Statistical Analysis Plan

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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
AE	adverse event
ApoA1	apolipoprotein A1
ApoB	apolipoprotein B
BP	blood pressure
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DIIR	data issue identification and resolution
DRE	disease-related event
eCRF	electronic case report form
EOS	end of study
FAS	full analysis set
GSO-DM	global study operation-data management
HDL-C	high-density lipoprotein cholesterol
HoFH	homozygous familial hypercholesterolemia
HR	heart rate
IP	investigational product
IPD	important protocol deviation
LDL-C	low-density lipoprotein cholesterol
Lp(a)	lipoprotein(a)
MedDRA	Medical Dictionary for Regulatory Activities
PCSK9	proprotein convertase subtilisin/kexin type 9
QM	once monthly
SC	subcutaneous
VLDL-C	very low-density lipoprotein cholesterol
WHODRUG	World Health Organization Drug

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for study 20170199, AMG 145 dated 16 August 2017. The scope of this plan includes the analyses 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 characterize the safety and tolerability in homozygous familial hypercholesterolemia HoFH patients in India exposed to 12 weeks of Repatha	• Subject incidence of treatment-emergent adverse events
Secondary	
• To characterize the efficacy of 12 weeks of Repatha on low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (ApoB) and lipoprotein(a) [Lp(a)] in HoFH patients in India	• Percent change from baseline in LDL-C at week 12 • Percent change from baseline in ApoB at week 12 • Percent change from baseline in Lp(a) at week 12

2.2 Hypotheses

This phase 4 study is descriptive in nature, describing safety and tolerability of Repatha in subjects with HoFH in India.

3. Study Overview

3.1 Study Design

This open-label, multicenter, non-comparative phase 4 study of Repatha is part of Amgen's post marketing requirement to the Indian Regulatory Authority. The study population consists of approximately 30 Indian subjects with HoFH and for whom Repatha is indicated in accordance with the approved prescribing information in India.

The assignment of subjects to protocol treatment will be decided by the investigator according to inclusion/exclusion criteria and laboratory assessments at screening (including fasting lipids). Subjects who are enrolled will be instructed to continue to follow a diet limiting saturated fat to less than 7% of total daily calories and will be required to maintain their current lipid-lowering drug therapy throughout the duration of the trial. Subjects will receive Repatha 420 mg once monthly (QM) subcutaneous (SC) and study visits will occur approximately every 4 weeks. For subjects on

apheresis, they may receive Repatha 420 mg SC every 2 weeks to correspond with their apheresis schedule. Final administration of Repatha will occur at week 8. The end of study (EOS) visit and the last estimation of lipids will occur at week 12 for all subjects.

3.2 Sample Size

Approximately 30 subjects with HoFH will be enrolled in the study.

3.3 Adaptive Design

Not Applicable.

4. Covariates and Subgroups

4.1 Planned Covariates

No covariates will be used in this study.

4.2 Subgroups

No subgroups will be used in this study.

5. Definitions

5.1 Study Time Points

Enrollment Date

The enrollment date is defined as the date collected on the electronic case report form (eCRF).

Study Day 1

For each subject, Study Day 1 is defined as the first day of IP administration in this study. 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 study visit date, Study Day is defined as the number of days since Study Day 1:

Study Day = (study visit date – Study Day 1 date) + 1

If the date of interest is prior to the Study Day 1:

Study Day = (study visit date – Study Day 1 date), so that the day prior to Study Day 1 is study day -1.

End of Investigational Product (EOIP) Date

For each subject, the end of investigational product date is defined as the date of decision was made to end investigational product recorded on the End of Investigational Product Administration form in eCRF.

End of Study (EOS) Date

For each subject, the end of study date is the date recorded on the End of Study eCRF.

Last IP Dose Date

For each subject, the Last IP Dose Date is defined as the last day of IP administration in this study:

- If the last dose was administered non-clinic, then Last IP Dose Date is defined as the final dose date reported by the subject on the Non-Clinic Final Investigational Product Dose Date Form in eCRF.
- If the last dose was administered in-clinic, then Last IP Dose Date is the last start date captured on the Investigational Product Administration (In-clinic) form in eCRF.

Study End Date

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

5.2 Demographics and Baseline Related Definitions

Age

Age at enrollment is the subject's age in years that derived in the clinical database.

Baseline Lipid and Lipid-related Values

The baseline for fasting lipids (total cholesterol, HDL-C, LDL-C, VLDL-C and non-hdl-c), ApoA1, ApoB, Lp(a) and their derived parameters (eg, ratio between them) is 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.

Other Baseline Values

For PCSK9 and all other variables, the baseline value is defined as the last non-missing value collected prior to or on Study Day 1.

Change from Study Day 1

The arithmetic difference between a post Study Day 1 value and Study Day 1 value for a given time point:

Change from Study Day 1 = (post Study Day value – Study Day 1 value)

Percent Change from Study Day 1

100 x [(post Study Day value – Study Day 1 value) / Study Day 1 value]

Change from Baseline

The arithmetic difference between a post-baseline value and baseline for a given time point: Change from baseline = (Post-baseline value – Baseline value)

Percent Change from Baseline

100 x [(Post-baseline value – Baseline value) / Baseline value]

Baseline CHD Risk Factors 2 or more (yes/no)

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 and family history of premature CHD as recoded in the eCRF form, and low HDL-C defined as baseline HDL-C < 40 mg/dL in men and < 50 mg/dL in women.

5.3 Other Related Definitions

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)

IP is Repatha 420 mg QM SC.

IP Exposure Period in Months

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

Treatment Emergent Adverse Events

Events are categorized as Adverse Events (AEs) starting on or after first dose of investigational product as determined by the flag indicating if the value of the Events eCRF question “Did event start before first dose of investigational product?” is No or

missing and up to including 30 days after the end of investigational product or the End of Study date, whichever is earlier.

Treatment Emergent Disease-Related Events

Treatment emergent disease-related events are events categorized as Disease-related Events (DREs) starting on or after first dose of investigational product as determined by the flag indicating if the value of the Events eCRF question "Did event start before first dose of investigational product?" is No or missing and up to including 30 days after the end of investigational product or the End of Study date, whichever is earlier.

Reflexive Approach for LDL-C and VLDL-C

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

6. Analysis Sets

6.1 Full Analysis Set

The full analysis set includes all enrolled subjects who have received at least 1 dose of Repatha. Unless specified otherwise, the FAS will be the default analysis set in this study.

6.1.1 Primary Analysis Set

The primary analysis set is the full analysis set (FAS).

6.2 Safety Analysis Set

The safety analysis set is the full analysis set (FAS).

6.3 Per Protocol Set(s)

Not applicable.

6.4 Health-related Quality-of-Life or Health Economics Analyses Set(s)

Not applicable.

6.5 Pharmacokinetic/Pharmacodynamic Analyses Set(s)

Not applicable.

6.6 Interim Analyses Set(s)

There is no planned interim analysis for this study.

6.7 Study-specific Analysis Sets

Not applicable.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

There is no planned interim analysis for this study.

7.2 Primary Analysis

Not applicable.

7.3 Final Analysis

The final analysis will be performed at the end of the study (defined as when the last subject enrolled has completed the safety follow-up/EOS visit).

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. In the Data Issue Identification and Resolution (DIIR) processes, queries will be made to the sites to distinguish true missing values from other unknown values (eg, 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.

There will be no imputation for missing data.

8.3.2 Handling of Incomplete Dates

Adverse event and concomitant medications with completely or partially missing dates will be queried. After the query is resolved, 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:

Table 8-1. 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 Study Day 1

8.4 Detection of Bias

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

Because of its prospective, observational nature, this study is more greatly affected by bias than interventional clinical trials. Missing or incomplete data is a potential risk for bias. Before the study begins, initiation visits will be carried out to complete site trainings for the protocol and other study specific procedures. The investigator will be given clear guidelines for CRF completion for this study to ensure that he/she makes every effort to collect complete data. In the Data Issue Identification and Resolution (DIIR) process, queries will be made to the sites minimize the missing data as described in Section 8.3.1.

8.5 Outliers

Various methods, including univariate summaries, histograms, scatterplots, 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.

8.6 Distributional Characteristics

Statistical analyses in this study are descriptive in nature. There are no distributional requirements for the planned analyses.

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 study will be descriptive in nature. No statistical inference is planned. There will be no imputation for missing data.

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, minimum and maximum. For categorical variables, the frequency and percentage will be given.

Final analyses will be based on data collected from this study. 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 locked. All endpoints will be analyzed based on this snapshot.

9.2 Subject Accountability

The number of subjects screened, enrolled, receiving IP, and completing the study will be summarized from all enrolled subjects. Study discontinuation and IP discontinuation will be tabulated separately by reasons for discontinuation from all enrolled subjects.

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

9.3 Important Protocol Deviations

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

prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol.

9.4 Demographic and Baseline Characteristics

Baseline demographics, weight, cardiovascular medical history, laboratory parameters, vital signs and concomitant medication will be summarized for all enrolled subjects.

9.5 Efficacy Analyses

The percent change from baseline to week 12 for LDL-C, ApoB and Lp(a) will be summarized. In addition, descriptive statistics of actual values and change from baseline will be provided.

9.5.1 Analyses of Primary Efficacy Endpoint(s)

Not applicable.

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

Descriptive statistics will be summarized for each secondary endpoint.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

Not applicable.

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

Subject incidence of treatment-emergent adverse events will be summarized.

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version [21.0] or later will be used to code all events categorized as adverse events and disease-related events to a system organ class and a preferred term.

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, fatal adverse events and adverse events of interest.

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.

Subject incidence of events of interest (standardized MedDRA queries and/or Amgen customized queries) will also be summarized according to their categories and preferred term. Current event of interest to be analyzed is hypersensitivity for this study.

Summaries of treatment-emergent and serious adverse events will be tabulated by system organ class and preferred term.

Subject incidence of disease-related events will be summarized for all treatment-emergent disease-related events and fatal disease-related events.

9.6.3 Laboratory Test Results

Descriptive statistics will be provided for actual values and changes from baseline in selected laboratory parameters at protocol-specified scheduled visits provided in the protocol Table 2-1. Laboratory analytes are provided in the protocol Table 12-1.

9.6.4 Vital Signs

Systolic and diastolic blood pressure and heart rate will be summarized using descriptive statistics at each scheduled visit. Summaries will also include the change from baseline at each scheduled visit.

9.6.5 Physical Measurements

Weight (in kilograms) will be summarized as baseline characteristics. Descriptive statistics will be provided.

9.6.6 Electrocardiogram

Not applicable.

9.6.7 Antibody Formation

Not applicable.

9.6.8 Exposure to Investigational Product

Descriptive statistics will be produced to describe the patient-month exposure to investigational product and patient-month duration of study participation.

9.6.9 Exposure to Non-investigational Product

Not applicable.

9.6.10 Exposure to Other Protocol-required Therapy

Not applicable.

9.6.11 Exposure to Concomitant Medication

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in protocol Section 7.1.7. The number and proportion of subjects receiving concomitant therapies will be summarized by preferred term as coded by the World Health Organization Drug (WHO DRUG) dictionary.

9.7 Other Analyses

Not applicable.

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

Not applicable.

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

There are no changes to the protocol-specified analyses.

11. Literature Citations / References

National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation.* 2002;106:3143-3421.

12. Prioritization of Analyses

Not applicable.

13. Data Not Covered by This Plan

Currently there are no pre-planned analyses for the biochemical cardiovascular biomarker objective.

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 table.

Scheduled Visit Week	Target Study Day	Vital Signs (BP, HR)	Physical Examinations	Fasting lipids, ApoA1, ApoB	Lp(a)
Week 1 (Day1)	1	< =1	< =1	< =1	< =1
Week 8	57	(1,70]	N/A	(1,70]	(1,70]
Week 12	85	> 70	> 1	> 70	> 70

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 study day of that specific study week (7×study week). 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 Adverse Events

Refer to the NCI Common Terminology Criteria for AEs (CTCAE) Version 4.0, published: May 29, 2009 (v4.03: June 14, 2010) for AE and lab shift grading and information. The CTCAE is available at the following link: http://evs.nci.nih.gov/ftp1/CTCAE/About.html