addition to Optimal Stable Background Statin Therapy in Chinese Subjects with Primary Hypercholesterolemia and Mixed Dyslipidemia
Short Protocol Title:	**Safety and Efficacy of Evolocumab in CHinese SUbjects with PrimAry HypercholesTerolemia and Mixed Myslipidemia on BackgroUnd Oral Statin Therapy (HUA TUO 华佗)**
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	12 JUN 2019	N/A
Amendment 1 (v2.0)	30 NOV 2020	• Added short protocol title. • Updated Section 3.2 to include details on the subjects not to be included in the analysis. • Updated the definition of Enrolment date and End of IP date in Section 5.1. • Updated the definition of TEAE in Section 5.3. • Updated Table 9-1 to include all the supplementary analysis defined in Section 9.5.1.1. • Added an additional sensitivity analysis of applying separated analytical window for subjects who report protocol deviation code 953 in Section 9.5.1.1. • Updated Section 9.5.3 to include additional exploratory analysis. • Updated Section 9.6.1 to clarify that summary of treatment emergent adverse events will include treatment emergent adverse events and disease related events and a separate table for disease related events will be provided as per suggestion from ASAE Adoption Committee (AAC). • Combined previously numbered Sections 9.6.9 and 9.6.10 to one section to avoid duplicated information. • Added an additional analytical window for subjects reporting protocol deviation code 953 in Appendix F.

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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
ACC	American College of Cardiology
AE	Adverse event
AHA	American Heart Association
AI	Autoinjector
ALT	Alanine aminotransferase
ApoA1	Apolipoprotein A-I
ApoB	Apolipoprotein B
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
CAS	Completer analysis set
CHD	Coronary heart disease
CK	Creatine phosphokinase
CMH	Cochran mantel-haenszel
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
EAS	European Atherosclerosis Society
eCRF	Electronic case report form
EOIP	End of Investigational Product
EOS	End of study
ESC	European Society of Cardiology
FAS	Full analysis set
GSO-DM	Global study operations-data management
HbA1c	Hemoglobin a1c
HDL-C	High-density lipoprotein cholesterol
HGRAC	**Human Genetic Resource Administration office of China**
IP	Investigational product
IPDs	Important protocol deviations
IVRS	Interactive Voice Response System
LDL-C	Low-density lipoprotein cholesterol
LFT	Liver function test
Lp(a)	Lipoprotein(a)
MedDRA	Medical Dictionary for Regulatory Activities
NCEP ATP III	National Cholesterol Education Panel Adult Treatment Panel III

PCSK9	Proprotein convertase subtilisin/kexin type 9
Q2W	Once in 2 Weeks
QM	Once monthly
SAE	Serious Adverse Event
SC	Subcutaneous
SCORE	Systematic Coronary Risk Estimation
SD	Standard deviation
TEAE	Treatment emergent adverse event
UC	Ultracentrifugation
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol
WHO DRUG	World Health Organization drug

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for study 20150172, Evolocumab dated 06 June 2016. The scope of this plan includes the primary analysis that is planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of 12 weeks of subcutaneous (SC) evolocumab every 2 weeks or every 4 weeks compared with placebo, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) when used in addition to optimal stable background statin therapy in Chinese subjects with primary hypercholesterolemia and mixed dyslipidemia.	• Mean percent change from baseline in LDL-C at weeks 10 and 12 • Percent change from baseline in LDL-C at week 12

The co-primary estimands consist of:

- Target population, which is adult Chinese subjects diagnosed with primary hypercholesterolemia and mixed dyslipidemia receiving optimal stable background statin therapy.
- The co-primary variables, which are
  - mean percent change from baseline in LDL-C at weeks 10 and 12
  - percent change from baseline in LDL-C at week 12
- The intercurrent events are discontinuation of investigational product or commencing commercial proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. For the primary estimands, the treatment effects will be estimated for all patients who receive at least one dose of investigational product, and regardless of the intercurrent events described above.
- Summary measures, which are
  - Least squares mean (LSM) difference between evolocumab SC 140 mg Q2W and placebo SC Q2W for mean percent change from baseline in LDL-C at weeks 10 and 12
  - LSM difference between evolocumab SC 420 mg QM and placebo SC QM for mean percent change from baseline in LDL-C at weeks 10 and 12.
  - LSM difference between evolocumab SC 140 mg Q2W and placebo SC Q2W for percent change from baseline in LDL-C at week 12.
  - LSM difference between evolocumab SC 420 mg QM and placebo SC QM for percent change from baseline in LDL-C at week 12.

The co-primary estimands are:

For the target population described above, who received at least one dose of IP and regardless of the intercurrent events described above:

1. LSM difference between evolocumab SC 140 mg Q2W and placebo SC Q2W for mean percent change from baseline in LDL-C at weeks 10 and 12.
2. LSM difference between evolocumab SC 420 mg QM and placebo SC QM for mean percent change from baseline in LDL-C at weeks 10 and 12.
3. LSM difference between evolocumab SC 140 mg Q2W and placebo SC Q2W for percent change from baseline in LDL-C at week 12.
4. LSM difference between evolocumab SC 420 mg QM and placebo SC QM for percent change from baseline in LDL-C at week 12.

Secondary	
• To evaluate the effect of 12 weeks of SC evolocumab Q2W or QM, compared with placebo, on change from baseline in LDL-C, achievement of target LDL-C < 70 mg/dL (1.8 mmol/L), LDL-C response (50% reduction of LDL-C from baseline) and percent change from baseline in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol, lipoprotein(a) [Lp(a)], triglycerides, HDL-C, very low-density lipoprotein cholesterol (VLDL-C) when used in addition to optimal stable background statin therapy in Chinese subjects with primary hypercholesterolemia and mixed dyslipidemia.	The mean of weeks 10 and 12 and for week 12 for the following. **Tier 1** • Change from baseline in LDL-C • Percent change from baseline in non-HDL-C • Percent change from baseline in ApoB • Percent change from baseline in total cholesterol • Achievement of target LDL-C < 70 mg/dL (1.8 mmol/L) • LDL-C response (50% reduction of LDL-C from baseline) **Tier 2** • Percent change from baseline in Lp(a) • Percent change from baseline in triglycerides • Percent change from baseline in HDL-C • Percent change from baseline in VLDL-C

<u>Secondary Estimands</u>

The descriptions for the estimands supporting the secondary objectives are the same as for the primary estimands, except the variable attribute will change for each of the Tier 1 and Tier 2 endpoints listed. Exceptions include the endpoints achieving the target LDL-C < 70 mg/dL and LDL-C response (50% reduction of LDL-C from baseline) where the summary measure is the difference in proportions rather than LSM difference.

Exploratory	
• To evaluate the effect of 12 weeks of SC evolocumab Q2W or QM, compared with placebo on change from baseline in high sensitivity C-reactive protein (hsCRP) and on percent change from baseline in apolipoprotein A1 (Apo A1) when used in addition to optimal stable background statin therapy in Chinese subjects with primary hypercholesterolemia and mixed dyslipidemia.	• Mean percent change from baseline in Apo A1 at weeks 10 and 12 • Percent change from baseline in Apo A1 at week 12 • Change from baseline in hsCRP
• To evaluate the effect over time of SC evolocumab Q2W or QM, compared with placebo, 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, apolipotrotein B (ApoB), VLDL-C, HDL-C, ApoA1, triglycerides and Lp(a) when used in addition to optimal stable background statin therapy in Chinese subjects with primary hypercholesterolemia and mixed dyslipidemia.	• PCSK9 change from baseline at each scheduled assessment • Change and percent change from baseline at each scheduled assessment in each of the following parameters: o LDL-C o Total cholesterol o Non-HDL-C o ApoB o VLDL-C o HDL-C o ApoA1 o Triglycerides o Lp(a)
Safety	
• To evaluate the safety and tolerability of SC evolocumab Q2W and QM when used in combination with optimal stable background statin therapy in Chinese subjects with primary hypercholesterolemia and mixed dyslipidemia	• Subject incidence of treatment emergent adverse events • Safety laboratory values and vital signs at each scheduled assessment • Incidence of anti-evolocumab antibody (binding and neutralizing) formation

2.2 Hypotheses and/or Estimations

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

Within each dose frequency, the null hypothesis is that there is no difference in means, in the mean percent change from baseline at weeks 10 and 12, or in the percent change from baseline at week 12 in LDL-C, between evolocumab and placebo, when used in combination with optimal stable background statin therapy in Chinese subjects with primary hypercholesterolemia and mixed dyslipidemia. The alternative hypothesis is that a mean difference does exist.

3. Study Overview

3.1 Study Design

This is a phase 3, multicenter, double-blind, randomized, placebo-controlled study of evolocumab in Chinese subjects with hypercholesterolemia and mixed dyslipidemia. Subjects, who have signed the informed consent form (ICF), will have fasting lipids measured and all inclusion and exclusion criteria assessed. Subjects should maintain their current diet and exercise regimen. Subjects who, in the opinion of the investigator require statin up-titration or dietary adjustment can be rescreened after 1 month. Subjects can only be rescreened once. Statins may not be down-titrated with subsequent rescreened. Subjects who screen fail due to the LDL-C below the limit for eligibility during final screening cannot be rescreened. Baseline statin therapy is expected to be continued unchanged throughout the study. Subjects will be randomized 2:2:1:1 into the following treatment arms:

- Evolocumab SC 140 mg Q2W,
- Evolocumab SC 420 mg QM,
- Placebo SC Q2W, or
- Placebo SC QM.

Randomization will be stratified by entry CV risk (high/very high CV risk vs. not high/very high CV risk).

The overall sample size will be approximately 450 subjects (150 subjects for each evolocumab dosing regimen). The sample size for each placebo will be approximately 75 subjects.

Evolocumab and placebo will be administered SC at the study site or in an appropriate non-clinic setting (eg, at home) by spring based prefilled autoinjector/pen (AI/Pen). Observed, in clinic dosing will occur at day 1, Week 8 (± 3 days) and Week 10 (± 3 days)

(as applicable). The dose frequencies of Q2W and QM will not be blinded but the identity of investigational product (evolocumab or matching SC placebo) will be blinded.

Subjects must tolerate a SC injection of placebo with a prefilled AI/Pen device to be used during the study prior to randomization.

All central laboratory results of ApoA1, ApoB, lipoprotein(a), PCSK9, hsCRP will be blinded from day 1 until unblinding of the clinical database and will not be reported to the investigator. Central laboratory results of the lipid panel will be blinded from day 1 until unblinding of the clinical database and will not be reported to the investigator. Investigators should not perform non protocol testing of these analytes during a subject's study participation and until at least 12 weeks after last investigational product administration, or the subject's end of study (EOS), whichever is later.

Approximately 40 sites in China will participate in this study. Treatment and follow-up period will be 12 weeks with an additional phone call or other subject contact at week 14 for subjects receiving investigational product Q2W. The EOS for subjects on QM investigational product is at the week 12 visit which must be at least 30 days post last dose of investigational product. The EOS for subjects on Q2W investigational product is a telephone call from the site at week 14 (and at least 30 days post last dose of investigational product) for any potential adverse events, adverse device effects (ADEs), disease related events (DREs) and serious adverse events. Subjects will be encouraged to complete all planned visits regardless of their adherence to investigational product administration.

3.2 Sample Size

The sample size for this study has been considered to meet the requirement from regulatory authority (Drug Registration Regulation No 28; Oct 2007).

The planned total sample size is 450 subjects (150 randomized to evolocumab SC 140 mg Q2W, 150 randomized to evolocumab SC 420 mg QM, 75 randomized to placebo Q2W and 75 randomized to placebo QM). The primary analysis will require the tests of each co-primary endpoint to be significant at level of 0.05. The sample size should provide adequate power to determine the superiority of evolocumab (either Q2W or QM) relative to respective placebo (Q2W or QM) as measured by the co-primary endpoints.

From the phase 3 study 20120122 and phase 2 study 20110155, the mean treatment effect of evolocumab 140 mg Q2W and 420 mg QM compared to placebo in percent

change from baseline in LDL-C at week 12 was at least -50.3%, with the smallest treatment effect of -44.6% estimated from 95% confidence intervals. For the co-primary endpoint of mean percent change from baseline in LDL-C at weeks 10 and 12, the mean treatment effect of evolocumab 140 mg Q2W and 420 mg QM compared to placebo was at least -62.4%, with the smallest treatment effect of -57.2% estimated from 95% confidence intervals.

The assumed treatment effect of evolocumab in LDL-C reduction is 40%, with a common SD of 25%. As the co-primary endpoints are correlated, the planned sample size will provide approximately at least 98% (99% x 99%) power in testing the superiority of each evolocumab dosing regimen over placebo on the co-primary endpoints, assuming a 10% drop out rate.

Since the testing statistics from Q2W and QM groups are independent, there is a 96% chance (98% x 98%) to show the superiority of both evolocumab dosing regimens over placebo.

The power calculation is derived using SAS Enterprise Guide version 6.1.

Seventeen subjects who were enrolled in the study will be excluded from all analyses (both efficacy and safety) because they would require additional Human Genetic Resource Administration office of China (HGRAC) approvals, as follows:

- **According to the Administrative Regulations on Human Genetic Resources of the People's Republic of China, effective on 01 July 2019, if a study screens ≥ 500 Chinese subjects, the study must complete the HGRAC sample collection application. Twelve subjects in Study 20150172 were enrolled after screening had reached 500; therefore, these 12 subjects will be excluded from the analyses.**
- **Under this same regulation, foreign-invested hospitals cannot participate in this application. Suzhou Kowloon Hospital, which enrolled 5 subjects in Study 20150172, is a Hong Kong-invested hospital, according to Implementation Regulations for Foreign Investment Law of P.R. China: "Investments in Mainland China by investors from Hong Kong Special Administrative Region shall be handled with reference to the Foreign Investment Law". [redacted], the 5 subjects enrolled at this site [redacted] will be excluded from the analysis.**

3.3 Adaptive Design

Not applicable

4. Covariates and Subgroups

4.1 Planned Covariates

- **Stratification factor -** Entry CV risk (high/very high CV risk vs. not high/very high CV risk).

4.2 Subgroups

Subgroup by stratification factor

- Entry CV risk (high/very high CV risk vs. not high/very high CV risk).

Subgroup by baseline characteristics

- Age (< 65 years, ≥ 65 years)
- Sex (female, male)
- Medical history of Diabetes Mellitus (yes/no)
- Baseline LDL-C (< median, ≥ median)
- Family history of premature CHD (yes, no)
- Baseline PCSK9: (< median, ≥ median)
- Body Mass Index (BMI; < 25 kg/m^2, 25 - < 30 kg/m^2, ≥ 30 kg/m^2)
- Hypertension (yes, no)
- Current smoker (yes, no)
- Baseline CHD risk factors ≥ 2 (yes, no)
- Baseline triglycerides (< median, ≥ median)
- Diagnosis of HeFH according to protocol defined criteria (yes/no)

5. Definitions

5.1 Study Time Points

Enrollment Date

Enrollment date is defined as the date **collected on the eCRF**.

Randomization Date

Randomization Date is defined as the date subject was allocated to a treatment group.

First Dose Date of SC Investigational Product (First SCIPD)

For each subject, the first dose date of SC investigational product is defined as the date of first administration of the SC IP.

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 last administration of the SC IP.

Study Day 1

Study Day 1 is defined as the date of first investigational product (IP) administration or the date of randomization for subjects who are not administered any dose of IP.

Study Day

For each subject, and for a given date of interest, study day is defined as the number of days since Study Day 1:

Study day = (date of interest – Study Day 1 date) + 1.

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

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

End of Investigational Product (EOIP) Date

End of IP date for each subject is defined as **the date the decision was made to end the IP as recorded on the End of IP eCRF page.**

End of Study (EOS) Date

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

Study End Date

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

5.2 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 lipids (total cholesterol, HDL-C, **non-HDL-C,** LDL-C, VLDL-C and triglycerides), ApoA1, ApoB, Lp(a) and their derived parameters (eg, ratio between them) are defined as the mean of the two most recent non-missing 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 all other variables, the baseline value is defined as the last non-missing value collected prior to or on Study Day 1.

Change (absolute change) from Baseline

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

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

Percent Change from Baseline

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

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

Baseline CHD Risk Factors

A subject will be categorized as having two or more CHD Risk Factors (Y/N) if they have at least two 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.

Framingham Risk Score (FRS)

10-year cardiovascular risk will be calculated using the Framingham Risk Score (FRS). The method to calculate the FRS is described in Appendix C.

ACC/AHA Risk Estimator

10-year risk of ASCVD will be calculated using the Pooled Cohort Equations from the 2013 ACC/AHA cardiovascular risk assessment guideline (Goff et al, 2013; Appendix D).

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.

5.3 Other Study Related Definitions

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)

SC IP includes Evolocumab SC 140 mg Q2W, Evolocumab SC 420 mg QM and their corresponding SC placebo.

IP Exposure Period in Months

For each Q2W subject:

IP Exposure Period = [min (Last SCIPD + 14 days, EOS Date) - First SCIPD + 1]/ 365.25 * 12

For each QM subject:

IP Exposure Period = [min (Last SCIPD + 28 days, EOS Date) - First SCIPD +1] / 365.25 * 12

Study Exposure Period in Months

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

Treatment Emergent Adverse Event (TEAE)

Events categorized as Adverse Events (AEs) starting on or after first dose of investigational product as determined by **"Did event start before first dose of**

investigational product" equal to "No" or missing on the Events eCRF, and up to 30 days after the last dose of investigational product or EOS date, whichever is earlier.

Treatment Emergent Serious Adverse Event (**TE**SAE)

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

Reflexive Approach for LDL-C and VLDL-C

For all analyses related to LDL-C and VLDL-C, unless specified otherwise, the following reflexive approach will be used. When calculated LDL-C is less than 40 mg/dL or triglycerides > 400 mg/dL, the UC LDL-C value from the same blood sample will be used instead of calculated LDL-C and the UC VLDL-C value from the same blood sample will be used instead of calculated VLDL-C, 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 10 and 12 is defined using the mean of non-missing LDL-C values at those two timepoints (if one is missing, mean equals the available one). If both the values at weeks 10 and 12 are missing, the subject is considered without the achievement.

LDL-C response (50% reduction from baseline)

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

Mean response of LDL-C 50% reduction at weeks 10 and 12 is defined using the mean of non-missing LDL-C percent change from baseline values at those two timepoints (if one is missing, mean equals the available one). If both the values at weeks 10 and 12 are missing, the subject is considered without the response when statistical inference is performed.

6. Analysis Sets

6.1 Full Analysis Set

The full analysis set (FAS) includes all randomized subjects who received at least 1 dose of IP **excluding the 17 subjects that require additional Human Genetic Resource Administration office of China approval (Refer Section 3.2 for details)**. In efficacy analysis, subjects will be analyzed according to their randomized treatment group assignment.

6.2 Safety Analysis Set

Safety Analysis Set is same as the Full Analysis Set. For safety analyses, subjects will be grouped according to their actual treatment group (as defined in Section 5.3).

6.3 Study-specific Analysis Sets

Completers Analysis Set

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

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

No interim analysis is planned for this study.

7.2 Primary Analysis

The primary analysis will be performed, when all subjects have either completed the study, 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 **for analyses. Based on the snapshot, efficacy and safety analyses will be performed.**

7.3 Final Analysis

Not applicable for this study.

8. Data Screening and Acceptance

8.1 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.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses **including data from RAVE**

database and central lab data (outside of RAVE database). The database will be subjected to edit checks outlined in the Data Management Plan (DMP). Additional details will be provided in DMP and Data Acquisition Requirements Specifications (DARS).

8.3 Handling of Missing and Incomplete Data

8.3.1 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. All attempts will be made to capture missing or partial data for this trial prior to the database lock.

8.3.2 Missing Lipid Measurements

For efficacy endpoints, where the analysis method is repeated measures linear effects model, missing lipid measurements will not be imputed. The handling of missing LDL-C response (50% reduction of LDL-C from baseline) and achievement of target LDL-C < 70 mg/dL is provided in Section 5.3. Sensitivity analysis will be performed on the co-primary endpoints to evaluate the robustness of the missing at random assumption, used in the repeated measures linear effects model as described in Section 9.5.1.1.

8.3.3 Handling of Incomplete Dates

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

Table 8-1. Imputation Rule for Incomplete Dates

	Missing	Imputation	Exception
Start date (AE and concomitant medication)	Day	1	Default to Study Day 1 if an event starts the same year and month as Study Day 1
	Day/Month	1-Jan	Default to Study Day 1 if an event starts the same year as Study Day 1

8.4 Detection of Bias

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

- Major protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints.
- Subject level unblinding before final database lock and formal unblinding.

Important protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints will be tabulated in the Clinical Study Report (CSR).

Any unblinding of individual subjects prior to formal unblinding of the study will be documented in the CSR. The impact of such unblinding on the results observed will be assessed. Data from subjects whose treatment assignments are unblinded prior to formal unblinding will be listed. The timing and reason for unblinding will be included in these listings.

Additional sensitivity and/or supplementary analyses may be included to assess the impact of potential biases on the co-primary endpoints. If any sensitivity analyses are required to evaluate potential biases in the study's conclusions, then the sources of the potential biases and results of the sensitivity and/or supplementary analyses will be documented in the CSR.

8.5 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.

8.6 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.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained and, output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

The efficacy and safety analyses will be performed on the FAS. Unless specified otherwise, the FAS will be the default analysis set in this study and data will be summarized by randomized treatment group **using the analysis window specified in Table 12-1**. Analyses will be performed separately by each dose frequency (Q2W and QM) unless specified otherwise.

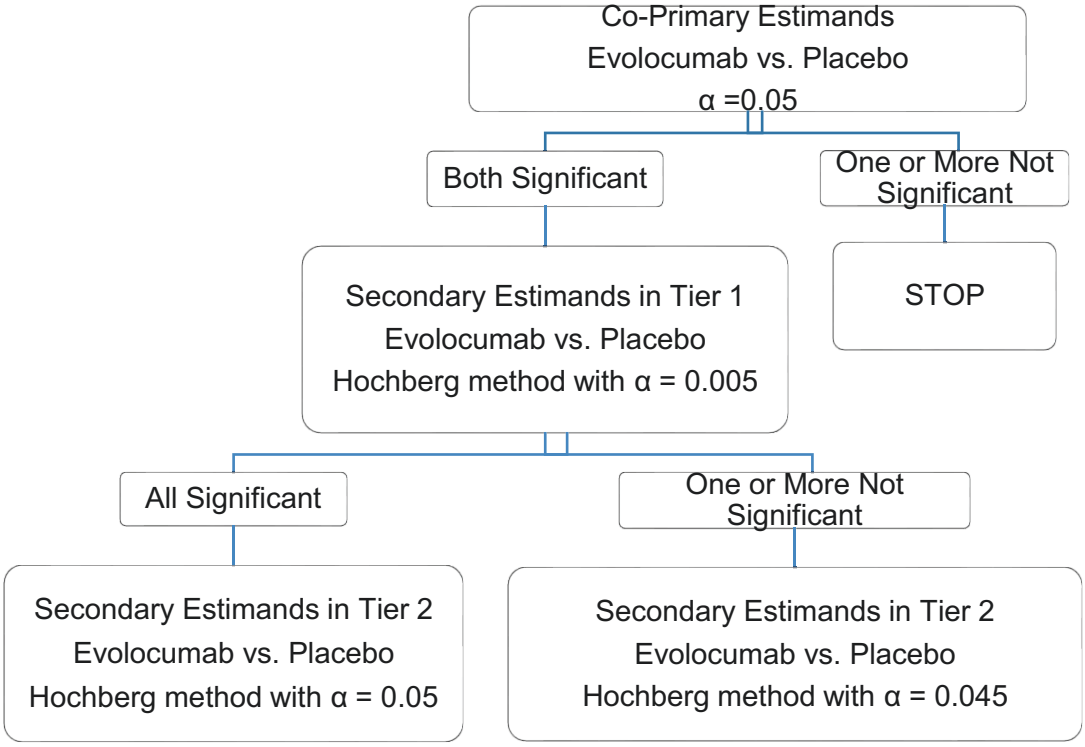
Subject disposition, demographics, baseline characteristics and exposure to IP will be summarized by treatment group. Summary statistics for continuous variables will include the number of subjects, mean, median, SD or standard error, minimum, and maximum. For categorical variables, the frequency and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

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

Multiplicity Adjustment Method

The analyses of Q2W and QM will be performed as 2 independent experiments. To preserve the familywise error rate at 0.05 within each independent experiment (Q2W and QM), methods of adjusting for multiplicity due to multiple estimands (co-primary and secondary efficacy estimands) within each dose frequency are described in the diagram below (Figure 9-1).

Figure 9-1. Multiplicity Adjustment Methods



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

1. If the treatment effect from the primary analysis of the co-primary estimands are both significant at a significance level of 0.05, statistical testing of the tier 1 secondary efficacy estimands will follow the Hochberg procedure at a significance level of 0.005 (Hochberg, 1988)
2. If all tier 1 secondary efficacy estimands are significant, the tier 2 secondary efficacy estimands will be tested using the Hochberg procedure at a significance level of 0.05.
3. If not all tier 1 secondary efficacy estimands are significant, the tier 2 secondary efficacy estimands 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.

9.2 Subject Accountability

The number of subjects who were screened, randomized, received IP, completed IP, discontinued IP and reasons for discontinuing, completed study, discontinued study and reasons for discontinuing**, including due to COVID-19, if applicable,** will be summarized by treatment group.

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

The number and percentage of subjects randomized will be tabulated by study site.

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

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

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol.

The number of subjects meeting Protocol Deviations due to COVID-19 will be summarized. A Protocol Deviations listing of subjects impacted due to COVID-19 will also be provided.

9.4 Demographic and Baseline Characteristics

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

9.5 Efficacy Analyses

Table 9-1. Primary Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	Sensitivity and/or Supplementary Analysis
• Mean percent change from baseline at weeks 10 and 12 in LDL-C • Percent change from baseline at week 12 in LDL-C	Repeated Measures Model assuming Missing at Random (MAR), including all values observed (on and off IP)	Sensitivity analysis: • Multiple imputation to handle missing primary variables • **Applying a separated analytical window to subjects who have protocol deviation code 953 (COVID-19 out-of-window visit).** Supplementary analysis: • **Primary analysis will be repeated using CAS** • Non-parametric analyses will be performed if assumption of normality is violated

Table 9-2. Secondary Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	Sensitivity Analysis
• Mean LDL-C achievement of target LDL-C < 70 mg/dL and LDL-C response of ≥ 50% reduction from baseline at weeks 10 and 12 • LDL-C achievement and response at week 12	Cochran Mantel-Haenszel (CMH) test	N/A
Mean percent change from baseline at weeks 10 and 12 Percent change from baseline at week 12 in each of the following lipid parameters: Lp(a), triglycerides, HDL-C and VLDL-C	Repeated measures model assuming MAR including all observed values (on and off IP)	N/A

9.5.1 Analyses of Primary Efficacy Endpoint(s)

To assess the co-primary endpoints as described in the co-primary estimands a repeated measures linear effects model including all observed values (on and off treatment) will be used on the FAS in each dose frequency to compare the efficacy of evolocumab with placebo. The repeated measures model will include terms for treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit. Missing values will not be imputed for primary analysis.

To account for the repeated LDL-C measurements within a subject across the visits, the repeated measures linear effects model will use an unstructured covariance.

Multiplicity adjustment procedures are defined in Section 9.1.

9.5.1.1 Sensitivity Analyses of Co-primary Endpoints

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

- Multiple imputation assuming MAR to handle missing primary variables
  - It will be assumed that the missing percent change values will be normally distributed with a mean 0 and a variance-covariance matrix the same as the observed variance-covariance matrix from subjects in the placebo group and have missing endpoint data.
  - If there are at least 25 subjects **in each treatment group** who discontinue **IP** but have non-missing endpoint data, an additional multiple imputation will be carried out utilizing the information from these subjects to impute the missing data for subjects **who discontinue IP** and have missing endpoint data.
- **An additional sensitivity analysis will be performed to evaluate the impact of COVID-related out of window visits. Primary analysis will be repeated using FAS. The subjects meeting protocol deviation code 953 (out-of-window visit) will use the analysis window defined in Table 12-2 and the remaining subjects will use the analysis window defined in Table 12-1 (ie, same visit window as the primary analysis).**

Supplementary analysis

- In addition to the sensitivity analysis, the primary analysis will be repeated using the CAS (described in Section 6.7) acknowledging there are limitations and biases with this analysis. A non-parametric analysis may also be performed if the assumption of normality is violated.

9.5.1.2 Covariate and Subgroup Analyses of Co-primary Endpoints

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

Subgroup analyses on the co-primary efficacy estimands will be conducted using the subgroups specified in Section 4.2. Treatment effect differences among subgroups, which represent subgroup by treatment interactions, will be estimated and tested based on statistics from the subgroup repeated measures models.

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

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

The statistical model and testing of the tier 1 secondary efficacy endpoints as described in estimands supporting the secondary objectives, will be similar to the primary analysis of the co-primary estimands. The secondary estimands of achievement of target LDL-C < 70 mg/dL and LDL-C response of ≥ 50% reduction from baseline will be analyzed using the Cochran-Mantel Haenszel (CMH) test adjusted by the stratification factor.

Analyses of the tier 2 secondary efficacy estimands will use the same analysis model as the tier 1 estimands, Refer to Section 9.1 and Figure 9-1 for multiplicity adjustment for multiple tier 1 and tier 2 secondary endpoints.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

Exploratory endpoints related to lipid parameters and PCSK9 will be summarized by randomized treatment group and by scheduled visit using descriptive statistics. Figures will be provided for change from baseline and percent change from baseline analyses.

Achievement of target LDL-C < 55 mg/dL and < 40 mg/dL will be analyzed using the Cochran-Mantel Haenszel (CMH) test adjusted by the stratification factor.

A shift table for hsCRP will be provided, for levels at baseline to maximum post-baseline value (<1, 1-3, >3 mg/L), by treatment group.

9.6 Safety Analyses

9.6.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 or later will be used to code all events categorized as adverse events (AEs) to a system organ class and a preferred term. Severity of AEs will be graded using the CTCAE and recorded on the eCRF. All treatment-emergent adverse event tables will be summarized by actual treatment group. Treatment-emergent adverse events are events with an onset after the administration of the first dose of IP as defined in Section 5.3.

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

Summaries of treatment-emergent and serious AEs occurring in at least 1% of the subjects by preferred term in any treatment arm will be provided in descending order of frequency.

All the summary of treatment-emergent adverse event/serious adverse event mentioned above will also include those reported as Disease Related Events (DRE). Subject incidence of DREs will be summarized **separately** by system organ class and preferred term for all treatment-emergent DREs and fatal DREs **as well**.

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

Subject incidence of treatment-emergent adverse events associated with injectable protein therapies will be summarized by category and preferred term:

- Injection site reactions
- Hypersensitivity or allergic reactions

9.6.2 Laboratory Test Results

Descriptive statistics will be provided for actual values and changes from baseline in select laboratory parameters at each protocol-specified scheduled visit. Laboratory analytes are provided in the protocol Table 2. Lab shift tables using the CTCAE grading scale v4.03 or later will be used for the select analytes of interest, when applicable.

In addition, CK and liver function test (LFT) abnormalities will be assessed by the incidence overall and by visits of the following categories:

- CK > 5 x ULN
- CK > 10 x ULN
- ALT or AST > 3 x ULN
- ALT or AST > 5 x ULN
- Total bilirubin > 2 x ULN
- (ALT or AST > 3 x ULN) and Total bilirubin > 2 x ULN and Alkaline Phosphatase < 2 x ULN

9.6.3 Vital Signs

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

9.6.4 Antibody Formation

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

9.6.5 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product by treatment group.

9.6.6 Exposure to Other Protocol-required Therapy

The number and proportion of subjects receiving selected lipid regulating medications captured on the **"Other Protocol Required Therapy – [Statin (Lipid Lowering Therapy)]"** eCRF will be summarized by **preferred term or category for each treatment group as coded by the World Health Organization Drug (WHO DRUG) dictionary**. Summaries will be provided for baseline use and use after Study Day 1. The subject incidence of changes in lipid regulating medications during the treatment period will also be provided by treatment group.

10. Changes From Protocol-specified Analyses

Eighteen subjects who were enrolled in the study will be excluded from all analyses (both efficacy and safety) because they would require additional Human Genetic Resource Administration office of China (HGRAC) approvals, as follows:

- **According to the Administrative Regulations on Human Genetic Resources of the People's Republic of China, effective on 01 July 2019, if a study screens 500 Chinese subjects, the study must complete the HGRAC sample collection application. Thirteen subjects in Study 20150172 were enrolled after screening had reached 500; therefore, these 13 subjects will be excluded from the analyses.**

- **Under this same regulation, foreign-invested hospitals cannot participate in this application. Suzhou Kowloon Hospital, which enrolled 5 subjects in Study 20150172, is a Hong Kong-invested hospital, according to Implementation Regulations for Foreign Investment Law of P.R. China: "Investments in Mainland China by investors from Hong Kong Special Administrative Region shall be handled with reference to the Foreign Investment Law". [redacted], the 5 subjects enrolled at this site [redacted] will be excluded from the analysis.**

11. Literature Citations / References

Goff DC, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk. *Circulation*. 2013;129:S49-S73.

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). ESC/EAS Guidelines for the management of dyslipidaemias. European Heart Journal. 2011; 32:1769–1818.

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

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

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

12. Appendices

Appendix A. Reference Values/Toxicity Grades

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 B. Lipid-lowering Background Therapy

Lipid Modifying Background Therapy Intensity

(Group A) Intensive statin usage	Subject has at least one of the following recorded for the last 4 weeks prior to screening: • Atorvastatin ≥ 40 mg QD • Rosuvastatin ≥ 20 mg QD • Simvastatin ≥ 80 mg QD (note that simvastatin 80 mg QD is not approved in some countries e.g., the United States) • Any statin[1] QD plus ezetimibe
(Group B) Non-intensive statin usage	Subject has been taking any dose of a statin at least weekly for the last 4 weeks prior to screening and is not included in Group A
(Group C) No statin	Subject is not included in Group A or Group B

Note:

[1] Statin includes atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin.

Appendix C. Framingham Risk Score

The method to calculate Framingham Risk Score is described below.

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 uses the following coefficients β_i, where *i* represent each of the independent variables. The values below are from the Framingham heart study (http://www.framinghamheartstudy.org/risk/hrdcoronary.html).

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

Men		
Independent variable	Coefficient βi	mean
ln(age)	52.00961	3.8926095
ln(t_chol)	20.014077	5.3441475
ln(hdl)	-0.905964	3.7731132
ln(sbp)	1.305784	4.8618212
trt_htn (spb>120)	0.241549	0.1180474
smoker	12.096316	0.335602
ln(age)* ln(t_chol)	-4.605038	20.8111562
ln(age)*smoker[1]	-2.84367	1.2890301
ln(age)*ln(age)	-2.93323	15.2144965
[1] if age>70 then ln(70)*smoker		

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

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

Men

For each subject:

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

Notes

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

Calculated scores should match the interactive calculator

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

Appendix D. Pooled Cohort Equations From 2013 ACC/AHA Cardiovascular Risk Assessment Guideline

Online ASCVD Risk Estimator: https://www.acc.org/tools-and-practice-support/mobile-resources/features/2013-prevention-guidelines-ascvd-risk-estimator.

	Cohorts			
	Men		Women	
	Non-African American/Black	African American/Black	Non-African American/Black	African American/Black
Parameter (Patient Level)	**Corresponding Coefficient** (β_i)			
x_1= Ln Age (years)	β_1= 12.344	β_1= 4.01	β_1 =-29.799	β_1 =17.114
x_2= (Ln Age)^2	β_2=N/A*	β_2=N/A	β_2=4.884	β_2=N/A
x_3= Ln Total Cholesterol(mg/dL)	β_3= 11.853	β_3= 5.36	β_3= 13.540	β_3= 0.940
x_4= Ln Age * Ln Total Cholesterol	β_4 =- 2.664	β_4 =N/A	β_4 =-3.114	β_4 =N/A
x_5= Ln HDL-C (mg/dL)	β_5= - 7.990	β_5=-0.307	β_5=-13.578	β_5=-18.920
x_6= Ln Age * Ln HDL-C	β_6=1.769	β_6=N/A	β_6=3.149	β_6=4.475
x_7= Ln Treated Systolic BP (mm Hg)	β_7=1.797	β_7=1.916	β_7=2.019	β_7=29.291
x_8= Ln Age * Ln treated Systolic BP	β_8=N/A	β_8=N/A	β_8=N/A	β_8=-6.432
x_9= Ln Untreated Systolic BP (mm Hg)	β_9=1.764	β_9=1.809	β_9=1.957	β_9=27.820
x_{10}= Ln Age * Ln Untreated Systolic BP	β_{10} =N/A	β_{10} =N/A	β_{10} =N/A	β_{10} =-6.087
x_{11}= Current Smoker (1=yes 0=No)	β_{11}=7.837	β_{11}=0.549	β_{11}=7.574	β_{11}=0.691
x_{12}= Ln Age * Current Smoker	β_{12}=-1.795	β_{12}=N/A	β_{12}=-1.665	β_{12}=N/A
x_{13}= Diabetes (1=Yes 0=No)	β_{13}=0.658	β_{13}=0.645	β_{13}=0.661	β_{13}=0.874
Parameter (Cohort Level)	**Given Value** (For each cohort)			
a=Cohort Constant	61.18	19.54	-29.18	86.16
b=Baseline Survival	0.9144	0.8954	0.9665	0.9533

For Patient level parameters (x_i for i in 1:13), multiply that patient's value by the appropriate coefficient (β_i) to get the patient-parameter value (z_i) then sum up the patient-parameter value of all the relevant parameters (z_1, z_2,…,z_{13}) to get the patient sum (y). Then, the estimated 10-year risk of first hard ASCVD is calculated as 1 minus the baseline survival, raised to the power of the exponent of the patient sum minus the Mean Value. Written as an equation this can be expressed as:

$$y = \sum_{i=1}^{n} \beta_i x_i$$

$$\text{Estimated } 10-\text{year risk of a first hard ASCVD} = 1 - b^{e^{y-a}}$$

*N/A means that particular parameter is not included in the calculation for that subgroup (can be thought of as β_i being equal to 0.)

Note: a=Cohort Constant, b=Baseline Survival, and β_i =Cohort Specific Parameter Coefficient are cohort specific values (eg, African American Woman), and x_i are patient specific values.

Example: White 43-year-old woman with Total-cholesterol=211mg/dL, HDL-C=52mg/dL, untreated systolic BP=117 mm Hg, smoker without diabetes. For this patient β_8 and β_{10} are not used due to being in the white female cohort. β_7 is also unused as they have untreated Systolic BP. x_{11}=1 and

x_{12}=ln(age)*1 as they are a smoker and x_{13}, x_{14}=0 as they do not have diabetes. In this case a=-29.18, b=0.9665 and β_i will be selected from the same column as a and b. The Final value this gives is

$$1 - 0.9665^{\exp(-27.546-(-29.18))} = 0.026 \text{ or } 2.6\% \text{ risk of hard ASCVD in 10-years}$$

Appendix E. Details of PK or PK/PD Methods for Modeling

Not applicable for this study.

Appendix F. Analytical Windows

Analytical Study Week Assignments

Analytical windows will be used to assign parameter measurements to study weeks. The algorithm is provided below.

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 12-1. Analytical Window for Primary Analysis

Analytical Study Week	Week 8	Week 10	Week 12
Scheduled Visit Day	57	71	85
Body Weight, Waist circumference, HbA1c, HCV, Hepatitis C viral load, hsCRP, Anti-evolocumab antibodies			>1
Chemistry, Hematology, Urinalysis	(1, 71]		(71, 91]
Vital Signs, Fasting Lipids, ApoA1, ApoB, Lp(a), PCSK9,	(1, 63]	(63, 77]	(77, 91]

Table 12-2. Analytical Window for Subjects Meeting PD 953 Used in Sensitivity Analysis

Analytical Study Week	**Week 8**	**Week 10**	**Week 12**
Scheduled Visit Day	**57**	**71**	**85**
Body Weight, Waist circumference, HbA1c, HCV, Hepatitis C viral load, hsCRP, Anti-evolocumab antibodies			**>1**
Chemistry, Hematology, Urinalysis	**(1, 71]**		**(71, 115]**
Vital Signs, Fasting Lipids, ApoA1, ApoB, Lp(a), PCSK9,	**(1, 63]**	**(63, 84]**	**(84, 99]**

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.