STATISTICAL ANALYSIS PLAN

A Double-blind, Randomized, Multicenter, Placebo-controlled, Parallel Group Study to Characterize the Efficacy, Safety, and Tolerability of 24 Weeks of Evolocumab for Low Density Lipoprotein-cholesterol (LDL-C) Reduction, as Add-on to Diet and Lipid-Lowering Therapy, in Pediatric Subjects 10 to 17 Years of Age With Heterozygous Familial Hypercholesterolemia (HeFH)

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Table of Abbreviations

Abbreviation or Term	Definition/Explanation
AE	Adverse Event
AHA	American Heart Association
AI	Autoinjector
ALT	alanine aminotransferase
ApoA1	Apolipoprotein A-1
ApoB	Apolipoprotein B
AST	aspartate aminotransferase
BMI	Body mass index
CAS	Completer analysis set
CEC	Clinical Events Committee
CHD	Coronary Heart Disease
CI	confidence interval
CK	Creatine phosphokinase
CV	Cardiovascular
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic blood pressure
DHEA-S	Dehydroepiandrosterone sulfate
DMC	Data Monitoring Committee
DQR	Data Quality Review
ECG	Electrocardiogram
eCRF	electronic case report form
EOI	Events of Interest
EOS	End of Study (end of trial), defined as the time when the last subject is assessed or receives an intervention for evaluation in the study.
FAS	Full analysis set
FDA	Food and Drug Administration
FRS	Framingham Risk Score
HepBsAg	Hepatitis B virus Surface Antigen
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous Familial Hypercholesterolemia
hsCRP	High sensitivity C-reactive protein
IBG	Independent biostatistical group
IEC/IRB	Independent Ethics Committee / Institutional Review Board
INR	International normalized ratio

Abbreviation or Term	Definition/Explanation
IP	investigational product
IPD	Important protocol deviation
IVRS	Interactive voice response system
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
LFT	Liver function test
LOCF	Last observation carried forward
Lp(a)	Lipoprotein(a)
MedDRA	Medical dictionary for regulatory activities
MoI	Medications of interest
NCEP	National Cholesterol Education Program
NCEP ATP III	National Cholesterol Education Panel Adult Treatment Panel III
NCI	National Cancer Institute
NHLBI	National Heart, Lung, and Blood Institute
[redacted]	[redacted]
PK	Pharmacokinetic(s)
PKDM	Pharmacokinetics and drug metabolism
QM	Monthly (Every 4 weeks)
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
TEAE	Treatment-Emergent Adverse Event
TIA	Transient ischemic attack
UC	Ultracentrifugation
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	22 Oct 2015	
Amendment 1 (v2.0)	16 Sep 2019	Section 6.1 Study Time Points Added the definition of First Dose Date of Investigational Product. Added the definition of Last Dose Date of Investigational Product. Removed the definition of End of Investigational Product (IP) Admin Date. Rationale: To align with other studies for the product. Section 6.3 Other Study Related Definition Updated the definition of IP Exposure Period in Months. Updated the definition of Treatment-emergent adverse event. Removed the definition of Treatment-emergent disease-related event. Updated the definition of Reflexive Approach for LDL-C and VLDL-C. Rationale: To align with other studies for the product. Section 9.3.2 Missing Lipid Measurements Removed sensitivity analysis using LOCF. Rationale: Analysis no longer being performed and to align with other studies for the product. Section 9.3.3 Handling of Incomplete Dates Updated the imputed rule in text toTable 1. Imputation Rules for Incomplete Dates Section 9.4 Detection of Bias Removed the listing of unblinding Section 10.2 Subject Accountability Added 'The number and percent of subjects randomized will be tabulated by the stratification factors.' Rationale: To align with other studies for the product.

		Section 10.4 Demographic and Baseline Characteristics Added detailed demographic and baseline disease characteristics. Rationale: To align with other studies for the product. Section 10.5 Efficacy Analyses Updated Table 1 with Table 2 Updated months with weeks in Table 2 Section 10.5.1.2 Sensitivity Analyses of Primary Efficacy Endpoints Added To evaluate the impact of missing data with missing value imputed. Added details to the multiple imputation using non-missing data from subjects who discontinued IP within the same treatment group. Rationale: To address feedback from FDA. Removed ANOCOVA using LOCF. Section 10.6.1 Adverse Events Updated MedDRA version 17.0 with 19.0. Removed all disease-related events (DREs) related content. Rationale: To align with the company policy regarding DRE and to align with other studies for the product. Updated all treatment-emergent with TE. Removed all adverse events associated with lipid-lowering therapies. Removed potential hepatitis C infections. Removed incidence of new-onset diabetes. Removed the High Level Group Terms of neurocognitive events. Rationale: To update the analyses to align with the product safety profile and also to align with other studies for the product. Section 10.7 Pharmacokinetic Analysis Added this section to include the PK analysis. Appendix Added day 175 as maximum value to Appendix A. Analytical Study Week

		Assignments. Updated day 196 with 175 for cIMT for the maximum window. Removed Appendix D. Definition of New-onset Diabetes Mellitus Removed Appendix E. Treatment Emergent Adverse Event Algorithm

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for evolocumab Study 20120123 dated 01 September 2015. The scope of this plan includes the final analyses that are planned and will be executed by the Biostatistics department unless otherwise specified.

2. Objectives

2.1 Primary

To evaluate the effect of 24 weeks of subcutaneous (SC) evolocumab compared with placebo, when added to standard of care, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in pediatric subjects 10 to 17 years of age with heterozygous familial hypercholesterolemia (HeFH).

2.2 Secondary Efficacy

- to assess the effects of SC evolocumab compared with placebo, when added to standard of care, on mean percent change from baseline to weeks 22 and 24 and change from baseline to week 24 in LDL-C, and on percent change from baseline to week 24 in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, and ApoB/Apolipoprotein A-1 (ApoA1) ratio, in pediatric subjects 10 to 17 years of age with HeFH

2.3 Secondary Safety

- to evaluate the safety of SC evolocumab compared with placebo, when added to standard of care, in pediatric subjects 10 to 17 years of age with HeFH

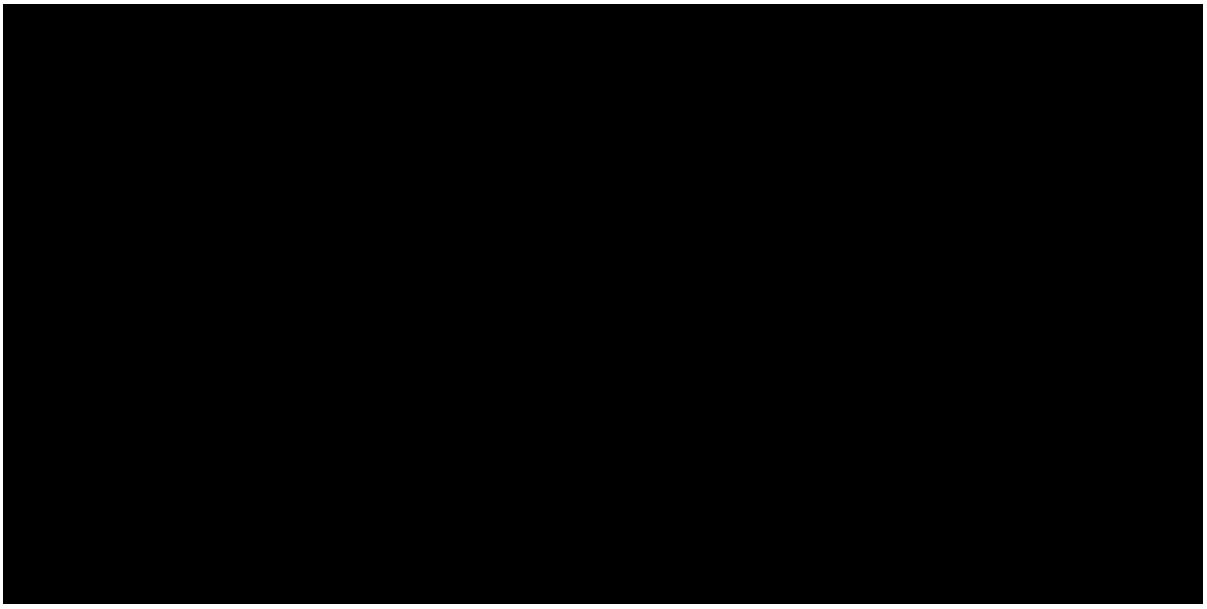
2.4 Secondary Pharmacokinetic

- to characterize pharmacokinetic (PK) exposure

2.5 Tertiary

- to assess the effects of SC evolocumab compared with placebo, when added to standard of care, on percent change from baseline to week 24 in total cholesterol, very low-density lipoprotein cholesterol (VLDL-C), HDL-C, ApoA1, triglycerides, and lipoprotein(a) [Lp(a)], in pediatric subjects 10 to 17 years of age with HeFH
- to assess the effects of SC evolocumab compared with placebo, when added to standard of care, on mean percent change from baseline to weeks 22 and 24 in non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio, total cholesterol, very low-density lipoprotein cholesterol (VLDL-C), HDL-C, ApoA1, triglycerides, and Lp(a), in pediatric subjects 10 to 17 years of age with HeFH

2.6 Exploratory



3. Study Overview

3.1 Study Design

This is a randomized, placebo-controlled, double-blind, parallel group, multicenter study. Subjects are eligible for screening if they are 10 to 17 years of age at time of randomization and have met the local applicable diagnostic criteria for HeFH. Subjects considered for enrollment will undergo screening assessments, including laboratory screening by central laboratory. Approximately 150 eligible subjects will be randomized in a 2:1 ratio to receive 24 weeks of QM evolocumab or placebo. Randomization will be stratified by screening LDL-C (< 160 mg/dL [4.1 mmol/L] vs ≥ 160 mg/dL) and age (< 14 years vs ≥ 14 years) at randomization.

The study includes collection of biomarker development samples. Where permitted by local regulations, subjects will be invited to consent to pharmacogenetic analyses.

Events of death, myocardial infarction (MI), hospitalization for unstable angina, coronary revascularization, stroke, transient ischemic attack (TIA), and hospitalization for heart failure will be adjudicated by an independent Clinical Events Committee (CEC). Subject incidence of exploratory endpoint events will be summarized for each treatment group. Processes of event identification and submission to the CEC are described in a CEC Endpoint Reporting Manual.

An independent data monitoring committee (DMC) will formally review the accumulating data from this and other completed and ongoing studies with evolocumab to ensure

there is no avoidable increased risk for harm to subjects. Analyses for the DMC will be provided by a group which is external to Amgen.

After completion of Study 20120123, subjects will be offered participation in an extension study where they will receive open-label evolocumab.

The overall study design is described by a study schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 4.1

3.2 Sample Size

This study is to provide clinical experience with evolocumab in approximately 150 pediatric subjects, compared to the current experience described in the Protocol Sections 2.3 and Section 2.4. Based on the treatment effect from the global phase 3 study in adult subjects with HeFH, evolocumab reduced LDL-C by approximately 55%. A planned total sample size of 150 pediatric subjects (100 randomized to evolocumab 420 mg QM and 50 randomized to placebo QM) will provide approximately 99% power in testing the superiority of evolocumab 420 mg QM over placebo. The sample size calculation is performed using a two-sided t-test with a 0.05 significance level, assuming a treatment effect of 40% reduction in LDL-C, a common standard deviation (SD) of 20%, and 20% of subjects discontinuing investigational product prior to completion of the study.

The power calculation is derived using nQuery version 7.01.

4. Study Endpoints and Covariates

4.1 Study Endpoints

4.1.1 Primary Efficacy Endpoint

- Percent change from baseline to week 24 in LDL-C

4.1.2 Secondary Efficacy Endpoints

- Mean percent change from baseline to weeks 22 and 24 in LDL-C[1]
- Change from baseline to week 24 in LDL-C[2]
- Percent change from baseline to week 24 in the following[3]:
  - non-HDL-C
  - ApoB
  - total cholesterol/HDL-C ratio
  - ApoB/ApoA1 ratio

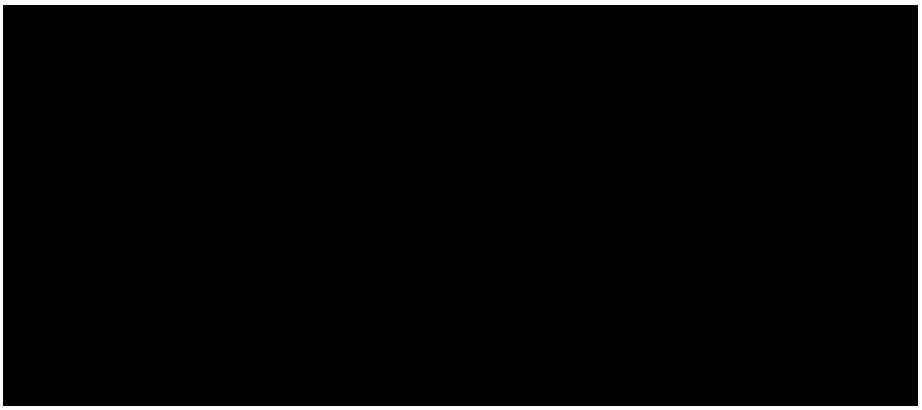
[1,2,3] See section 10.1 for detail on multiplicity adjustment

4.1.3 Tertiary Efficacy Endpoints

- Percent change from baseline to week 24 in the following:
  - total cholesterol
  - VLDL-C
  - HDL-C
  - ApoA1
  - Triglycerides
  - Lp(a)
- Mean percent change from baseline to weeks 22 and 24 in the following:
  - non-HDL-C
  - ApoB
  - total cholesterol/HDL-C ratio
  - ApoB/ApoA1 ratio
  - total cholesterol
  - VLDL-C
  - HDL-C
  - ApoA1
  - triglycerides
  - Lp(a)

4.1.4 Exploratory Endpoints

[redacted]



4.1.5 Secondary Safety Endpoints

- Subject incidence of treatment emergent adverse events
- Safety laboratory values and vital signs at each scheduled assessment
- Incidence of anti-evolocumab antibody (binding and neutralizing) formation

4.1.6 Secondary Pharmacokinetics Endpoints

- Serum concentration of evolocumab at each scheduled assessment

4.1.7 Other Safety Endpoints

- Change from baseline score in the components of the Cogstate battery at each scheduled administration

4.2 Planned Covariates

Stratification factors

- Screening LDL-C (< 160 mg/dL [4.1 mmol/L], ≥ 160 mg/dL)
- Age (< 14 years, ≥ 14 years)

Baseline characteristics

- Gender
- Race (black, white, and other)
- Region (North America, Europe, other)
- LDL-C (< baseline median, ≥ baseline median)
- Glucose tolerance status (type 2 diabetes mellitus, metabolic syndrome, neither type 2 diabetes mellitus nor metabolic syndrome)

- Lipid modifying background therapy (statin intensity defined based on modified ACC/AHA guidance, see Appendix C)

5. Hypotheses and/or Estimations

The primary hypothesis of the primary endpoint is: the null hypothesis is that there is no difference in the mean percent change from baseline at week 24 in LDL-C between

evolocumab and placebo, when added to standard of care, and the alternative hypothesis is that a mean difference does exist.

6. Definitions

6.1 Study Time Points

Enrollment Date

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

Randomization date

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

Study Day 1

For each subject, Study Day 1 is defined as the first day of investigational product (IP) administration.

Study Day

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

First Dose Date of Investigational Product

For each subject, the First Dose Date of Investigational Product is defined as the date of the first administration of IP as recorded on the IP administration eCRF, equivalent to study day 1.

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 IP.

End of Study (EOS) Date

End of study for each subject is defined as the date the subject last completed a protocol-specified procedure. The date will be recorded on the End of Study CRF page.

Study End Date

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

6.2 Demographics and Baseline Related Definitions

Age

Age at randomization will be derived in years in the clinical database.

Baseline Lipid and Lipid-related Parameters

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

BMI

Subject's BMI will be derived in kg/m^2 in the clinical database.

Other Baseline Values

For ECG, the baseline value is defined as the mean over all non-missing triplicate averages of 3 (or all available) readings from each set of triplicate taken prior to or on Study Day 1.

For [redacted] the baseline value is defined as the average of the last two non-missing values collected prior to first IP administration. If for any reason only 1 value is available, then that value will be used as baseline.

For cIMT, the baseline value is defined as the non-missing value collected on or prior to study day 28.

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

Change (absolute change) from Baseline

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

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

Percent Change from Baseline

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

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

Baseline Metabolic Syndrome

For each subject without type 2 diabetes mellitus, metabolic syndrome is identified by the presence of 3 or more of the components listed below (modified AHA/NHLBI criteria, Fryar et al 2012, Ji et al 2010). Subjects with type II diabetes cannot be categorized as having metabolic syndrome.

Age 10 to <16 years

Risk Factor	Defining Level
Elevated waist circumference:	Obesity ≥ 90 percentile or adult cut-off if lower (refer to the cut-offs below)
Non-Asian (Fryar et al., 2012):	
Male:	
Age 10	≥ 85.6 cm
Age 11	≥ 90.4 cm
Age 12	≥ 93.7 cm
Age 13	≥ 96.7 cm
Age 14	≥ 101.3 cm
Age 15	≥ 99.9 cm
Female:	
Age 10	≥ 84.1 cm
Age 11	≥ 88 cm
Age 12	≥ 88 cm
Age 13	≥ 88 cm
Age 14	≥ 88 cm
Age 15	≥ 88 cm
Asian (Ji et al, 2010):	
Male:	
Age 10	≥ 73.1 cm
Age 11	≥ 75.6 cm
Age 12	≥ 77.4 cm
Age 13	≥ 78.6 cm
Age 14	≥ 79.6 cm
Age 15	≥ 80.5 cm
Female:	
Age 10	≥ 67.8 cm
Age 11	≥ 70.4 cm
Age 12	≥ 72.6 cm
Age 13	≥ 74.0 cm
Age 14	≥ 74.9 cm
Age 15	≥ 75.5 cm
Triglycerides	≥ 1.7 mmol/L (150 mg/dL)

HDL cholesterol	<1.03 mmol/L (40 mg/dL)
Blood pressure	SBP ≥ 130 mmHg or DBP ≥ 85 mmHg OR Hypertension checked 'yes' on CV Medical History eCRF
Fasting glucose	≥ 5.6 mmol/L (100 mg/dL)

For Age >=16 years

Risk Factor	Defining Level
Elevated waist circumference:	
Non-Asian:	
Male	≥ 102 cm
Female	≥ 88 cm
Asian:	
Male	≥ 90 cm
Female	≥ 80 cm
Triglycerides	≥ 1.7 mmol/L (150 mg/dL)
HDL cholesterol	
Male	<1.03 mmol/L (40 mg/dL)
Female	< 1.29 mmol/L (50 mg/dL)
Blood pressure	SBP ≥ 130 mmHg or DBP ≥ 85 mmHg OR Hypertension checked 'yes' on CV Medical History eCRF
Fasting glucose	≥ 5.6 mmol/L (100 mg/dL)

Baseline CHD Risk Factors

A subject will be categorized as having 2 or more CHD Risk Factors (Y/N) from the list of the modified NCEP ATP III risk factors:

- current cigarette smoking
- hypertension
- type II diabetes mellitus
- family history of premature CHD as recorded on the eCRF
- low HDL-C defined as baseline HDL-C < 40 mg/dL for both males and females with age 10 to < 16 years; < 40 mg/dL in male and < 50 mg/dL in female with age >= 16 years.

6.3 Other Study Related Definitions

Analytical Study Week Assignments

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

Actual Treatment Group

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

Investigational Product (IP)

Evolocumab SC 420 mg QM and placebo SC QM.

Study Exposure Period in Months

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

IP Exposure Period in Months

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

Treatment-emergent adverse event

Treatment emergent adverse events are events categorized as Adverse Events (AEs) starting on or after first dose of investigational product as determined by "Did event start before first dose of investigational product" equal to No or missing on the Events eCRF and up to and including 30 days after last dose of investigational product or the EOS date, whichever is earlier. Any AE that cannot be defined clearly as a TEAE will be considered a TEAE in the database.

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 > 400 mg/dL, the UC LDL-C **value from** the same blood sample will be used instead **of calculated LDL-C and the UC VLDL-C value from the same blood sample will be used instead of calculated VLDL-C**, if available.

7. Analysis Subsets

7.1 Full Analysis Set

The full analysis set (FAS) includes all randomized subjects who received at least 1 dose of IP. It will be used for both efficacy and safety analyses. In efficacy analyses,

subjects will be grouped according to their randomized treatment group assignment, regardless of the treatment received. For safety analyses, subjects will be grouped according to their actual treatment group (as defined in Section 6.3).

7.2 Completer Analysis Set

The completer analysis set (CAS) includes subjects in the FAS who adhered to the scheduled IP and have observed values for the primary endpoints. The completer analysis set will be used in sensitivity analyses of the primary endpoints.

7.3 Subgroup Analyses

Subgroup by stratification factor

- Screening LDL-C (< 160 mg/dL, ≥ 160 mg/dL)
- Age (< 14 years, ≥ 14 years)

Subgroup by baseline characteristics

- Gender
- Race (black, white, and other)
- Region (North America, Europe, other)
- LDL-C (< baseline median, ≥ baseline median)
- Glucose tolerance status (type 2 diabetes mellitus, metabolic syndrome, neither type 2 diabetes mellitus nor metabolic syndrome)
- [redacted]
- Lipid modifying background therapy (statin intensity defined based on modified ACC/AHA guidance, see Appendix C)

8. Interim Analysis and Early Stopping Guidelines

No interim analysis is planned for this study.

An external independent DMC has been established to formally review the accumulating data from this and other completed and ongoing studies with evolocumab to ensure there is no avoidable increased risk of harm to subjects. The independent DMC is chaired by an external academic cardiologist who is an expert in lipids and clinical trials. Analyses for the DMC are provided by the Independent Biostatistical Group (IBG), which is external to Amgen.

9. Data Screening and Acceptance

9.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

9.2 Data Handling and Electronic Transfer of Data

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. Final PK data for all randomized subjects will be transferred from statistical programming to Amgen's PKDM group. Unblinded subject and box ID randomization lists will be provided by Amgen's randomization group and the IVRS when the study stops. Details on data transfer will be provided in the Data Transfer Plan.

9.3 Handling of Missing and Incomplete Data

9.3.1 Patterns of Missing Data

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

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

9.3.2 Missing Lipid Measurements

For primary efficacy endpoint, the primary analysis will be performed using repeated measures linear effects model without imputation**. To assess the impact of missing data,** sensitivity analyses will be performed based on multiple imputation **(details in section 10.5.1)**.

Imputation will not be performed for other efficacy endpoints.

9.3.3 Handling of Incomplete Dates

Adverse event and concomitant medication with completely or partially missing start dates will be queried. After the issue is queried, if the date is still incomplete with year only or year and month only, the start date will be imputed as described in Table 1 below.

Table 1. Imputation Rules for Incomplete Dates

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

9.4 Detection of Bias

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

- major protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints
- subject level unblinding before final database lock and formal unblinding
- DMC related analyses

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

Any unblinding of individual subjects prior to formal unblinding of the study will be documented in the CSR. The impact of such unblinding on the results observed will be assessed.

For DMC related analyses, details of access to subject level treatment assignments are provided in the protocol, Section 10.3.

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

9.5 Outliers

Various methods, including univariate summaries, histograms, scatter plots, box plots, and line graphs, may be used to identify outliers in key safety and efficacy variables. Extreme data points will be identified during the blinded review of the data prior to database lock. Such data points will be reviewed with clinical data management to ensure accuracy. The primary analyses will include outliers in the data. Sensitivity analyses may be undertaken if extreme outliers for a variable are observed.

9.6 Distributional Characteristics

Distributional assumptions for the primary and secondary endpoints will be assessed. If the assumptions are not met, then alternative methods will be utilized. The use of alternative methods will be fully justified in the CSR.

9.7 Validation of Statistical Analyses

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

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

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.3 or later.

10. Statistical Methods of Analysis

10.1 General Principles

The final analysis will be conducted when all subjects have either completed all the scheduled study visits or have early terminated from the study. At that time, the database will be cleaned, processed and a snapshot will be taken; the study will also be unblinded. Based on the snapshot, efficacy and safety analyses will be performed on the FAS. Unless specified otherwise, the FAS will be the default analysis set in this study and data will be summarized by randomized treatment group. The superiority of evolocumab to placebo will be assessed for all efficacy endpoints.

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

Summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation or standard error, minimum, and maximum. For categorical variables, the frequency and percentage will be summarized.

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

Multiplicity Adjustment Method

In order to preserve the familywise error rate at 0.05, multiplicity adjustment for the multiple endpoints (**primary efficacy endpoint: percent change from baseline to week 24 in LDL-C and secondary efficacy endpoints: mean percent change from**

baseline to weeks 22 and 24 in LDL-C, change from baseline to week 24 in LDL-C and percent change from baseline to week 24 in non-HDL-C, ApoB, total cholesterol/HDL-C ratio and ApoB/ApoA1 ratio) will be performed using sequential gatekeeping and Hochberg procedures (Hochberg, 1988) as follows:

1. If the treatment effect from the primary analysis of the primary endpoint is significant at a significance level of 0.05, statistical testing of the **mean percent change from baseline to weeks 22 and 24 in LDL-C and change from baseline to week 24 in LDL-C** will proceed using the sequential procedure with a significance level of 0.05 (ie, **change from baseline to week 24 in LDL-C** will be tested only if **mean percent change from baseline to weeks 22 and 24 in LDL-C** is statistically significant at 0.05 significance level).
2. If the treatment effect from **change from baseline to week 24 in LDL-C** is significant at a significance level of 0.05, statistical testing of the **percent change from baseline to week 24 in non-HDL-C, ApoB, total cholesterol/HDL-C ratio and ApoB/ApoA1 ratio** will follow the Hochberg procedure at a significance level of 0.05.

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

10.2 Subject Accountability

The number of subjects screened, randomized, receiving IP, and completing the study will be summarized. Key study dates for the first subject enrolled, last subject enrolled and last subject's end of study will be presented.

Study discontinuation and IP discontinuation will be tabulated separately by reasons for discontinuation.

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

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

10.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's visit and updated during the IPD reviews throughout the study prior to

database lock. These definitions of IPD categories, sub-category codes, and descriptions will be used during the course of the study.

Eligibility deviations are defined in the protocol.

10.4 Demographic and Baseline Characteristics

Demographic (**ie, gender, race, region**) and baseline disease characteristics (**cardiovascular medical history, laboratory parameters and lipid-regulating medication**) will be summarized by treatment group and overall using descriptive statistics. If multiple races have been reported for a subject, the subject will be categorized as multiple race.

10.5 Efficacy Analyses

The following table summarizes the key efficacy analyses that will be conducted:

Table 2. Key Efficacy Analyses Summary Table

Endpoint	Statistical Analysis Method	P-values from the Statistical Tests	Hierarchical Testing Procedure for testing of Treatment Effect vs. Placebo. As specified in the Multiplicity Adjustment Method diagram
Primary Endpoint			
Percent change in LDL-C from baseline to week 24	Repeated measures model	P1= the p-values for the primary endpoint	P1 compare to α = 0.05
Secondary Endpoint[1]			
Mean percent change from baseline at weeks 22 and 24 in LDL-C	Repeated measures model	P2a=the p-values for the secondary endpoint[1]	If P1 < 0.05 ➔ P2a will be tested and compare to α = 0.05 Else(i.e. primary endpoint is not significant) ➔ No further testing
Secondary Endpoint[2]			
Change from baseline to week 24 in LDL-C	Repeated measures model	P2b= the p-values for the secondary endpoint[2]	If P2a < 0.05 ➔ P2b tested and compare to α = 0.05 Else(i.e. secondary endpoint[1] is not significant) ➔ No further testing

Table 2. Key Efficacy Analyses Summary Table

Endpoint	Statistical Analysis Method	P-values from the Statistical Tests	Hierarchical Testing Procedure for testing of Treatment Effect vs. Placebo. As specified in the Multiplicity Adjustment Method diagram
Secondary Endpoints[3] Percent change from baseline to 24 **weeks** In each of the following lipid parameters: • non-HDL-C • ApoB • total cholesterol/HDL-C ratio • ApoB/ApoA1 ratio	Repeated measures model	For each lipid parameter P2c= p-values for each lipid parameter	If P2b < 0.05, ➔ All P2c's from each lipid parameter will be tested through Hochberg method with α = 0.05 Else(i.e. secondary endpoint[2] is not significant) ➔ No further testing

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10.5.1 Analyses of Primary Endpoints

10.5.1.1 Primary Analysis of Primary Efficacy Endpoints

The estimand of primary interest is the difference in mean percent change from baseline in LDL-C at week 24 regardless of treatment adherence for subjects in FAS. A repeated measures linear effects model (Littell et al, 2000) will be used to compare the efficacy of evolocumab with placebo. The repeated measures model will include terms for treatment group, stratification factors (as appropriate), scheduled visit and the interaction of treatment with scheduled visit. To account for the repeated LDL-C measurements within a subject across the visits, the repeated measures linear effects model will use an unstructured covariance. Missing values will not be imputed when the repeated measures linear effects model is used. The analysis will use LDL-C values measured regardless of treatment adherence.

Multiplicity adjustment procedures are defined in Section 10.1.

10.5.1.2 Sensitivity Analyses of Primary Efficacy Endpoints

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

- The primary analysis will be repeated using the CAS.
- Non-parametric analyses (Quade test).
- **To evaluate the impact of missing data,**
  - A sensitivity analysis under the assumption that subjects that discontinued IP and have missing endpoint data have a mean zero percent change from baseline will be conducted using multiple imputation.
  - **If there are at least 25 subjects who discontinue IP but have non-missing week 24 endpoint data, the primary analysis model will be repeated using FAS with missing values imputed for subjects who discontinued IP. Missing values will be imputed using non-missing data from subjects who discontinued IP within the same treatment group.**

If there is notable number of subjects randomized but did not receive IP, ad hoc analysis (e.g. repeating primary analysis using all randomized subjects) may be performed.

10.5.1.3 Subgroup Analyses of Primary Efficacy Endpoints

Subgroup analyses on the primary efficacy endpoints will be conducted using the subgroups specified in Section 7.3. Treatment effect differences among subgroups, which represent subgroup by treatment interactions, will be estimated and tested based on statistics from the subgroup repeated measures models.

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

10.5.2 Analyses of Secondary Efficacy Endpoints

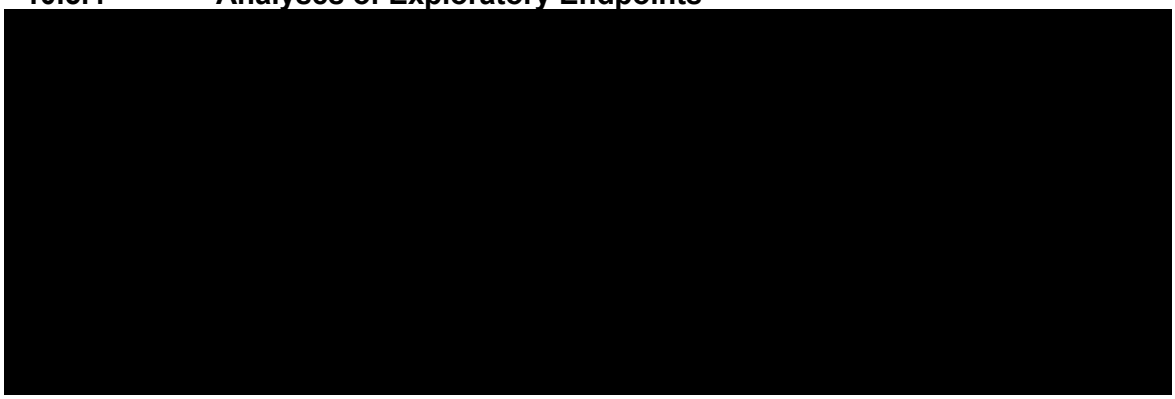
The statistical model and testing of the secondary efficacy endpoints will be similar to the primary analysis of the primary endpoint.

Multiplicity adjustment procedures are defined in Section 10.1

10.5.3 Analyses of Tertiary Efficacy Endpoints

Analysis of the tertiary efficacy endpoints will be similar to the primary analysis of the primary endpoints. No multiplicity adjustment will be applied.

10.5.4 Analyses of Exploratory Endpoints



10.6 Safety Analyses

10.6.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version **19.0** or later will be used to code all events categorized as adverse events (AE) to a system organ class and a preferred term. Severity of AEs will be graded using the CTCAE (Appendix B) and recorded on the eCRF. All adverse event tables will be summarized by actual treatment group. Treatment-emergent adverse events are events with an onset after the administration of the first dose of IP.

Subject Incidence of AEs will be summarized for all TEAEs, TE serious AEs, TEAE leading to withdrawal of investigational product and fatal TEAEs. Subject incidence of all treatment-emergent AEs, serious TEAEs, TEAEs leading to withdrawal of investigational product and fatal TEAE will be tabulated by system organ class, high level group term and preferred term.

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

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

Subject incidence of adverse events associated with injectable protein therapies:

- Injection site reactions
- Hypersensitivity or allergic reactions
- potential neurocognitive events

will be summarized by category and preferred term.

Tanner stage will be summarized by treatment group and gender. A shift table for hsCRP will be provided, for levels at baseline to maximum post-baseline value (<1, 1-3, >3 mg/L), by treatment group. HbA1c, carotid intimal-medial thickness (cIMT) and steroid hormones will be summarized at each scheduled assessment by treatment group.

10.6.2 Laboratory Test Results

Descriptive statistics will be provided for actual values and changes from baseline in select laboratory parameters at each protocol-specified scheduled visit. Laboratory analytes are provided in the protocol Table 2. Lab shift tables using the CTCAE v4.03 or later grading will be used for analytes of interest, when applicable. The results will be based on the maximum (ie, worst) shift from baseline to the EOS. In addition, CK and liver function test (LFT) abnormalities will be assessed by the incidence overall and by visits of the following categories:

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

10.6.3 Vital Signs

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

10.6.4 Electrocardiogram (ECG)

For post-baseline assessments where ECG is performed in triplicate, the average of the 3 (or all available) readings will be used for analysis. Observations with the following diagnosis or findings will be excluded from analysis: artificial pacemaker, atrial

fibrillation, atrial flutter, left bundle branch block, and right bundle branch block. PR, QRS, QT, QTc and RR intervals and their change from baseline will be summarized for each treatment group by scheduled visit. In each treatment group, subjects will be categorized and summarized per their maximum post-baseline absolute QTc interval using limits of 450 ms, 480 ms, and 500 ms. They will also be categorized per their maximum change from baseline QTc interval using limits of 30 ms and 60 ms.

10.6.5 Neurologic Examination

The incidence of abnormal neurologic findings overall and in each exam area will be summarized by treatment group.

10.6.6 Cogstate Neurocognitive Assessment

For each test, the change from baseline to EOS in the standardized score will be summarized by treatment group.

10.6.7 Antibody Formation

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

10.6.8 Exposure to Investigational Product

Descriptive statistics will be produced to describe the patient-month exposure to investigational product and the categorical representation of dose received. Exposure definitions are provided in Section 6.3.

10.6.9 Exposure to Concomitant Medication

The number and proportion of subjects receiving the lipid regulating medications of interest (MOI) will be summarized by category and preferred term for each treatment group as coded by the World Health Organization Drug (WHODRUG) dictionary.

10.7 Pharmacokinetic Analyses

Individual and mean serum evolocumab and [redacted] concentration-time profiles will be provided nominal times. The data set will be analyzed and stored in the Pharsight Knowledgebase Server (PKS) data repository using the current version of Phoenix WinNonlin.Evolocumab or [redacted] serum concentrations with values below the lower limit of quantification will be reported as less than their respective values but will be set to zero for analysis. PK parameters following the last dose will include but not limited to the maximum and minimum evolocumab serum concentrations observed at the collected timepoints. Individual and summary statistics for PK concentrations will be provided.

These analyses will be performed by the PKDM group.

Compartmental exposure-response analyses will not be specified in this analysis plan but may be included in a subsequent population PK analysis using a single study or as part of a metadata analysis.

11. Changes From Protocol-specified Analyses

As per the memo dated 11th March 2019, Disease-Related Events (DREs) will be removed from protocols and no longer need to be collected by Investigators.

The 20120123 protocol is not being amended to reflect this change since it is an ongoing study close to primary analysis. However, the SAP has been modified to remove all DRE language. DREs will not be reported separately (as specified in the protocol) but will be included as AEs.

12. Literature Citations / References

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Fryar CD, Gu Q, Ogden CL. Anthropometric Reference Data for Children and Adults: United Stages, 2007-2010. Vital Health Stat 11. 2012 Oct; (252): 1-48.

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13. 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:

Analytical Study week	Week 4	Week 8	Week 12	Week 16	Week 20	Week 22	Week 24
Scheduled Visit day	29	57	85	113	141	155	169
Vital Signs(sitting BP, HR)	(1,56]		(56,112]		(112,147]	(147,161]	(161,175]
Physical exam(including neurologic examination)							(1,175]
Body weight, waist circumference, Tanner staging, Body height							(1,175]
cIMT							(29,196]
Cogstate neurocognitive assessment							(1,175]
12 lead ECG			(1,126]				(126,175]
Fasting Lipids			(1,119]			(119,161]	(161,175]
Lp(a), ApoA1, ApoB			(1,119]			(119,161]	(161,175]
PK, [redacted]			(1,119]			(119,161]	(161,175]
Chemistry, including fasting glucose			(1,126]				(126,175]
Hematology			(1,126]				(126,175]
Estradiol (females) / testosterone (males)							(1,175]
HbA1c, hsCRP, CK, FSH, LH, ACTH, DHEA-S, cortisol							(1,175]
Anti-evolocumab antibodies			(1,126]				(126,175]
HCV viral load							(1,175]
Urinalysis, urine microalbumin			(1,126]				(126,175]

Handling multiple records assigned to an analytical study week:

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

Appendix B. Common Terminology Criteria for AEs (CTCAE)

Refer to the NCI Common Terminology Criteria for Adverse Events (CTCAE) for adverse event grading and information. The CTCAE is available at the following link: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Appendix C. Lipid Modifying Background Therapy

Criteria modified from ACC/AHA guidelines:

	HIGH-INTENSITY STATIN THERAPY	MODERATE-INTENSITY STATIN THERAPY	LOW-INTENSITY STATIN THERAPY	Notes (modifications from ACC/AHA guideline)
Atorvastatin	40 mg or greater QD	10 mg QD up to less than 40 mg QD	Less than 10 mg QD	Atorvastatin 30 mg QD is Moderate intensity.
Rosuvastatin	20 mg or greater QD	5 – < 20 mg QD	less than 5 mg QD	Rosuvastatin < 5 mg QD is low intensity , Rosuvastatin 15 mg QD = moderate
Simvastatin	80 mg or greater QD	20-80 mg QD	< 20 mg QD	And Simvastatin > 40 and < 80 mg QD is moderate, Simvastatin 80 mg or greater QD = high, Simvastatin < 20 mg QD is low-intensity
Pravastatin		40 mg or greater QD	less than 40 mg QD	Pravastatin < 10 mg QD is low intensity
Lovastatin		40 mg or greater QD	less than 40 mg QD	Lovastatin 80 mg QD = moderate, Lovastatin 10 mg QD = Low-intensity
Fluvastatin		80 mg QD	less than 80 mg QD	Fluvastatin 10 mg QD = Low-intensity
Pitavastatin		≥ 2 mg QD	< 2 mg QD	

UNKNOWN-INTENSITY STATIN THERAPY if dose frequency is other or dose unit is other and therefore total daily dose in mg cannot be derived; NO STATIN THERAPY if subject does not use any statin at baseline.