Statistical Analysis Plan

Protocol Title:	A Multicenter, Open-label, Single-arm, Extension Study to Assess Long-term Safety of Evolocumab Therapy in Subjects With Clinically Evident Cardiovascular Disease in Selected European Countries
Short Protocol Title:	FOURIER-OLE
Protocol Number:	20160250
NCT Number:	NCT03080935
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SAP Date:	**Document Version** — **Date** **Original** — **29 March 2019** **Amendment 1 (v2.0)** — **27 May 2020** **Amendment 2 (v3.0)** — **24 March 2022**

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	29MAR2019	
Amendment 1 (v2.0)	27MAY2020	**Changes** 1. Change one of the authors from [redacted] to [redacted] Rationale: Study statistician role had been transitioned from [redacted] to [redacted]. 2. Update statistical analysis plan (SAP) version and date throughout this SAP Rationale: Statistical analysis plan was amended 3. Replace one of the cardiovascular events of interest :revascularization with coronary revascularization throughout this SAP Rationale: To identify the specific vascular territory of interest, which is the coronary circulation 4. Change the definition of age in section 5.2 Rationale: To clarify age at enrollment is the subject's age in years as recorded on Demographics eCRF of the parent study 5. Remove adverse event events of interest (EOIs) throughout this SAP Rationale: Events of interest (EOIs) are no longer pre-specified in the protocol 6. Update the wording of the primary endpoint in Table 9-1 Rationale: This change is to make it clear that all events listed are treatment emergent 7. Update the language in Section 9.5.1 Analyses of Primary Endpoint Rationale: To clarify that all adverse event summaries will include not only Clinical Events Committee (CEC) reviewed events but also disease related events; to clarify that subject incidence and exposure-adjusted subject incidence rate will be tabulated by system organ class, high level term and preferred term which is similar to how they were summarized for the parent study; to clarify that disease related events will be coded with Medical Dictionary for Regulatory Activities (MedDRA) 8. Remove the fifth and the seventh paragraphs in section 9.5.1 Rationale: The third paragraph has captured the information

		9. Remove efficacy from the title in section 9.5.2 and 9.5.3 Rationale: To align with the title in section 9.5.1 10. Replace “serious AE” with “serious TEAE” in section 9.6.1 Rationale: To clarify only serious AEs which are treatment emergent 11. Specify the analysis set in section 9.6.2 and 9.6.3 Rationale: To clarify that laboratory test results and vital signs will only be summarized based on the OLE safety analysis set 12. Remove the change of exploratory objective in section 10 Rationale: The exploratory objective not included in Protocol Amendment 1 are now included in Protocol Amendment 2 13. Remove End of Investigational Product Administration (EOIP) in Appendix. A Rationale: To realign with the 20130295 sister study and to clarify that week 260 visit applies 14. Add one analysis in section 9.7 Rationale: The team agree on adding a listing for events which occurred in the time between the subject’s EOS date in parent study and the enrolment date of the OLE

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Amendment 2 (v3.0)	24March2022	**Changes:** 1. Change in one of the author of Study Statistician from [redacted] to [redacted] 2. Update statistical analysis plan (SAP) version and date throughout this SAP Rationale: Statistical analysis plan was amended 3. Removed long-term safety analysis set (including parent [FOURIER] subjects who did not rollover into this OLE study) and related analysis from SAP and clarified the rationale in section 10. Rationale: The pre-specified planned analyses in the SAP focus on the long term safety data in the subjects who enrolled into this OLE study (i.e., OLE safety analysis set) rather than the long-term safety analysis set which also includes parent study subjects who did not rollover into this OLE study. We will include parent studydata and OLE data from those that enrolled in the OLE for the analysis. More details will be provided in SAP section 9. 4. Add the explanations for “ABI” and “PAD” in the list of abbreviations Rationale: To explain the abbreviation of a new definition added in section 5.2 5. Added explanation for “K-M” in the list of abbreviations as included for efficacy tables. 6. Added a new subgroup analysis in the list per request from Clinical team to analyze the long term exposure effect in subjects with evolocumab. 7. Update the definition of planned covariates in section 4.1 Rationale: Since this study is for estimation and summarizes descriptive statistics. Covariate analysis involves modelling; therefore, covariate analysis is not applicable for this study. 8. Update section 5 to include definition of censoring date and time to event Rationale: We need those to be able to compare the results of OLE vs parent study. 9. Provided more details on the definition of last dose date in section 5.1 and apparently updated language

		in definition for Enrollment date and Study day 1. 10. Added Categories of Time to first-event Endpoints with definitions and derivations in section 5.1 11. Rationale – To incorporate the last known survival status information when censoring for mortality endpoints especially for those lost to follow up patients or patients that withdrew consent. 12. Updated derivation for patient years of follow up for TEAE. Rationale – To count parent study and OLE period as two distinct periods which are added together, rather than 1 period from parent study's first dose to end of OLE 13. Update IP and Study Exposure Derivation for the combined parent and OLE study period. Rationale – To only sum of the two separate study exposure from the parent study and OLE studies (i.e., excluding the gap time between end of parent study and start of OLE) instead of the continuous study exposure from start of parent study till end of OLE (i.e., including the gap time between end of parent study and start of OLE. 14. Update section 8.3.2 to include imputation methods for handling partial dates of the CEC reviewed events and death events. Rationale: To be consistent with Fourier reporting. 15. Update the wording of the primary endpoint in Table 9-1 Rationale: This change is to clarify that all events listed are treatment emergent 16. Updated section 9.3 to include COVID-19 related protocol deviations and important protocol deviations Rationale: Per GDE-409220, the COVID-19 related PD and IPD will also be summarized and listed as per Amgen standard 17. Update the language in section 9.5.1 Analyses of Primary Endpoint Rationale: To clarify that all adverse event summaries will include not only Clinical Events Committee (CEC) reviewed events but also disease related events; to clarify that disease related events will be coded with

		Medical Dictionary for Regulatory Activities (MedDRA) 18. Updated section 9.5.2 and section 9.5.3 Rationale – To specify that those would be analyzed. 19. Update the LDL-C subgroup to LDL-C<40 mg/dl in section 9.6.1 Rationale: LDL-C < 40 mg/dl is used to be consistent with other low LDL-C achievement analysis 20. Updated section 9.5.3 for sensitivity analysis Rationale – To perform analysis for cardiovascular events that occurred during the gap (i.e.between subjects EOS date in parent study and OLE study enrolment date). 21. Specified the analysis set in section 9.6.1, 9.6.2, 9.6.3, 9.6.4 and 9.6.5. 22. Updated the analysis window for week 260 Rationale: to make sure the lipid assessments are properly included for the analysis 23. Updated term from “FOURIER” to “parent” study. 24. Added Appendix D. Rationale – To understand the ACC/AHA guidelines for lipid modifying background therapy.

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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
ABI	**Ankle-brachial index**
AE	Adverse event
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase (serum glutamic-pyruvic transaminase)
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
AST (SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
CEC	Clinical events committee
CI	Confidence Interval
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CVD	Cardiovascular disease
DRE	Disease-related event
eCRF	Electronic case report form
EOI	Event of interest
EOIP	End of investigational product
EOS	End of study
FOURIER	Study 20110118; the parent study for this open-label extension study
FOURIER OLE	Open-label extension study of the FOURIER study (Study)
GSO-DM	Amgen global study operations - data management
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
hsCRP	High sensitivity C-reactive protein
IP	Investigational product
IPD	Important protocol deviation
K-M	**Kaplan-Meier**
LDL-C	Low-density lipoprotein cholesterol
LLT	Lipid-lowering therapy
Lp(a)	Lipoprotein(a)
MI	Myocardial infarction
MedDRA	Medical Dictionary for Regulatory Activities
non-HDL-C	Non-high-density lipoprotein cholesterol
OLE	Open-label extension
PAD	**Peripheral arterial disease**

Abbreviation or Term	Definition/Explanation
PCSK9	Proprotein convertase subtilisin/kexin type 9
Q1	The first quartile
Q2W	Every 2 weeks
Q3	The third quartile
QM	Monthly; defined as every 4 weeks
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
TEAE	Treatment emergent adverse event
TIA	Transient ischemic attack
UC	Ultracentrifugation
VLDL-C	Very low-density lipoprotein cholesterol
WHO DRUG	World Health Organization Drug

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol amendment **2** for study 20160250, AMG 145 evolocumab dated **19 February 2020**. The scope of this plan includes the pre-specified analyses and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To describe the safety and tolerability of long-term administration of evolocumab	• Subject incidence of adverse events
Secondary	
• To describe the effects of long-term administration of evolocumab on low density lipoprotein cholesterol (LDL-C) levels • To describe the effects of long-term administration of evolocumab in subjects achieving an LDL-C level of < 40 mg/dL (1.03 mmol/L)	• Percent change of LDL-C from baseline at each scheduled visit • Achievement of an LDL-C level < 40 mg/dL (1.03 mmol/L) at each scheduled visit
Exploratory	

• To describe the effects of long-term administration on non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol, lipoprotein(a) (Lp[a]), triglycerides, high-density lipoprotein cholesterol (HDL-C), LDL-C, very low-density lipoprotein (VLDL-C), and apolipoprotein A1 (ApoA1) levels
• To describe the effects of long-term administration of evolocumab on subject incidence of death and cardiovascular events of interest
	• Change and percent change from baseline at each scheduled visit in each of the following lipid parameters:
	  • non-HDL-C
	  • ApoB
	  • Total cholesterol
	  • Lp(a)
	  • Triglycerides
	  • HDL-C
	  • LDL-C
	  • VLDL-C
	  • ApoA1
	• Subject incidence of events positively reviewed by the CEC:
	  • All deaths
	  • Cardiovascular events of interest:
	  o Myocardial Infarction (MI)
	  o Stroke
	  o Coronary revascularization
	  o Hospitalization for unstable angina
	  o Hospitalization for heart failure
	  o Transient Ischemic Attack (TIA)

2.2 Hypotheses and/or Estimations

The primary clinical hypothesis is that long-term exposure of evolocumab will be safe and well tolerated in subjects with clinically evident atherosclerotic cardiovascular disease (CVD).

3. Study Overview

3.1 Study Design

This is a multicenter, open-label extension (OLE) study designed to assess the extended long-term safety of evolocumab in subjects who have completed the FOURIER trial (Study 20110118). FOURIER is a randomized placebo-controlled study of evolocumab, in patients with clinically evident atherosclerotic CVD on stable effective statin therapy. Subjects at sites participating in FOURIER OLE (Study 20160250) who are eligible and have signed the FOURIER OLE informed consent will be enrolled after completion of FOURIER.

The FOURIER OLE study requires laboratory assessments at day 1, week 12, and thereafter approximately every 6 months from day 1; the corresponding blood samples will be processed using a central laboratory.

Upon enrollment in FOURIER OLE study, subjects will receive evolocumab 140 mg every 2 weeks (Q2W) or 420 mg monthly (QM) according to their preference. Frequency and corresponding dose of administration can be changed at any scheduled time point where evolocumab is supplied to the subject, provided the appropriate supply is available. It is recommended that subjects continue the same background lipid-lowering therapy (LLT), including statin, as taken during FOURIER.

This study will continue for 260 weeks (approximately 5 years). Subjects ending administration of evolocumab should continue study assessments until the end of study.

All subjects will be followed and complete procedures/assessments from enrollment through the date of study termination unless the subject has withdrawn consent, irrespective of whether the subject is continuing to receive treatment. All deaths and cardiovascular events of interest will be reviewed by an independent external Clinical Events Committee (CEC), using standardized definitions.

3.2 Sample Size

It is estimated approximately 1600 subjects who completed the FOURIER trial will be enrolled. Based on sample size of 1600 subjects, Table 3-1 lists the width of 95% confidence interval (CI) for a range of various underlying adverse event rates.

Table 3-1. Confidence Interval Width for Adverse Event Rates

Underlying Adverse Event Rate (%)	Width of 95% Confidence Interval
0.01	0.098
0.05	0.219
0.10	0.310
1.00	0.975
2.00	1.372
3.00	1.672
4.00	1.920
5.00	2.136

4. Covariates and Subgroups

4.1 Planned Covariates

Not applicable

4.2 Subgroups

The planned subgroups include the following:

- Baseline age (< 65 years, ≥ 65 years; < 75 years, ≥ 75 years)
- Sex (male, female)
- Race (white, non-white)
- Prior non-hemorrhagic stroke (yes, no)
- Symptomatic PAD (yes, no)
- Prior MI (No, < 1 year, 1 - < 2 years, ≥ 2 years)
- Baseline PCSK9 level (< median, ≥ median)
- Baseline LDL-C by quartiles (Q1, median, Q3)
- Baseline HDL-C by quartiles (Q1, median, Q3)
- Baseline triglycerides by quartiles (Q1, median, Q3)
- Baseline hsCRP (< 2 mg/L, ≥ 2 mg/L)
- Ezetimibe use at baseline (yes, no)
- ACC/AHA high statin background therapy intensity at baseline (yes, no)
- History of type 2 diabetes (yes, no)
- Heterozygous Familial Hypercholesterolemia (HeFH) at OLE enrollment (definite, probable, neither definite nor probable)
- **Subjects who were randomized to and received evolocumab group in the parent (i.e., FOURIER) study with ≥ 7 years of the combined exposure for evolocumab across the parent and OLE studies.**

5. Definitions

5.1 Study Time Points

Baseline

The baseline value is defined as the subject's baseline value from the parent study (FOURIER), unless otherwise specified.

First Dose Date of Investigational Product (IP)

For each subject, the first dose date of IP is the date of the first administration of evolocumab in **this OLE study**.

End of Investigational Product (EOIP) Date

For each subject, end of investigational product is the date reported on End of Investigational Product Administration eCRF.

Last Dose Date of Investigational Product

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

If the last dose was administered in-clinic, then the Last IP Dose Date is the last start date captured on the IP Administration (In-Clinic) eCRF page.

If the last dose was administered at a non-investigator site location, then the Last IP Dose Date is defined as the final dose date reported by the subject on the Non-Clinic Final Investigational Product Dose Date eCRF page.

End of Study (EOS) Date

For each subject, the end of study date is defined as the last day that protocol-specified procedures are conducted for an individual subject, including safety follow-up and survival assessment. The EOS date is recorded on the End of Study eCRF.

Enrollment Date

The enrollment date for each subject is recorded on the Subject Enrollment eCRF **in the OLE study**.

Study Day 1

Study day 1 is defined as the day of the first administration of evolocumab in the study or the day of enrollment for subjects who are not administered any dose of evolocumab.

Study Day

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

Study day = (date of interest – study day 1 date) + 1

If the date of interest is prior to the study day 1:

Study day = (date of interest – study day 1 date)

Study End Date

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

Categories of Time-to-first-event Endpoints

All time-to-first-event endpoints in this study are categorized below.

- **Composite**
  - **time to cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary revascularization, whichever occurs first**
  - **time to cardiovascular death, myocardial infarction, or stroke, whichever occurs first**
  - **time to cardiovascular death or hospitalization for worsening heart failure, whichever occurs first**
  - **time to ischemic fatal or non-fatal stroke or transient ischemic attack, whichever occurs first**
  - **time to the first fatal and non-fatal myocardial infarction**
  - **time to the first fatal and non-fatal stroke**
- **Non-mortality**
  - **time to the first coronary revascularization**
- **Mortality**
  - **time to cardiovascular death**
  - **time to coronary death**
  - **time to death by any cause**

Censoring date

Endpoints are censored differently according to the endpoint categories. The censoring schema are described in below:

- **censoring date for the composite and non-mortality endpoints is the EOS date in the OLE study.**
- **censoring (or time-to-event) for mortality endpoints are detained in appendix C.**

Time-to-first-event Definition

- **For the time-to-first-event analysis based on combined the parent and OLE data,** the events adjudicated as positive in the parent study and occurred prior to or on subject last confirmed survival status date in the parent study (i.e., primary analysis in the parent study; please see the definition in the parent study SAP version 3.1 dated Aug 09, 2016) are included in addition to the events reviewed as positive in the OLE study (defined as below).

  For the time-to-first-event analysis based on the OLE data only, mortality events reviewed as positive and occurred prior to or on later of (the EOS date or last known survival status date from eCRF page(s) in this OLE study) and non-mortality events reviewed as positive and occurred prior to or on the EOS date are included. For those subjects who already experience such event in the parent study, their time to event and censor flag are same as those in the parent study.
- **For those subjects who didn't experience such event in the parent study, the derivation of the time-to-event and censoring date is presented below**

For analyses combined both the parent and OLE studies		
Endpoint	**Time-to-event for subjects with events**	**Censoring date for subjects without events**
Composite or Non-mortality	**First event onset date reviewed by CEC in OLE study – randomization date in the parent study +1**	**EOS date in OLE study**

Mortality	**Death endpoint date reviewed by CEC in OLE study – randomization date in the parent study +1**	**For subjects who died not due to death endpoint, the censoring date is the death date (reviewed by CEC) in OLE study** **For remaining subjects, the censoring date is max (EOS date, last known survival status date from eCRF page(s)) in the OLE study**
For analyses based on OLE data only		
Composite or Non-mortality	**First event onset date reviewed by CEC in OLE – enrolment date in OLE study +1**	**EOS date in OLE study**
Mortality	**Death endpoint date reviewed by CEC in OLE study – enrolment date in OLE study +1**	**For subjects who died not due to death endpoint, the censoring date is the death date (reviewed by CEC) in OLE study** **For remaining subjects, the censoring date is max (EOS date, last known survival status date from eCRF page(s)) in the OLE study**

<u>Patient-years of follow-up for treatment emergent adverse events</u>

For analyses based on combined both the parent and OLE studies:

1) **Subjects had first event in parent study: date (first event) – date (first dose date in FOURIER) + 1**
2) **Subjects had first event in OLE: study exposure in parent study + (date (first event) – first dose date in OLE + 1)**
3) **Subjects didn't have events: study exposure in parent study + (min [date (EOS in OLE), date (last dose date in OLE)+30] – first dose date in OLE + 1)**

For analyses based on OLE study:

1) **Subjects had events: date (first event in OLE) – date (first dose date in OLE) + 1**

2) **Subjects didn't have events: min [date (EOS in OLE), date (last dose date in OLE)+30] – date (first dose date in OLE) + 1**

5.2 Demographic and Baseline-related Definitions

Age

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

Baseline Lipid and Lipid-related Parameters

Baseline values for lipids (total cholesterol, HDL-C, non-HDL-C, LDL-C, VLDL-C, and triglycerides), ApoA1, ApoB, hsCRP, Lp(a) and their derived parameters (eg, ratio between them) are defined as the two most recent non-missing concentrations measured through central lab prior to or on the **parent** study randomization date. If for only reason only 1 value is available, then that value will be used as baseline.

Change (absolute change) From Baseline

The arithmetic difference from baseline at a given time point:

Change from baseline = (value at given time point – baseline value)

Percent Change From Baseline

The percent change from baseline for a given variable at a given time point is defined as: 100 x (change from baseline / baseline value)

Baseline Metabolic Syndrome

Baseline metabolic syndrome is defined as the eCRF data of history history of metabolic syndrome at **parent** study baseline.

Baseline Major Risk Factors

Baseline major risk factors are defined at FOURIER study baseline:

- Diabetes (type 1 or type 2)
- Age ≥ 65 years at randomization in parent study (and ≤ 85 years at time of informed consent in parent study)
- MI or non-hemorrhagic stroke within 6 months of screening in parent study
- Additional diagnosis of myocardial infarction or non-hemorrhagic stroke excluding qualifying MI or non-hemorrhagic stroke
- Current daily cigarette smoking

- History of symptomatic PAD (intermittent claudication with ABI < 0.85, or peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease) if eligible by MI or stroke history

Baseline Minor Risk Factors

Baseline minor risk factors are defined at **parent** study baseline:

- History of non-MI related coronary revascularization
- Residual coronary artery disease with ≥ 40% stenosis in ≥ 2 large vessels
- Most recent HDL-C < 40 mg/dL (1.0 mmol/L) for men and < 50 mg/dL (1.3 mmol/L) for women by central laboratory before randomization
- Most recent hsCRP > 2.0 mg/L by central laboratory before randomization
- Most recent LDL-C ≥ 130 mg/dL (3.4 mmol/L) or non-HDL-C ≥ 160 mg/dL (4.1 mmol/L) by central laboratory before randomization
- Metabolic syndrome

Other Baseline Values

Other baseline values are defined at FOURIER study baseline.

For targeted concomitant medications data, the medication taken at baseline is defined as the medication collected at day 1 visit (ie, currently medications taken at time of day 1 visit) in **parent** study.

For all other variables, the baseline value is defined as the last non-missing value collected prior to or on randomization date in **parent** study.

5.3 Other Study Related Definitions

Treatment-emergent adverse event

Events are categorized as Adverse Events (AEs) **or Disease-related Events (DREs)** starting on or after first dose of investigational product as determined by the flag indicating if the event started prior to the first dose on the Events eCRF and up to the EOS/Safety Follow-up visit or 30 days after the last administration of evolocumab, whichever is earlier.

Treatment-Emergent Disease-Related Events

Events categorized as Disease-related Events (DREs) defined in Protocol Section 9.1.1 starting on or after first dose of investigational product as determined by the flag indicating if the disease-related event started prior to the first dose on the Events eCRF and up to the EOS/Safety Follow-up visit or 30 days after the last administration of evolocumab, whichever is earlier.

Analytical Study Week Assignments

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

Investigational Product (IP)

Investigational product includes evolocumab 140 mg every two weeks (Q2W) and 420 mg monthly (QM).

IP Exposure Period in Months (Parent study)

For subjects whose last IP dose is Q2W:

IP exposure period = [min(last IP dose date in parent study + 14 days, EOS date) – first IP dose date in parent study + 1] / 365.25 x 12

For subjects whose last IP dose is QM:

IP exposure period = [min(last IP dose date in parent study + 28 days, EOS date) – first IP dose date in parent study + 1] / 365.25 x 12

IP Exposure Period in Months **(For OLE period)**

For subjects whose last IP dose is Q2W:

IP exposure period **in OLE period**= [min(last IP dose date **in OLE period** + 14 days, EOS date) – first IP dose date **in OLE period** + 1] / 365.25 x 12

For subjects whose last IP dose is QM:

IP exposure period **in OLE period**= [min(last IP dose date **in OLE period** + 28 days, EOS date) – first IP dose date **in OLE period** + 1] / 365.25 x 12

IP Exposure Period in Months (For the combined parent and OLE periods)

For each subject, IP exposure in combined periods is the sum of the IP exposure in the parent study (defined above) plus the IP exposure in the OLE period (defined above).

Study Exposure Period in Months (Parent study)

For each randomized subject, study exposure period = [(EOS date in parent study – Randomization date) + 1] / 365.25 x 12

Study Exposure Period in Months **(For OLE period)**

For each subject, study exposure period in OLE period = [(EOS date – enrollment date) + 1] / 365.25 x 12

Study Exposure Period in Months (For the combined parent and OLE periods)

For each subject, study exposure in combined periods is the sum of the study exposure in the parent study (defined above) plus the study exposure in the OLE period (defined above).

Reflexive Approach for LDL-C and VLDL-C

For all analyses related to LDL-C and VLDL-C, unless specified otherwise, an LDL-C reflexive approach will be used. When calculated LDL-C is less than 40 mg/dL or triglycerides are > 400 mg/dL, the ultracentrifugation (UC) LDL-C value and UC VLDL-C value from the same blood sample will be used instead, if available.

Two Consecutive LDL-C Values < **cutoff (25 mg/dL and 40 mg/dl)**The algorithm for defining the 2 consecutive LDL-C values < 25 mg/dL **/ 40 mg/dL** separated by at least 21 days within OLE study period is summarized below:

1) For each blood sample draw date that has at least one LDL-C value within OLE study period, identify the lowest LDL-C value
    a. If UC values exist regardless of the presence of calculated LDL-C values, the lowest UC LDL-C value will be used
    b. If only calculated LDL-C values exist, the lowest calculated LDL-C value will be used
2) If a subject has 2 consecutive (separated by at least 21 days) LDL-C values that are < 25 mg/dL **/ 40 mg/dL** within OLE study period, then the subject will be considered as a subject with two consecutive LDL-C values < 25 mg/dL **/ 40 mg/dL** within OLE study period.

Two consecutive LDL-C in the parent study has been defined and derived in the same way as above.

6. Analysis Sets

6.1 OLE Safety Analysis Set

The OLE safety analysis set includes all subjects who received at least 1 dose of open-label evolocumab in the OLE study.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

Interim analysis will be performed to support safety data reporting and assessments of other listed endpoints.

7.2 Primary Analysis

Primary analysis activities are commenced based on achieving the EOS milestone described in Protocol Section 3.5.2.

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.

All data collected in the eCRF will be extracted from RAVE. Protocol deviations will be transferred from eClinical. Details on data transfer will be provided in the Data Transfer Plan.

8.3 Handling of Missing and Incomplete Data

8.3.1 Patterns of Missing Data

Subjects may be missing specific data points for various reasons. In general, data may be missing due to a subject's early withdrawal from study, a missed visit, or non-evaluability of a data point or an endpoint at a particular point in time. All attempts will be made to capture missing or partial data for this trial prior to the data cutoff date.

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

There will be no imputation for missing data other than date imputation described in the next section.

8.3.2 Handling of Missing Data

Missing and partially missing dates will be queried. Partial/missing EOS dates will be imputed as the maximum of (last dose date of IP, vital signs assessments, lab assessments, AE start dates, concomitant medication start dates and imputed EOS date if partially missing). Partial/missing onset dates (reviewed by CEC) of

time-to- first-event endpoints will be imputed using the following algorithm, with the reference date being the enrollment date.

- **Impute the missing year as the year of the reference date**
- **Impute the missing month as January**
- **Impute the missing day as 1st**

Partial/missing start dates of adverse events and disease-related adverse events will be imputed using the following algorithm, with the reference date being the first dose date.

- **Impute the missing year as the year of the reference date**
- **Impute the missing month as January**
- **Impute the missing day as 1st**

If any of the resulting dates are prior to the reference date, the imputed date will be reset to the reference date. Please note for completely missing start dates of adverse-events and disease-related adverse where 'Did event start before first dose of investigational product?' on eCRF is recorded as 'Yes' will not be imputed. In addition, any imputed death dates will be the maximum of (the all adverse event start dates [use imputed event dates if missing], subject EOS dates [use imputed EOS dates if missing], and subject last confirmed survival status date recorded on the survival status eCRF page). For CEC death events and AE death event start dates, missing or partial missing dates will use the imputed death dates.

Adverse events with a valid answer to the question 'Did event start before first dose of investigational product?' on eCRF can be well defined based on the answer regardless of dates being completely or partially missing. Adverse events that cannot be determined as prior to IP or not either by the question above or by the onset date will be counted as treatment-emergent adverse events.

Concomitant medication with completely or partially missing start dates will be queried. After the query is resolved and the date is still incomplete with year only or year and month only, the start date will be imputed as described in Table 8-1 below.

Table 8-1. Imputation Rules for Incomplete Dates

	Missing	Imputation	Exception

Start date	Day	1	Default to Study Day 1 if an event starts the same year and month as Study Day 1
	Day-Month	1-Jan	Default to Study Day 1 if an event started the same year as Day 1

There are two cases for start date is missing:

- **End date is after first dose date or missing (i.e. medication is ongoing), the medication will be considered as being taken at OLE study baseline and post baseline.**
- **End date is prior to first dose date, the medication will not be considered as being taken at OLE study baseline or post baseline.**

Partial/missing start dates of cardiovascular medical history events which occurred during the gap between subjects' EOS date in the parent study and OLE study enrolment date will be imputed as follows for the sensitivity analysis:

- **If day is missing, impute to 1st of the month. If the partial start date is the same month as EOS date in parent study, impute to EOS date in parent study +1**
- **If day and month are missing, impute to 1st Jan of that year. If the partial start date is the same year as parent study EOS date, impute to EOS date in parent study +1**
- **If start date is completely unknown, no imputation and event will not be considered in the gap**

8.4 Detection of Bias

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

If any sensitivity analyses are required to evaluate potential biases in the study's conclusions, the sources of the potential biases and results of the sensitivity analyses will be documented in the CSR.

8.5 Outliers

Various methods, including univariate summaries, histograms, scatter plots, box plots, and line graphs, will be used to identify outliers in key variables. Extreme data points will

be identified during the review of the data prior to database snapshot. Such data points will be reviewed with clinical data management to ensure accuracy. Unless specified otherwise, all analyses will include outliers in the data. Sensitivity analyses may be undertaken if extreme outliers for a variable are observed.

8.6 Distributional Characteristics

There are no distributional requirements for the planned analyses. Therefore, no assessment will be made.

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

Statistical analyses in this open-label study are descriptive in nature. No formal hypothesis will be tested in this study. No statistical inference is planned.

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

Summary statistics for continuous variables will include the number of subjects (n), mean, standard deviation (SD) or standard error (SE), median, the first (Q1) and third (Q3) quartiles, minimum, and maximum. For categorical variables, the frequency and percentage will be given. The baseline value is defined as the subject's baseline value from the **parent** study as defined in Section 5.2, unless specified otherwise. All analyses will be performed on the OLE safety analysis set.

Interim and final analyses will be based on data collected from this study combined with the data from the FOURIER study as applicable. For all endpoints, results will be summarized by the randomized treatment group from the parent study and overall, unless specified otherwise.

All deaths and cardiovascular events of interest (MI, stroke, coronary revascularization, hospitalization for unstable angina, hospitalization for heart failure, and TIA) will be reviewed by an independent external CEC, using standardized definitions. The CEC is external to Amgen and primarily comprises both academic clinical physicians (to include cardiologists) 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 reviews events according to pre-specified criteria defined in the CEC charter. The CEC will be blinded to the original randomized treatment group from the **parent** study.

There will be no imputation for missing data other than date imputation described in Section 8.3.2

9.2 Subject Accountability

The number and percent of subjects who were enrolled into the OLE study, received IP, completed IP, discontinued IP and reasons for discontinuing during the OLE study, completed the OLE study, and discontinued the OLE study and reasons for discontinuing will be summarized by the randomized treatment group in parent study and overall.

OLE enrollment by region, country and investigator and, key study dates for the first subject enrolled, last subject enrolled and last subject's end of study will be presented.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, 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 and Important Protocol Deviations due to COVID-19 impact will be summarized in a table. A Protocol Deviation listing of subjects impacted due to COVID-19 impact will also be provided.

9.4 Demographic and Baseline Characteristics

All baseline tables will be summarized by the randomized treatment groups in **parent** study. Baseline tables will summarize the following: baseline characteristics, demographics, cardiovascular medical history, laboratory parameters, physical measurements and lipid regulating medication.

9.5 Efficacy Analyses

Table 9-1. Endpoint Summary Table

Endpoint	Primary Summary (Long-Term Safety Analysis Set and OLE Safety Analysis Set)
Primary Endpoint	
Treatment emergent adverse events • Adverse events • Serious adverse events • Fatal adverse events • AEs leading to withdrawal from IP • Device-related adverse events • Disease related events	Subject incidence and exposure adjusted subject incidence rate
Secondary Endpoints	
Percent change of LDL-C from baseline	Summary statistics at each scheduled visit
Achieving an LDL-C level < 40 mg/dL	Summary statistics at each scheduled visit
Exploratory Endpoints	
Change and percent change from baseline • non-HDL-C • ApoB • Total cholesterol • Lp(a) • Triglycerides • HDL-C • LDL-C • VLDL-C • ApoA1	Summary statistics at each scheduled visit

Endpoint	Primary Summary (Long-Term Safety Analysis Set and OLE Safety Analysis Set)
Subject incidence of events positively reviewed by the CEC: ○ All deaths ▪ Cardiovascular death ▪ Non-cardiovascular death ▪ Undetermined Cause of death ○ Cardiovascular events of interest: ▪ Myocardial Infarction (MI) ▪ Coronary revascularization ▪ Hospitalization for unstable angina ▪ Heart failure ▪ Cerebrovascular Events ▪ Coronary heart disease death	Subject incidence of events positively reviewed by the CEC

9.5.1 Analyses of Primary Endpoint

The current Medical Dictionary for Regulatory Activities version at the time of data lock will be used to code all adverse events (AEs) and disease related events to a system organ class and a preferred term.

Treatment-emergent adverse events are events with an onset after the administration of the first dose of investigational product as defined in Section 5.3.

The subject incidence and exposure-adjusted subject incidence rate of all treatment-emergent adverse events, serious adverse events, fatal adverse events, adverse events leading to withdrawal of evolocumab, device-related adverse events, and disease-related events will be tabulated by system organ class (SOC), high level term (HLT), and preferred term (PT) in alphabetical order for the overall OLE study period using the OLE safety analysis set. These events will also be presented by yearly subject exposure time intervals. All adverse event summaries for the primary analysis of the primary endpoint will include all treatment-emergent events reported on the Event eCRF, including CEC reviewed events and disease related events.

The analyses described above (subject incidence, exposure-adjusted subject incidence rate) will also be performed combining data from the OLE study and the **parent** study

using the **OLE safety analysis set and also be analyzed separately for the subgroup of subjects who were randomized to and received evolocumab group in the parent study with ≥ 7 years of the combined exposure for evolocumab across the parent and OLE study.** Events from **parent** study classified as Target IP TEAEs will be included (adverse events occurring from the first dose of IP date to 30 days after the last dose of IP date or EOS, whichever occurs first). Disease-related events from the OLE study will be reclassified as adverse events and positively reviewed events from the OLE study will not be included to remain consistent with **parent** study adverse event reporting. This analysis will be presented by the **randomized treatment in the parent study**.

Subject incidence of treatment emergent and serious adverse events occurring in at least 1% of the subjects by preferred term will be provided in descending order of frequency for the overall OLE study period only **and combined parent and OLE study periods.**

9.5.2 Analyses of Secondary Endpoints

Summary statistics of the secondary endpoints (percent change of LDL-C from baseline and achieving an LDL-C level < 40 mg/dL) will be analyzed based on the OLE Safety Analysis Set at each scheduled visit **for the overall parent and OLE study periods**.

9.5.3 Analyses of Exploratory Endpoints

The change and percent change from baseline in lipid parameters at each scheduled visit will be summarized based on the OLE Safety Analysis Set **for the overall parent and OLE study periods**. For continuous exploratory endpoints, summary statistics (number of subjects, mean, median, standard deviation or standard error, first and third quartiles, minimum, and maximum) at all scheduled visits will be calculated. Subject incidence, **exposure-adjusted subject incidence rate, and yearly Kaplan Meier (K-M) estimates of** positively reviewed events (by an independent external CEC) will be summarized **for both the OLE study period and combined parent and OLE study periods**. **All deaths will be summarized by cardiovascular death (including coronary heart disease death), non-cardiovascular death and undetermined cause of death. A sensitivity analysis will be performed for the following composite endpoints:**

- **time to cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary revascularization, whichever occurs first**
- **time to cardiovascular death, myocardial infarction, or stroke, whichever occurs first**

In this analysis, cardiovascular events which occurred during the gap between subjects End of Study date in the parent study and OLE study enrolment date will be included in the time to event analysis.

9.6 Safety Analyses

9.6.1 Safety Analysis of Low LDL-C

The safety analyses (TEAE and serious TEAE) will be summarized for subjects with any postbaseline LDL-C and all postbaseline LDL-C with the cutoffs of **<** 25 mg/dL, **< 40 mg/dL** and ≥ 40 mg/dL **for the OLE study period using the OLE safety analysis set**. In addition, the safety analyses will be summarized in subjects with 2 consecutive postbaseline LDL-C < 25 mg/dL and LDL-C **< 40 mg/dL** separated by at least 21 days.

9.6.2 Vital Signs

Systolic and diastolic blood pressure and heart rate will be summarized using descriptive statistics at each scheduled visit based on the OLE Safety Analysis Set **for the OLE study period**.

9.6.3 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product **for both the overall OLE study period and combined parent and OLE study periods using the** OLE Safety Analysis Set.

9.6.4 Exposure to Other Protocol-specified Treatment

The number and proportion of subjects receiving protocol specified lipid regulating medications captured on the **related concomitant medication** eCRF will be summarized. The subject incidence of changes in protocol specified background lipid regulating medications during the treatment period will also be provided **for the overall OLE study period using the** OLE Safety Analysis Set **(Appendix D).**

9.6.5 Exposure to Concomitant Medication

The number and proportion of subjects receiving therapies of interest will be summarized by preferred term or category as coded by the World Health Organization Drug (WHO DRUG) dictionary **using the** OLE Safety Analysis Set.

9.7 Other Analyses

A listing will be provided for events which occurred in the time between the subject's EOS date in the parent study and the enrolment date of the OLE (recorded on the medical history eCRF for the OLE).

10. Changes From Protocol-specified Analyses

Removed long-term safety analysis set and related analysis from SAP.

Rationale: The pre-specified planned analyses in the SAP focus on the long term safety data in the subjects who enrolled into this OLE study (i.e., OLE safety analysis set) rather than the long-term safety analysis set which also includes the subjects from the parent study who did not enroll into this OLE study.

11. Literature Citations / References

There are no references in this document.

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.

If there is more than one record in a given analytical window, the analytical record for that scheduled visit will be defined as the record closest to the scheduled visit day (7 days x Number of Study Weeks + 1) for that scheduled visit. If two records are equidistant from the scheduled visit day, then the earlier record will be chosen. If there are multiple records on the same day, the last record will be used.

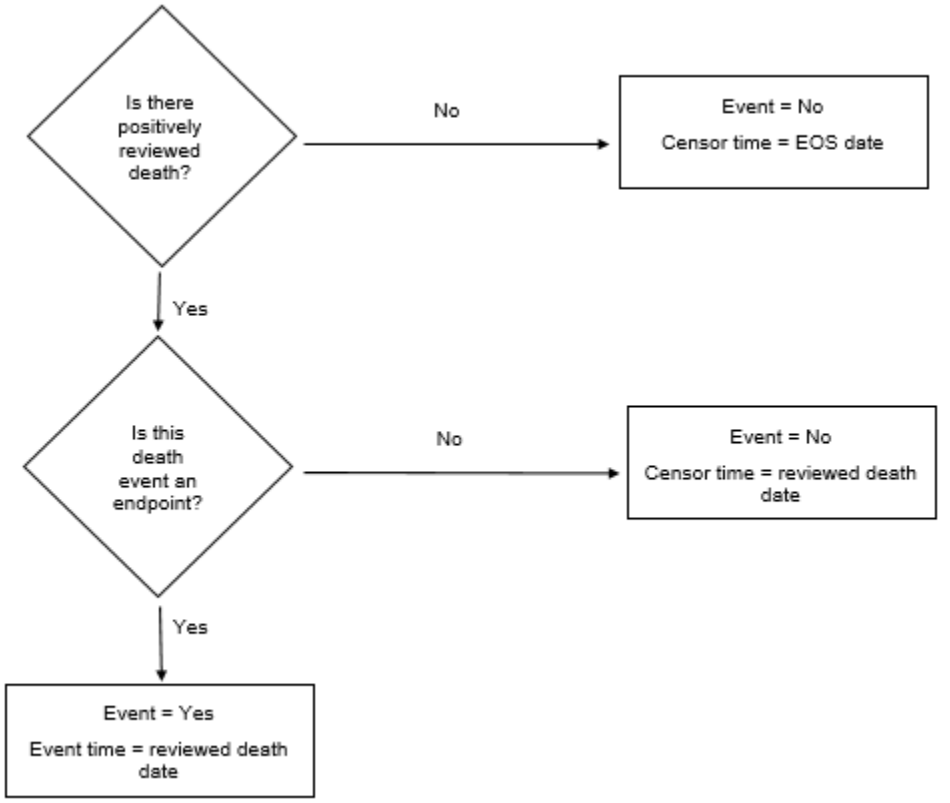
Analytical Study Week	Scheduled Visit Day	Vital signs **Body weight** Laboratory (lipid panel, ApoA1, ApoB, Lp(a), and serum pregnancy)	**Concomitant therapy**	**Physical exam**
Week 12	85	(1, 126]	**(1, 126]**	
Week 24	169	(126, 252]	**(126, 252]**	
Week 48	337	(252, 420]	**(252, 420]**	
Week 72	505	(420, 588]	**(420, 588]**	
Week 96	673	(588, 756]	**(588, 756]**	
Week 120	841	(756, 924]	**(756, 924]**	
Week 144	1009	(924, 1092]	**(924, 1092]**	
Week 168	1177	(1092, 1260]	**(1092, 1260]**	
Week 192	1345	(1260, 1428]	**(1260, 1428]**	
Week 216	1513	(1428, 1666]	**(1428, 1596]**	
Week 240	1681		**(1596, 1750]**	
Week 260	1821	(1666, **EOS**]	**(1750, 1836]**	**> 1**
EOS	**1851**		**> 1836**	

Appendix B. Common Terminology Criteria for AEs (CTCAE)

Refer to the NCI Common Terminology Criteria for AEs (CTCAE) Version 4.03, published: May 28, 2009 (v4.03: June 14, 2010) for AEs and lab shift grading and information. The CTCAE is available at the following link:

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Appendix C. Mortality Endpoints Censoring



Appendix D. Lipid Modifying Background Therapy

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	≥ 80 mg QD	20 – < 80 mg QD	< 20 mg QD	0.5
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	10

*** includes immediate-release capsules and prolonged-release tablets**

High-intensity lipid-lowering regimen is defined as:

- **A high intensity statin (e.g. atorvastatin ≥ 40 mg QD, rosuvastatin ≥ 20 mg QD, or simvastatin ≥ 80 mg QD); or**
- **A combination of any statin at any approved daily dose plus ezetimibe ≥ 10mg QD**