Summary Table of Study Protocol

Title	Observational Serial Chart Review of Repatha® Use in European Subjects With Hyperlipidaemia
Protocol version identifier	**Amendment 2**
Date of last version of the protocol	**13 February 2018**
EU Post Authorisation Study (PAS) Register No	EUPAS13328
Active Substance	Evolocumab
Medicinal Product	Repatha®
Product Reference	EU/1/15/1016
Procedure Number	EMA/H/C/3766
NCT Number	**NCT02770131**
Marketing Authorisation Holder(s)	Amgen Europe B.V.
Joint PASS	NA
Research Question and Objectives	Research Question: What are the clinical characteristics of patients who are prescribed Repatha® in the post-launch period, and how is their treatment managed? Primary Objective: To describe the clinical characteristics of subjects at initiation of Repatha® Secondary Objective: To describe parameters associated with clinical management of hyperlipidaemia, in subjects initiated on Repatha® treatment
Countries of Study	Multiple countries across Europe
Author	PPD [redacted] Amgen Ltd 1 Uxbridge Business Park Sanderson Road Uxbridge UB8 1DH UK

Marketing Authorisation Holder

Marketing authorisation holder(s)	Amgen Europe B.V.
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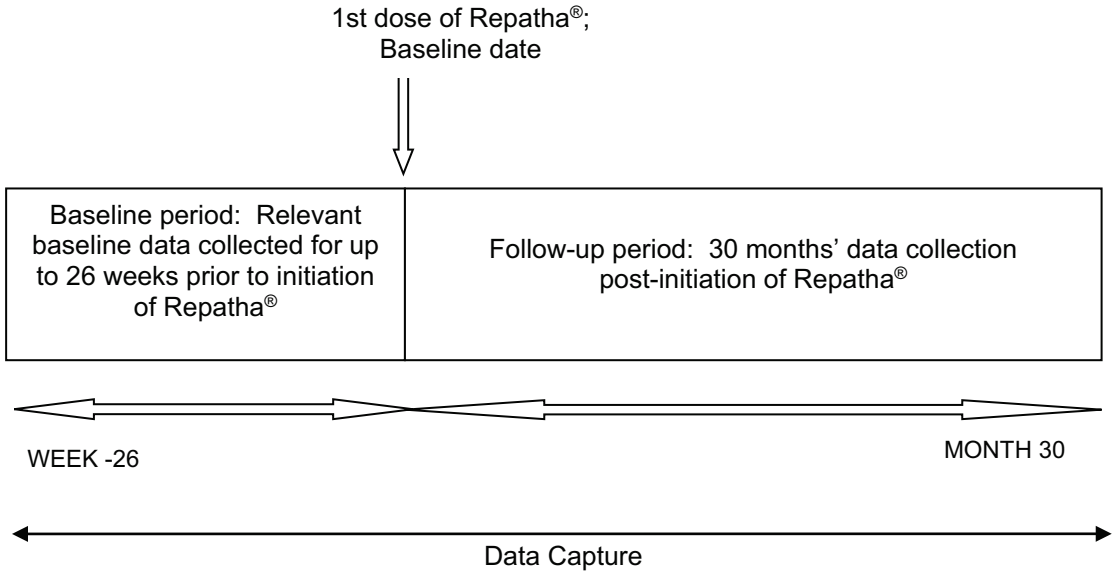
Investigator's Agreement

I have read the attached protocol entitled "Observational Serial Chart Review of Repatha® Use in European Subjects with Hyperlipidaemia", dated **20 December 2018**, and agree to abide by all provisions set forth therein.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature	
Name of Investigator	Date (DD Month YYYY)

Study Design Schema



- Enrolment occurs only after initiation of Repatha® at physician discretion, independent of study protocol
- Where enrolment into study occurs after Repatha® initiation; all relevant follow-up data between Repatha® initiation and prior to study enrolment will be captured in a retrospective manner
- Calendar time for enrolment period at a country level is dependent on launch in each country; the enrolment period for the study on the whole is anticipated to span from Q1 2016 to Q4 2018
- Follow-up at the individual subject level continues for up to 30 months from start of Repatha® treatment irrespective of whether subject continues to receive Repatha®

1. Table of Contents

List of Appendices

2. List of Abbreviations

Abbreviation	Meaning
Adherence	A derived measure describing both persistence and compliance combined at a specific point in time
ADR	Adverse drug reaction
BMI	Body mass index
Compliance	A measurement of how often a patient follows a particular dose and dosing schedule
CRF	**Case report form**
CTT	Cholesterol Treatment Trialists
CV	Cardiovascular
CVD	Cardiovascular disease
eCRF	Electronic case report form
EDC	**Electronic data capture**
EMA	European Medicines Agency
Enrolment	Subject is considered enrolled when informed consent/notification has occurred (if applicable according to local requirements), eligibility has been determined and data entry initiated confirming eligibility on the Meets Eligibility Form in the eCRF.
FH	Familial hypercholesterolaemia
HDL-C	High density lipoprotein-cholesterol
ICH GCP	International Committee for Harmonisation Good Clinical Practice
ICMJE	International Committee of Medical Journal Editors
IRB/IEC	Institutional Review Board/Institutional Ethics Committee
LDL-C	Low density lipoprotein-cholesterol
LLT	Lipid lowering therapy
LMT	Lipid-modifying therapy
MAN	Manual
Persistence	Individual subject time on therapy
SOP	Standard Operating Procedure
Source data	Information from an original record or certified as a copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations or other activities in a study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies). (ICH Guideline E6).
Study start	Date on which data for first enrolled subject is first entered into EDC
WHO	World Health Organisation

3. Responsible Parties

Amgen Ltd is responsible for all aspects of study execution, conduct and reporting.

4. Abstract

- Study Title: Observational Serial Chart Review of Repatha® Use in European Subjects with Hyperlipidaemia
- Study Background and Rationale:

Cardiovascular disease (CVD) represents the leading cause of death and disability in the world, comprising over 10% of the global total disease burden. In 2008, the World Health Organization (WHO) reported that CVD accounted for over 17 million deaths, nearly 80% of which were due to heart attacks and strokes alone.

Elevated cholesterol is among the leading risk factors for cardiovascular deaths, with an estimated prevalence of 39% globally among all adults (greater in high-income countries). It is estimated that up to 50% of the European population aged 35-64 years has a total cholesterol > 6.5 mmol/L (Tolonen et al, 2005), (equivalent to > 254 mg/dL). This high prevalence of dyslipidemia translates into significant cardiovascular morbidity and mortality.

Over 50 million patients in the United States, Europe, and Japan are currently treated with lipid lowering therapies (LLTs). The rationale for treatment of dyslipidemia derives from extensive clinical trial data which demonstrate that the reduction in total cholesterol, non-high density lipoprotein-C (HDL-C), and most importantly, low density lipoprotein-C (LDL-C) through pharmacological therapies lowers the risk of CVD events (Kannel et al, 1974; Kannel, 1995; Kannel et al, 1979). A recent Cholesterol Treatment Trialists' (CTT) Collaboration (CTT et al, 2010) meta-analysis which included 21 randomized controlled trials involving nearly 170,000 patients showed that for every 1 mmol/L (equivalent to 39 mg/dL) reduction of LDL-C there was a 20% reduction in the risk of major vascular events (coronary death, non-fatal myocardial infarction, coronary revascularisation, or stroke).

A serine protease expressed predominantly in the liver, kidney and intestine (Seidah, 2003), proprotein convertase subtilisin/kexin type 9 (PCSK9), plays an important role in the recycling and regulation of the LDL receptor (Horton et al, 2007; Brown and Goldstein, 2006). PCSK9 acts via direct binding to the LDL receptor, resulting in post-translational down-regulation of receptor expression on the hepatic cell surface. This in turn leads to increased levels of circulating LDL-C. Repatha® (evolocumab) is a fully human monoclonal immunoglobulin (Ig) G2 that binds specifically

to human PCSK9. Following parenteral administration, it inhibits circulating PCSK9 from binding to the low-density lipoprotein receptor (LDLR) on the liver cell surface, thus preventing PCSK9-mediated LDLR degradation. It increases liver LDLR levels resulting in associated reductions in serum LDL-C.

Repatha® is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet, in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL C goals with the maximum tolerated dose of a statin or, alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated. (Repatha® EPAR)

European Medicines Agency (EMA) approval for Repatha® was granted on 17th July 2015. The data submitted in support of the filing were generated from an extensive interventional clinical trial programme in which selected populations were enrolled and managed according to strictly-defined protocols in a controlled setting. More recently, the 27,564 patient FOURIER trial which evaluated the effect of lowering LDL-C with evolocumab in subjects with established atherosclerotic disease reported a 20% relative risk reduction in major adverse cardiac events compared to those on optimized oral lipid lowering therapy (Sabatine et al, 2017). However such data can not necessarily be generalised to routine clinical practice especially given the varying reimbursement rules and availability of the drug in participating countries, and at present there is little information describing Repatha® use in a real-world setting.

Across Europe, country health authorities grant local access approvals based on clinical trial data; it is recognised that local conditions may limit the population eligible to receive Repatha® through application of criteria other than the terms of the label. As the next step, real world evidence describing product use in routine clinical practice is required, for continuation and/or reassessment of access.

The design and objectives of this study address the requests being made by the health authorities. In particular, authorities require local real-world data on the patient population which is receiving Repatha®, including patient characteristics, dosing patterns and effectiveness in lowering LDL-C. The study will be conducted only in countries which require real world data to be collected in the post-launch setting and where it is allowed as per local regulations to study the use of a single treatment in clinical practice.

Data obtained from this study are intended to fulfil health authorities' requirements and to provide a robust source of published information for physicians.

- Research Question and Objectives
  - Primary Objective:
    To describe the clinical characteristics of subjects at initiation of Repatha®
  - Secondary Objectives are to describe the following:
    - LDL-C and other cholesterol values over time
    - Repatha® use over time (dose, dose frequency)
    - Use of other lipid-modifying therapies (LMTs) over time (type, dose, dose frequency)
    - Physician visits (dates and reason)
    - Hospitalisation (dates and reason)
- Hypothesis

No formal hypothesis will be tested in this observational study

- Study Design/Type

Observational cohort study collecting data through serial chart review

- Study Population

The study population comprises patients from European countries, who have received Repatha® as part of routine clinical management of their hyperlipidaemia, between August 2015 and June 2021.

- Summary of Subject Eligibility Criteria
  - All inclusion criteria need to be met, as follows:
    - Adults (≥ 18 years)
    - Provided informed consent if applicable according to local requirements
    - Initiated on Repatha® at physician's discretion, after 1st August 2015
    - Received at least one dose of Repatha®
- If at least one exclusion criterion is met, subject is not eligible for participation in the study, as follows:
    - Enrolled in an interventional study of PCSK9 inhibitor within 12 weeks prior to initiation of Repatha®
    - Received commercially available PCSK9 inhibitor within 12 weeks prior to initiation of Repatha®
- Follow-up

Individual observation period is up to 36 months; capture of baseline data from up to 6 months prior to the date of initiation of Repatha® and a maximum of 30 months of follow-up data after the date of Repatha® initiation.

The study period is expected to extend from 1st August 2015 to 30 June 2021.

- Variables

Outcome Variables:

Baseline period

- Demographics: age (at initiation of Repatha®), gender, country
- Cardiovascular risk factors, including body mass index (BMI), smoking status, vascular bed involvement, chronic kidney disease status (CKD), history of hypertension (see also Appendix B)
- Familial hypercholesterolaemia (FH) status
- Diabetic status including type 1 or 2, and HbA1C (closest to initiation of Repatha®)
- Cardiovascular history (see Appendix B for list of applicable conditions/events)
- Cholesterol values including total cholesterol, LDL-C, HDL-C, non-HDL-C, triglycerides
- Dose, dose frequency, commencement date of Repatha® administration
- Type, dose, dose frequency, commencement and discontinuation dates of other LMT administration including apheresis
- History of statin intolerance (y,n)
- Dates and reason for hospital admittance/final diagnosis
- Dates of physician visits and reason for attendance

Follow-up period

- Cholesterol values including total cholesterol, LDL-C, HDL-C, non-HDL-C, triglycerides
- Dose, dose frequency, commencement and discontinuation dates of Repatha®administration
- Type, dose, dose frequency, commencement and discontinuation dates of other LMT administration including apheresis
- Dates and reason for hospital admittance/final diagnosis
- Dates of physician visits and reason for attendance
- Medication persistence
- Medication adherence

End of study

- Date of last Repatha® dose
- Reason for cessation of Repatha® therapy, if stopped within the observation period
- Primary reason for ending study

- Study Sample Size

The primary outcome measures for the study involve estimating the percentage of subjects with clinical characteristics of interest (FH, diabetes, CV history) and also estimating the baseline LDL-C levels. The intention is to perform the analyses by country. The planned sample size for the study is 2000 subjects across approximately 15 countries; an average of approximately 130 subjects per country.

The sample size is expected to enable precise estimates of the primary outcome measures to be obtained for each participating country.

- Data Analysis

All summaries of the data will be descriptive in nature. For categorical variables the frequency and percentage, with 95% confidence interval, will be given.

Summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation or standard error, 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum.

5. Amendments and Updates

Amendment or Update No.	Date	Section of Study Protocol	Amendment or Update	Reason
1	13 Feb 2018		See summary of changes	
2	**20 December 2018**		**See summary of changes**	

6. Milestones

Milestone	Planned date
Start of data collection	April 2016
Interim analysis 1	March 2017
Interim analysis 2	June 2017
Interim analysis 3	August 2017
Interim analysis 4	November 2017
Interim analysis 5	Q2 2018
Interim analysis 6	2019
Interim analysis 7	2020
End of data collection	June 2021
Final report of study results	Dec 2021

7. Rationale and Background

7.1 Diseases and Therapeutic Area

Cardiovascular disease (CVD) represents the leading cause of death and disability in the world, comprising over 10% of the global total disease burden. In 2008, the World Health Organization (WHO) reported that CVD accounted for over 17 million deaths, nearly 80% of which were due to heart attacks and strokes alone.

Elevated cholesterol is among the leading risk factors for cardiovascular deaths, with an estimated prevalence of 39% globally among all adults (greater in high-income countries). It is estimated that up to 50% of the European population aged 35-64 years has a total cholesterol > 6.5 mmol/L (Tolonen et al, 2005) (equivalent to > 254 mg/dL). This high prevalence of dyslipidemia translates into significant cardiovascular morbidity and mortality.

Over 50 million patients in the US, Europe, and Japan are currently treated with lipid lowering therapies (LLTs). The rationale for treatment of dyslipidemia derives from extensive clinical trial data which demonstrate that the reduction in total cholesterol, non-HDL-C, and most importantly, LDL-C through pharmacological therapies lowers the risk of CVD events (Kannel et al, 1974; Kannel, 1995; Kannel et al, 1979). A recent Cholesterol Treatment Trialists' (CTT) Collaboration (CTT et al, 2010) meta-analysis which included 21 randomized controlled trials involving nearly 170,000 patients showed that for every 1 mmol/L (equivalent to 39 mg/dL) reduction of LDL-C there was a 20% reduction in the risk of major vascular events (coronary death, non-fatal myocardial infarction, coronary revascularisation, or stroke).

Repatha® (evolocumab) is a fully human monoclonal IgG2 antibody directed against proprotein convertase subtilisin/kexin type 9 (PCSK9). Following parenteral administration, it inhibits circulating PCSK9 from binding to the low-density lipoprotein receptor (LDLR) on the liver cell surface, thus preventing PCSK9-mediated LDLR degradation. It increases liver LDLR levels resulting in associated reductions in serum LDL-C.

Repatha® is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non familial) or mixed dyslipidaemia, as an adjunct to diet, in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL C goals with the maximum tolerated dose of a statin or, alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

7.2 Rationale

EMA approval for Repatha® was granted on 17th July 2015. The data submitted in support of the filing were generated from an extensive interventional clinical trial programme in which selected populations were enrolled and managed according to strictly-defined protocols in a controlled setting. More recently, the 27,564 patient FOURIER trial which evaluated the effect of lowering LDL-C with evolocumab in subjects with established atherosclerotic disease reported a 20% relative risk reduction in major adverse cardiac events compared to those on optimized oral lipid lowering therapy (Sabatine et al, 2017). However, such data can not necessarily be generalised to routine clinical practice especially given the varying reimbursement rules and availability of the drug in participating countries, and at present there is little information describing Repatha® use in a real-world setting.

Across Europe, country health authorities grant local access approvals based on clinical trial data. As the next step, real world evidence describing product use in routine clinical practice are required, for continuation and/or reassessment of access. The design and objectives of this study address the anticipated requests being made by the health authorities. In particular, authorities require local real-world data on the patient population which is receiving Repatha®, including patient characteristics, dosing patterns and effectiveness in lowering LDL-C. The study will be conducted only in countries which require real world data to be collected in the post-launch setting and where it is allowed as per local regulations to study the use of a single treatment in clinical practice.

Data obtained from this study are intended to fulfil health authorities' requirements and to provide a robust source of published information for physicians.

7.3 Statistical Inference (Hypothesis)

No formal hypothesis will be tested in this observational study. The study aims to describe the characteristics of subjects who commence treatment with Repatha®. The sample size is expected to enable sufficiently precise estimates of the primary outcome measures to be obtained for each participating country.

8. Research Question and Objectives

Research Question: What are the clinical characteristics of patients prescribed Repatha® in the post-launch period, and how is their treatment managed?

8.1 Primary Objective

To describe the clinical characteristics of subjects at initiation of Repatha®

8.2 Secondary Objectives

- To describe LDL-C and other cholesterol concentrations over time
- To describe treatment patterns of use of Repatha® over time
- To describe treatment patterns of use of other lipid modifying therapies over time
- To describe Health Resource Utilisation components, including hospitalisations and physician visits

8.3 Exploratory Objective

To evaluate incidence of LDL-C below 50 mg/dL (below 1.3 mmol/L)

9. Research Methods

9.1 Study Design

This cohort study is a multicountry, observational, serial chart review study of European patients receiving Repatha® as part of routine clinical management of their hyperlipidaemia. It is designed to capture data on clinical parameters relevant to health authorities and physicians.

Following approval of Repatha®, which was granted after review of data from an extensive interventional clinical trial programme, health authorities and other bodies now require real-world evidence on the clinical profile of patients who receive Repatha® in the immediate post-launch period, hence a non-interventional design is essential.

Enrolment will not be stratified by population characteristics, although a cap will be placed on total enrolment per country.

This study protocol is for a non-interventional, observational study and does not alter the clinical management of patients.

9.2 Setting and Study Population

9.2.1 Study Period

At the individual subject level, data will be captured for up to 36 months (up to 6 months pre-initiation of Repatha® and up to 30 months follow-up post-initiation of Repatha®).

At the study level, data will be captured for the periods spanning February 2015 (includes the 6-month period prior to the earliest possible prescription of commercial Repatha®) and June 2021.

9.2.2 Selection and Number of Sites

Sites in Europe where patients are being treated with commercially available Repatha® will be considered for inclusion. These are anticipated to be specialist sites which treat patients at high or very high risk of experiencing a CV event, including but not limited to FH patients.

Potential sites will be identified, approached and selection confirmed according to Amgen standard operating procedures (SOPs); selection is based on interest in participation as a study site, willingness and ability to comply with the protocol and data entry conventions, and agreement to follow the subjects throughout the observation period.

9.2.3 Subject Eligibility

9.2.3.1 Inclusion Criteria

All inclusion criteria need to be met, as follows:

- Adults (≥ 18 years)
- Provided informed consent if applicable according to local requirements
- Initiated on Repatha® at physician's discretion, after 1st August 2015
- Received at least one dose of Repatha®

9.2.3.2 Exclusion Criteria

If at least one exclusion criterion is met, subject is not eligible for participation in the study, as follows:

- Enrolled in an interventional study of PCSK9 inhibitor within 12 weeks prior to initiation of Repatha®
- Received commercially available PCSK9 inhibitor within 12 weeks prior to initiation of Repatha®

9.2.4 Matching

NA

9.2.5 Baseline Period

The baseline period is from the 6 months prior to the first dose of Repatha® through to the date of administration of the first dose of Repatha®. Therefore, the end of the baseline period coincides with the first dose of Repatha®.

9.2.6 Study Follow-up

Follow-up of each subject will be for 30 months after date of first administration of Repatha®, death, withdrawal of consent or loss to follow-up (whichever occurs earliest). Subjects will be followed regardless of continuation/discontinuation of Repatha®, including for subjects who received only one dose of Repatha®.

If subjects are lost to follow-up, the site will be encouraged to confirm the reason, which may include withdrawal of consent or relocation to a different physician.

Study duration is considered sufficient to allow an estimation of Repatha® and other LMT usage and LDL-C concentrations over time, following initiation of Repatha®.

9.3 Variables

9.3.1 Exposure Assessment

Exposure to Repatha® and other LMT will be assessed through review of medical charts.

9.3.2 Outcome Assessment

Outcome measures reflect parameters used in routine clinical management, and are expected to provide data which are of interest to physicians and health authorities, as these measures are directly relevant to current clinical practice.

To provide baseline information for each subject, in addition to demographic data (age, gender, country) and established cardiovascular risk factors (BMI, hypertension, CKD, smoking status, vascular bed involvement), data on other key variables will also be collected such as history of statin intolerance and also current aspirin use. For an overview which assessments are recorded into an electronic case report form (eCRF) at which points in a subject's observation period, please also refer to Appendix C.

9.3.2.1 Primary Outcome

Clinical characteristics at time of initiation of Repatha® as assessed in relation to:

- FH status (diagnosed/not diagnosed)
- CV history (see Appendix B for a list of diagnoses/events)

- Diabetic status (diabetic/not diabetic; Type 1 or Type II; HbA1C measurement closest to initiation of Repatha®)
- Cholesterol values including total cholesterol, LDL-C, HDL-C, non-HDL-C, triglycerides (value(s) available in the 26-week baseline period)
- Demographics (age at initiation of Repatha®, gender, country)
- Cardiovascular risk factors (body mass index (BMI), smoking status, chronic kidney disease, history of hypertension, vascular bed involvement (see also Appendix B)
- History of statin intolerance (y,n)
- Dose, dose frequency, commencement date of Repatha® administration
- Type, dose, dose frequency, commencement and discontinuation dates of other LMT administration including apheresis
- Dates and reason for hospital admittance/final diagnosis
- Dates of physician visits and reason for attendance

Of note, LMT use (including apheresis) over the 6 months prior to initiation of Repatha® will be summarised and the regimen in place at the time of Repatha® initiation will be regarded as the baseline.

In addition, LDL-C and other relevant lipid panel measurements and HbA1C as assessed within 6 months prior to initiation of Repatha® (or the mean of the two most recent LDL-C measurements, if there is more than one) will be regarded as the respective baseline values.

All CV history and diabetic status will be reported as baseline data

9.3.2.2 Secondary Outcomes

- Age at initiation of Repatha®
- Gender
- Country of residence
- Relevant laboratory measures including LDL-C, other test results of the lipid panel (over time; values available during the 30-month follow-up period)
- Use of Repatha® (at initiation of Repatha® and during the 30-month follow-up period; type, dose, frequency, switching)
- LMTs (over the full observation period (ie, from baseline throughout the 30-month follow-up period); type, dose, frequency, switching)
- Medication persistence
- Medication adherence
- Incidence of hospitalisation (dates, including reason for admittance/final diagnosis)
- Incidence of physician visits (dates, including reason for attendance)

9.3.2.3 Exploratory Outcome

- Incidence of LDL-C < 50 mg/dL (< 1.3 mmol/L)

9.3.3 Covariate Assessment

NA

9.3.4 Validity and Reliability

Study variables stated in this protocol are objective, relevant to the question under study and are accepted as appropriate by regulatory authorities. Variables to be evaluated in the study are parameters which are routinely measured as part of clinical management of patients with hyperlipidaemia.

Data for this non-interventional, observational study are collected through serial review of subjects' charts. Clinical management of enrolled subjects will not be altered through the study protocol. Therefore, data from subjects' medical records is expected to be valid and reliable in reflecting their routine clinical management.

9.4 Data Sources

Study site staff will abstract data from subject medical notes and enter these into eCRF pages of the sponsor's electronic database. Sites participating in the study will be fully trained by Amgen in data entry and use of the study-specific database and eCRFs.

Chart reviews and data abstraction will be conducted periodically (at a minimum 3-monthly). Data capture comprises the baseline and follow-up periods as described in Section 9.2.5 and Section 9.2.6**,** respectively.

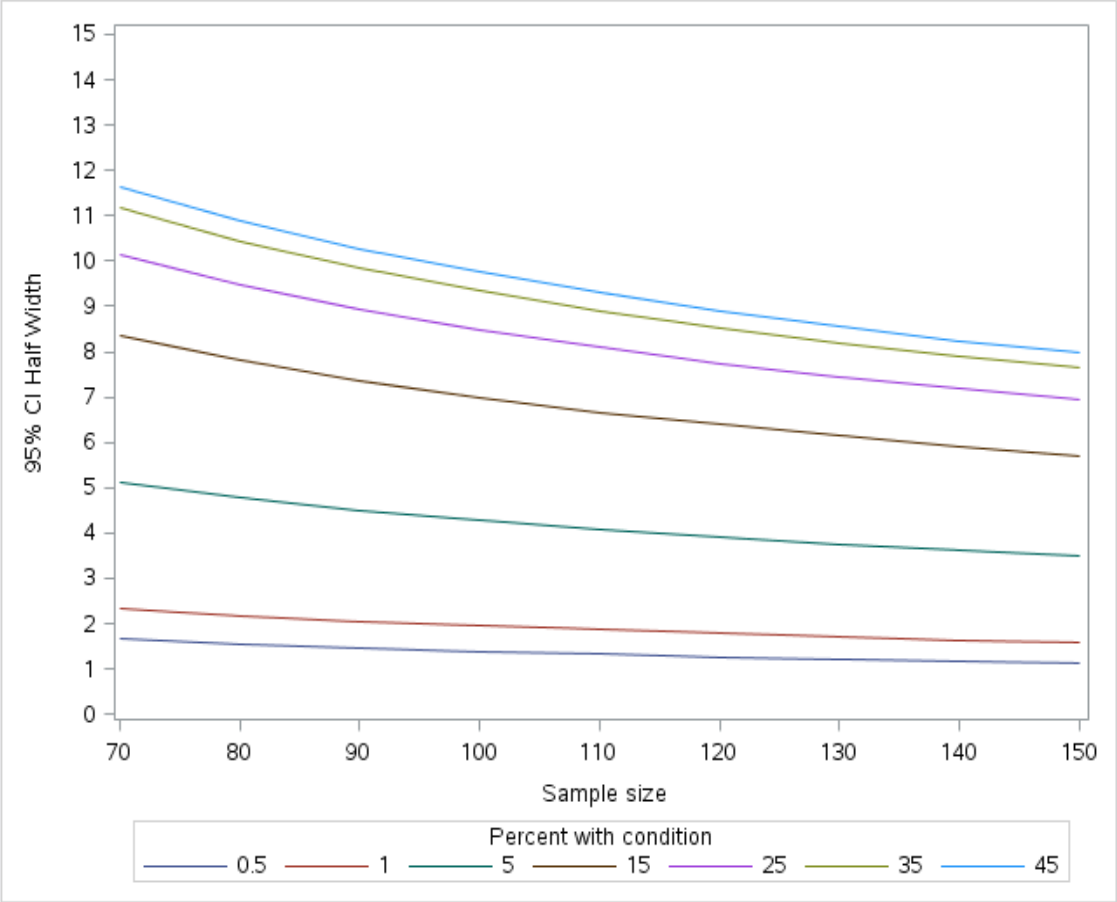
The first data abstraction into the CRF should occur as soon as the patient is enrolled into the study.

The periodic data abstractions are expected to occur once every 3 months thereafter.

9.5 Study Size

The primary outcome measures for the study involve estimating the percentage of subjects with clinical characteristics of interest (FH, CV history, diabetes - yes or no for each outcome measure) and also estimating the baseline LDL-C levels. The intention is to perform the analyses by country. The planned sample size for the study is 2000 subjects across approximately 15 countries; an average of approximately 130 subjects per country. The figure below shows the expected precision of estimates of the binary outcome measures for a range of sample sizes above and below 130 and for a range of percentages of subjects with and without the conditions of interest. This

gives an indication of the likely precision of estimates and demonstrates that the sample size per country will enable sufficiently precise estimates to be obtained for the primary outcome measures. For example, with a sample size of 130 in the country and assuming 35% of subjects have the condition being summarised, the ½ width of the 95% confidence interval around the estimate would be approximately 8%.



The table below shows the estimated precision of the continuous primary outcome measure, the mean LDL-C value prior to initiation of Repatha®, assuming a range of sample sizes and standard deviations (standard deviations based on those observed in phase 3 studies).

	½ width of 95% CI in mg/dL			
Standard deviation	N = 70	N = 100	N = 130	N = 150
40	9.37	7.84	6.88	6.40
45	10.54	8.82	7.74	7.20
50	11.71	9.80	8.60	8.00
55	12.89	10.78	9.46	8.80

The sample size will also enable the secondary outcome measures to be precisely estimated. This includes the LDL-C over time after initiation of Repatha, after allowing for missing data due to subject withdrawal (expected to be up to 10% per year over the 30 months follow-up period).

9.6 Data Management

Data are abstracted by site staff from subject notes into an electronic database provided by the sponsor. The sponsor provides protocol-specific training to all site staff delegated to abstract subject data.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg**,** CRFs and other pertinent data) provided that subject confidentiality is respected.

The Clinical Monitor or designee is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of research. The Clinical Monitor, or designee is to have access to subject medical records and other study-related records needed to verify the entries on the CRFs in accordance with the local laws and regulations.

The Investigator agrees to cooperate with the Clinical Monitor, or designee to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or designees). Review of study-related records will occur to evaluate the study conduct and compliance with the protocol, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the electronic CRFs must be maintained and available upon request.
- Updates to electronic CRFs will be automatically documented through the software's "audit trail".

- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data is checked for consistency, omissions, and any apparent discrepancies. To resolve any questions arising from the clinical data management review process, data queries are created in the EDC system database for site resolution and closed by Amgen reviewer.
- The Investigator **applies an electronic signature in the electronic data capture (EDC) database. This signature indicates that investigator inspected or reviewed the data on the CRF, the data queries, and agrees with the content.**

9.6.1 Obtaining Data Files

NA

9.6.2 Linking Data Files

NA

9.6.3 Review and Verification of Data Quality

Automatic edit checks within the database and further manual review by the sponsor help to ensure quality and completeness of the data. Data queries are sent to site for clarification and resolution of discrepancies.

9.7 Data Analysis

9.7.1 Planned Analyses

9.7.1.1 Interim Analyses

Interim analyses (IAs) will be performed according to individual country need, where possible, to provide a timely snapshot of essential data prior to the final analysis (see also Section 6). Country-specific analyses will be provided at the interim analysis stage where possible, according to enrolment and duration of follow-up (for some countries baseline data only may be presented at the interim analyses).

9.7.1.2 Primary Analysis

The summaries of FH status, CV history and diabetic status and the summary statistics of LDL-C will be presented for the time of initiation of Repatha®.

9.7.2 Planned Method of Analysis

All summaries of the data will be descriptive in nature. For categorical variables the frequency and percentage, with 95% confidence interval, will be given.

Summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation or standard error, 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum.

For the outcome measure of LDL-C and other cholesterol values over time, the data collection period (up to 6 months pre-initiation of Repatha® and up to 30 months post-initiation of Repatha®) will be divided into time windows. For each subject the mean LDL-C and other cholesterol values during each time period will be obtained, and summary statistics will be produced based on these mean values. In order to optimally utilize the available LDL-C and other cholesterol data, the following time windows will be used:

Definition 1: Period of 6 months duration pre-initiation of Repatha® (to obtain baseline LDL-C), windows of 3 months duration post initiation of Repatha® (months 1-3, months 4-6, months 7-9 and so on, through months 28-30)

Definition 2: Period of 6 months duration pre-initiation of Repatha® (to obtain baseline LDL-C), windows of 6 months duration post initiation of Repatha® (months 1-6, months 7-12, months 13-18 and so on through months 25-30)

9.7.2.1 General Considerations

Statistical analyses will be descriptive only. No statistical inference or imputations of missing data are planned.

Subject 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 reported.

At the individual subject level, collection of data may be both retrospective and prospective, or prospective only. This depends on whether the subject enrolled some time after initiation of Repatha® (in which case their follow-up data is captured partially retrospectively) or whether the subject enrolled upon initiation of Repatha® (in which case the subject's follow-up data is collected prospectively in its entirety). Data obtained from subjects whose follow-up data are in part collected retrospectively may be reported separately from those with data collected fully prospectively to assess the potential for systematic differences between these subject groups.

9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

The primary outcome measures are commonly recorded and/or already known to the treating physician. Incomplete information is not expected in this regard.

To evaluate the secondary objectives**,** the study intends to capture variables expected to be recorded as part of routine follow-up in this cardiovascular high risk population.

Measurement of laboratory variables (eg LDL-C) may be infrequent, however Investigators are expected to be interested in checking this parameter more closely following administration of a novel therapeutic, hence it is expected that LDL-C measurements will be taken during the follow-up period of all subjects enrolled in the study. Likewise, accuracy in reporting use of Repatha® and concomitant LMTs can be expected in this situation.

Where data appears to be incomplete in the study database, the study monitor will encourage sites to provide as much information as possible, from patient notes.

For relevant calendar dates that are partially complete, where possible an algorithm will be utilised to impute eg the missing day. Details of this algorithm are described in the statistical analysis plan. There will be no imputation for any other missing data fields.

Based upon data from the long-term Phase III studies Descartes and Osler (Blom et al 2014, Sabatine et al 2015), a lost-to-follow-up rate of around 10% might be expected in this study. However, the low dropout rate in long-term interventional Phase III studies of evolocumab indicates subjects' willingness to continue on therapy. The incidence of discontinuation may be expected to be lower in an observational study, which does not carry the burden of additional study visits and invasive laboratory investigations.

Subjects lost to follow up will not be replaced.

9.7.2.3 Descriptive Analysis

9.7.2.3.1 Description of Study Enrolment

Eligible patients at each study site will be invited by the Investigator to provide informed consent to be enrolled into the study.

9.7.2.3.2 Description of Subject/Patient Characteristics

Subjects are adult patients who have been prescribed Repatha® as part of routine treatment at centres in Europe, and who provide informed consent to participate in the study.

Inclusion criteria have been written to be as inclusive as possible of the population initiated on Repatha® in the post-launch period.

9.7.2.4 Analysis of the Primary, Secondary and Exploratory Endpoints

9.7.2.4.1 Analysis of Primary Endpoints

Summaries displaying frequency and percentage, with 95% confidence intervals will be presented for FH status, CV history and diabetic status at the time of initiation of Repatha®.

Summary statistics displaying the number of subjects, mean, median, standard deviationor standard error, 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum will be presented for LDL-C and HbA1C levels) at the time of initiation of Repatha®.

9.7.2.4.2 Analysis of Secondary Endpoints

Summaries displaying frequency and percentage, with 95% confidence intervals will be presented for gender, country, use of Repatha® (at initiation of Repatha® and over time), lipid-modifying therapies (at initiation of Repatha® and over time), medication adherence, medication persistence, incidence of hospitalization (including reason for admittance/final diagnosis), and incidence of physician visits.

Summary statistics displaying the number of subjects, mean, median, standard deviation or standard error, 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum will be presented for age (at initiation of Repatha®) and LDL-C over time.

9.7.2.4.3 Exploratory Endpoint

A Summary displaying frequency and percentage, with 95% confidence intervals will be presented for incidence of LDL-C < 50 mg/dL (< 1.3 mmol/L)

9.7.2.5 Sensitivity Analysis

The primary analysis, summarizing data for each country separately, will include all data pooled, regardless of whether the data was collected retrospectively or prospectively. Sensitivity analyses will be performed subsetting the data according to the amount of retrospective data capture post-Repatha® initiation, to assess any differences in data completion for subjects with a greater or smaller duration of retrospective data capture.

9.7.2.5.1 Subgroup Analysis

Subgroup analysis will be conducted to be supportive of the primary analysis of the primary, secondary and exploratory endpoints. The subgroup analysis will be the planned analysis stratified by country. In addition, a selection of outputs will be generated for subgroups defined based on their status at Repatha® initiation: FH status

(HeFH, HoFH, no); Diabetic status (Type I, Type II, no); CV History (yes, no); Baseline LDL-C (< median, ≥ median); Age (< 65 years, ≥ 65 years).

9.7.3 Analysis of Safety Endpoint(s)/Outcome(s)

No formal analysis of Safety data is planned for this study. ADRs will be summarised.

9.8 Quality Control

Source data verification will be performed at the study site, in accordance with Amgen SOPs.

The Investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRF, informed consent forms, as applicable, and subject identification list
- Study files containing the protocol with all amendments, copies of pre-study documentation, and all correspondence to and from the IRB/IEC or other relevant ethical review board and Amgen

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

Retention of study documents will be governed by the contractual agreement with Amgen.

Amgen retains all data, programs and outputs generated for the study. At study close, data are uploaded from the Medidata Rave database and stored in accordance with Amgen SOPs. Statistical programming and outputs are locked in the analysis environment and no updates are permitted; standard programming procedures will apply.

9.9 Limitations of the Research Methods

9.9.1 Internal Validity of Study Design

9.9.1.1 Information Bias

For the primary objective, information bias is not anticipated to be applicable, as Investigators will be aware of the subjects' age and gender, and will have paid particular attention to their CV history as they have been referred for CV cause. It is possible that lipids may be measured more frequently in very high risk and/or sicker patients, which could influence the baseline LDL-C; to help prevent this, a maximum of two LDL-C values in the 6 months prior to initiation of Repatha® will be considered for inclusion in the baseline, and these will be the two most recent values prior to the initiation date.

For the secondary objectives, it is expected that Investigators will follow all subjects closely as: 1. they have been initiated on a novel therapeutic in the immediate post-launch period. LDL-C values and use of Repatha® and any concomitant medications will be significant markers of clinical care, and are likely to be assessed on an ongoing basis over the observation period. 2. Subjects are high risk patients in secondary care.

9.9.1.2 Selection Bias

At the site level, to avoid enrolment bias via selective invitation of a particular subject profile to participate in the study, all eligible patients will be invited to enrol in chronological order of attending the clinic, until the local enrolment cap has been reached. This also minimises selection of study subjects based on patient progress through the 30 month follow-up period.

It is possible that there could be differential follow-up over the 30 month post-initiation if subjects with certain characteristics, eg**,** those with less elevated LDL-C, were more likely to drop out than others. To explore this, an analysis set of study completers will be defined, and the primary outcome measure for that analysis set will be presented along with the primary analysis for the full analysis set (ie**,** all eligible subjects enrolled).

Patients who have received one dose of Repatha® only are also eligible to participate in the study, reducing the potential for selection bias to only those patients who remain on therapy for sufficient time to enrol into the study.

9.9.1.3 Confounding

NA

9.9.2 External Validity of Study Design

It is unlikely that Repatha® will be available to all patients eligible to receive it according to the guidance in the European label. Regional health authorities' access policies will determine which patients are eligible for prescription. It is expected that patients refractory or intolerant to conventional lipid-lowering therapy (eg statins) and at highest risk of a CV event will be those deemed to be eligible to receive Repatha® treatment, hence the study population will comprise mainly high risk and secondary prevention patients.

In addition, access to Repatha® may vary from region to region, so the populations enrolled in each country may differ in their clinical characteristics. Data at the local level will not necessarily be generalizable to the entire CV population, nor to the overall European population with elevated LDL-C. However, the primary objective of the study is to provide a country-level picture of the clinical characteristics of patients who are prescribed Repatha®, and data will not be interpreted as being more broadly generalizable.

9.9.3 Limitations Due to Missing Data and/or Incomplete Data

Missing/incomplete data is a possibility on this study, but is not expected to be significant: Subjects are expected to be followed closely by their specialist physicians and the variables collected in the eCRF are those captured as part of routine care of this patient population. Additionally, Amgen will review all study data thoroughly on an ongoing basis throughout the study conduct period, and will follow up directly with study sites to query for information which seems to be missing from the study database.

A dropout rate of approximately 10% is possible; this number has been taken into account when considering the feasibility of addressing the study secondary objectives, which involve capturing data over time, post initiation of Repatha®.

10. Protection of Human Subjects

10.1 Informed Consent

An initial sample informed consent form is provided for the Investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Clinical Study Manager to the Investigator. The written informed consent document is to be prepared in the language(s) of the potential subject population.

Before a subject's participation in the study, the Investigator is responsible for obtaining written informed consent, where applicable by local regulations, from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific activities/assessments are conducted. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a subject/patient, to the subject's/patient's participation in the study.

The acquisition of informed consent and the subject's/patient's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject or legally acceptable representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the Investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

10.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

A copy of the protocol, proposed informed consent form, as applicable, other written subject/patient information, and any proposed advertising material must be submitted to the IRB/IEC or other relevant ethical review board for written approval. A copy of the written approval of the protocol, and informed consent form, as applicable must be received by Amgen before the study can be initiated.

The Investigator must submit and, where necessary, obtain approval from the IRB/IEC or other relevant ethical review board for all subsequent protocol amendments and changes to the informed consent document, as applicable. The Investigator is to notify the IRB/IEC or other relevant ethical review board of deviations from the protocol or serious adverse event(s) occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The Investigator is responsible for obtaining annual IRB/IEC or other relevant ethical review board approval /renewal throughout the duration of the study. Copies of the

Investigator's reports, where applicable by local regulations and the IRB/IEC or other relevant ethical review board continuance of approval must be sent to Amgen.

10.3 Subject Confidentiality

The Investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRFs demographics page, in addition to the unique subject identification number, include the age at time of initiation of Repatha®.
- Documents that are not for submission to Amgen (eg, signed informed consent forms, as applicable) are to be kept in confidence by the Investigator, except as described below.

In compliance with Local country regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC or other relevant ethical review board direct access to review the subject's original medical records for verification of study-related activities and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

11. Collection of Safety Information and Product Complaints

11.1 Definition of Safety Events

11.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a subject/patient administered a pharmaceutical product(s) irrespective of a causal relationship with this treatment.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product(s), whether or not considered related to the product(s). The definition of an adverse event includes:

- Worsening of a pre-existing condition or underlying disease
- Events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)

It is the investigator's responsibility to evaluate whether an adverse event is related to an Amgen product prior to reporting the adverse event to Amgen.

An adverse device effect is any adverse event related to the use of a medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

11.1.2 Serious Adverse Events

A serious adverse event is any adverse event as defined above that meets at least one of the following serious criteria:

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an "other significant medical hazard" that does not meet any of the above criteria

A hospitalization meeting the regulatory definition for "serious" is any in-patient hospital admission that includes a minimum of an overnight stay in a healthcare facility.

"Other significant medical hazards" refer to important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

11.1.3 Other Safety Findings

Other Safety Findings (regardless of association with an adverse event) include:

- Medication errors, overdose, whether accidental or intentional, misuse, or abuse, involving an Amgen product,
- Pregnancy and lactation exposure,
- Transmission of infectious agents,
- Reports of uses outside the terms for authorized use of the product including off-label use,
- Occupational exposure,
- Any lack or loss of intended effect of the product(s).

11.1.4 Product Complaints

Product Complaints include any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product or device after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug(s) or device(s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) includes investigational product.

This study will collect Product Complaints to Repatha® and devices used in the administration of Repatha®.

11.2 Safety Reporting Requirements

The Investigator is responsible for ensuring that safety events (adverse events considered by the Investigator to be causally related to administration of Repatha®, product complaints and other safety findings) observed by the Investigator or reported by the subject that occur during the observation period are recorded in the subject's appropriate study documentation. **The observation period for this study consists of 2 distinct periods: 1) the retrospective observational period that is defined as the time between initiation of Repatha® and a subject's enrolment into the study and, 2) the prospective observation period defined as the time between a subject's enrolment date until the end of follow-up.**

For safety events that occurred in the retrospective observation period, the date on which the Investigator accessed the subject's medical notes to abstract the relevant retrospective information should be entered into the field "Date Investigator became aware of this Event" on the Event eCRF. Safety events **occurring in the prospective observation period** must be submitted as individual case safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of Investigator awareness **for serious events and 15 days of Investigator awareness for non-serious events**.

If the EDC system is unavailable to the site staff to report the safety event, the information is to be reported to Amgen via a paper Safety Reporting Form within 1 business day of the Investigator's awareness. For EDC studies where the first notification of a safety event is reported to Amgen via the Safety Reporting Form, the data must be entered into the EDC system when the system is again available.

See Appendix C for sample Safety Reporting Form, Appendix D for Additional Safety Reporting Information regarding the adverse event grading scale used in this study, and Appendix E for sample Pregnancy and Lactation Notification Worksheets.

The Investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded on study Case Report Forms (CRFs) where safety data may also be recorded (eg, Event CRF).

11.2.1 Protocol Exempt Safety Information

Only those adverse events considered by the Investigator to be causally related to Repatha® administration are required to be reported. These events are to be reported as they are of specific interest to health authorities and other bodies.

Exempted events are those adverse events not considered by the Investigator to have a causal relationship with Repatha® administration. Repatha® has a well characterized safety profile based on the experience of greater than 26,000 subjects exposed to Repatha® in clinical trials as well as experience obtained from post-marketing sources. Collection of adverse events not considered related to Repatha® in this observational serial chart review is not expected to further inform the Repatha® safety profile.

All safety information that is not specified in this section including all fatal events are to be collected and submitted to Amgen within the specified time frame.

11.2.2 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required to regulatory authorities, Investigators/institutions, IRBs/IECs or other relevant ethical review board(s) in accordance with Pharmacovigilance guidelines and in compliance with local regulations. The Investigator is to notify the appropriate IRB/IEC or other relevant ethical review board of Serious Adverse Events in accordance with local procedures and statutes.

12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations. The IRB/IEC or other relevant ethical review board must be informed of all amendments and give approval. The Investigator must send a copy of the approval letter from the IRB/IEC or other relevant ethical review board to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the contractual agreement. The Investigator is to notify the IRB/IEC or other relevant ethical review board in writing of the study's completion or early termination and send a copy of the notification to Amgen.

13. Plans for Disseminating and Communicating Study Results

The intent is to publish the results from this study. Publication may be in the form of Congress abstracts or posters, and/or manuscript(s).

13.1 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

14. References

Blom DJ, et al A 52-Week Placebo-Controlled Trial of Evolocumab in Hyperlipidemia. NEJM 2014; 370: 1809-1819

Brown MS, Goldstein JL. Biomedicine. Lowering LDL--not only how low, but how long? Science. 2006; 311:1721-1723

Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376:1670-1681

Horton JD, Cohen JC, Hobbs HH. Molecular biology of PCSK9: its role in LDL metabolism. Trends Biochem Sci. 2007; 32:71-77

Kannel WB, et al. The Framingham Study: An epidemiological investigation of cardiovascular disease, Section 30. Some characteristics related to the incidence of cardiovascular disease and death: The Framingham Study. 18-year followup. Washington, D.C., Dept.of Health, Education, and Welfare, Publication No. (NIH) 74599, 1974

Kannel WB, Castelli WP, Gordon T. Lipoprotein cholesterol in the prediction of atherosclerotic disease: New perspectives based on the Framingham Study. Ann Int Med. 1979;90:85-91

Kannel WB. Range of serum cholesterol values in the population developing coronary artery disease.Am J Cardiol.1995;76:69C-77C

Repatha® EPAR; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/003766/WC500191401.pdf

Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events. NEJM 2015; 372(16) 1500-1509.

Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. NEJM 2017; 376(18):1713-1722.

Seidah NG, Benjannet S, Wickham L, et al. The secretory proprotein convertase neural apoptosis-regulated convertase 1 (NARC-1): liver regeneration and neuronal differentiation. Proc Natl Acad Sci USA 2003;100:928-933

Tolonen H, Keil U, Ferrario M, Evans A, WHO MONICA Project. Prevalence, awareness and treatment of hypercholesterolaemia in 32 populations: results from the WHO MONICA Project. Int J Epidemiol. 2005;34:181-192

15. Appendices

Appendix A. List of Stand-alone Documents

None

Appendix B. Cardiovascular History Variables

- Coronary Thrombosis (acute, non-acute)
- Acute coronary Syndrome
- Angina (stable, unstable)
- Coronary Artery Disease
- Ischaemic Heart Disease
- Myocardial Infarction (NSTEMI/STEMI)
- Coronary Artery Bypass Grafting (CABG)
- Percutaneous Coronary Intervention (PCI)

Components of Cerebrovascular or Peripheral Vascular Disease (CVD / PVD)

- Peripheral Artery Disease
- Claudication intermittens
- Critical limb ischemia
- Atherosclerosis
- Carotid Artery Disease
- Ischaemic Stroke
- Transient Ischaemic Attack (TIA)

Additional risk factors:

- Smoking status/history
- History of hypertension
- History of CKD
- Vascular bed involvement

Appendix C. Schedule of Observations

	Observation Period		
Data to be collected	Baseline[a]	3 monthly follow-up data[b]	EOS[h]
Demographics	X		
Meets Eligibility Criteria	X		
Subject Enrollment	X		
Cardiovascular Medical History	X		
Diabetes Medical History	X		
Details of HbA1C Assessments	X		
Site Characteristics[c]	X		
History of Statin Intolerance	X		
Initiation of Repatha®	X		
Cardiovascular Risk	X		
FH Status[d]	X		
Additional Consents/Withdrawal of Consent[e]	(X)	(X)	
Events Summary[f]		X	
Product Complaints[g]		(X)	
Concomitant Medications			
Other Lipid Modifying Therapy	X	X	
Study Log Pages			
Repatha® Administration		X	
Missed Repatha Dose		X	
Details of Cholesterol Assessments	X	X	
Hospitalizations	X	X	
Non-Hospitalization Health Visits			
Healthcare Visit	X	X	
Apheresis Healthcare Visits	X	X	
End of Study			
End of Study			X
Last Repatha® Dose			X

[a] Baseline data to be entered into the eCRF within 7 calendar days of enrollment
[b] Follow up data to be entered into the eCRF within 15 calendar days of the chart review, or routine subject visit
[c] Completed for first subject at each site only
[d] Completed if FH diagnosis confirmed on Cardiovascular Risk page
[e] To be added if applicable - via Add Event button in eCRF
[f] All Repatha® related events [(S)ADRs], any non-related fatal events, any other safety findings – To be completed within 1 business day of awareness
[g] To be completed when applicable within 1 business day of awareness – via Add Event button in eCRF
[h] EOS – Up to 30 months from the initiation of Repatha® (regardless of continuation/discontinuation of Repatha®) unless subject dies, is lost to follow up, or withdraws consent.

Appendix D. Sample Safety Reporting Forms

AMGEN Study # 20130296 Repatha	Electronic Adverse Event Contingency Report Form For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

<<For completion by COM/Study manager/Author prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____
and start date: Day ____ Month ____ Year _____

3. ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day___ Month___ Year___

Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of drug under study	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by, Amgen drug under study or an Amgen device used to administer the Amgen drug under study?								Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
						<drug/device> No✓	<drug/device> Yes✓	<drug/device> No✓	<drug/device> Yes✓	<drug/device> No✓	<drug/device> Yes✓	<drug/device> No✓	<drug/device> Yes✓		
				☐Yes ☐No											
				☐Yes ☐No											
				☐Yes ☐No											

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly / birth defect; 06 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

AMGEN
Study # 20130296
Repatha

Electronic Adverse Event Contingency Report Form

For Restricted Use

Site Number	Subject ID Number

5. Was drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

Amgen Drug/Amgen Device:		Date of Initial Dose (Day Month Year)	Prior to, or at time of Event: Date of Dose (Day Month Year)	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
<<Drug/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<< Drug/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Test												
Date (Day Month Year)	Unit											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20130296 Repatha	Electronic Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee -	Title	Date
I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.		

Appendix E. Additional Safety Reporting Information

Adverse Event Severity Scoring System

Grade	Amgen Standard Adverse Event Severity Scoring System
1	MILD: Aware of sign or symptom, but easily tolerated
2	MODERATE: Discomfort enough to cause interference with usual activity
3	SEVERE: Incapacitating with inability to work or do usual activity

Appendix F. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20130296

Study Design: ☐ Interventional ■ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____) _____ **Fax** (____) _____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm ____ / dd ____ / yyyy ____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm ____ /dd ____ /yyyy ____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____ /dd ____ /yyyy ____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm ____ / dd ____ / yyyy ____ ☐ Unknown

Estimated date of delivery mm ____ / dd ____ / yyyy ____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm ____ / dd ____ / yyyy ____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm ____ / dd ____ / yyyy ____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details: _____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

****

Effective Date: March 27, 2011

Page 1 of 1

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: 20130296

Study Design: ☐ Interventional ☑ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm____ / dd____ / yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

****

Effective Date: 03 April 2012, version 2.

Page 1 of 1

Appendix G. ENCePP Checklist for Study Protocols

Study title:
Observational Serial Chart Review of Repatha® Use in European Subjects with Hyperlipidaemia

Study reference number:
20130296

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	Section 6
1.1.2 End of data collection[2]	☒	☐	☐	Section 6
1.1.3 Study progress report(s)	☐	☒	☐	
1.1.4 Interim progress report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS register	☒	☐	☐	1
1.1.6 Final report of study results.	☒	☐	☐	Section 6

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	Sctn 4,7.2
2.1.2 The objective(s) of the study?	☒	☐	☐	Sctn 8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	Sctn 9
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☒	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	Sctn 7

Comments:
There is no formal hypothesis

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	Sctn 9
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	Sctn 9.3
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☒	☐	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	Sctn 9
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	Sctn 9
4.2.2 Age and sex?	☒	☐	☐	Sctn 9.2
4.2.3 Country of origin?	☒	☐	☐	Sctn 9.2
4.2.4 Disease/indication?	☒	☐	☐	Sctn 7
4.2.5 Co-morbidity?	☐	☒	☐	
4.2.6 Seasonality?	☐	☒	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	Sctn 9.9

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☐	☐	☒	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective				

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	Sctn 9.3
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	Sctn 9.3

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Confounding is not applicable; no association is examined in this stiudy

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☐	☐	☒	
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	Sctn 9.4
8.1.3 Covariates?	☒	☐	☐	Sctn 9.4
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	Sctn 9.7
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	Sctn 9.7
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☒	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☒	☐	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	Sctn 9.5

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☒	☐	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	Sctn 9.7
10.3 Are descriptive analyses included?	☒	☐	☐	Sctn 9.7
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	Sctn 9.7
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	Sctn 9.6
11.3 Are methods of quality assurance described?	☒	☐	☐	Sctn 9.6
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	Sctn 9.7
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	Sctn 9.9
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	Sctn 9.9
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☒	☐	
12.3 Does the protocol address other limitations?	☒	☐	☐	Sctn 9.9

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	Sctn 10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	Sctn 10

Comments:

No EC review has yet taken place.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	Sctn 5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☐	☒	☐	
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	Sctn 13

Comments:

Name of the main author of the protocol: PPD

Date: 10 /12/ 2015

Signature: PPD

Amendment 2

Protocol Title: Observational Serial Chart Review of Repatha® Use in European Subjects With Hyperlipidaemia

Amgen Protocol Number (Repatha®) 20130296

NCT Number: NCT02770131

Amendment Date: 20 December 2018

Rationale:

The main purpose of this protocol amendment is to clarify safety reporting requirements and to align data management-specific language with current requirements.

Description of Changes:

Section: Global

Change: Version date updated throughout document from 13 February 2018 to **20 December 2018**.

Section: Global

Change: Editorial changes (including typographical, grammatical, and formatting) have been made throughout the document.

Section: Title Page

Replace:

Protocol version identifier	Amendment 1

With:

Protocol version identifier	**Amendment 2**

Section: Title Page

Replace:

Date of last version of the protocol	19th November 2015

With:

Date of last version of the protocol	**13 February 2018**

Section: Title Page

Add:

NCT Number	**NCT02770131**

Section: 2 List of Abbreviations

Add:

CRF	**Case report form**
EDC	**Electronic data capture**

Section: 5. Amendments and Updates

Add:

Amendment or Update No.	Date	Section of Study Protocol	Amendment or Update	Reason
1	13 Feb 2018		See summary of changes	
2	**20 December 2018**		**See summary of changes**	

Section: 9.6 Data Management, Paragraph 1

Delete:

~~An eCRF Completion Guideline is provided.~~

Section: 9.6 Data Management, Paragraph 6, Bullet 3

Delete:

- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data is checked for consistency, omissions, and any apparent discrepancies. To resolve any questions arising from the clinical data management review process, data queries ~~and/or site notifications~~ are created in the EDC system database for site resolution and closed by Amgen reviewer.

Section: 9.6 Data Management, Paragraph 6, Bullet 4

Replace:

- The Investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that the Investigator inspected or reviewed the data on the CRF, the data queries, and site notifications, and agrees with the content.

With:

- The Investigator **applies an electronic signature in the electronic data capture (EDC) database. This signature indicates that investigator inspected or reviewed the data on the CRF, the data queries, and agrees with the content.**

Section: 11.2 Safety Reporting Requirements, Paragraph 1

Replace:

The Investigator is responsible for ensuring that safety events (adverse events considered by the Investigator to be causally related to administration of Repatha®, product complaints and other safety findings) observed by the Investigator or reported by

the subject that occur during the study observation period through to the final study contact are recorded in the subject's appropriate study documentation. Safety events must be submitted as individual case safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of Investigator awareness.

With:

The Investigator is responsible for ensuring that safety events (adverse events considered by the Investigator to be causally related to administration of Repatha®, product complaints and other safety findings) observed by the Investigator or reported by the subject that occur during the observation period are recorded in the subject's appropriate study documentation. **The observation period for this study consists of 2 distinct periods: 1) the retrospective observational period that is defined as the time between initiation of Repatha® and a subject's enrolment into the study and, 2) the prospective observation period defined as the time between a subject's enrolment date until the end of follow-up.**

For safety events that occurred in the retrospective observation period, the date on which the Investigator accessed the subject's medical notes to abstract the relevant retrospective information should be entered into the field "Date Investigator became aware of this Event" on the Event eCRF. Safety events **occurring in the prospective observation period** must be submitted as individual case safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of Investigator awareness **for serious events and 15 days of Investigator awareness for non-serious events**.