Statistical Analysis Plan

Protocol Title:	A Multicenter, Open-label, Single-arm, Extension Study to Assess Long-term Safey of Evolocumab Therapy in Patients with Clinically Evident Cardiovascular Disease
Short Protocol Title:	FOURIER-OLE
Protocol Number:	20130295
NCT Number:	NCT02867813
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	10JUN2019	
Amendment 1 (v2.0)	21 DEC 2021	**Changes** 1. Change one of the authors from [redacted] and then author added [redacted] Rationale: Study lead statistician role had been transitioned to [redacted]. Study lead transition role transitioned from [redacted] to [redacted]. Study Statistician role also transition from [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 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 FOURIER subjects who did not rollover into this OLE study. We will include FOURIER data 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 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 FOURIER. 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. Rationale: to clarify the definition in both in-clinic and non-clinic settings. 10. 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 11. Remove the second paragraph in sections 6.1 and 6.2 Rationale: Sections 9.5 and 9.6 have covered the information 12. Update the definition of OLE CANTAB analysis set in section 6.3 Rationale: To clarify this analysis set and align with the protocol 13. Update section 8.3.2 to include imputation methods for handling CEC reviewed events and death date. Rationale: To be consistent with Fourier reporting. 14. Update the wording of the primary endpoint in Table 9-1 Rationale: This change is to clarify that all events listed are treatment emergent 15. Remove disease-related events from the primary summary of primary endpoint in Table 9-1 Rationale: These will be reclassified as AEs in the long-term safety analysis set 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. Remove the last two paragraphs in section 9.5.1 Rationale: The third paragraph has captured the information 19. Replace “serious AE” with “serious TEAE” in section 9.6.1 Rationale: To clarify only serious AEs which are treatment emergent will be summarized 20. 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 21. Update the wording in section 9.6.6 Exposure to Concomitant Medication Rationale: To clarify that concomitant medication analysis will use the terms as coded by WHO Drug 22. Add the description in section 9.6.6 Exposure to Concomitant Medication Rationale: To clarify that how to handle the completely blank start date. 23. Add one analysis in section 9.7 Rationale: Team agreed on adding a listing for events which occurred in the time between the subject’s EOS date in FOURIER and the enrolment date of the OLE 24. Add the time point of End of Study (EOS), the assessments of Body weight, Concomitant therapy and Physical exam in Appendix A Rationale: To add the analysis windows at EOS visit, and add the

		items of body weight, concomitant therapy and physical exam 25. Updated the analysis window for week 260 Rationale: to make sure the lipid assessments are properly included for the analysis
Amendment 2 (v3.0)	08 MAR 2021	26. Update censoring date definition in section 5 for mortality endpoints 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 27. Provided reasons for subjects from site which may be removed from analysis sets Rationale: The site which has issue to provide the source documentation for clinical trial data verification needs to be removed from analysis 28. Update the imputation methods for missing EOS date, survival status date and death dates. Rationale: to help address partial/missing EOS dates, survival status dates and death dates 29. 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 30. Removed the toxicity shift table Rationale: Safety lab data were not collected in this study. 31. Updated the plot in appendix C based on the new censoring date Rationale: to reflect the new censoring date which considers the last known survival status date

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List of Abbreviations

Abbreviation	Explanation
ABI	**Ankle-brachial index**
AE	Adverse event
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
CANTAB	Cambridge neuropsychological test automated battery
CEC	Clinical events committee
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CVD	Cardiovascular disease
DRE	Disease-related event
eCRF	Electronic case report form
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
non-HDL-C	Non-high-density lipoprotein cholesterol
OLE	Open-label extension
PAD	**Peripheral arterial disease**
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

SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SWM	Spatial working memory
TEAE	Treatment emergent adverse event
TIA	Transient ischemic attack
UC	Ultracentrifugation
VLDL-C	Very low-density lipoprotein cholesterol

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 **3** for study 20130295, AMG 145 evolocumab dated **26 February 2020**. The scope of this plan includes interim analyses and the primary analysis that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To 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	• Percent change of LDL-C from baseline at each scheduled visit
• 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)	• Achievement of an LDL-C level < 40 mg/dL (1.03 mmol/L) at each scheduled visit

Exploratory	
In subjects who completed the EBBINGHAUS study (Study 20130385): • To evaluate long-term change over time in executive function, as assessed by the Cambridge Neuropsychological Test Automated Battery (CANTAB) Spatial Working Memory (SWM) strategy index of executive function • To evaluate long-term change over time in working memory, as assessed by the CANTAB SWM test between-errors score • To evaluate long-term change over time in memory function, as	In subjects who completed the EBBINGHAUS study: Change from baseline in • SWM strategy index of executive function • SWM between-errors score • PAL total errors adjusted • RTI median 5-choice reaction time

assessed by the CANTAB Paired Associates Learning (PAL) test • To evaluate long-term change over time in psychomotor speed, as assessed by the CANTAB Reaction Time (RTI) test	
In all subjects: • 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	In all subjects: ▪ Change and percent change from baseline at each scheduled visit in each of the following lipid parameters: o Total cholesterol o Triglycerides o LDL-C o HDL-C o VLDL-C o non-HDL-C o ApoA1 o ApoB o Lp(a) ▪ Subject incidence of events positively reviewed by the CEC: o All deaths o Cardiovascular events of interest: ▪ Myocardial Infarction (MI) ▪ Stroke ▪ Coronary revascularization ▪ Hospitalization for unstable angina ▪ Hospitalization for heart failure ▪ 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 study designed to assess the long-term safety of evolocumab in subjects who completed the FOURIER study (Study 20110118), a randomized placebo-controlled study of evolocumab in subjects with clinically evident

atherosclerotic CVD on stable effective statin therapy. Eligible subjects at sites participating in FOURIER OLE who have signed the FOURIER OLE informed consent may be enrolled at the completion of FOURIER. Enrollment of eligible subjects may be limited at the site level to maintain a 1:1 ratio between the following subject populations:

- subjects with ≥ 2 years of study exposure in FOURIER and
- subjects who have less than 2 years of study exposure in FOURIER and did not participate in EBBINGHAUS

In this study (FOURIER OLE), laboratory assessments will be performed at week 12 and thereafter approximately every 24 weeks from day 1; the corresponding blood samples will be processed using a central laboratory. To preserve the integrity of FOURIER blinding, no local lipid assessments may be performed until either FOURIER is unblinded or at least 12 weeks after a subject's last administration of FOURIER investigational product (evolocumab or placebo), whichever is first.

Upon enrollment in this study (FOURIER OLE), 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 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 (EOS).

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 (MI, stroke, coronary revascularization, hospitalization for unstable angina, hospitalization for heart failure, and transient ischemic attack [TIA]) will be reviewed by an independent external Clinical Events Committee (CEC), using standardized definitions.

3.2 Sample Size

It is estimated approximately 5000 subjects who completed the FOURIER study will be enrolled. Based on a sample size of 5000 subjects, Table 3-1 lists the width of 95% confidence intervals for a range of various underlying adverse event rates.

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

Percent Underlying Adverse Event	Width of 95% Confidence Interval
0.01%	0.056%
0.05%	0.124%
0.10%	0.176%
1.00%	0.552%
2.00%	0.776%
3.00%	0.946%
4.00%	1.086%
5.00%	1.208%

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 study and this OLE study**

5. Definitions

5.1 Study Time Points

Baseline

The baseline value is defined as the subject's baseline value from the parent study, 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 individual 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

The date of the first administration of evolocumab in the OLE study or the **enrollment date** 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.

Endpoint Categories

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 study and this OLE study		
Endpoint	Time-to-first-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	For subjects who died not due to death endpoint, the censoring date is the death

	study – randomization date in the parent study +1	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 study– 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**

Patient-years of follow-up for treatment emergent adverse events

For analyses based on combined both the parent study and this OLE study:

1) Subjects had events: date (first event) – date (first dose date in FOURIER) + 1
2) Subjects didn't have events: min [date (EOS in OLE), date (last dose date in OLE)+30] – date (first dose date in FOURIER) + 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 is the subject's age at the parent study baseline. 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 mean of 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 for a given variable 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 × (change from baseline / baseline value)

Baseline Metabolic Syndrome

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

Baseline Major Risk Factors

Baseline major risk factors are defined at parent 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 parent 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 (TEAE)

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 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 (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 ×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 ×12

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

For subjects whose last IP dose is Q2W:

IP exposure period in combined periods= [min(last IP dose date in OLE period + 14 days, EOS date in OLE period) – first IP dose date in the parent period + 1] / 365.25 ×12

For subjects whose last IP dose is QM:

IP exposure period in combined periods= [min(last IP dose date in OLE period + 28 days, EOS date in OLE period) – first IP dose date in the parent period + 1] / 365.25 ×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 ×12

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

For each subject, study exposure period in combined periods = [(EOS date in OLE – randomization date in the parent study) + 1] / 365.25 ×12

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.

SWM strategy 6-8 boxes (SWMS68) raw score

SWMS68 raw score is the number of times that a subject begins a search with a different box in a Spatial Working Memory test having six boxes or more. A high score represents an inefficient use of strategy and planning and a low score represents an efficient use of strategy (Owen et al, 1990). SWMS68 is a discrete ordinal variable with a range of 4 to 28.

SWM between errors (SWMBE48) raw score

SWMBE48 raw score is the number of times that a subject revisits a box in which a token has previously been found in a Spatial Working Memory test having four boxes or more. A lower score indicates better performance. SWMBE48 is a discrete ordinal variable with range of 0 to 279.

PAL total errors adjusted (PALTEA) raw score

PALTEA is comprised of the number of errors committed by a subject in a Paired Associates Learning test plus an adjustment for the estimated number of errors the subject would have made on any stages that were not reached. A lower score indicates better performance. PALTEA is a discrete ordinal variable with a range of 0 to 70.

RTI median 5-choice reaction time (RTIMDFRT) raw score

RTIMDFRT is the median duration between the onset of the stimulus and the release of the button in a Reaction Time test. A lower score indicates better performance. RTIMDFRT is a continuous variable with a range of 100 to 5100

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. **There may be sites which enrolled subjects and closed due to COVID, and those sites may have issues providing source documentation for clinical trial data verification. We will exclude the subjects from those sites for all analysis sets if their data are not able to be verified successfully via the full source documentation verification process. Since only a minimal number of subjects' data are excluded compared with the number of subjects enrolled in this study, no sensitivity analyses will be performed.**

6.2 OLE CANTAB Analysis Set

The OLE CANTAB analysis set (OLE study only) includes all subjects who enrolled in the EBBINGHAUS study and 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 analyses will be performed to support safety data reporting and assessments of other listed endpoints. The study is not anticipated to stop early unless an unexpected safety signal is detected that is assessed by Amgen to warrant study stop.

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 Incomplete Dates

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 above 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 the **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 **the first dose date,** the medication will not be considered as being taken at OLE study baseline or post baseline.

8.4 Detection of Bias

To preserve the integrity of parent study blinding, no local lipid assessments may be performed until either parent study is unblinded or at least 12 weeks after a subject's last administration of parent study investigational product (evolocumab or placebo), whichever is first. 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 statistical inference is planned. No formal hypothesis will be tested in this study.

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.

For all endpoints, results will be summarized by the randomized treatment group from the parent study and overall, unless specified otherwise.

The analysis of all primary, secondary, and exploratory endpoints will use data from the OLE study only as well as the combined data from parent and OLE studies as applicable.

All deaths and cardiovascular events of interest (MI, coronary revascularization, hospitalization for unstable angina, heart failure, cerebrovascular events and coronary heart disease death) 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 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 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	
In subjects who completed the EBBINGHAUS study: Change from baseline in • SWM strategy index of executive function • SWM between-errors score • PAL total errors adjusted • RTI median 5-choice reaction time In all subjects: 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
Subject incidence of events positively reviewed by the CEC: o All deaths ▪ Cardiovascular death	Subject incidence of events positively reviewed by the CEC

▪ 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	

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 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 OLE only 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 **combined** 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 OLE **only** study period **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 combined** parent **and** OLE study periods.

9.5.3 Analyses of Exploratory Endpoints

In subjects who completed the EBBINGHAUS study (Study 20130385), descriptive statistics for the exploratory endpoints (raw score and change from baseline of SWM strategy index of executive function, SWM between-errors score, PAL total errors adjusted and RTI median 5-choice reaction time) will be provided by each scheduled visit for OLE CANTAB analysis set.

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 **combined 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 only 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.

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 **only** 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 Laboratory Test Results

This study did not collect any laboratory parameters for safety analysis.

9.6.3 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 **only** study period.

9.6.4 Exposure to Investigational Product

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

9.6.5 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 lipid regulating medications during the treatment period will also be provided for the OLE **only** study period using the OLE Safety Analysis Set **(Appendix D).**

9.6.6 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). **In addition, for those subjects who were excluded from the OLE Safety Analysis Set due to data without fully source data verification, a key safety data listing on disposition, survival status, serious TEAE and important protocol/eligibility deviations will be provided.**

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.

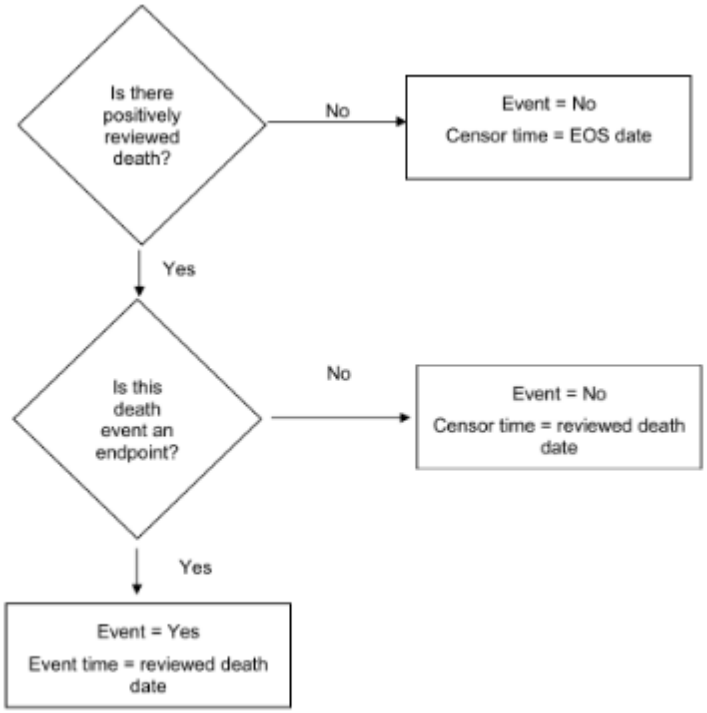
Analytical Study Week	Scheduled Visit Day	Vital signs **Body weight** Laboratory (lipid panel, ApoA1, ApoB, Lp(a), and serum pregnancy)	**Concomitant therapy**	**Physical exam**	CANTAB assessment
Week 12	85	(1, 126]	**(1, 126]**		
Week 24	169	(126, 252]	**(126, 252]**		
Week 48	337	(252, 420]	**(252, 420]**		(1, 504]
Week 72	505	(420, 588]	**(420, 588]**		
Week 96	673	(588, 756]	**(588, 756]**		(504, 840]
Week 120	841	(756, 924]	**(756, 924]**		
Week 144	1009	(924, 1092]	**(924, 1092]**		(840, 1176]
Week 168	1177	(1092, 1260]	**(1092, 1260]**		
Week 192	1345	(1260, 1428]	**(1260, 1428]**		(1176, 1582]
Week 216	1513	(1428, 1666]	**(1428, 1595]**		
Week 240	1681		**(1596, 1750]**		
Week 260	1821	(1666, **EOS**]	**(1750, 1836]**	**> 1**	(1582, **EOS**]

Appendix B. Common Terminology Criteria for AE's (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**