Statistical Analysis Plan

Protocol Title:	Open-label, Single-arm, Multicenter Study to Evaluate the Safety, Tolerability and Efficacy of Evolocumab for LDL-C Reduction, as Add-on to Diet and Lipid-lowering Therapy, in Pediatric Subjects From 10 to 17 Years of Age With Heterozygous Familial Hypercholesterolemia (HeFH) or Homozygous Familial Hypercholesterolemia (HoFH)
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	17OCT2019	Original version
Amendment 1 (v2.0)	29MAY2020	• Endpoint updates per protocol (amendment 4, 14 May 2020). Removed “subject incidence” from endpoints • Updated sample size in section 3.1 and 3.2 following protocol (amendment 4, 14 May 2020) • Removed DRE related sentences following protocol (amendment 4, 14 May 2020) • Added interim analysis and early stopping guideline in section 7.1 and 7.2 following protocol (amendment 4, 14 May 2020) • Updated study exposure period in months, IP exposure period in months and TEAE definition in section 5.3 for the inclusion of interim analysis • Updated Study Cohort in section 5.3 following protocol (amendment 4, 14 May 2020) • Updated full analysis set definition in Section 6 to align with other studies for the product • Updated section 9.1 to include interim analysis, scope of interim analysis, and analysis set to be used for this study • Included interim analysis and added “For the interim analyses, the numbers of ongoing subjects and the data cut-off date will also be presented.” in section 9.2 • Updated section 9.3 to include COVID-19 related PD • Updated section 9.5.3 on shift table levels for hsCRP to align with other studies for the product • Removed “is the primary safety endpoint” from section 9.6.1 following protocol (amendment 4, 14 May 2020) • Removed “Diabetes-related”, “Muscle-related”, “Liver-related associated with injectable protein therapies”, and “incidence of new-onset diabetes from section 9.6.2 • Updated section 9.6.3 on Total bilirubin to align with other studies for the product • Updated section 9.7.1 to include the PK analysis to align with other studies for the product • Update section 10 to remove previous changes from protocol-specified analysis • Updated footnote for Appendix A and included Appendix C to align with other studies for the product

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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
AE	Adverse event
AHA	American Heart Association
ALT (SGPT)	Alanine aminotransferase (serum glutamic-pyruvic transaminase)
ApoA1	Apolipoprotein A-1
ApoB	Apolipoprotein B
AST (SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
BMI	Body mass index
BP	Blood pressure
CHD	Coronary heart disease
cIMT	carotid intima-media thickness
CK	Creatine kinase
CRP	C-reactive protein
CSR	Clinical study report
CTCAE	NCI Common Terminology Criteria for AEs
DBP	Diastolic blood pressure
DIIR	Data Issue Identification and Resolution
DMC	Data monitoring committee (Efficacy and Safety Evaluation Committee)
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of Study
eSAE	Electronic serious adverse event
FAS	Full analysis set
FH	Familial hypercholesterolemia
FSH	Follicle-stimulating hormone
HDL-C	High density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
HoFH	Homozygous familial hypercholesterolemia
HR	Heart Rate
hsCRP	High sensitivity CRP
IP	Investigational product
LDL-C	Low-density lipoprotein cholesterol
LFT	Liver function test
Lp(a)	Lipoprotein(a)
MedDRA	Medical dictionary for regulatory activities

Abbreviation or Term	Definition/Explanation
MOI	Medications of Interest
NCEP	National Cholesterol Education Program
NCEP ATP III	National Cholesterol Education Panel Adult Treatment Panel III
NHLBI	National Heart, Lung, and Blood Institute
PCSK9	Proprotein convertase subtilisin/kexin type 9
PK	Pharmacokinetic
QM	Every 4 weeks
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
TC	Total cholesterol
TEAE	Treatment-Emergent Adverse Event
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol
WHODRUG	World Health Organization Drug dictionary

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 4 for study 20120124, AMG 145 dated **14 May 2020.** The scope of this plan includes the **interim analysis and** 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 80 weeks of SC evolocumab when added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH	• Treatment emergent adverse events at week 80
Secondary	
• To describe percent change and change from baseline in LDL-C, and on percent change from baseline 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 or HoFH after 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH	• Percent change from baseline at week 80 in: − LDL-C − Non-HDL-C − ApoB − Total cholesterol/HDL-C ratio − ApoB/ApoA1 ratio • Change from baseline in LDL-C at week 80
• To describe change from baseline in steroid hormones and the subject incidence of abnormal muscle and liver enzyme levels after 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH	• Change from baseline in steroid hormones (FSH, LH, ACTH, DHEA-S, cortisol, estradiol/testosterone [females/males, respectively]) at week 80 • Abnormal muscle and liver enzyme levels (CK, AST, ALT) at week 80
• To describe changes from baseline in carotid intima-media thickness (cIMT) after 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH	• Change from baseline in cIMT at week 80

Secondary	
• To describe change from baseline in growth and pubertal development parameters at measured timepoints with 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH	• Change from baseline in growth (height and weight) and pubertal development (Tanner staging) at weeks 24, 48 and 80
Exploratory	
• To describe change and percent change at measured timepoints in LDL-C, total cholesterol, non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio, triglycerides, VLDL-C, HDL-C, ApoA1, lipoprotein(a) [Lp(a)], with 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH	• Change from baseline and percent change from baseline at each scheduled assessment in the following: − LDL-C − Total cholesterol − Non-HDL-C − ApoB − Total cholesterol/HDL-C ratio − ApoB/ApoA1 ratio − Triglycerides − VLDL-C − HDL-C − ApoA1 − Lp(a)
• To describe change at measured timepoints in proprotein convertase subtilisin/kexin type 9 (PCSK9) and high sensitivity C-reactive protein (hsCRP) with 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH	• Change from baseline at each scheduled assessment in the following: − Proprotein convertase subtilisin/kexin type 9 (PCSK9) − High sensitivity C-reactive protein (hsCRP)
• To evaluate the incidence of abnormal neurological examination findings after 80 weeks of SC evolocumab added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH	• Abnormal neurological examination findings
• To assess cognitive function, assessed using the change from baseline in the components of the Cogstate battery at each scheduled administration, after 80 weeks of SC evolocumab added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH	• Change from baseline score in the components of the Cogstate battery at each scheduled administration

Exploratory	
• To investigate the relationship between novel and established biochemical cardiovascular and lipid biomarkers and effects of evolocumab in pediatric subjects 10 to 17 years of age with HeFH	• Select safety laboratory values and vital signs at each scheduled assessment • Anti-evolocumab antibody (binding and neutralizing) formation • ECG parameters (such as RR, PR, QRS, QT, and QTc intervals) at each scheduled assessment
• In subjects consenting to the optional pharmacogenetics analysis, to investigate potential correlations of study data including the subject response to evolocumab with genetic variation in markers of (PCSK9) signaling, low-density lipoprotein receptor (LDLR) turnover, cholesterol metabolism, inflammation, and plaque stability	• Serum concentration of evolocumab at each scheduled assessment

2.2 Hypotheses and/or Estimations

The primary hypothesis is that SC evolocumab will be well tolerated when added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH.

3. Study Overview

3.1 Study Design

This is an open-label, single-arm, multicenter study. Subjects are eligible for screening if they have completed Study 20120123 (and did not experience a treatment-related serious adverse event) or if they are 10 to 17 years of age at time of enrollment and have HoFH. The minimum expected enrollment of HeFH (rollover) subjects is approximately 70% of subjects enrolled in Study 20120123 or approximately **111** subjects. In addition, approximately 10 subjects with HoFH (and without prior participation in an evolocumab study) will be enrolled for an expected total enrollment of approximately **124** subjects. Depending on willingness of 20120123 subjects to continue evolocumab administration, final enrollment may be smaller or greater.

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

3.2 Sample Size

Approximately **124** subjects are anticipated to enroll in this trial. This corresponds to an estimated 70% rollover for subjects with HeFH from the parent study 20120123 and approximately 10 subjects with HoFH enrolling in this study. Depending on rollover rate from study 20120123, final enrollment may be smaller or greater.

3.3 Adaptive Design

Not applicable.

4. Covariates and Subgroups

4.1 Planned Covariates

No planned covariates will be included in the analysis.

4.2 Subgroups

No subgroup analysis will be included in the analysis.

5. Definitions

5.1 Study Timepoints

Enrollment Date

The enrollment date is defined as the date collected on the Subject Enrollment eCRF.

Study Day 1

For each subject, Study Day 1 is defined as the first day of investigational product administration. If a subject never received IP, then Study Day 1 is defined as the date of enrollment.

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 first administration date of the IP as recorded on the IP 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 the IP:

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

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

End of Study (EOS) Date **for Each Subject**

End of study for each subject is defined as the last day on which the enrolled subject in this study completes the end-of-study visit (week 80) or terminates the study early. The date will be recorded on the End of Study eCRF page.

Study End Date **for the Overall Study**

The study end date is defined as the date when the last enrolled subject has completed the end-of-study visit (week 80) (ie, last subject last visit).

5.2 Demographics and Baseline Related Definitions

Age at Enrollment

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

Baseline Lipid and Lipid-related Parameters

For subjects with HeFH rolling over from parent study 20120123, baseline lipid and lipid-related parameters are defined as parent study baseline lipid and lipid-related parameters. For lipids (total cholesterol, HDL-C, LDL-C, VLDL-C and triglycerides), ApoA1, ApoB, hsCRP, Lp(a) and their derived parameters (eg, ratio between them) of de novo subjects with HoFH, the baseline values are defined as the mean of the two most recent non-missing concentrations measured through central lab prior to or on Study Day 1. If for any reason only 1 value is available, then that value will be used as baseline for de novo subjects.

Other Baseline Values

For subjects with HeFH rolling over from parent study 20120123, other baseline values (ECG, PCSK9, and other variables) are defined as parent study baseline values.

For de novo subjects with HoFH, the baseline ECG 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 PCSK9, 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 all other variables, the baseline value is defined as the last non-missing value collected prior to first IP administration.

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 2 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) or known type 2 diabetes mellitus

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	≥ 150 mg/dL
HDL cholesterol	
Male	< 40 mg/dL
Female	< 50 mg/dL
Blood pressure	SBP ≥ 130 mmHg or DBP ≥ 85 mmHg OR Hypertension checked 'yes' on CV Medical History eCRF
Fasting glucose	≥ 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.

5.3 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.

Investigational Product (IP)

IP refers to Evolocumab SC 420 mg QM.

Study Cohort

The enrolled subjects consist of two study cohorts: HeFH subjects (roll-over subjects from the parent study of 20120123) and HoFH subjects (new enrolled subjects in this study)

For the HeFH subjects rolled over from the parent study, those subjects will be categorized according to the treatment groups they were randomized to in their parent study. All analyses will be summarized based on the followings:

- **Roll-over HeFH subjects randomized to AMG 145 in parent study**
- **Roll-over HeFH subjects randomized to Placebo in parent study**
- **De-novo HoFH subjects**

Study Exposure Period in months:

Interim analysis

- **For ongoing subjects, Study Exposure Period = (data cutoff date – Enrollment Date + 1) / 365.25 * 12**
- **For subjects who completed study or early terminated from the study, Study Exposure Period = [min(EOS date, data cutoff date) – Enrollment Date + 1] / 365.25 * 12**

Primary analysis

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

IP exposure period in months:

Interim analysis

- **For ongoing subjects, IP Exposure Period = [min (Last IP dose date + 28 days, data cutoff date) - Study Day 1 + 1]/ 365.25 * 12**
- **For subjects who completed study or early terminated from the study, IP Exposure Period = [min (Last IP dose date + 28 days, EOS Date, data cutoff date) - Study Day 1 + 1]/ 365.25 * 12**

Primary analysis

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

Treatment Emergent Adverse Event (TEAE)

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 the last dose of investigational product or the EOS date or the data cutoff date, whichever is earlier for interim analysis. For primary analysis, 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 the 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, the following reflexive approach will be used. When calculated LDL-C is less than 40 mg/dL or triglycerides > 400 mg/dL, the UC LDL-C value from the same blood sample will be used instead of calculated LDL-C and the UC VLDL-C value from the same blood sample will be used instead of calculated VLDL-C, if available.

6. Analysis Sets

The full analysis set (FAS) includes all subjects with HeFH from parent study 20120123 who are enrolled **and dosed** and all subjects with HoFH who are enrolled and dosed in this study.

Unless specified otherwise, the FAS will be the default analysis set in this study.

7. Planned Analyses

7.1 Data Monitoring Committee (DMC)

An external independent DMC has been established to formally review the accumulating data from this study to ensure there is no avoidable increased risk for harm to subjects. The independent DMC is chaired by an external academic cardiologist who is an expert in lipids and clinical trials. Details are provided in the DMC charter.

7.2 Interim Analysis and Early Stopping Guidelines

The interim analysis will be conducted when all the enrolled subjects in the study have opportunity to experience 28 weeks of investigation product exposure or have early terminated from the study. At that time, the database related to the interim analyses of the study will be cleaned, processed and a snapshot will be taken. Unless specified otherwise, the FAS will be the default analysis set in this

study. Similar to the primary analysis, the interim data will be summarized by cohort (HeFH and HoFH). Statistical analysis in this interim analysis is descriptive in nature for all safety and efficacy endpoints if applicable. No statistical hypotheses testing or missing value imputation is planned. There is no study stopping rule for either futility or efficacy and the current design or execution of the study will continue without any changes regardless of the result of the interim analysis.

7.3 Primary Analysis

To evaluate the safety, tolerability and effect of 80 weeks of SC evolocumab when added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH, the primary analysis will be conducted when all the enrolled subjects in the study have either completed all the scheduled visits up to and including week 80 or have early terminated from the study. At the time of the primary analysis, the database will be cleaned, processed and locked. Unless specified otherwise, the FAS will be the default analysis set in this study and data will be summarized by cohort (HeFH and HoFH) **as well as by the randomized treatment group of the parent study for HeFH cohort (as defined in** section 5.3). All analyses will include estimation for all the endpoints. No formal hypotheses will be tested in this study.

7.4 Final Analysis

Not applicable.

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. Final PK data will be transferred from statistical programming to Amgen's PKDM group. 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. In the Data Issue Identification and Resolution (DIIR) process, queries will be made to the sites to distinguish true missing values from other unknown values (eg, due to measurement processing error). 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 efficacy endpoints will be assessed through descriptive summaries of the measurements over time.

There will be no imputation for missing data except the incomplete date imputation for AE and concomitant medication.

8.3.2 Handling of Incomplete Dates

Adverse event and concomitant medication (eg, lipid regulatory 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 below.

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

8.4 Detection of Bias

This study has been designed to minimize potential bias. For subjects rolling over from study 20120123, central laboratory results of the lipid panel, as well as ApoA1, ApoB, Lp(a), and PCSK9 will be blinded until the subject has reached week 12 in Study 20120124. For these subjects, vitamins A, D, E and K will also be blinded until the study 20120123 database is locked. In addition, investigators and staff involved with this trial and all medical staff involved in the subject's medical care should refrain from obtaining lipid panels until week 12 in Study 20120124 and, if a lipid panel is drawn, all reasonable

steps must be undertaken to avoid informing the subject and study personnel of the results.

Factors that may bias the results of the study include:

- Major protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints

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

8.5 Outliers

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

8.6 Distributional Characteristics

Statistical analyses in this study are descriptive in nature. No statistical inference is planned. No distributional characteristics will be assessed in this study.

8.7 Validation of Statistical Analyses

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

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

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

9. Statistical Methods of Analysis

9.1 General Considerations

The interim analysis will be conducted when all the enrolled subjects in the study have opportunity to experience 28 weeks of investigation product exposure or have early terminated from the study. At that time, the database related to the interim analyses of the study (on or before the data cutoff date) will be cleaned,

processed and a snapshot will be taken. All analyses for the interim analyses will be based on the interim data on or before the data cutoff date. The scope of the interim analyses includes all endpoints specified in the protocol amendment 4 dated 14 May 2020.

To evaluate the safety, tolerability and effect of 80 weeks of SC evolocumab when added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH, the primary analysis will be conducted when all the enrolled subjects in the study have either completed all the scheduled visits up to and including week 80 or have early terminated from the study. At that time, the database will be cleaned, processed and locked. All endpoints will be analyzed based on this snapshot.

All analyses **for both the interim and primary analyses** will be descriptive. Missing data will not be imputed for safety endpoints. Statistical analyses in this open label study are descriptive in nature. No statistical inference or missing value imputation is planned. **Unless specified otherwise, the FAS will be the default analysis set in this study and data will be summarized by cohort (HeFH and HoFH) as well as by the randomized treatment group of the parent study for HeFH cohort (as defined in section 5.3). Due to the open-label study design, all analyses for both interim and primary analyses will also be summarized by cohort for the overall subjects.**

Subject disposition, demographics and baseline characteristics will be summarized.

Summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation or standard error, first quartile (Q1), third quartile (Q3), minimum, and maximum. For categorical variables, the frequency and percentage will be given.

Unless specified otherwise, the FAS will be the default analysis set in this study and subjects will be summarized by 3-level groups defined in section 5.3.

9.2 Subject Accountability

The number of subjects screened, enrolled, receiving IP, and completing the study will be summarized. Key study dates for the first subject enrolled, last subject enrolled, last subject's end of study **for primary analysis and for interim analysis** will be presented. **For the interim analyses, the numbers of ongoing subjects and the data cut-off date will also be presented.**

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

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

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol. **In addition, COVID-19 related protocol deviations will also be summarized and listed.**

9.4 Demographic and Baseline Characteristics

The descriptive statistics of baseline characteristics will summarize the following: baseline characteristics, demographics, cardiovascular medical history, laboratory parameters, and lipid-regulating concomitant medications.

9.5 Efficacy Analyses

9.5.1 Analyses of Primary Efficacy Endpoint(s)

Not applicable.

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

Descriptive statistics of percent change from baseline will be provided for the following efficacy parameters at week 80

- LDL-C
- Non-HDL-C
- ApoB
- Total cholesterol/HDL-C ratio
- ApoB/ApoA1 ratio

In addition, the descriptive statistics in change from baseline will be provided for LDL-C at week 80.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

Descriptive statistics summarized by 3-level groups will be provided for actual value, change from baseline and percent change from baseline at each protocol-specified visit in the following

- LDL-C
- Total cholesterol
- Non-HDL-C

- ApoB
- Total cholesterol/HDL-C ratio
- ApoB/ApoA1 ratio
- Triglycerides
- VLDL-C
- HDL-C
- ApoA1
- Lp(a)

Descriptive statistics will be provided for actual value and change from baseline at each protocol-specified visit in the following

- Proprotein convertase subtilisin/kexin type 9 (PCSK9)
- High sensitivity C-reactive protein (hsCRP)

In addition, a shift table for hsCRP will also be provided, for levels at baseline to maximum post-baseline value (<1, 1-3, >3 **mg/L**)

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

Subject incidence of treatment emergent adverse events at week 80 **will be summarized.**

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 or later will be used to code all events categorized as adverse events 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.

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

Subject incidence of all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product and fatal adverse events will be tabulated by system organ class and preferred term in alphabetical order.

In addition, summaries 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.

Subject incidence of adverse events associated with lipid lowering therapies:

- **Injection site reactions**
- **Hypersensitivity or allergic reactions**

will be summarized by category and preferred term.

Subject neurocognitive events will also be summarized.

9.6.3 Analyses of Secondary Safety Endpoints

Descriptive statistics of change from baseline will be provided for the following safety parameters at week 80.

- Steroid hormone levels (FSH, LH, ACTH, DHEA-S, cortisol, estradiol in females, testosterone in males).
- Carotid intima-media thickness (cIMT)

Summary of subject incidence of abnormal muscle and liver enzymes at week 80 will also be provided.

Abnormalities of muscle and liver enzymes will be assessed by 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

Descriptive statistics of change from baseline in growth (height and weight) will be provided at week 24, 48 and 80 by study cohort, parent study treatment and gender.

Shift from baseline in Tanner staging at weeks 24, 48 and 80 will be summarized by study cohort, parent study treatment and gender.

9.6.4 Laboratory Test Results

Descriptive statistics will be provided for actual values and changes from baseline in select laboratory parameters at select protocol-specified scheduled visit. Laboratory

analytes are provided in the protocol Table 3. CTCAE grading v5.0 or later will be used for lab shift table for liver function test (LFT).

9.6.5 Vital Signs

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

9.6.6 Physical Measurements

Physical measurements will be summarized using descriptive statistics at each scheduled visit.

9.6.7 Electrocardiogram

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 by scheduled visit. 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.

9.6.8 Antibody Formation

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

9.6.9 Neurologic examination

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

The neurologic examination includes assessments of motor, sensory, reflexes, coordination and gait. On the relevant eCRF, each area is described as normal or abnormal. Overall neurologic finding will be based on all 5 assessments. It will be defined as abnormal if any of these 5 assessments is abnormal.

9.6.10 Cogstate Battery

Change from baseline score in the components of the Cogstate battery at each scheduled administration will be summarized using descriptive statistics.

9.6.11 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product by 3-level group.

9.6.12 Exposure to Other Protocol-required Therapy

The number and proportion of subjects receiving selected lipid regulating medications captured on the Lipid Regulating Concomitant Medications eCRF will be summarized for baseline use and post-baseline use. The subject incidence of changes in lipid regulating medications during the treatment period will also be provided **(**Appendix C**)**.

9.6.13 Exposure to Concomitant Medication

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

9.7 Other Analyses

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

Individual and mean serum evolocumab and PCSK9 concentration-time profiles will be provided at 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 PCSK9 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 on or before data cutoff date for interim analysis or the last dose for primary analysis 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 for both interim and primary analysis.

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.

9.7.2 Analyses of Clinical Outcome Assessments

Not applicable.

9.7.3 Analyses of Health Economic Endpoints

Not applicable.

9.7.4 Analyses of Biomarker Endpoints

Not applicable.

10. Changes From Protocol-specified Analyses

Not applicable.

11. Literature Citations / References

Study AMG145 20120124 protocol Amendment 3 dated on 26 April, 2017

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.

Ji C et al. Waist Circumference Distribution of Chinese School-age Children and Adolescents. *Biomedical and Environmental Sciences*. 2010; 23 (1): 12-20.

12. Prioritization of Analyses

Not applicable.

13. Data Not Covered by This Plan

Not applicable.

14. 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, with scheduled visit time being the center of each interval. The mapping intervals for all distinct schedules are summarized in the following tables.

Tests / Analytical Visit Window	Week 4	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 80
Target day	29	85	169	253	337	421	505	561
Vital Signs (sitting BP, HR)	(1, 56]	(56, 126]	(126, 252]		(252, 448]			(448, EOS]
Physical exam (including neurologic examination)								(1, EOS]
Height, weight, cIMT[a], Tanner staging			(1, 252]		(252, 448]			(448, EOS]
Neurocognitive assessment (Cogstate battery) - HoFH			(1, 252]		(252, 448]			(448, EOS]
Neurocognitive assessment (Cogstate battery) - HeFH			(1, 364]					(364, EOS]
12 lead ECG								(1, EOS]
Lipids		(1, 210]			(210, 448]			(448, EOS]
ApoA1, ApoB100, Lp(a)		(1, 322]						(322, EOS]
PK (evolocumab), PCSK9		(1, 322]						(322, EOS]
Chemistry, including glucose		(1, 210]			(210, 448]			(448, EOS]
Hematology					(1, 448]			(448, EOS]
Estradiol (females) / testosterone (males)								(1, EOS]
HbA1c, FSH, LH, ACTH, DHEA-S, cortisol, hsCRP, vitamins A/D/E/K								(1, EOS]
CK		(1, 210]			(210, 448]			(448, EOS]
Biomarkers (blood)								(1, EOS]
Anti-evolocumab antibodies								(1, EOS]
HCV viral load					(1, 448]			(448, EOS]
Urinalysis, urine microalbumin, urine creatinine, urine albumin/creatinine ratio								(1, EOS]

[a] cIMT assessments conducted up to and including study day 28 are considered baseline values.

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
Atorvastatin	≥ 40 mg QD	10 – < 40 mg QD	< 10 mg QD
Rosuvastatin	≥ 20 mg QD	5 – < 20 mg QD	< 5 mg QD
Simvastatin	≥ 80 mg QD	20 – < 80 mg QD	< 20 mg QD
Pravastatin		≥ 40 mg QD	< 40 mg QD
Lovastatin		≥ 40 mg QD	< 40 mg QD
Fluvastatin XL		80 mg QD	< 80 mg QD
Fluvastatin		40 mg BID	< 40 mg BID
Pitavastatin		1 – 4 mg QD	< 1 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.