Statistical Analysis Plan

Protocol Title:	A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate the Impact of Evolocumab on Major Cardiovascular Events in Patients at High Cardiovascular Risk Without Prior Myocardial Infarction or Stroke
Short Protocol Title:	Effect of Evolocumab in Patients at High Cardiovascular Risk Without Prior Myocardial Infarction or Stroke
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Version Number	Date	Summary of Changes, including rationale for changes
Original (v1.0)	29 May 2019	N/A

Amendment 1 (v2.0)	06 March 2020	• Updates to study design section to be consistent with protocol amendment 2
		  ○ Updated lipid-lowering background therapy for at least 2 weeks from 4 weeks, and 'Subjects must be receiving stable, lipid-lowering background therapy as per local guidelines, starting at least 2 weeks prior to the qualifying lipid panel.'
		  ○ Added 'Optimized lipid-lowering therapy could be high, moderate, or low dose.'
		  ○ Added fasting to central laboratory results of the lipid panel
		  ○ Replaced 'should' with 'must' in vital status collection section
		• Addition of two exploratory efficacy endpoints, new or worsening aortic valve stenosis and new or recurrent venous thromboembolism, to be consistent with protocol amendment 2
		• Updates to sample size section
		  ○ Sample size reduction to 12,000 patients due to the annualized event rates of the primary endpoints in the placebo arm were updated based on Bhatt et al, 2019 and Steg et al, 2019
		  ○ Statistical power reduction to 95.6% at the time of 751 subjects with the primary triple component endpoint observed, and approximately 1254 subjects with the primary quadruple component endpoint observed
		  ○ Added 'two-sided' for significance level of type I error for each of the primary estimands
		• Added details on IDMC interim analyses to be consistent with the DMC charter and per FDA request
		• Added further details for tipping point analysis for primary efficacy endpoints per FDA request, including:
		  ○ Definition of missing follow-up data
		  ○ Assumptions for hazard rates and hazard ratios for the imputation of missing follow-up data
		  ○ Use of Rubin's rule to combine results from the analysis of the combined imputed and observed datasets

		• Added multiple imputation analysis to assess the impact of missing follow-up data on the primary estimands as an additional sensitivity analysis per FDA request • Added the programming codes for efficacy analysis in Appendix per FDA request • Added a covariate/subgroup 'Diabetes mellitus without significant coronary artery disease, atherosclerotic cerebrovascular disease, or peripheral arterial disease, and without a known arterial stenosis of 50% or more' in addition to inclusion criteria 104/108. • Other minor updates to be aligned with protocol amendment 2 o Removed 'subject incidence of' from subject incidence of treatment emergent (serious) adverse events in safety endpoints o LDL-C level 160 mg/dL [4.2 mmol/L] updated to [4.14 mmol/L] o Updated anticipated median baseline LDL-C to approximately 120 mg/dL from at least 125 mg/dL o Added 'potential' to be 'potential use of commercially available PCSK9 inhibitors' o Updated anticipated LDL-C difference between the evolocumab and placebo arms at the midpoint of the trial to approximately 1.7 mmol/L from at least 1.7 mmol/L o Covariate/subgroup: Race (white, non-white) updated to Race (white, black, other); other category in geographic region updated to others o Inclusion criteria 104 updated to 104/108 o Added 'major' for the subjects in the primary analysis as 'subjects at high risk of major cardiovascular events without prior MI or stroke' o Added 'All primary and secondary endpoint events reported and adjudicated at the time of database lock will be included in the primary analysis.'
Amendment 2 (v3.0)	06 September 2022	• Added coauthor [redacted], and document version and date • Updates to be aligned with protocol amendment 4 dated 31Aug2022 o Added IWRS to be 'IVRS/IWRS' o Added 'unless a change is clinically necessary' for lipid lowering background therapy o Replaced 'screening LDL-C/HDL-C/triglycerides' with 'LDL-C/HDL-C/triglycerides used for eligibility' and added 'The most recent LDL-C value (historical or screening) must be used.'

		○ Updated 'results may be requested by the investigator after unblinding of the clinical database' for the central laboratory results ○ Removed 'or the EOS, whichever is later' from the end of 'Investigators and staff involved with this trial should not perform non-protocol lipid panel testing during a subject's study participation and until at least 12 weeks after the subject's last administration of investigational product or the EOS, whichever is later' ○ Replaced 'geographic' region with 'geographical' region ○ Removed 'and the Executive Committee Chair, and Co-Chair' from the list that the DMC will communicate to ○ Updated intercurrent event strategy for the primary estimands and additional estimands to handle permanent IP discontinuation at site due to natural disaster or other significant event independent of the study and restructured estimand format ○ Added additional secondary endpoint – Time to CHD death or MI ○ Updated 3rd secondary endpoint to include ischemic stroke ○ Updated figure 9-1 to reflect changes to secondary endpoints ○ Added exploratory objective and endpoints for cardiovascular biomarkers, plasma proteome, and proteomic risk score, and their relationship to cardiovascular events ○ Updated subject follow-up to be a median of at least 4.5 years ○ Updated interim analysis schedule – one Interim Analysis at 75% of subjects with primary events. • Added 'Statin intolerance at screening (yes, no) [defined as no statin use at screening due to demonstrated intolerance to 2 or more statins]' and 'Use of lipid lowering therapy at baseline (yes, no)' as a subgroup and a planned covariate • Added including cigarette, pipe and cigar smokers for current smoker covariate and subgroup, SCORE categories, Framingham Risk Score for clarity • Clarified in Section 5. Definitions ○ Updated definitions of last dose date of investigational product (LDDIP) and vital status to align with database migration. The calculations of IP exposure period in months, treatment-emergent adverse event, and on-treatment estimand that involved LDDIP were updated accordingly.

		○ In the definition of baseline lipid and lipid-related parameters, added 'prior to the first dose of IP will be used' for both local and central laboratory. For central laboratory, the randomization date will be used when the first dose of IP is missing. ○ Updated ESC/EAS guidelines from 2011 to 2019 ○ Added 'Treatment-emergent' for serious adverse event ○ In Low-density Lipoprotein Cholesterol (LDL-C) definition, added Martin-Hopkins formula for the calculation of LDL-C ○ Added Coronary Heart Disease (CHD) Death • Added Lipid Sub-study Analysis Set in Section 6 • Added details about the Data Access Plan • Removed SOP-024846 • Updated 8.3.1 Handling of Incomplete Dates according to the current SAP template for CEC adjudicated events, adverse events, and non-lipid regulating concomitant medication, added imputation rules for partial date of change lipid regulating medication and local laboratory collection, and added an example of historical events which is more relevant to the study • Added 'The number of subjects who discontinue study due to administrative reasons (eg, site closure) will be summarized.' and 'The number and percent of subjects randomized will be tabulated by study site.' to 9.2 Subject Accountability • Added COVID-19 impact analyses to assess the impact due to COVID-19 control measures in Section 9.2 and 9.3 • Added 'COVID-19 contribution to death will be summarized as definite, possible, and none.' to Section 9.5, based on Clinical Events Committee charter version 3.0 • Added statin intolerance history to Baseline Characteristics • Updated LDL-C values to be assigned to yearly windows and analyzed according to yearly windows as appropriate • Added for subgroup analysis "All races (if appropriate) with less than 5% of the total enrolled subjects will be pooled together for summary purposes." • Added 'occurring between randomization and prior to or on the LCSSD' for aortic valve stenosis and venous thromboembolism exploratory endpoints; added patients with aortic valve replacement between randomization and LCSSD will be considered as an aortic valve stenosis event.

		• Updated MedDRA to version 25.0 • In Exposure to Concomitant Medication, added 'All statins will be converted to an atorvastatin equivalent dose in order to calculate total statin intensity for subjects taking more than one type of statins (Appendix D).', added atorvastatin equivalent factor and clarified high-intensity lipid-lowering regimen according to protocol in Appendix D • Added Hosmer and Lemeshow 1999 in citations • Updated Appendix A for lipid panel and vital signs • Updated URL for Framingham heart study, and removed the interactive calculator URL in Appendix B • Corrected the parameters for African American and added a note in Appendix C • Added Handling of Incomplete Dates for Lipid Regulating Concomitant Medication to Appendix F, Handling of Dates, Incomplete Dates and Missing Dates to Appendix G, Martin-Hopkins Formula to Estimate LDL-C to Appendix H, and moved Efficacy Analysis Code to Appendix I • Rearranged the sensitivity analyses in Appendix I

Amendment 3 (v4.0)	31 March 2023	• Updated coauthor from [redacted] to [redacted], updated document version and date, updated protocol version
		• Updated Study Day 1 to be defined as the randomization date for each subject in section 5.1
		• Updated LPEPD definition in section 5.1 to truncate LPEPD at death date
		• Added "Data supporting the primary and secondary endpoints at the interim analysis will be locked to prevent further changes" in Section 7.1
		• Added summary of subjects who discontinue IP due to IP supply discontinuation at site due to natural disaster/other significant event independent of the study to section 9.2
		• Updates based on Response to 10 November 2022 FDA Advice/Information Request Letter
		  ○ Added lag model as additional sensitivity analysis for adjusting for treatment lag in Section 8.6 and Section 9.5.1
		  ○ Updated tipping point analysis in Section 9.5.1 to explore piecewise hazard rates to impute the missing follow-up data if the constant hazard rate assumption is violated. Clarified that when using follow-up data from subjects who discontinue IP to impute missing follow-up data, only data after the last IP dose will be used.

		○ Added an additional analysis using a proportional hazards model for the subdistribution of a competing risk to further investigate the impact of non-CHD deaths as a competing event on the primary estimand in Section 9.5.1 ○ Clarified when atorvastatin equivalent factor will be used. Updated atorvastatin equivalent factor for Simvastatin and Pitavastatin in Appendix D. Removed Simvastatin 80mg from high-intensity statin definition. ○ Added Fine and Gray 1999 and Luo et al 1997 in citations • Replaced high intensity lipid lowering regimen definition with lipid lowering therapy intensity including bempedoic acid and ezetimibe to Appendix D. Added subgroup and covariate analysis for lipid lowering therapy intensity to section 4. Added analysis of change in lipid lowering therapy intensity to section 9.6.4. • Updated the analysis of aortic valve stenosis and venous thromboembolism exploratory endpoints to stratified log rank test and stratified Cox model. • Updated calculation in Appendix C for subjects who have values outside of the reliable ranges to use the closest in-range value • Updated stop date imputation rule for medication end date for subjects who have died in Appendix G. • Minor administrative and grammatical updates
Amendment 4 (v5.0)	18 Jul 2024	• Added author [redacted] • Updated labels and/or descriptions to Covariates and Subgroups in Section 4 • Added definition for End of Investigational Product (EOIP) Date, clarified LPEPD definition, and added time to EOS and time to EOIP definitions in Section 5.1 • Clarified testing strategy that will be followed if the study will or will not terminated at the interim analysis and removed text about locking data in Section 7.1. • Added description of imputation rules that will be used for missing EOIP and EOS dates/reasons in Section 8.3 • Clarified how reported endpoint events will be summarized in final analysis (efficacy vs. safety tables) in Section 9.6. Appendix J was added to fully describe these details. • Changed all instances of "lipid lowering therapy" to "LDL-C lowering therapy." • Added text in Section 9.6.4 clarifying that only medication dose/intensity changes that last ^{3}14 days will be summarized/ • Added a clarifying footnote to Appendix A on defining analytical study week assignments.

		• Added a clarifying footnote to Appendix E for handling subjects without an on-study LPEPD. • Additional text and clarifications for imputation rules were added to Appendix G, including a full description of the imputation rules for EOIP/EOS dates. • Minor administrative and grammatical updates • Added text considering competing risks in Section 9.5.2
Superseding Amendment 4 (v6.0)	10 Dec 2024	• Administrative changes needed prior to regulatory submission – fix hyperlinks and table of contents • Updated author name to [redacted]

Amendment 5 (v7.0)	**18 Jul 2025**	• **Removed the co-author [redacted], and updated document version and date.**
		• **Added the explanations for CABG, eGFR, GCP and PCI to the list of abbreviations, updated the explanation for IWRS.**
		• **Added two covariates and two subgroups in Section 4.**
		• **Clarified in Section 5 Definitions:**
		  ○ **Updated the definition of subject last confirmed survival status date (LCSSD) to compare to the death date or last known alive date in Section 5.1.**
		  ○ **Updated the definitions of baseline lipid and lipid-related parameters and other baseline values to consider the subjects who did not receive any IP in Section 5.2.**
		  ○ **Updated the definition of low-density lipoprotein cholesterol (LDL-C) to clarify the Martin-Hopkins formula in Section 5.3.**
		  ○ **Added definitions for trial follow-up time and trial midpoint for landmark estimands of primary endpoints, conversion factors, estimated glomerular filtration rate (eGFR) and time potentially lost to follow-up in Section 5.3**
		• **Updated analysis set definitions in Section 6 to exclude all 44 subjects from Poland site 48030 from efficacy, safety and lipid sub-study analyses.**
		• **Updated the description of imputation rules that will be used for missing EOS date/reason in Section 8.3.**
		• **Changed the missing EOS date imputation formula from max(LCSSD + 1, EOIP date) to max(LCSSD, EOIP date) in Section 8.3.1 and Appendix G.**
		• **Added the description for screened subjects in Section 9.1.**
		• **Added summarization of cardiovascular and diabetes medications in Section 9.4.**

		• **Added the description for sensitivity analyses in Table 9-1.** • **Updated the approaches for sensitivity analysis and additional sensitivity analysis for primary estimands in Section 9.5.1.** • **Changed the wording from patients to subjects for additional estimands in Section 9.5.1 and Section 9.5.3.** • **Changed the wording from mortality to fatal in Section 9.5.2, Appendix E and Appendix I.** • **Added the summarization approaches for treatment-emergent adverse events, exposure adjusted treatment-emergent adverse events and exposure adjusted serious treatment-emergent adverse events in Section 9.6.1.** • **Added the description for tabulating each subject's medications taken at baseline and end of study in Section 9.6.4.** • **Added a reference (Stevens et al, 2007) for eGFR in Section 11.** • **Added the description to consider the subjects without a qualifying positively adjudicated event during the event coverage period in Appendix E.** • **Updated the imputation rule for partial medication start date in Appendix F.** • **Corrected the medians for the ratio of triglycerides to VLDL-C in Appendix H to align with the literature reference's values.** • **Updated descriptions and code in Appendix I**

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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
ACC/AHA	American College of Cardiology/American Heart Association
AE	Adverse event
ASCVD	Atherosclerotic cardiovascular disease
BID	Twice a day
CABG	**Coronary Artery Bypass Graft**
CEC	Clinical Events Committee
CHD	Coronary heart disease
CI	Confidence interval
CIF	Cumulative incidence function
CSR	Clinical Study Report
CV	Cardiovascular
DMC	Data Monitoring Committee
EAS	European Atherosclerosis Society
eCRF	Electronic case report form
EDEVP	End date of EOS visit period
EDPM	End date of previous medication
eGFR	**Estimated Glomerular Filtration Rate**
EOIP	End of Investigational Product
EOS	End of study
ESC	European Society of Cardiology
FAS	Full analysis set
FDA	Food and Drug Administration
FRS	Framingham Risk Score
GCP	**Good Clinical Practice**
GSO-DM	Global Study Operations-Data Management
HDL-C	High-density lipoprotein cholesterol
HLGT	High level group term
HLT	High level term
HR	Hazard ratio
IBG	Independent Biostatistics Group
IP	Investigational product
IPD	Important protocol deviation
IVRS	Interactive Voice Response System; telecommunication technology that is linked to a central computer in real time as an interface to collect and process information

Abbreviation or Term	Definition/Explanation
IWRS	Interactive Web Response System; **web-based** technology that is linked to a central computer in real time as an interface to collect and process information
K-M	Kaplan-Meier
LCSSD	Subject last confirmed survival status date
LDDIP	Last dose date of investigational product
LDL-C	Low-density lipoprotein cholesterol
LPEPD	Subject last non-fatal potential endpoint collection date
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
PAD	Peripheral arterial disease
PCI	**Percutaneous Coronary Intervention**
PCSK9	Proprotein convertase subtilisin/kexin type 9
PEP	Potential endpoint
Q1	The first quartile
Q3	The third quartile
QD	Every day
SAP	Statistical Analysis Plan
SCORE	Systematic coronary risk estimation
SD	Standard deviation
SDEVP	Start date of EOS visit period
SDNM	Start date of new medication
SE	Standard error
TIMI	Thrombolysis in Myocardial Infarction
TMF	Trial master file
WLW method	Wei-Lin-Weissfeld (WLW) method

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol amendment 6 for study 20170625, Evolocumab dated 12 June 2023. 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. There will be a separate academic SAP developed by the Thrombolysis in Myocardial Infarction (TIMI) study group which will contain pre-specification of additional analyses to be performed by TIMI.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for coronary heart disease (CHD) death, myocardial infarction (MI), or ischemic stroke, whichever occurs first, in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to CHD death, MI, or ischemic stroke, whichever occurs first
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization, whichever occurs first, in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization, whichever occurs first
Primary Estimands	
The primary estimands consist of: Population: Adults at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy who are randomized Variables: • time to CHD death, MI, or ischemic stroke, whichever occurs first • time to CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization, whichever occurs first Treatments: Evolocumab Q2W compared to placebo Q2W Summary Measure: Hazard ratio (HR) comparing the hazard in the evolocumab group to the hazard in the placebo group Intercurrent events:	

Objectives	Endpoints
• Discontinuation of investigational product or commencing commercial proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. For the primary estimand, the treatment effect will be estimated regardless of the occurrence of these events. • IP supply discontinuation at site due to natural disasters (eg, earthquake, hurricane) or other significant event independent of the study (eg, riots, civil commotion, political disturbances, international conflicts, terrorism). For the primary estimand, data after the subject has discontinued IP for these reasons will be treated as missing at random.	
Secondary	
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for MI, ischemic stroke, or any ischemia-driven arterial revascularization in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to MI, ischemic stroke, or any ischemia-driven arterial revascularization
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for CHD death, MI, or any ischemia-driven arterial revascularization in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to CHD death, MI, or any ischemia-driven arterial revascularization
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for cardiovascular death, MI, or ischemic stroke in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to cardiovascular death, MI, or ischemic stroke
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for CHD death or MI in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid lowering therapy.	• Time to CHD death or MI
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for MI in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to MI
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for any ischemia driven arterial revascularization in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to any ischemia-driven arterial revascularization
• To evaluate the effect of treatment with evolocumab, compared with placebo, on	• Time to CHD death

Objectives	Endpoints
the risk for CHD death, in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for cardiovascular death, in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to cardiovascular death
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for all cause of death, in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to all cause of death
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for ischemic stroke in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Time to ischemic stroke
Secondary Estimands	
The population, treatments, summary measures and intercurrent event strategy for the secondary estimands are the same as the primary estimands. The variables for the secondary estimands are: • time to MI, ischemic stroke, or any ischemia-driven arterial revascularization • time to CHD death, MI, or any ischemia-driven arterial revascularization • time to cardiovascular death, MI, or ischemic stroke • time to CHD death or MI • time to MI • time to any ischemia driven arterial revascularization • time to CHD death • time to cardiovascular death • time to all cause of death • time to ischemic stroke	
Safety	
• To evaluate the safety and tolerability of evolocumab treatment, compared with placebo, in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• Treatment-emergent adverse events leading to investigational product discontinuation • Treatment-emergent serious adverse events

Exploratory	
• To evaluate the effect of treatment with evolocumab, compared with placebo, on change and percent change from baseline of low-density lipoprotein cholesterol (LDL-C), in subjects at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy	• LDL-C change and percent change from baseline
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the incidence of new or worsening aortic valve stenosis	• New or worsening aortic valve stenosis
• To evaluate the effect of treatment with evolocumab, compared with placebo, on the incidence of new or recurrent venous thromboembolism	• New or recurrent venous thromboembolism (pulmonary embolus and/or deep venous thrombosis)
• To explore the effect of evolocumab versus placebo treatment, on individual cardiovascular biomarkers and/or the plasma proteome and proteomic risk scores, to explore the relationship between baseline biomarker levels, risk of major cardiovascular events and efficacy of evolocumab, and to explore how changes from baseline in biomarkers and/or proteomic risk scores relate to subsequent risk of major cardiovascular events	• Cardiovascular biomarker values, protein expression levels, and change in protein expression from baseline to post-baseline and time to major cardiovascular events.

2.2 Hypotheses and/or Estimations

The primary hypothesis is that additional LDL-C lowering with evolocumab when used in addition to optimized lipid-lowering therapy decreases:

- the risk of CHD death, MI, or ischemic stroke
- the risk of CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization

in adults without a prior MI or stroke at high risk of major cardiovascular events.

The primary hypothesis will be tested using the primary estimands.

3. Study Overview

3.1 Study Design

This is a phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group, cardiovascular outcomes study for evolocumab in subjects at high cardiovascular risk without prior MI or stroke. Subjects must be receiving stable, lipid-lowering background therapy as per local guidelines, starting at least 2 weeks prior to the qualifying lipid panel. Such therapy must include optimized statin therapy, except in

subjects with documented statin intolerance. Optimized lipid-lowering therapy could be high, moderate, or low dose. Lipid-lowering background therapy should remain unchanged throughout the duration of the study, unless a change is clinically necessary.

Eligible subjects will be randomized with an allocation ratio of 1:1 to either receive evolocumab or placebo. Randomization will be stratified by the LDL-C level used for eligibility (< 160 mg/dL [4.14 mmol/L] vs ≥ 160 mg/dL) and by geographical region (North America, Europe, and others). The most recent LDL-C value (historical or screening) must be used. Evolocumab and placebo will be blinded. Central laboratory results of the lipid panel (fasting or non-fasting; only collected in a subset of subjects) will be blinded on study; results may be requested by the investigator after unblinding of the clinical database. Investigators and staff involved with this trial should not perform non-protocol lipid panel testing during a subject's study participation and until at least 12 weeks after the subject's last administration of investigational product (to avoid potential unblinding). The study includes collection of biomarker samples, unless prohibited by local law or regulations. Follow-up of all randomized subjects is planned to continue for a median of at least 4.5 years and until at least 751 subjects have experienced a primary triple component endpoint event (CHD death, MI, ischemic stroke) and 1254 subjects have experienced a primary quadruple component endpoint event (CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization). Subjects will be requested to complete all planned visits regardless of their adherence to investigational product. At minimum, vital status must be collected on day 1 and every 16 weeks and must be obtained at the end of the study for all subjects including those who withdraw consent, unless prohibited by local law.

3.2 Sample Size

The calculation of sample size is based on the primary endpoints in this study (triple component of CHD death, MI, or ischemic stroke; quadruple component of CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization).

Based on the lipid entry criteria, it is anticipated that the median baseline LDL-C will be approximately 120 mg/dL. Taking into account premature discontinuation of study drug and potential use of commercially available PCSK9 inhibitors, it is anticipated that the LDL-C difference between the evolocumab and placebo arms will be approximately 1.7 mmol/L at the midpoint of the trial. After accounting for a 12-month treatment lag at the beginning of the trial, and assuming a median follow-up of at least 4.5 years, the anticipated HRs over the duration of this entire study for the primary endpoints will be

0.77 for primary triple component endpoint and 0.80 for primary quadruple component endpoint.

The annualized event rate of the primary triple endpoint and the primary quadruple endpoint in the placebo arm are estimated approximately 1.63% and 2.72%, respectively (Bhatt et al, 2019; Steg et al, 2019).

The two-sided 0.025 significance level of type I error is used for each of the primary estimands.

Assuming a 15-month enrollment period, a 1% of loss to follow-up rate per year, and a total study duration of 63 months, a total sample size of at least 12000 subjects, with approximately 751 subjects experiencing a primary triple component endpoint, is required to ensure approximately 90.5% power (Shih, 1995) based on a 2-sided log-rank test of demonstrating the superiority of evolocumab over placebo. At the time of 751 subjects with the primary triple component endpoint observed, there will be approximately 1254 subjects with the primary quadruple component endpoint, which will ensure a power of 95.6% to demonstrate superiority for that component endpoint of evolocumab over placebo.

Based on the accumulating event rate in the pooled blinded treatment groups, the sample size and/or study duration may be altered in order to complete the trial with at least 751 subjects with the primary triple component events and at least approximately 1254 subjects with the primary quadruple observed in approximately 63 months.

4. Covariates and Subgroups

4.1 Planned Covariates

- Stratification factors
  - LDL-C level (< 160 mg/dL [4.14 mmol/L], ≥ 160 mg/dL) used for eligibility
  - geographical region (North America, Europe, others)
- Age (continuous)
- Sex (male, female)
- Race (white, non-white)
- Baseline LDL-C (continuous) used for eligibility (refer to section 5.2 for definition)
- Baseline HDL-C (continuous) used for eligibility (refer to section 5.2 for definition)
- Baseline triglycerides (continuous) used for eligibility (refer to section 5.2 for definition)
- Ezetimibe use at baseline (yes, no)

- ACC/AHA high intensity statin background therapy at baseline (yes, no) [See Appendix D for full definition]
- LDL-C lowering therapy intensity at baseline (high, moderate, low, none) [See Appendix D for full definition]
- Statin intolerance at screening (yes, no) [defined as no statin use at screening due to demonstrated intolerance to 2 or more statins]
- Use of LDL-C lowering therapy at baseline (yes, no)
- History of diabetes mellitus (yes, no), where this variable indicates subjects with medical history of either Type 1 or Type 2 diabetes mellitus
- History of metabolic syndrome (yes, no) [defined in protocol Appendix 9]
- History of coronary artery disease (yes, no)
- History of atherosclerotic cerebrovascular disease (yes, no)
- History of peripheral arterial disease (yes, no)
- History of hypertension (yes, no)
- Family history of premature coronary heart disease (yes, no)
- Current smoker, including cigarette, pipe and cigar smokers (yes, no)
- Significant coronary artery disease, as defined in inclusion criteria 104/108 (yes, no)
- Significant atherosclerotic cerebrovascular disease, as defined in inclusion criteria 104/108 (yes, no)
- Significant peripheral arterial disease, as defined in inclusion criteria 104/108 (yes, no)
- High risk diabetes mellitus**,** as defined as those with at least 1 additional risk factor, using inclusion criteria 104/108 (yes, no)
- High risk diabetes mellitus without significant coronary artery disease, atherosclerotic cerebrovascular disease, or peripheral arterial disease, and without a known arterial stenosis of 50% or more (yes, no)
- **History of coronary artery bypass graft (CABG) or percutaneous coronary intervention [PCI] (yes, no)**
- **History of any revascularization (yes, no)**

4.2 Subgroups

- Stratification factors
  - LDL-C level (< 160 mg/dL [4.14 mmol/L], ≥ 160 mg/dL) used for eligibility
  - geographical region (North America, Europe, others)
- Age (< 65 years, ≥ 65 years)
- Sex (male, female)
- Race (white, non-white)
- Baseline LDL-C by quartiles used for eligibility (refer to section 5.2 for definition)
- Baseline HDL-C by quartiles used for eligibility (refer to section 5.2 for definition)

- Baseline triglycerides by quartiles used for eligibility (refer to section 5.2 for definition)
- Ezetimibe use at baseline (yes, no)
- ACC/AHA high intensity statin background therapy at baseline (yes, no) [See Appendix D for full definition]
- LDL-C lowering therapy intensity at baseline (high, moderate, low, none) [See Appendix D for full definition]
- Statin intolerance at screening (yes, no) [defined as no statin use at screening due to demonstrated intolerance to 2 or more statins]
- Use of LDL-C lowering therapy at baseline (yes, no)
- History of diabetes mellitus (yes, no), where this variable indicates subjects with medical history of either Type 1 or Type 2 diabetes mellitus
- History of metabolic syndrome (yes, no) [defined in protocol Appendix 9]
- History of coronary artery disease (yes, no)
- History of atherosclerotic cerebrovascular disease (yes, no)
- History of peripheral arterial disease (yes, no)
- History of hypertension (yes, no)
- Family history of premature coronary heart disease (yes, no)
- Current smoker, including cigarette, pipe and cigar smokers (yes, no)
- Significant coronary artery disease, as defined in inclusion criteria 104/108 (yes, no)
- Significant atherosclerotic cerebrovascular disease, as defined in inclusion criteria 104/108 (yes, no)
- Significant peripheral arterial disease, as defined in inclusion criteria 104/108 (yes, no)
- High risk diabetes mellitus, as defined as those with at least 1 additional risk factor using inclusion criteria 104/108 (yes, no)
- High risk diabetes mellitus without significant coronary artery disease, atherosclerotic cerebrovascular disease, or peripheral arterial disease, and without a known arterial stenosis of 50% or more (yes, no)
- **History of CABG or PCI (yes, no)**
- **History of any revascularization (yes, no)**

5. Definitions

5.1 Study Time Points

Randomization Date

The randomization date for each subject is the date the investigator (or designee) confirms in the Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) that the subject has met all eligibility criteria and is randomized as recorded on Subject Enrollment electronic case report form (eCRF).

Enrollment Date

The enrollment date is the same as the randomization date.

Study Day 1

Study Day 1 for each subject is the randomization date.

Study Day

For each subject and 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).

First Dose Date of Investigational Product

For each subject, the first dose date of investigational product is defined as the date of the first administration of investigational product (evolocumab or placebo)

Last Dose Date of Investigational Product (LDDIP)

For each subject, the last dose date is defined as the minimum of [EOS date, derived last IP dose date (defined below)]

Derived last IP dose date is the maximum of:

- Last in-clinic dose date
- Estimated last non-clinic dose date

The estimated last non-clinic dose date will be calculated based on the number of full administrations, assuming the subject administered the IP every 14 days.

Subject End of Investigational Product (EOIP) Date

For each subject, the EOIP date is the date recorded on the EOIP electronic case report form (eCRF).

Subject End of Study (EOS) Date

For each subject, the EOS date is the date recorded on the EOS electronic case report form (eCRF).

Overall-trial Study End Date

The study end date is the last EOS date of all randomized subjects.

Start Date of EOS Visit Period (SDEVP)

The study is event driven. Amgen and the Executive Committee will monitor the overall event rate and will set the start date for the EOS visit period based on the anticipated date when at least 751 subjects have experienced an adjudicated primary triple component endpoint and at least 1254 subjects have experienced an adjudicated primary quadruple component endpoint.

End Date of EOS Visit Period (EDEVP)

The end date of EOS visit period is approximately 10 weeks from SDEVP. The actual EDEVP will be included in the analysis data set for analysis purpose.

Subject Last Non-fatal Potential Endpoint Collection Date (LPEPD)

For each subject, the LPEPD is the last non-fatal PEP ascertainment date which is latest date that sites evaluate and ascertain whether subjects had any non-fatal PEPs since the previous visit. If the LPEPD is after death date, the LPEPD will be set to the death date.

Vital Status

Vital status will be recorded using the survival status eCRF. For subjects who withdraw early from the study with reasons of withdrawal of consent, decision by sponsor or lost to follow-up, an assessment of vital status will be performed up to the EOS visit period, as allowed by local law, and recorded on the eCRF.

Death recorded from vital status assessment will be a potential endpoint and adjudicated by the Clinical Events Committee (CEC).

Subject Last Confirmed Survival Status Date (LCSSD)

For each subject, the LCSSD is based on the evaluation of his or her vital status defined above. **A subject's LCSSD cannot exceed the EDEVP. Subject's LCSSD is defined as follows using information obtained during vital status assessments:**

- **Death date for subjects who have died. Adjudicated death date is prioritized when available, but site-reported death date will be used if adjudicated death date is not available.**
- **Otherwise, last known alive date, which is defined as the most recent status date from a subject's survival status forms, with survival status =**

"Alive" or "Unknown". "Unknown" survival status records are considered above because sites are instructed to copy the last known alive date from the previous entry with most recently confirmed survival status whenever no new information can be found (i.e., current survival status check results in "Unknown").

Start Date of Commercial PCSK9 Inhibitor Therapy (SDCPIT)

For each subject who commenced commercial PCSK9 inhibitor therapy post-baseline, the SDCPIT is defined as the start date of commercial PCSK9 inhibitor therapy as recorded on the concomitant medication eCRF.

Time-to-event Definition

Only events adjudicated as positive (see Appendix J) and occurred prior to or on the event coverage date (See Appendix E) are included in the time-to-event efficacy analysis.

- For subjects who experienced such event,
    - event = yes (ie, censor = no)
    - time-to-event (days) = adjudicated onset date – randomization date + 1
- For subjects who do not experienced such event,
    - event = no (ie, censor = yes)
    - time-to-event (days) = censoring date – randomization date + 1

For the primary analysis of the primary, composite, and **non-fatal** secondary estimands, the censoring date will be the LPEPD. **Fatal** secondary estimands will use the LCSSD as the censoring date. See Appendix E for further details on the censoring dates used for sensitivity analyses and additional estimands.

For the final analysis, time to EOS will be defined:

- Subjects with EOS reason = (Death or Completed) will be censored at EOS date.
- For subjects with other EOS reasons, time to EOS will be calculated using EOS date (event date). This includes subjects with EOS reason = "Unknown".

For the final analysis, time to EOIP (final analysis) will be defined:

- Subjects with EOIP reason = Completed will be censored at min(last dose date + 14, EOS date).
- Subjects with EOIP reason = Death will be censored at death date.
- Last dose date (event date) will be used to calculate time to EOIP for all other subjects.

5.2 Demographics and Baseline Related Definitions

Age

Age will be collected as the subject's age in years at enrollment as recorded on the eCRF.

Baseline Lipid and Lipid-related Parameters

For subgroup and covariate analysis, the lipid value used for eligibility will be used for all subjects. This is defined as the last non-missing value (historical or at screening) measured through local laboratories prior to or on the **date of the** first dose of IP. **For subjects not receiving any IP, the last non-missing value measured prior to or on the randomization date will be used.**

The analysis of the exploratory endpoint for LDL-C will use change and percent change from baseline for the subset of subjects with additional lipid panel testing at the central laboratory. Day 1 is the baseline measurement per schedule of assessments in the protocol. In this analysis, baseline is defined as the last non-missing value measured through central laboratory prior to **or on** the **date of the** first dose of IP. **For subjects not receiving any IP, baseline is defined as the last non-missing value measured prior to or on the randomization date.**

Other Baseline Values

For all other variables, the baseline value is defined as the last non-missing value collected prior to or on **the date of the first dose date of IP. For subjects not receiving any IP, baseline is defined as the last non-missing value measured prior to or on the randomization date.**

Change from Baseline

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

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

Percent Change from Baseline

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

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

Framingham Risk Score (FRS)

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

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 C). Subjects will be categorized using the categories from the 2018 ACC/AHA guidelines (Grundy et al, 2018):

- Low risk: < 5%
- Borderline risk: 5 - <7.5%
- Intermediate risk: 7.5 - <20%
- High risk: ≥20%

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 2019). The SCORE risk estimates will be computed from the high and low risk region tables based on sex and baseline smoking status (including cigarettes, pipes and cigars), systolic blood pressure, total cholesterol and age.

5.3 Other study related definitions

Analytical Study Week Assignments

Analytical windows will be used to assign parameters to study weeks. The algorithm is provided in Appendix A.

Actual Treatment Group

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

IP Exposure Period in Months

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

Study Exposure Period in Months

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

Treatment-emergent Adverse Event

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 and including 30 days after the LDDIP or the EOS date, whichever is earlier. Potential endpoints which have been negatively adjudicated, will be counted as adverse events.

Treatment-emergent Serious Adverse Event

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

Low-density Lipoprotein Cholesterol (LDL-C)

For lipid panel testing measured through local laboratories used for eligibility, the LDL-C value recorded by the local laboratory will be used. If this is missing, but total cholesterol, HDL-C, and triglycerides from the same sample collection are available, then LDL-C will be calculated using the Martin-Hopkins formula (Appendix H; Martin et al, 2013). **When using Martin-Hopkins formula to calculate LDL-C, non-HDL-C derived using reported Total Cholesterol minus reported HDL will be prioritized instead of using reported non-HDL-C values.**

For the subset of subjects who have additional lipid panel testing, the central laboratory will use the Martin-Hopkins formula for the calculation of LDL-C.

Coronary Heart Disease (CHD) Death

Coronary heart disease (CHD) death is defined as death due to or in the setting of:

- acute myocardial infarction,
- coronary revascularization procedure, or
- sudden cardiac death without evidence of a likely non-coronary cause of death.

Further details are provided in the CEC charter.

Trial Follow-up time and Trial Midpoint for Landmark Estimands of Primary Endpoints

To assess the impact of a potential treatment lag in the primary endpoints, landmark estimands with respect to the trial midpoint will be implemented. The trial midpoint is defined as the day where the subject with the longest follow-up in the trial completed 50% of their total follow-up.

Trial follow-up time is defined as:

- **Follow-up (months) = (adjudicated death date – randomization date + 1) / 365.25 * 12 for subjects with EOS reason = 'Death'. If adjudicated death date is not available, site reported death date will be used.**
- **Follow-up (months) = (last non-fatal potential endpoint collection date – randomization date + 1) / 365.25 * 12 for other subjects.**

Conversion Factors (days/months/years)

The following conversion factors will be used for all applicable analyses:

- **To convert from days to months, divide by 30.4375 (365.25/12).**
- **To convert from days to years, divide by 365.25.**

Estimated Glomerular Filtration Rate (eGFR)

For eGFR, if the value is missing but serum creatinine is available, then eGFR is calculated as: 175 x (serum creatinine in mg/dL$^{-1.154}$) x (Age$^{-0.203}$) x 1.212 (if subject is Black or African American) x 0.742 (if subject is Female) (Stevens et al, 2007).

Time potentially lost to follow-up

For subjects with final EOS reason = "Completed", the amount of time a subject was previously missing survival status information will be defined as:

- **(LCSSD) minus (most recent Alive/Unknown status date occurring prior to min[LCSSD, SDEVP])**

Since survival status searches are conducted approximately every 16 weeks per protocol, we expect the above calculation to be approximately ≤16 weeks for subjects who are on track and not potentially lost to follow-up. Subjects who are potentially lost to follow-up will have missing survival status information for longer than approximately 16 weeks. The number of potentially lost to follow-up subjects with missing survival status information for ≥6 months, ≥12 months, ≥18 months, ≥24 months may be summarized.

6. Analysis Sets

Due to site-wide serious breach and good clinical practice (GCP) violations, data from 44 subjects randomized at site 48030 (including 5 subjects who have experienced a primary endpoint event) will be excluded from all primary analyses of efficacy and safety endpoints to eliminate potential risk of obscuring the overall study results. Given the small number of subjects and events being excluded

relative to study overall population and event counts, the overall validity and scientific integrity of the study is not impacted. However, summaries containing "all randomized subjects," such as screen failure summaries and summaries of enrolment by country/region, will still include the 44 subjects enrolled at site 48030. A now planned sensitivity analysis will be performed to further assess primary/secondary endpoint results when incorporating subject data from site 48030, including the additional 5 primary endpoint events reported at site 48030.

6.1 Full Analysis Set

The primary efficacy analysis set is the full analysis set (FAS), which includes all randomized subjects who provide informed consent**, excluding the 44 subjects enrolled at site 48030 due to site-wide serious breach and GCP violations.** All subjects will be analyzed according to their randomized treatment assignment.

6.2 Safety Analysis Set

Safety analyses will be performed on the safety analysis set, which includes all randomized subjects who received at least 1 dose of investigational product**, excluding the 44 subjects enrolled at site 48030 due to site-wide serious breach and GCP violations.** For safety analyses, subjects will be grouped according to their actual treatment group.

6.3 Lipid Sub-study Analysis Set

The lipid sub-study analysis set is defined as all randomized subjects who received at least 1 dose of investigational product and had at least 1 lipid measurement available from central laboratory**, excluding the 44 subjects enrolled at site 48030 due to site-wide serious breach and GCP violations. All subjects will be analyzed according to their randomized treatment assignment.**

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

An Independent Biostatistics Group (IBG) will perform the interim analysis and provide the interim report to an independent Data Monitoring Committee (DMC). The DMC will review all available safety data periodically (approximately every 6 months) and will consider a recommendation for early termination of the study based on their review of the totality of evidence at a single pre-specified interim analyses. The IBG and DMC will have access to subjects' individual treatment assignments. To minimize the potential introduction of bias to the conduct of the study, members of the DMC and IBG will not have any direct contact with study site personnel or subjects. The DMC will

communicate major safety concerns and recommendations regarding study modification or termination based on the safety and efficacy parameters to Amgen in accordance with the DMC charter.

The independent DMC will not review the unblinded CV endpoints prior to the pre-specified interim analysis and will consider a recommendation for early termination of the study based on efficacy at a single pre-specified interim analysis. The interim analysis for the DMC reviewing the unblinded CV endpoints will occur when at least 564 subjects have experienced the primary triple component event and at least 941 subjects have experienced the primary quadruple component event (75% of targeted number of events).

A summary of the timing and corresponding two-sided alpha level for the interim analysis is detailed below.

Timing of IA: % of endpoints	Estimated median study duration	Haybittle-Peto alpha spending approach	
		Test statistics (Z) for log-rank test	Corresponding two-sided alpha level
75% of subjects with targeted # of endpoints for the primary triple component endpoint and the primary quadruple endpoint	~3.5 years	3.291	0.001

The DMC will recommend alteration or early termination based on a totality of evidence that will include proof beyond a reasonable doubt that is likely to influence clinical practice. Additional specific factors to be considered by the DMC will include:

(1) no major safety concerns

AND

(2) there is sufficient follow up time to adequately characterize the long-term efficacy profile of evolocumab in this patient population studied (ie, median duration of at least 3.5 years)

AND

(3) A two-sided $p < 0.001$ in both primary pre-specified endpoints with consistency in major subgroups and a definite reduction in coronary, cardiovascular, and total mortality.

In the case where the DMC recommends to terminate the study early based on the prespecified decision rules at the planned interim analysis, Amgen may review the unblinded results to endorse a final decision. Details will be described in a Data Access Plan. If the study is terminated at the planned interim analysis, the secondary endpoints will be tested sequentially using the interim analysis snapshot data. The sequential ordering will follow the order specified in Figure 9-1.

If the study is not terminated at the planned interim analysis, the overall alpha left used for the primary analysis which will be conducted by the sponsor will be 0.05 based on Haybittle-Peto spending approach spent on a single pre-specified interim analysis by the DMC.

Records of all meetings will be maintained by the DMC for the duration of the study. Records of all meetings will be transferred and stored in the trial master file at the conclusion of the study. Further details are provided in the DMC charter.

7.2 Primary Analysis

The primary objectives of the primary analysis will be to assess the study hypotheses that treatment with evolocumab when used in addition to stable optimized lipid-lowering background therapy, reduces the risk for CHD death, MI, ischemic stroke, whichever occurs first, and/or reduces the risk for CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization in subjects at high risk of major cardiovascular events without prior MI or stroke. All secondary and exploratory objectives will also be assessed at the time of the primary analysis. The primary analysis will occur at the primary completion date, when at least 751 subjects have experienced the primary triple component event and at least 1254 subjects have experienced the primary quadruple component event. At this time, the data will be cleaned, processed, and locked; the study will then be unblinded. All primary and secondary endpoint events reported and adjudicated at the time of database lock will be included in the primary analysis.

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. This study will use the RAVE database. Protocol deviations will be transferred from eClinical.

8.3 Handling of Missing and Incomplete Data

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

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

For all time-to-event endpoints, there will be no imputation of the data, except for incomplete dates of the events. Incomplete dates for adverse events, concomitant medication, historical events, and local laboratory results collected will be imputed**.** For all other efficacy and safety endpoints, unless specified otherwise, missing data will not be imputed.

Missing EOIP reasons will be imputed as "Unknown." **Subjects whose EOS date (observed or imputed) falls** within 16 weeks of site closure date **(applicable to any site the subject belonged to during study conduct) and whose site-reported EOS reason is not "Completed" or "Death" will have their final EOS reason updated to "Administrative reasons".** Otherwise, missing EOS reasons will be imputed as "Unknown."

8.3.1 Handling of Incomplete Dates

Missing and incomplete dates for CEC adjudicated events, adverse events, local laboratory collection, and non-lipid regulating concomitant medication will be imputed as outlined in Appendix G. Partial or missing death dates will be imputed prior to derivation of any endpoint that utilizes the date of death.

For historical events (eg, date of prior revascularization in the targeted medical history) that will be used to summarize as baseline data, the imputation rules are as follows: if the day is missing, default to 1; if both month and day are missing, default to Jan 1. If the imputed date is on or after the randomization date, default to the randomization date minus 1. Missing years will not be imputed under any condition.

Lipid regulating concomitant medication with partially missing start and end dates will be imputed as described in Appendix F.

Completely missing start dates for any concomitant medication will be queried in the database to confirm the medication started prior to study enrolment. The start date will not be imputed, but the medication will be flagged as starting prior to study enrolment.

Missing End of Study dates will be imputed to max(**LCSSD**, EOIP date). Missing End of IP dates will not be imputed.

8.4 Detection of Bias

This study has been designed to minimize potential bias by the use of stratified randomization of subjects into treatment groups and the use of blinding. It is not expected that any study conduct procedures or statistical analyses will introduce bias in the study results or conclusions. However, potential sources of bias in this study include:

- Major protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints
- Subject level unblinding before final database lock and formal unblinding
- DMC related analyses
- Informative censoring

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

Any inadvertent breaking of the blind 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 12.3. Analyses for the DMC will be provided by the IBG, which is external to Amgen, the Executive Committee, and the Study Investigators. Details for the committee will be provided in a committee charter. Any additional unblinding beyond protocol specified will be documented in the CSR. No impact from the DMC review of unblinded data is expected since all of DMC members and the IBG supporting DMC are independent to the Amgen study team, the Executive Committee, and the Investigators.

Reasons for study withdrawal will be summarized in the CSR. If there is a differential study withdrawal rate (lost to follow-up or full consent withdrawn) between treatment arms, then the impact on primary and secondary estimands will be explored. To assess

the impact of missing follow-up data on the primary estimands, and to explore potential non-informative censoring, a tipping point analysis for each primary estimand will be performed (Section 9.5.1).

Additional supplemental estimands may be included to assess the impact of any potential biases on the primary and secondary estimands. If any additional supplemental estimand analyses are required to evaluate potential biases in the study's conclusions, then the sources of the potential biases and the analysis results of the additional supplemental estimand 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. 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

Statistical assumptions for each planned method of analysis will be assessed. If the distributional or other assumptions are not met, then transformations, alternative parametric models, or nonparametric methods will be utilized. The use of alternative methods will be fully justified in the CSR.

The proportional hazards assumption in the Cox model will be assessed by the following 2 methods:

1. Visual inspection of parallel lines in the log(-log(survival)) vs log of survival time graph (Hosmer, 1999)
2. Including an interaction term of log(time) and randomized treatment group as a time dependent covariate in the Cox model

Inference from the Cox model is generally fairly robust with modest violation of the proportional hazards assumption, however, a piecewise Cox model will be considered if there is evidence of a strong non-proportionality in hazards over time.

In addition, the lag model will be considered as additional sensitivity analysis for adjusting for treatment lag in the primary analysis if the proportional hazards assumption is not held (eg, due to treatment lag).

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

Unless specified otherwise, efficacy analyses will be performed on the full analysis set by randomized treatment group; and safety analyses will be performed on the safety analysis set by actual treatment group.

Subject disposition, demographics, baseline characteristics, and exposure to investigational product will be summarized. **Additionally, the number of subjects screened, number of subjects screened by not randomized, reasons for screen failure (by inclusion/exclusion criteria), and the number of subjects that did not randomize (although met all eligibility criteria) will be summarized.**

All continuous variables will be summarized using descriptive statistics, including the number of observations (n), mean, standard deviation (SD), standard error (SE), median, the first (Q1) and third (Q3) quartiles, minimum, and maximum. All categorical variables will be summarized using the number and percent of subjects.

All deaths and individual components of the primary and secondary endpoints (MI, stroke, and ischemia-driven arterial revascularization) will be adjudicated by an independent external CEC, using standardized definitions. The exploratory endpoints aortic valve stenosis and venous thromboembolic events (pulmonary embolism and/or deep vein thrombosis) will not be adjudicated. The CEC is external to Amgen and primarily comprises both academic clinical physicians (to include cardiologists and neurologists for stroke endpoints) and medical reviewers trained on the clinical trial protocol, the CEC charter, and CEC processes. The chairman of the CEC is responsible for overseeing the operations in conformance with the CEC charter and for supervising the flow of data between the sponsor/data management and the CEC. Committee members are qualified in the appropriate subspecialty and free of conflict of interest. The CEC is blinded to treatment allocation and reviews events according to pre-specified criteria defined in the CEC charter.

In order to preserve the overall type I error rate at 0.05 in the primary analysis of the primary estimands in the primary endpoint family and secondary estimands in the secondary endpoint family, a parallel gatekeeping strategy will be applied. The primary endpoint family includes the primary triple component (positively adjudicated CHD death, MI, or ischemic stroke) and the primary quadruple component (positively adjudicated CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization); the secondary endpoint family includes all positively adjudicated secondary endpoints described in Section 2.1.

The multiplicity adjustment procedure used within the primary estimands is the truncated Hochberg procedure (US FDA, 2017). The truncated Hochberg procedure is based on the 2-sided alpha level of 0.05. The truncated Hochberg procedure can pass the unused alpha from the primary estimands to the secondary estimands if at least 1 of the primary estimands is successful (Figure 9-1). The following estimand-specific alpha levels for the truncated Hochberg are constructed by combining the estimand-specific alpha levels of the conventional Hochberg method with the pre-specified truncation fraction of 0.5.

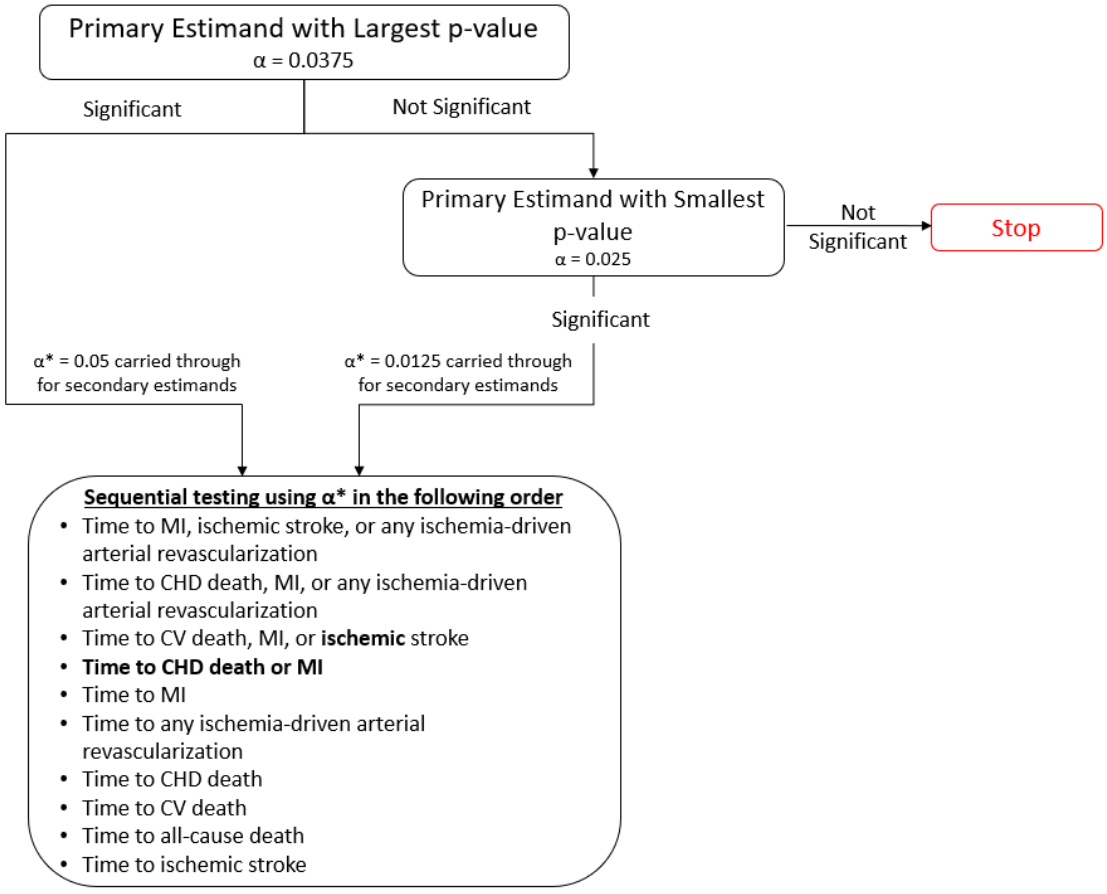
- The first test from the primary estimands (ie, the larger p-value for the primary estimands) for the truncated Hochberg test is performed at alpha level of 0.0375. If the first test is successful, then the remaining test is also considered successful.
- The remaining test from the primary estimands, after the first test is not successful, is performed at alpha level of 0.025.

The multiplicity adjustment procedure used within the secondary estimands is fixed sequence testing procedure. The specific 2-sided alpha level (α*) is used for the secondary estimands depending on the statistically significant results of the primary estimands and the details are described below.

- α*= 0.05, if the first test from the primary estimands (ie, the larger p-value for the primary estimands) is successful. Note: If the first test is successful, then the remaining test is also considered successful. In this case, each of the secondary estimands are tested at an alpha level of 0.05 in the fixed sequential order the secondary endpoints are listed in Figure 9-1.
- α*= 0.0125, if the first test from the primary estimands is not successful (ie, the larger p-value for the primary estimands $>$ 0.0375) and the remaining test from the primary estimands is successful (ie, the smaller p-value in the primary estimands $\leq$ 0.025). In this case, each of the secondary estimands are tested at an alpha level of 0.0125 in the fixed sequential order the secondary endpoints are listed in Figure 9-1.
- α*= 0, if both tests from the primary estimands are not successful.

No multiplicity adjustment will be used for exploratory or sensitivity analyses.

Figure 9-1. Parallel Gatekeeping Procedure



CHD = coronary heart disease; CV = cardiovascular; MI = myocardial infarction.

9.2 Subject Accountability

The number of subjects screened, randomized, receiving IP, and completing the study will be summarized by randomized treatment group. Study discontinuation and IP discontinuation will be tabulated separately by reasons for discontinuation, including due to COVID-19 control measures if applicable. The number of subjects who discontinue study due to administrative reasons (eg, site closure) will be summarized. The number of subjects who discontinue IP due to IP supply discontinuation at site due to natural disasters or other significant event independent of the study will be summarized. The time of withdrawal from IP and study (with reasons other than death) will be analyzed graphically by treatment arm. The number and percent of subjects randomized will be tabulated by country and study site. The number of subjects included in and excluded from each analysis set will 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 reporting protocol deviations related to COVID-19 control measures will be summarized. A protocol deviation listing of subjects impacted due to COVID-19 will also be provided.

9.4 Demographic and Baseline Characteristics

All baseline tables will be summarized by randomized treatment group and for all subjects in FAS. Baseline tables will summarize the following: baseline characteristics, demographics, targeted medical history, baseline cardiovascular risk using FRS and ACC/AHA guidelines, laboratory parameters, lipid regulating medication, including statin intensity based on ACC/AHA guidelines (Grundy et al, 2018; Appendix D), **cardiovascular medications, diabetes medications,** and statin intolerance history (including number of statins with demonstrated intolerance and intolerance symptoms) for subjects not on a high-intensity statin and for subjects on no statin at baseline who have demonstrated intolerance recorded as the primary reason in Statin Intolerance eCRF. If multiple races have been reported for a subject, the subject will be categorized as multiple race.

9.5 Efficacy Analyses

FAS will be used as the primary analysis set for the primary analysis of the primary and secondary estimands. For each subject, the date of randomization will be used as the starting point for all time-to-event calculation. For each event, the onset date adjudicated by CEC will be used as event onset date for time-to-event calculation. Subject incidence of positively adjudicated events occurring between randomization and LCSSD will be summarized by adjudication term. In addition, subject incidence of on-treatment positively adjudicated events (events that occur after randomization and before commencing commercial PCSK9 inhibitor therapy or the minimum of [LDDIP + 30 days, SDCPIT, LCSSD], whichever is earlier) will also be summarized by adjudication term. For subjects who discontinued study early (due to consent withdraw or loss-to-follow up), their vital status data will be collected up to the EOS visit period and prior to the overall-trial study end date. All adjudicated death cases collected up to the overall-trial end date of EOS visit period (EDEVP; defined in Section 5.1) will be summarized based on CEC adjudicated results (CV deaths, non-CV deaths, and undetermined deaths). COVID-19 contribution to death will be summarized as definite, possible, and none.

For the primary analyses for the primary and secondary endpoints, the stratification factors from the IVRS/IWRS will be used in the model. For covariate and subgroup analyses, the stratification factors from the eCRF will be used. Differences in stratum assignment between IVRS/IWRS and eCRF will be tabulated.

Table 9-1. Primary Efficacy Estimand Summary Table

Estimands	Primary Summary and Analysis Method	Sensitivity Analysis
The primary estimands consist of: Population: Adults at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy who are randomized Variables: • time to CHD death, MI, or ischemic stroke, whichever occurs first • time to CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization, whichever occurs first Treatments: Evolocumab Q2W compared to placebo Q2W Summary Measure: Hazard ratio (HR) comparing the hazard in the evolocumab group to the hazard in the placebo group Intercurrent events: • Discontinuation of investigational product or commencing commercial proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. For the primary estimand, the treatment effect will be estimated regardless of the occurrence of these events. • IP supply discontinuation at site due to natural disasters (eg, earthquake, hurricane)	The following analyses will be performed for each primary estimand. Subject count by event status will be provided by treatment group. Kaplan-Meier curves will be estimated and graphically displayed for each randomized treatment group. The primary test comparing the 2 survival functions will be performed using a 2-sided log-rank test stratified by randomization stratification factors. Yearly K-M estimates and 95% CIs will be calculated by each randomized treatment group. The HR and its corresponding 95% CI will be estimated from a stratified Cox model, stratified by the randomization stratification factors.	The primary analysis of the primary estimands will be repeated using the LCSSD as the censoring date, instead of the LPEPD and additionally including only events occurring before min (SDEVP, LCSSD) (see Section 9.5.1 and Appendix E for further details). To assess the impact of missing follow-up data on the primary estimands, a tipping point analysis for each primary estimand will be performed. In addition, multiple imputation analysis will be performed **if greater than 5% of subjects in the full analysis set do not experience a primary endpoint event and are missing follow-up time for primary endpoint assessment. Multiple imputation will be** based on retrieved drop-outs **to impute missing follow-up time** for **these** subjects. If the discrepancy in stratum assignment between IVRS/IWRS and eCRF occurred in more than 5% subjects, the primary analysis of the primary estimands will be repeated with stratifying the models by the stratification from eCRF.

Estimands	Primary Summary and Analysis Method	Sensitivity Analysis
or other significant event independent of the study (eg, riots, civil commotion, political disturbances, international conflicts, terrorism). For the primary estimand, data after the subject has discontinued IP for these reasons will be treated as missing at random.		

SDEVP: Start Date of EOS Visit Period
LCSSD: Subject Last Confirmed Survival Status Date
LPEPD: Subject Last Non-Fatal Potential Endpoint Collection Date
See Section 5.1 for full definitions

Table 9-2. Secondary Efficacy Estimand Summary Table

Estimands	Primary Summary and Analysis Method
The population, treatments, summary measures and intercurrent event strategy for the secondary estimands are the same as the primary estimands. The variables for the secondary estimands are: • time to MI, ischemic stroke, or any ischemia-driven arterial revascularization • time to CHD death, MI, or any ischemia-driven arterial revascularization • time to cardiovascular death, MI, or ischemic stroke • time to CHD death or MI • time to MI • time to any ischemia driven arterial revascularization • time to CHD death • time to cardiovascular death • time to all cause of death • time to ischemic stroke	The analysis of the secondary estimands will be similar to the primary analysis of the primary estimands. Kaplan-Meier (K-M) curves will be estimated and graphically displayed. The 2 survival functions will be compared using a 2-sided log-rank test stratified by randomization stratification factors. Yearly K-M estimates and 95% CIs will be calculated by each randomized treatment group. The HR and its corresponding 95% CI will be estimated from a stratified Cox model, stratified by the randomization stratification factors.

Table 9-3. Exploratory Efficacy Estimand Summary Table

Estimand	Primary Summary and Analysis Method
Difference in mean change and percent change from baseline in LDL-C between evolocumab and placebo for adults at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy, who are randomized, regardless of discontinuation of investigational product or commencing commercial PCSK9 inhibitors	The repeated measures linear mixed effects model will be used to compare the change and percent change from baseline between treatment groups by using all measurements from baseline up to EOS for subjects with additional lipid laboratory testing. The model will include terms for treatment group, stratification factors, scheduled visit and the interaction of treatment with scheduled visit. Missing values will not be imputed when the repeated measures linear mixed effects model is used. LDL-C values will be assigned to yearly windows (see Appendix A). Yearly windows may be combined to enable the repeated measures model to converge.
The difference of subject incidence of new or worsening aortic valve stenosis between evolocumab and placebo for adults at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy, who are randomized, regardless of discontinuation of investigational product or commencing commercial PCSK9 inhibitors	The survival functions between the randomized treatment groups will be compared using a 2-sided log-rank test stratified by randomization stratification factors. The HR and its corresponding 95% CI will be estimated from a stratified Cox model, stratified by the randomization stratification factors.
The difference of subject incidence of new or recurrent venous thromboembolism between evolocumab and placebo for adults at high cardiovascular risk without prior MI or stroke and receiving optimized lipid-lowering therapy, who are randomized, regardless of discontinuation of investigational product or commencing commercial PCSK9 inhibitors	The survival functions between the randomized treatment groups will be compared using a 2-sided log-rank test stratified by randomization stratification factors. The HR and its corresponding 95% CI will be estimated from a stratified Cox model, stratified by the randomization stratification factors.

9.5.1 Analyses of Primary Efficacy Estimands

Primary analysis of the primary estimands:

The following analyses will be performed for each primary estimand. Subject count by event status will be provided by treatment group. Kaplan-Meier curves will be estimated and graphically displayed for each randomized treatment group. The primary test comparing the 2 survival functions will be performed using a 2-sided log-rank test stratified by randomization stratification factors. Yearly K-M estimates and 95% CIs will be calculated by each randomized treatment group. The HR and its corresponding 95% CI will be estimated from a stratified Cox model, stratified by the randomization stratification factors. All positively adjudicated events occurring prior to or on the LCSSD (or prior to LDDIP + 30 days for subjects who discontinue IP due to permanent IP supply discontinuation at site) will be included in the primary analysis of the primary estimands. The censoring date for subjects without an event at LCSSD, will be the LPEPD date (or LDDIP + 30 days for subjects who discontinue IP due to permanent IP supply discontinuation at site). See Appendix E for further details on the event coverage and censoring dates.

Sensitivity analysis for primary estimands:

- The primary analysis of the primary estimands will be repeated using the LCSSD date as the censoring date for subjects without an event (in this analysis, all positively adjudicated events occurring prior to or on the LCSSD will be included as per the primary analysis, see Appendix E).
- The primary analysis of the primary estimands will be repeated including positively adjudicated events occurring prior to or on the earlier of the SDEVP and LCSSD. The censoring date for subjects without an event at this time will be the earlier of the SDEVP and LPEPD (see Appendix E).
- To assess the impact of missing follow-up data on the primary estimands, a tipping point analysis for each primary endpoint will be performed. Subjects will be considered to have missing follow-up data if they have not experienced a primary endpoint event and their LPEPD is prior to the SDEVP. This will include subjects who fully withdrew consent, as well as those lost to follow-up. Subjects will not be considered to have missing follow-up data if a non-CHD death occurred within 16 weeks of LPEPD. Event data for the missing days will be simulated using an exponential distribution. Assumptions will be made on the following parameters:
  - The hazard rate for the missing time in the placebo arm and
  - The hazard ratio (HR) comparing the evolocumab arm to the placebo arm for the missing follow-up data.

  The following assumptions for the hazard rates and HRs will be used:

Three different hazard rates are considered for the missing follow-up data in the placebo arm:

- Use the observed hazard rate during the study for all subjects randomized to placebo
- Use the observed hazard rate after LDDIP in the subjects (pooled evolocumab and placebo treatment groups) who discontinue investigational product but continue with study follow up
- Use the highest annual hazard rate observed during the study in the placebo group

The hazard rates described above (from lowest to highest) will be investigated for each HR assumed (see below).

For each of the 3 hazard rates assumed for the missing follow-up data in the placebo arm, hypothetical HRs will be assumed, starting from 1 until either a tipping point (defined below) is reached, or the HR is equal to 5.

Appropriate increments for the hazard ratio will be decided based on the analysis results on the combinations of hazard rates and HRs assumed above. For example, if the analysis reaches a hazard ratio of 5 without tipping, then increments of 1 may be used. However, if a tipping point is reached at a lower hazard ratio (eg, HR = 1.5), then increments of 0.1 may be used.

If the constant hazard assumption **is violated, a** piecewise hazard **model could be considered** to impute the missing follow-up data.

The imputed data under these assumptions will be used for the missing follow-up data in the study along with the actual observed data. At least 100 simulations will be performed for each scenario. Analyses of the primary endpoints based on the **simulated** data sets will **use a Cox model with randomization stratification factors to obtain Hazard Ratio and 95% confidence interval estimates for each iteration. For each scenario, Rubin's rule will be used to combine the** Hazard Ratio **and** 95% confidence interval **estimates across iterations (observed + imputed datasets). The p-value corresponding to this combined hazard ratio** will be presented for each scenario.

The assumptions on the missing follow-up data will be varied (as described above) to create different scenarios until a scenario is observed where the results tip from being statistically significant to being non-significant – the "tipping point". The point at which the results tip statistically is when the p-values exceed the

adjusted alpha rates based on the truncated Hochberg procedure (see multiplicity adjustment in Section 9.1).

- An additional sensitivity analysis will be performed using multiple imputation to assess the impact of missing follow-up data on the primary analysis if greater than 5% of subjects **in the full analysis set** do not experience a primary endpoint event and **are missing follow-up time for primary endpoint assessment** (**i.e., for subjects not previously experiencing a primary endpoint event: LPEPD < non-CHD death date for subjects with EOS reason = "Death" due to non-CHD death,** LPEPD < SDEVP **for all other EOS reasons**). Data after LDDIP from retrieved drop-outs subjects who discontinued treatment and did not experience the primary endpoint prior to treatment discontinuation, **but** remained in study until occurrence of primary endpoint or EOS, will be used to impute the hazard rate of subjects who do not experience a primary endpoint event **and are missing follow-up time for primary endpoint assessment if sufficient data exists to support imputation assumptions. The** imputed remaining time to an event will be integrated with the observed data to generate **at least** 100 imputed datasets for subjects who do not experience a primary endpoint event and **are missing follow-up time for primary endpoint assessment.** The remaining time to an event will be imputed stratified by treatment. The hazard rate from the retrieved drop-out data will be evaluated to assess if the hazard rate is constant and use piecewise exponential distribution (if applicable) to impute the remaining time to event with hazard rates dependent on the year the subject discontinued study. Results from multiple imputation will be combined using Rubin's rule.
- If the discrepancy in stratum assignment between IVRS/IWRS and eCRF occurred in more than 5% subjects, the primary analysis of the primary estimands will be repeated with stratifying the models by the stratification from eCRF.
- The lag model will be considered as additional sensitivity analysis for the primary endpoints to adjust for treatment lag if the proportional hazards assumption is not held (eg, due to treatment lag). The lag model (Luo et al, 1997) is a modification of the Cox model that includes a threshold lag effect of treatment. The threshold lag effect of treatment is considered as the change point in the hazard function of the treatment group. The lag effect and the regression coefficient of treatment will

be estimated by maximizing the partial likelihood function via a grid search. With the fixed lag effect of treatment, the observed HR and 95% CIs (after treatment lag) will be estimated from stratified Cox model with a time dependent treatment effect as covariate and stratified by the randomization stratification factors collected via IVRS/IWRS.

Additional analysis for the primary estimands:

- Covariate analyses of the primary estimands using Cox model will be performed. Baseline covariates listed in Section 4.1 will be included in the model one at a time.
- Subgroup analyses on the primary estimands will be conducted using the stratification factors and baseline covariates listed in Section 4.2. The interaction between each subgroup and the treatment group will be evaluated. A forest plot will be created to summarize the variability in the HRs across subgroups. All races (if appropriate) with less than 5% of the total enrolled subjects will be pooled together for summary purposes.
- The trend and consistency of the treatment effect on the components of the primary estimands will be examined and tested for heterogeneity by using the Wei-Lin-Weissfeld (WLW) method (Wei et al, 1989). The components are:
  - CHD death
  - MI
  - ischemic stroke
  - Any ischemia-driven arterial revascularization
- Estimation of the Cumulative Incidence Function (CIF), the p-value for the statistical test comparing the CIF between evolocumab and placebo (Gray, 1988), and a proportional hazards model for the subdistribution of a competing risk (Fine and Gray, 1999) will be used to assess the primary estimands whilst taking competing risk of non-CHD deaths into account. The model will include terms for treatment group and the randomization stratification factors.

Additional estimands:

The on-treatment estimands will use the same population, variables, treatments, and summary measure as the primary estimands, but the intercurrent event strategy is defined as:

- Discontinuation of investigational product for any reason or commencing commercial proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Data after discontinuation of IP or after initiation of commercial PCSK9 inhibitor will not be included.

Only events that occur after randomization and before commencing commercial PCSK9 inhibitor therapy or the minimum of (LDDIP + 30 days, SDCPIT, LPEPD), whichever is earlier, are included (see Appendix E).

The on-treatment estimands will be analyzed as per the primary analysis of the primary estimands.

To assess the impact of a potential treatment lag, Landmark Estimands will be defined as follows:

1. For the primary variables of time to CHD death, MI, ischemic stroke, whichever occurs first.
    a. The HR comparing evolocumab and placebo including only those events which occur between year 0 and the end of year 1
    b. The HR comparing evolocumab and placebo including only those events which occur beyond year 1

    The **subjects** at risk for the analysis of year 0-1 will include all **subjects in the full analysis set**. For beyond year 1, the **subjects** at risk will include those who are alive and still in follow up at the end of year 1.

2. The above estimand will be repeated for the primary variable of time to CHD death, MI, ischemic stroke, or any ischemia driven arterial revascularization, whichever occurs first.

The landmark estimands will be repeated for year 0 to the midpoint of the trial, and beyond the midpoint of the trial. The midpoint is defined as the day in which the subject with the longest **follow-up** in the trial completed 50% of their total **follow-up**. The **subjects** at risk for the analysis of year 0 to the midpoint will include all **subjects in the full analysis set**. For beyond the midpoint, the **subjects** at risk will include those who are alive and still in follow up the day after the midpoint. The population and intercurrent event strategy for the landmark estimands will be the same as the primary estimands.

The Total Event Estimand will be defined as follows:

The rate ratio comparing the incidence of CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization between evolocumab and placebo using the negative binomial model. The population and intercurrent event strategy for the total event estimand will be the same as the primary estimands.

Summary statistics for the total number of quadruple component endpoint events will also be provided.

The All Cause Death Estimands will be defined as follows:

The HR comparing evolocumab and placebo for time to all cause death, MI, ischemic stroke, whichever occurs first, and the HR comparing evolocumab and placebo for time to all cause death, MI, ischemic stroke, or any ischemia-driven arterial revascularization, whichever occurs first. The population and intercurrent event strategy will be the same as the primary estimands.

9.5.2 Analyses of Secondary Efficacy Estimands

The secondary efficacy estimands described in Section 2.1 will be analyzed as per the primary analysis of the primary estimands. Composite and **non-fatal** endpoints will use the LPEPD as the censoring date for subjects without an event. **Fatal** endpoints will use the LCSSD as the censoring date for subjects without an event.

Additional analyses may be performed to evaluate impact of competing risks for applicable endpoints.

9.5.3 Analyses of Exploratory Efficacy Estimands

LDL-C values will be assigned to yearly windows (see Appendix A). Change and percent change in LDL-C will be analyzed using the repeated measures liner mixed effects model, including all available yearly values from Day 1 up to EOS for subjects in the lipid sub-study analysis set. The model will include terms for treatment group, stratification factors, year and the interaction of treatment with year. Missing values will not be imputed when the repeated measures linear mixed effects model is used. Yearly windows may be combined to enable the repeated measures model to converge.

The effect of treatment with evolocumab, compared with placebo, on the subject incidence of new or worsening aortic valve stenosis occurring between randomization and prior to or on the LCSSD will be analyzed using a 2-sided log-rank test stratified by randomization stratification factors and a stratified Cox model, stratified by the randomization stratification factors. **Subjects** with aortic valve replacement between randomization and LCSSD will be considered as an aortic valve stenosis event.

Similarly, the effect of treatment with evolocumab, compared with placebo, on the subject incidence of new or recurrent venous thromboembolism occurring between randomization and prior to or on the LCSSD will be analyzed using a 2-sided log-rank test stratified by randomization stratification factors and a stratified Cox model, stratified by the randomization stratification factors.

Analysis of change in protein expression from baseline to post-baseline, and the relationship to time to major cardiovascular events will be described in a supplemental SAP.

9.6 Safety Analyses

9.6.1 Adverse Events and Disease-related Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 or later will be used to code all events categorized as adverse events to a system organ class and a preferred term.

The subject incidence of adverse events will be summarized for all treatment-emergent serious adverse events and adverse events leading to withdrawal of investigational product.

Subject incidence of all treatment-emergent serious adverse events and adverse events leading to withdrawal of investigational product, will be tabulated by system organ class, high level group term (HLGT), high level term (HLT), and preferred term in alphabetical order.

All treatment-emergent adverse events will be summarized by system organ class and preferred term within the following subgroups: Age (<65 years, ≥65 years), Sex (Male, Female), Race (White, Non-white).

Exposure adjusted summaries of all treatment-emergent adverse events will be tabulated by severity, seriousness, and if the event led to withdrawal of investigational product. To create exposure adjusted summaries, total years at risk are calculated as the sum of time on treatment up to the first qualifying event for those with events, and time on treatment up to min(last dose date + 30 days, EOS date) for those without events.

Exposure adjusted summaries of serious treatment-emergent adverse events with preferred terms reported in ≥ 0.5% of subjects in any treatment group will be presented. Similarly, exposure adjusted summaries of treatment-emergent adverse events leading to withdrawal of investigational product will be summarized for preferred terms reported in ≥ 0.1% of subjects in any treatment group.

As defined in Section 5.3, negatively adjudicated potential endpoints will be included in the definition of treatment-emergent adverse events. Any negatively adjudicated potential endpoints which are not classified as serious adverse events or adverse events

leading to withdrawal of investigational product will be tabulated separately by system organ class and preferred term.

Subject incidence of negatively adjudicated myocardial infarction and stroke endpoint events will be summarized by system organ class and preferred term, while negatively adjudicated potential ischemia driven revascularizations will be summarized by investigator reported procedure type.

Details on endpoint events to be included in safety analysis summaries can be found in Appendix J.

9.6.2 Vital Signs

The analyses of vital signs will include summary statistics at baseline and EOS by treatment group.

9.6.3 Exposure to Investigational Product

The exposure to investigational product will be summarized using descriptive statistics by treatment group.

9.6.4 Exposure to Concomitant Medication

Number and proportion of subjects receiving therapies of interest, including lipid-lowering therapy, will be summarized for each treatment group.

The number and proportion of subjects who stayed at the same statin dose, increased their statin dose, decreased their statin dose, or discontinued statin therapy (with discontinuation reason) will be provided for each treatment group. In addition, the number and proportion of subjects who stayed at the same statin intensity, increased their statin intensity, or decreased their statin intensity per ACC/AHA guidelines (Grundy et al, 2018; Appendix D) and the number and proportion of subjects who stayed at the same LDL-C lowering therapy intensity, increased their LDL-C lowering therapy intensity, or decreased LDL-C lowering therapy intensity (Appendix D) will be provided for each treatment group.

For subjects who were not on a statin at baseline, the number of subjects who started statin therapy during the study will be provided. **The number of subjects that initiated or stopped the following medications since baseline will be tabulated by comparing each subject's medications taken at baseline and end of study: Ezetimibe, PCSK9i, Bempedoic acid, SGLT2i, and GLP-1RA.**

Only medication dose/intensity changes which last ≥14 days will be summarized.

10. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

11. Literature Citations / References

Bhatt DL, Steg G, Miller M, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N Eng J Med.* 2019;380:11-22.

Fine, JP and Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *Journal of the American Statistical Association* 94, no. 446 (1999): 496–509.

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

Gray RJ. Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. *The Annals of Statistics*. 1988;16:1141-1154.

Grundy SM, Stone NJ, Bailey AL et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;pii:S0735-1097(18)39033-39038.

Hosmer DW, Lemeshow S. Applied Survival Analysis: Regression Modeling of Time to Event Data. John Wiley and Sons, New York. 1999.

Lipkovich I, Ratitch B, O'Kelly M. Sensitivity to censored-at-random assumption in the analysis of time-to-event endpoints. *Pharmaceutical Statistics* 2016; 15(3):216-229

Luo X, Turnbull BW, and Clark LC. Likelihood Ratio Tests for a Change Point With Survival Data. *Biometrika*. 1997;84(3):555-565.

Martin SS, Blaha MJ, Elshazly MB, et al. Comparison of a novel method vs the Friedewald equation for estimating low-density lipoprotein cholesterol levels from the standard lipid profile. *JAMA*. 2013;310:2061-2068.

Moscovici JL, Ratitch B. Combining Survival Analysis Results after Multiple Imputation of Censored Event Times. *Proceedings of the Pharmaceutical SAS Users Group Conference (PharmaSUG-2017)*, Paper SP05. Cary, NC: SAS Institute Inc

Shih JH. Sample size calculation for complex clinical trials with survival endpoints. *Control Clin Trials.* 1995;16:395-407.

Steg PG, Bhatt DL, Simon T, et al. Ticagrelor in Patients with Stable Coronary Disease and Diabetes. *N Engl J Med*. 2019;381:1309-1320.

Stevens LA, Manzi J, Levey AS, Chen J, Deysher AE, Greene T, Poggio ED, Schmid CH, Steffes MW, Zhang Y, Lente FV, Coresh J. Impact of Creatinine Calibration on Performance of GFR Estimation Equations in a Pooled Individual Patient Database. American Journal of Kidney Diseases. 2007; Volume 50, Issue 1: 21-35.

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). 2019 ESC/EAS Guidelines for the management of dyslipidaemias. *European Heart Journal.* 2020; 41:111–188.

US Department of Health and Human Services, Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Multiple Endpoints in Clinical Trials (Guidance for Industry). 2017. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm536750.pdf.

Wei LJ, Lin DY and Weissfeld L. Regression Analysis of Multivariate Incomplete Failure Time Data by Modeling Marginal Distributions. *Journal of the American Statistical Society.* 1989; *84*: 1075-1073

12. Appendices

Appendix A. Analytical Study Week Assignments

Selected endpoints will be summarized by scheduled study visits in descriptive analyses. Since the actual visits may not exactly coincide with their scheduled visit day, the actual visit day is mapped to the study visit generally by non-overlapping consecutive intervals covering the entire time continuum. The mapping intervals for all distinct schedules are summarized in the following table:

Scheduled Visit	Scheduled visit day	Lipid panel	Vital signs
Week 48 (~ 1 year)	337	(1, 504]	
Week 96 (~ 2 years)	673	(504, 884]	
Year 3	1097	(884, 1279]	
Year 4	1462	(1279, 1644]	
Year 5	1827	(1644, 2009]	
Year 6	2193	(2009, 2375]	
EOS	2193	N/A	(1, EOS]

Analytical study week assignments for laboratory values only apply to post-baseline laboratory values.

Handling multiple records assigned to an analytical study week or year:

If there is more than one record in a study week or year interval, the analytical record for that specific study week or year will be defined as the record closest to the scheduled visit day of that specific study week (7 x study week + 1) or study year (365.25 x study year + 1). If two records are equidistant from the scheduled day, then the earlier record will be chosen. If there are multiple records on the same day, the last record will be used.

Appendix B. Framingham Risk Score (FRS)

Method to calculate the Framingham Risk Score (FRS):

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

The calculation is different for men and women and use the following coefficients β_i, where *i* represents each of the independent variables. The values below are from the Framingham heart study.

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

Men			Women		
Independent variable	Coefficient βi	mean	Independent variable	Coefficient βi	mean
ln(age)	52.00961	3.8926095	ln(age)	31.764001	3.9213204
ln(t_chol)	20.014077	5.3441475	ln(t_chol)	22.465206	5.3628984
ln(hdl)	-0.905964	3.7731132	ln(hdl)	-1.187731	4.0146369
ln(sbp)	1.305784	4.8618212	ln(sbp)	2.552905	4.8376494
trt_htn (sbp>120)	0.241549	0.1180474	trt_htn (sbp>120)	0.420251	0.142802
smoker	12.096316	0.335602	smoker	13.07543	0.3236202
ln(age)* ln(t_chol)	-4.605038	20.8111562	ln(age)* ln(t_chol)	-5.060998	21.0557746
ln(age)* smoker[1]	-2.84367	1.2890301	ln(age)* smoker[2]	-2.996945	1.2519882
ln(age)*ln(age)	-2.93323	15.2144965			
[1] if age>70 then ln(70)*smoker			[2] if age>78 then ln(78)*smoker		

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

Men

For each subject:

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

2. Calculate $A_{men} = L_{men} - 172.300168$ (note: the value of 172.300168 was derived based on the mean columns in above table)
3. Calculate $B_{men} = \exp(A_{men})$
4. Calculate $P_{men} = 1 - 0.9402^{B_{men}}$
5. $FRS_{men} = P_{men} * 100$ (rounded to nearest integer)

Women

For each subject:

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

Appendix C. Pooled Cohort Equations from 2013 ACC/AHA cardiovascular risk assessment guideline

	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 = 2.469	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 = 0.302	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, including cigarette, pipe and cigar smokers (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	86.61
b= Baseline Survival	0.9144	0.8954	0.9665	0.9533

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

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 = 211 mg/dL, HDL-C = 52 mg/dL, untreated systolic BP = 117 mmHg, 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 $x_{12} = \ln(\text{age})*1$ as they are a smoker and $x_{13} = 0$ 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

$1 - 0.9665^{\exp(-\mathbf{29.427} - (-29.18))} = 0.026$ or 2.6% risk of hard ASCVD in 10-years.

Note: The risk calculation is reliable when age is between 40-79 years, total cholesterol 130-320 mg/dL, HDL 20-100 mg/dL, and SBP 90-200 mmHg. Based on clinical practice, for values outside the range, the value that is the closest and in the range will be used for estimating risk.

Appendix D. Lipid Modifying Background Therapy

Statin Intensity based on ACC/AHA 2018 guidelines:

	HIGH-INTENSITY STATIN THERAPY	MODERATE-INTENSITY STATIN THERAPY	LOW-INTENSITY STATIN THERAPY	Atorvastatin equivalent factor†
Atorvastatin	≥ 40 mg QD	10 – < 40 mg QD	< 10 mg QD	1
Rosuvastatin	≥ 20 mg QD	5 – < 20 mg QD	< 5 mg QD	2
Simvastatin		≥ 20 mg QD	< 20 mg QD	0.5 up to 80mg, 0.25 for ≥80mg
Pravastatin		≥ 40 mg QD	< 40 mg QD	0.25
Lovastatin		≥ 40 mg QD	< 40 mg QD	0.25
Fluvastatin*		80 mg QD	< 80 mg QD	0.125
Pitavastatin		1 – 4 mg QD	<1 mg QD	5

* includes immediate-release capsules and prolonged-release tablets
† atorvastatin equivalent factor will be used to determine overall statin intensity for subjects taking >1 type of statin concurrently

LDL-C lowering therapy intensity:

HIGH-INTENSITY LDL-C lowering therapy	MODERATE-INTENSITY LDL-C lowering therapy	LOW-INTENSITY LDL-C lowering therapy	No LDL-C lowering therapy
• Any PCSK9 inhibitor • High intensity statin • Moderate intensity statin plus Ezetimibe 10mg QD • Moderate intensity statin plus Bempedoic Acid 180mg • Any statin plus Bempedoic Acid 180mg QD and Ezetimibe 10mg QD	• Moderate intensity statin with no Bempedoic acid 180mg QD /Ezetimibe 10mg QD • Low intensity statin plus Ezetimibe 10mg QD • Low intensity statin plus Bempedoic Acid 180mg QD • Bempedoic Acid 180mg QD plus Ezetimibe 10mg QD	• Low intensity statin with no Bempedoic acid 180mg QD /Ezetimibe 10mg QD • Ezetimibe 10mg QD with no statin /Bempedoic Acid 180mg QD • Bempedoic Acid 180mg QD with no statin /Ezetimibe 10mg QD	• Not on any statin, Bempedoic Acid 180mg QD, Ezetimibe 10mg QD, or any PCSK9 inhibitor

Appendix E. Event Coverage and Censoring Dates

	Site IP supply discontinuation*	Primary Analysis	Sensitivity Analysis / Supplemental Estimands		
			LCSSD	SDEVP	On-Treatment Estimand
Event Coverage	No	Events ≤ LCSSD	Events ≤ LCSSD	Events ≤ min (LCSSD, SDEVP)	Events ≤ min (LCSSD, SDCPIT, LDDIP + 30 days)
	Yes	Events ≤ min (LCSSD, LDDIP + 30 days)	Events ≤ min (LCSSD, LDDIP + 30 days)	Events ≤ min (LCSSD, SDEVP, LDDIP + 30 days)	Events ≤ min (LCSSD, SDCPIT, LDDIP + 30 days)
Censoring Date					
Composite or **non-fatal**	No	LPEPD	LCSSD	min (LPEPD, SDEVP)	min (LPEPD, SDCPIT, LDDIP + 30 days)
	Yes	min(LPEPD, LDDIP + 30 days)	min(LCSSD, LDDIP + 30 days)	min (LPEPD, SDEVP, LDDIP + 30 days)	min (LPEPD, SDCPIT, LDDIP + 30 days)
Fatal	No	LCSSD	NA	NA	NA
	Yes	min(LCSSD, LDDIP + 30 days)	NA	NA	NA

Subjects without an on-study LPEPD **and without a qualifying positively adjudicated event during the event coverage period** will be censored at Day 1 (**e.g.,** if a subject **has a non-CHD death** between Day 1 and Week 16, the subject would be censored at Day 1 for non-fatal and composite endpoints).

*Subject is considered to have site IP supply discontinuation if the subject discontinued IP due to permanent IP supply discontinuation at site due to natural disasters (eg, earthquake, hurricane) or other significant event independent of the study (eg, riots, civil commotion, political disturbances, international conflicts, terrorism)LCSSD = subject last confirmed survival status date; LDDIP = last dose date of investigational product; LPEPD = subject last non-fatal potential endpoint collection date; SDCPIT = start date of commercial PCSK9 inhibitor therapy; SDEVP = start date of EOS visit period

See Section 5.1 for full definitions.

Appendix F. Handling of Incomplete Dates for Lipid Regulating Concomitant Medication

Missing and incomplete dates for new concomitant medication initiated which is not replacing previous medication and concomitant medication ended which has no replacement therapy started will be imputed as outlined in Appendix G.

New concomitant medication initiated as a replacement for a previous medication (including dose changes):

- EDPM – End date of previous medication
- SDNM – Start date of new medication

Full date recorded for SDNM	
EDPM missing	Imputation
Day	If partial EDPM is the same month as SDNM, impute EDPM as the day before SDNM If partial EDPM is not the same month as SDNM, impute EDPM as the last day of the month
Month-Day	If partial EDPM is the same year, imputed EDPM as the day before SDNM If partial EDPM is not the same year as SDNM, impute EDPM as 31st December

Full date recorded for EDPM	
SDNM missing	Imputation
Day	If EDPM is the same month as partial SDNM, impute SDNM as the day after the EDPM If EDPM is not the same month as partial SDNM, impute SDNM as the 1st of the month
Month-Day	If EDPM is the same year as partial SDNM, impute SDNM as the day after EDPM If EDPM is not the same year as partial SDNM, impute SDNM as the 1st Jan

EDPM missing day (month and year present)	
SDNM missing	Imputation

Day	If partial EDPM is the same month as partial SDNM, impute SDNM as the 16th day of the month and impute EDPM as the 15th day of the month If partial EDPM is not the same month as partial SDNM, impute SDNM as the 1st of the month and impute EDPM as the last date of the month
Month-Day	If partial EDPM is the same year as partial SDNM, impute SDNM as the 16th day of the month from partial EDPM, and impute EDPM as the 15th day of the month. If partial EDPM is not the same year as partial SDNM, impute SDNM as the 1st Jan and impute the EDPM as the last date of the month.

EDPM missing day and month (year present)	
SDNM missing	Imputation
Day	If partial EDPM is in the same year as the partial SDNM, impute the SDNM as the 16th of the month, and impute EDPM as the 15th of the month from partial SDNM If partial EDPM is not the same year as the partial SDNM, impute SDNM as the 1st of the month and impute EDPM as the 31st December.
Month-Day	If partial EDPM is in the same year as the partial SDNM, impute SDNM as the 1st July and impute EDPM as the 30th June If partial EDPM is not the same year as the partial SDNM, impute SDNM as the 1st of January and impute the EDPM as the 31st December.

If **the month/year of partial medication start date matches with the month/year of** Study Day 1, **then medication start date is imputed** to Study Day 1.

If imputed end date is after EOS, default to EOS. If imputed end date is before the start date (imputed or original) of the same medication record, the end date will default to the start date.

Years will not be imputed.

Appendix G. Handling of Dates, Incomplete Dates and Missing Dates

Imputation Rules for Partial or Missing Start Dates (concomitant medications, events, procedures)

The reference date for the following rules is the date of first dose of IP.

Start Date		Stop Date						
		Complete: *yyyymmdd*		**Partial: *yyyymm***		**Partial: *yyyy***		**Missing**
		< 1st dose	**≥ 1st dose**	**< 1st dose *yyyymm***	**≥ 1st dose *yyyymm***	**< 1st dose *yyyy***	**≥ 1st dose *yyyy***	
Partial: *yyyymm*	**= 1st dose *yyyymm***	2	1	n/a	1	n/a	1	1
	≠ 1st dose *yyyymm*		2	2	2	2	2	2
Partial: *yyyy*	**= 1st dose *yyyy***	3	1	3	1	n/a	1	1
	≠ 1st dose *yyyy*		3		3	3	3	3

1=Impute the date of first dose; 2=Impute the first of the month; 3=Impute January 1 of the year
Note:
If the start date is entirely missing, assume the medication is started prior to baseline.
For subjects who were never treated (first dose date is missing), first dose date will be replaced by the randomization date in the table.

If a procedure with a partial date is linked to an event with a complete date and the procedure's partial date (MonthYear/Year) matches the linked event's start date, impute the procedure date to the event's start date.

Imputation Rules for Partial or Missing Stop Dates (concomitant medications, events, procedures)

Initial imputation

- If the month and year are present, impute the last day of that month.
- If only the year is present, impute December 31 of that year.
- If subject ends the study due to death with missing medication stop date, impute missing stop date to death date. Otherwise, if the stop date is entirely missing at end of study, assume the event or medication is ongoing at end of study.

If the imputed stop date is before the start date, set stop date to missing.

If the imputed stop date is after the EOS date and the start date is on or prior to the EOS date, impute stop date as the EOS date.

Imputation Rules for Partial or Missing Death Dates

If death year and month are available but day is missing:

- If yyyymm for the date last known to be alive equals yyyymm for death date, set death date to the day after the date last known to be alive.
- If yyyymm for the date last known to be alive is less than the yyyymm for death date, set death date to the first day of the death month.
- If yyyymm for the date last known to be alive is greater than yyyymm for death date, set death date to the first day of the death month.

If month and day are missing and year of death is known:

- If yyyy for the date last known to be alive equals yyyy for death date, set death date to the day after last known to be alive date.
- If yyyy for the date last known to be alive is less than yyyy for death date, set death date to the first day of the death year.
- If yyyy for the date last known to be alive is greater than yyyy for death date, set death date to the first day of the death year.

If a death date is totally missing:

- Set death date to the day after the date last known to be alive. If the date last known to be alive is a partial date, set it to the first day of the month last known to be alive or first day of the year last known to be alive if month is also missing.

Imputation Rules for Missing EOIP and EOS dates

- Missing EOIP dates will not be imputed.
- Missing EOS dates will be imputed as max(**LCSSD**, EOIP date).

Appendix H. Martin-Hopkins Formula to Estimate LDL-C

By using the Martin-Hopkins formula, LDL-C is estimated as non-high-density lipoprotein cholesterol (non-HDL-C) – (triglycerides / adjustable factor) in mg/dL, where the adjustable factor is determined as the median triglycerides to very low-density lipoprotein cholesterol (VLDL-C) ratio by non-HDL-C and triglyceride strata (Martin et al, 2013). The equation can be expressed as

Estimated LDL-C = non-HDL-C – (triglycerides / adjustable factor) in mg/dL,

where in this study, non-HDL-C will be calculated from (total cholesterol – HDL-C) in mg/dL, and total cholesterol, HDL-C, and triglycerides are from the same sample collection.

Strata-specific median for the ratio of triglycerides to VLDL-C:

Triglyceride Levels, mg/dL	Non-HDL-C, mg/dL					
	<100	100-129	130-159	160-189	190-219	≥220
7-49	3.5	3.4	3.3	3.3	3.2	3.1
50-56	4.0	3.9	3.7	3.6	3.6	3.4
57-61	4.3	4.1	4.0	3.9	3.8	3.6
62-66	4.5	4.3	4.1	4.0	3.9	3.9
67-71	4.7	4.4	4.3	4.2	4.1	3.9
72-75	4.8	4.6	4.4	4.2	4.2	4.1
76-79	4.9	4.6	4.5	4.3	4.3	4.2
80-83	5.0	4.8	4.6	4.4	4.3	4.2
84-87	**5.1**	4.8	4.6	4.5	4.4	4.3
88-92	5.2	4.9	4.7	4.6	4.4	4.3
93-96	5.3	5.0	4.8	4.7	4.5	4.4
97-100	5.4	5.1	4.8	4.7	4.5	4.3
101-105	5.5	5.2	5.0	4.7	4.6	4.5
106-110	5.6	5.3	5.0	4.8	4.6	4.5

111-115	5.7	5.4	5.1	4.9	4.7	4.5
116-120	5.8	5.5	5.2	5.0	4.8	4.6
121-126	6.0	5.5	5.3	5.0	4.8	4.6
127-132	6.1	5.7	5.3	5.1	4.9	4.7
133-138	6.2	5.8	5.4	5.2	5.0	4.7
139-146	6.3	5.9	5.6	5.3	5.0	4.8
147-154	6.5	6.0	5.7	5.4	5.1	4.8
155-163	6.7	6.2	5.8	5.4	5.2	4.9
164-173	6.8	6.3	5.9	5.5	5.3	5.0
174-185	7.0	6.5	6.0	5.7	5.4	5.1
186-201	7.3	6.7	6.2	5.8	5.5	5.2
202-220	7.6	6.9	6.4	6.0	5.6	5.3
221-247	8.0	7.2	6.6	6.2	5.9	5.4
248-292	8.5	7.6	7.0	6.5	6.1	5.6
293-399	9.5	**8.3**	7.5	7.0	6.5	5.9
400-13975	11.9	10.0	8.8	8.1	7.5	6.7

Appendix I. Efficacy Analysis Code

Primary analysis of the primary estimands

Hazard ratio and 95% confidence interval

```
proc phreg data=ep ;
           class trt strata   ;
           model  aval* cnsr(1) = trt / RISKLIMITS;
           strata strata ;
           hazardratio trt;
run;
```

Kaplan-Meier graph and yearly Kaplan-Meier estimates

```
proc lifetest data=ep method=km outsurv=out1 conftype=log
timelist= 12 24 36 48 60 66;
id subjid;
strata  trt;
time aval * cnsr(1);
run;
```

Stratified log rank test

```
proc lifetest data=ep;
id subjid;
strata strata / group = trt;
time aval * cnsr(1);
run;
```

ep = dataset containing time to event data for the endpoint of interest for all **subjects in the full analysis set**, 1 record per subject

trt = randomized treatment group

strata = stratification factor from IVRS/IWRS (6 levels, geographical region [Europe, North America, and Others] and LDL-C level [<160mg/dL, ≥160 mg/dL] used for eligibility)

aval = time variable (months). Subject who had a primary endpoint event, this variable is equal to the time of the first positively adjudicated primary endpoint event. Subjects without an event, this variable is equal to the time of the Last Potential Endpoint Assessment.

cnsr = censor indicator. Equal to 1 for subjects who were censored (ie, no primary endpoint event), and equal to 0 for subjects who experienced an event

subjid = subject identifier

The above analyses will be repeated for all secondary estimands. For **fatal** secondary estimands, the aval variable will be equal to the last confirmed survival status date for subjects who have not died.

Sensitivity analyses

Tipping point analysis

A published SAS macro from **literature** will be **referenced** :

[1] Moscovici JL, Ratitch B. Combining Survival Analysis Results after Multiple Imputation of Censored Event Times. *Proceedings of the Pharmaceutical SAS Users Group Conference (PharmaSUG-2017)*, Paper SP05. Cary, NC: SAS Institute Inc

Multiple imputation analysis

The same **stratified** Cox model used in the primary analysis of the primary estimands will be used to analyse each imputed dataset. Normalizing transformations before combining the results and back-transformed the combined results may be applied when needed. The following code will be used to combine the results using Rubin's rule:

```
proc mianalyze data= imputed_analysis;
           modeleffects teststat;
           stderr stderr;
run;
```

Imputed_analysis = dataset containing the analysis results from imputed datasets

Teststat = coefficient estimate (i.e., Hazard ratio from the Cox model)

Stderr = standard error for the estimate

Lag model

The following cox model will be run in R for each day in year 1:

fit <- coxph(Surv(tstart, aval, cnsr) ~ trt_time + strata(strata) + cluster(subject_id), data = ep_split)

ep_split: Time to event data for the endpoint of interest, split into 2 records per subject (time before lag and time after lag)

trt_time: equal to 0 for subjects randomized to placebo, equal to 1 for subjects randomized to evomab for time before lag, equal to 2 for subjects randomized to evomab for time after lag

tstart: start time for each record. Equal to 0 for the time segment before the lag, equal to date of lag for the time segment after the lag

Additional analyses

Covariate analysis

```
proc phreg data=ep ;
           class trt strata covar /*if binary or categorical
covariate*/ ;
           model  aval* cnsr(1) = trt covar/ RISKLIMITS;
           strata strata ;
           hazardratio trt;
run;
```

Variables as specified for the primary analysis of the primary estimand.

Covar = covariate of interest, listed in Section 4.1 of the SAP

Subgroup analysis

```
proc phreg data=ep ;
           class trt strata ;
           model  aval* cnsr(1) = trt / RISKLIMITS;
           strata strata ;
           hazardratio trt;
           by subgroup;
run;
```

Variables as specified for the primary analysis of the primary estimand.

subgroup = subgroup of interest, listed in Section 4.2 of the SAP

Trend and consistency of the treatment effect

```
proc phreg data=ep_WLW covs(aggregate);
    model aval*CNSR(1) = chd mi str / rl;
    strata strata paramcd;
    id subjid;
    test cvd=mi=str;
run;
```

aval, cnsr, strata, ep as specified for the primary analysis of the primary estimand.

ep_WLW = dataset containing time to event data for cardiovascular death, myocardial infarction, and ischemic stroke, for all **subjects in the full analysis set**, 3 records per subject

chd = CHD death indicator. Equal to 1 for CHD records of subjects randomized to AMG 145, otherwise equal to 0

mi = myocardial infarction indicator. Equal to 1 for MI records of subjects randomized to AMG 145, otherwise equal to 0

str = ischemic stroke indicator. Equal to 1 for STR records of subjects randomized to AMG 145otherwise equal to 0

NOTE: for the trend and consistency analysis of the quadruple component primary endpoint, an additional variable to indicate revascularization will be included.

subjid = unique subject identifier

paramcd = variable to indicate the type of event (cardiovascular death, myocardial infarction, or ischemic stroke)

Competing risk – non-CHD death

Cumulative Incidence Function:

```
proc lifetest data=ep plots=cif(test);
time aval*status(0) / eventcode=1;
strata trt;
run;
```

Proportional hazards model for the subdistribution of a competing risk:

```
proc phreg data=ep ;
                class trt strata ;
                model  aval* status(0) = trt / RISKLIMITS eventcode=1;
                strata strata ;
                hazardratio trt ;
run;
```

Variables as specified for the primary analysis of the primary estimand, except:

status = Equal to 0 for subjects who had no primary endpoint event and did not experience non-CHD death, equal to 1 for subjects who experienced a primary endpoint

event, and equal to 2 for subjects who did not experience a primary endpoint event prior to non-CHD death.

Additional estimands

On-treatment estimands

Analysis will be the same as the primary analysis of the primary estimands, except subjects will be censored after discontinuing investigational product or commencing commercial PCSK9 inhibitor therapy.

Landmark estimands

Analysis will be the same as the primary analysis of the primary estimands, except four sets of analysis will be produced per endpoint:

- Including only those events which occur between year 0 and the end of year 1
- Including only those events which occur beyond year 1
- Including only those events which occur between year 0 and the midpoint of the trial (defined as the day in which the subject with the longest **follow-up** completed 50% of their total follow-up)
- Including only those events which occur beyond the midpoint of the trial

Total event estimand

```
proc genmod data= ep_all ;
      class strata trt;
model count = strata trt /offset= lstyd link=log dist=negbin
scale=pearson;
      lsmeans trt / diff cl exp;
run;
```

ep_all = dataset containing the time to all primary endpoint events

strata and trt = as per primary analysis of the primary estimands

count = number of primary endpoint events per subject

lstyd = log(total study exposure)

Appendix J. Potential Endpoint Event Reporting in Final Analysis Tables

Event Type	Positively adjudicated	Negatively adjudicated
Any Death	Will be summarized in applicable primary and secondary efficacy tables. Will not be reported in safety tables.	N/A (all cause death is a secondary endpoint)
MI/Stroke	Will be summarized in applicable primary and secondary efficacy tables. Will not be reported in safety tables.	Will be summarized in safety tables by system organ class (SOC) and preferred term (PT).
Coronary/ Cerebrovascular/ Peripheral Revascularizations	Will be summarized in applicable primary and secondary efficacy tables. Will not be reported in safety tables.	Will be summarized in safety tables by investigator reported procedure type.
Deep Vein Thrombosis*	Will be reported in exploratory endpoint efficacy tables. Will not be reported in safety tables.	
Aortic Valve Stenosis*	Will be reported in exploratory endpoint efficacy tables. Will not be reported in safety tables.	
Aortic Valve Replacement*	Will be reported in exploratory endpoint efficacy tables. Will not be reported in safety tables.	

*Deep Vein Thrombosis, Aortic Valve Stenosis, and Aortic Valve Replacement potential endpoints did not undergo adjudication by the CEC.